THE EPIDEMIOLOGY AND COST-EFFECTIVENESS OF VACCINATION STRATEGIES AGAINST INFECTIOUS DISEASES: A FOCUS ON VARICELLA ZOSTER, PANDEMIC INFLUENZA A/H1N1 2009, AND STREPTOCOCCUS PNEUMONIAE

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DE EPIDEMIOLOGIE EN KOSTENEFFECTIVITEIT VAN VACCINATIE-STRATEGIEEN TEGEN INFECTIEZIEKTEN: EEN FOCUS OP VARICELLA ZOSTER, PANDEMISCHE GRIEP A/H1N1 EN STREPTOCOCCUS PNEUMONIAE

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chapter ONE

GENERAL INTRODUCTION

ONE

This thesis is concerned with the epidemiology of vaccine preventable diseases, quantifying their burden, and estimating the cost-effectiveness of alternative strategies to control them. This subject brings together three fields of research: health economics, vaccinology, and infectious disease epidemiology. Health economics is a branch of economics which focusses on the scarcity in the allocation of health and health care [1]. Within the field of health economics the framework of cost-effectiveness analysis was developed. The cost-effectiveness framework is focussed on analysing the costs of a new drug or health care intervention related to the (projected) health improvement. The outcome of the cost-effectiveness analysis enables a direct comparison between mutually exclusive products or interventions. Other research in the field of health economics is focussed on the development of tools to measure health states or quality of life, investigates methodological issues as time preferences and the application of sensitivity analysis [1]. The second field of research is the field of vaccinology, this is a science focussed on the development and application of vaccines [2]. The field is linked to other areas as immunology and bio-chemistry and has as goal to develop sustained immunity against pathogens by priming the immune system with a compound. Questions in vaccinology are for example the use of adjuvants, conjugation of antigens and optimisation of the prime-boosting schedule. The third field of research is infectious disease epidemiology. Infectious disease epidemiology tries to understand disease transmission and transmission control. In this thesis infectious disease epidemiology is applied by the use of infectious disease transmission models, risk factor analysis and the understanding of transmission patterns.

In this thesis there is a focus on three different pathogens; varicella zoster, influenza A/H1N1 2009 and Streptococcus pneumoniae, and for clarity the thesis is structured by these pathogens.

The main aim of the research described in this thesis was to support sound decision making in the application of vaccines. The research in this thesis did/will support five decisions in the use of vaccines in England and Wales and the Netherlands: introduction of Herpes Zoster vaccination among elderly (70+; England and Wales) [3], withholding of an introduction of childhood Varicella vaccination (England and Wales) [4], to focus the introduction of the pandemic H1N1/09 influenza vaccine on risk groups (England and Wales) [5] the introduction of a successor of the 7-valent pneumococcal conjugate vaccine (the Netherlands) and the decision whether or not to vaccinate pneumococcal risk groups with a pneumococcal conjugate vaccine (England and Wales).

In this general introduction the three pathogens and the individual chapters are introduced, and for each chapter the main aim and major issues or discussion points are described.

PART I

Varicella Zoster vaccination

Varicella Zoster virus (VZV), is a DNA virus from the Herpes family [6,7]. Members of this family are able to integrate their viral DNA into the nuclei of host cells, and in doing so the virus remains dormant within the human body. The first exposure to VZV causes varicella (chickenpox), a disease which in temperate climates mostly occurs in childhood [6,7]. After initial infection the virus remains dormant in the dorsal root ganglia [8]. Later in life the virus can reactivate, most likely due to a waning of cell mediated immunity, and causes Herpes Zoster (HZ; shingles). HZ can cause post herpetic neuralgia (PHN), a painful and long lasting complication [7]. Cell mediated specific immunity can be boosted by exogenous exposure to VZV [9]. Due to this relation of exposure and the activity of the cell mediated specific immunity there is a link between getting exposed to VZV via a varicella and/or HZ patients, and a reduced risk of reactivation of the dormant virus and subsequently HZ disease [10,11]. In this section of the thesis the impact of the introduction of a live attenuated VZV vaccine is investigated. There are two versions of the vaccine; a high concentrated version aimed at older adults, to boost immunity and prevent reactivation of the virus causing HZ, and a version to be used as a childhood vaccine against the initial infection. In this part of the thesis we investigate the impact of an introduction of HZ vaccination (chapter 2 and 3) and a combined use of the childhood and adult vaccine (chapter 4 and 5).

CHAPTER 2

Aim

Describe the cost effectiveness of Herpes Zoster vaccination for the 60 plus in England and Wales.

In 2005 the results of a large randomized, double-blind, placebo controlled clinical trial was published. The trial was performed in a cohort of 38,546 individuals aged 60 years and over and assessed the efficacy of a HZ vaccine at reducing the burden of HZ associated disease. The results showed that HZ vaccination reduced the incidence by 51.3% [12] in vaccinees compared to the placebo recipients. Following these results the vaccine was licensed by the Food and Drug Authority (FDA) in the US [13] and the European Medicines Agency (EMA) in the European Union [14]. The licensure of an effective vaccine against HZ necessitates a decision whether or not to introduce this vaccine in England and Wales.

To support this decision we investigated the cost-effectiveness of introducing HZ vaccination in older adults. The proposed schedule by the manufacturer was one dose at the age of 60, but also other ages of introduction were investigated. The greatest challenge in the analysis was incorporating various age effects; as there is

an increasing incidence of disease by age as well as an increasing severity, and the results of the clinical trial suggest that the vaccine is less efficacious among older recipients. Within the cost-effectiveness analysis the disease burden needs to be expressed in quality adjusted life years (QALYs) lost. QALYs combine the severity of disease with the duration of symptoms. The severity of disease is expressed as a QALY weight, a measure between 0 and 1. Unfortunately not many data was available measuring the QALY weight of HZ at different ages and at different intervals after disease onset, however what was available was the measurement of pain levels. Therefore we modelled pain levels by age and time after onset and subsequently translated those estimated pain levels and duration into QALY losses.

To use a realistic vaccine efficacy within the model we estimated the waning of immunity by comparing the incidence of disease in both arms (i.e. vaccine vs placebo) over the duration of the follow-up.

CHAPTER 3

Aim

Describe the cost effectiveness of Herpes Zoster vaccination for the 60 plus in the Netherlands.

The question of whether to introduce the vaccine was also raised in the Netherlands. In this chapter we describe the disease burden and implications of Herpes Zoster vaccination in the Netherlands using the checklist developed by the Dutch institute of Public Health and the Environment (RIVM) [15]. Doing so required re-parameterisation of the model developed in chapter 2 to the epidemiological setting of the Netherlands, as well as an adaptation of the cost-effectiveness model. The latter because there are different rules to perform cost-effectiveness modelling in the Netherlands compared to England. Firstly in the Netherlands a different perspective is applied, a societal perspective instead of a health care payer's perspective [16]. This means that in Netherlands interventions are evaluated based on a wider impact for society, including indirect costs such as work loss due to disease. In England only the direct effects on health outcomes and health care utilization are included in the base case [17]. Secondly in the Netherlands differential discounting is in place, this means that costs and health effects are discounted separately with each a different discount rate [16], this is different from England and Wales where the same discount rate is used for both costs and outcomes [17]. Thirdly there is a different threshold for which an intervention is considered to be cost effective. In England and Wales this threshold is between £20,000 and £30,000 in the Netherlands this was lower with €20,000 (£20,000 pounds was ~ €25,000 euro on 16 June 2012).

Given the differences in the applied criteria in the cost-effectiveness analyses the model outcome can be different despite the use of the same disease model.

CHAPTER 4

Aim

Describe the epidemiological effects of an introduction of a universal childhood vaccine against VZV.

After the focus on HZ and HZ vaccination in chapter 2 and 3 the next two chapters describe the impact of childhood vaccination against VZV on varicella and HZ.

It took around 200 years between the first description of varicella by William Heberden in 1767 to the isolation of the virus by Weller and Stoddard in 1952 [18].

Immediately after the isolation of the virus, researchers started to develop a vaccine. The vaccination was introduced in Japan (1987) and South Korea (1988) and in the United States in 1995 [19,20]. However until today this vaccine has not been introduced in England and Wales or the Netherlands, and most other countries. This is because of two reasons. The first is a possible increase in the average age of infection in case of a poor uptake of the vaccine. An indirect impact of vaccinating children is a reduced transmission of the virus, due to this reduced transmission it takes longer to infect a susceptible person. In practice this means that the patient, who was born susceptible, will be older when experiencing disease, compared to a situation without vaccination. In the case of VZV this possible increase in the average age of infection is important because varicella is more likely to be severe if acquired later in life, especially during pregnancy. Varicella during pregnancy can cause pneumonia and encephalitis in the mother, leading to severe complications, and foetal varicella syndrome in the unborn infant [6]. Due to these severe outcomes pregnant woman who are exposed to VZV are currently passively immunised with VZV-immunoglobulin; a costly intervention to prevent disease.

The second reason not to introduce the vaccine is because of the relation between waning cell mediated specific immunity against VZV and the reactivation of the virus as HZ. In normal life the reactivation of VZV is actively suppressed by the immune system, which is boosted on re-exposure to the wild type virus. Therefore when the transmission of wild virus declines due to vaccination there will be a decline in boosting events, and hence an increase of reactivation and HZ cases [10,11].

However, HZ vaccine might be able to mimic the re-exposures, possibly counter-balancing the decline of natural boosting.

In this chapter we build on the work of Marc Brisson, who previously developed a varicella transmission model [21,22]. Firstly we expand this model by incorporating vaccination against HZ. Secondly, since the contact between children and adults (driving the boosting) was based on assumptions we replaced those assumptions by real data. This contact data was collected as part of the European project Polymod, which documented epidemiologically relevant social contact patterns in 8 different countries [23]. To include this contact data in the model we had to solve some

methodological issues such as how to incorporate uncertainty, the transmission probability per contact and how to utilize information of the most likely contact structure given the disease pattern by age.

The final results of this chapter shows the incidence of varicella zoster and Herpes Zoster in England and Wales and the projected impact of several vaccination schedules (i.e. both with childhood and adult vaccination) on the disease incidence.

CHAPTER 5

Aim

Describe the cost-effectiveness of a varicella vaccination programme that includes both childhood vaccination against varicella and the vaccination of the elderly against HZ.

In this chapter we translated the epidemiological predictions from Chapter 4 into costs and QALY loss over time and undertake an economic analysis of the alternative policy options.

In the context of varicella zoster vaccination the time preference of the decision maker is very important. As explored in the previous chapter, exposure to VZV appears to act as a booster against HZ, therefore, when this booster falls away there is an estimated increase of HZ in the short and medium-term (up to 30-40 years) following introduction of the vaccine. This increase is reduced when the elderly receive HZ vaccine but it will not be prevented. However in the long run (80 years and over) there is a predicted decline in HZ. This decline is due to the fact that varicella vaccinated children are assumed to have a lower probability of developing HZ. So there is a negative effect in the medium-term and a positive effect in the long term, therefore time preferences of time become important in the interpretation of the results in the context of decisions making.

In cost-effectiveness modelling there are two ways to handle time preferences, this is by discounting and the time horizon. Discounting is to give less weight to cost and benefits in the future and the time horizon is the numbers of future years included in the analysis. In this chapter we extensively explore the effect of different assumptions regarding those two parameters, exploring different discount rates in combination with different time horizons, including an infinite one.

The overall conclusion regarding the cost-effectiveness of a combined vaccination schedule depends on the time preferences of the decision maker.

PART II

Vaccination against pandemic influenza A/H1N1 2009 influenza

In April 2009 a new strain of the influenza virus was recognised in Mexico and California (USA) which quickly spread around the world [24]. The World Health

Organisation declared a pandemic on the 11th June 2009 [25]. Influenza is a respiratory RNA virus which is transmitted among birds and mammals such as humans, swines and horses. The 2009 influenza strain was a A/H1N1 strain that circulated among swines but which adapted to human-to-human transmission [26]. This part of the thesis is about the severity of disease caused by pandemic influenza A/H1N1 and the cost-effectiveness of the use of pandemic A/H1N1 influenza vaccine. That is we attempted to measure the health "costs" of this novel strain of influenza in comparable units, and estimate the cost-effectiveness of vaccination in the same way that other vaccines are routinely evaluated in the UK.

The decision to purchase a vaccine was made quickly after the emergence of the new virus. The production of the vaccine is however a time consuming process which took around 5 to 6 months (the virus has to be identified, a vaccine strain has to be prepared, the vaccine strain has to be verified, reagents to test the vaccine has to be prepared, the growth conditions of the virus has to be optimized, the vaccine has to be manufactured in bulk, the quality of the produced vaccine has to be controlled, vaccine has to be filled in syringes and the vaccine has to be tested in clinical trials [27]). The vaccine became available in the UK on the 21st of October 2009 [28], and our analysis was performed therefore to inform decisions on vaccine implementation at around that date.

CHAPTER 6

Aim

Obtain the disease burden of pandemic influenza A/H1N1 2009 by estimating the loss of quality of life.

One of the key questions raised when a new disease emerges concerns that of the clinical severity of the disease caused by the new pathogen. Indicators of severity are hospitalisation and case fatality rates. Apart from these indicators in cost-effectiveness analysis the impact on the quality of life is considered, expressed as the QALYs lost. To calculate this it is necessary to estimate the QALY weight, this is the quality of life given the health status, and the duration of that health status. When you know both the total amount of QALY can be calculated by multiplying the QALY weight by the duration. Subsequently the QALY loss is the difference between the QALY in perfect health and the QALY given the disease health status.

To measure the QALY weight several methods have been developed within the discipline of health economics. These methods describe the quality of life with a value between 1 and 0, where 1 is perfect health and 0 death. The methods are the visual-analogue scale (VAS), the time trade-off (TTO) and the standard gamble (SG) [1]. In the visual-analogue scale the patient is asked to value their current health state between 0 and 100 (0 being the worst imaginable health state). In the time-trade off method respondents are asked how much life-expectancy they

would be willing to trade off to remove themselves from a certain health stage. In the standard-gamble method individuals are provided with a gamble that would either return them to full health (or some other state) or result in immediate death. They are then asked what the maximum probability of death they would accept.

The VAS is comparatively easy to administer, but has been criticised on empirical and theoretical grounds. The TTO and SG are very difficult to implement in practice. Hence, other methods have been developed that are comparatively easy to apply and yet have the ability to provide a preference-based measure of health related quality of life, that has the correct properties. One such method is EuroQoL (EQ-5D). The EQ-5D method assesses health related quality of life in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each of those dimensions can be: not affected, a little affected or a lot affected, resulting in 125 possible combinations (5^3). From a large number of these combinations a QALY weight was obtained based on the time-trade off method by asking the general public. This makes it possible to calculate QALY losses for patients if you know their score for those 5 dimensions. In this chapter we describe a survey among laboratory confirmed cases of H1N1 and H1N1 negative controls and estimate the impact on the quality of life by the use of the EQ-5D.

Issues related to the measurement of the quality of life, such as the problems in estimating the duration of disease are discussed. The outcomes are compared to previous estimates of the impact on the quality of life for influenza.

CHAPTER 7

Aim

Estimation of the cost-effectiveness of the A/H1N1 2009 pandemic influenza vaccine for different target groups taking into account the availability of the vaccine in respect to the on-going pandemic.

This chapter describes the analysis we performed to investigate the best use of the A/H1N1 2009 pandemic vaccine at the time of availability in October 2009. In this analysis we take into account the disease transmission, the disease outcome and the availability of vaccine over time.

During a pandemic it is difficult to make evidence based decisions, as there is not much time, and the numbers of options are limited as there are constraints on vaccine supply or lack of time to mount large programmes. There are broadly two vaccination options: to protect a certain group in the population or to control the spread of the disease in the whole population. For influenza this question can be very important. The main transmission of influenza is among children; however the main burden of disease tends to fall on the elderly. Therefore you can protect the elderly by vaccinating them directly, or you can try to control the spread by vaccinating the children and protect the elderly indirectly.

To be able to inform policy making on time we used a real-time modelling approach. A real time model is a contemporary exploration of the pandemic, making use of data which is collected while the pandemic is on-going. The model estimates are improved when there is more data available. There are numerous problems which had to be overcome to make a valid assessment of the situation and which are addressed in this chapter. The first problem is the estimation of the proportion of the population which is immune to the new disease; the base line immunity. The base line immunity is important because the total size of the pandemic is directly related to the total number of available susceptibles. An estimation of the people who are immune is therefore key. We used seroprevelance data as collected from residual laboratory samples to parameterize this variable. The second problem is the estimation of the cumulative number of infections; the total number of those susceptibles who have become immune. The estimation of this number based on health care consultations is problematic due to potential changes in health care seeking behaviour. The third problem is the change in contact patterns during the pandemic. Changes in the contact patterns can hugely affect the speed of the epidemic. These behavioural changes can be for example due to different time in the calendar such as holidays [29]. Using the original data from the Polymod study [23] it was possible to generate contact matrices for the holiday and non-holiday period. The fourth problem was the estimation of the relative risk of clinical disease and the hospitalisation and case fatality rate by age and risk group. Important parameters in the evaluation of a targeted vaccination approach.

In this chapter the fitting procedure is described, bringing together the information on the base line immunity, the epidemic curve (based on the estimated number of influenza cases in the health care system) and the observed growth rate after the school holidays. The fitted model allowed for an estimation of the timing of the peak and the expected number of remaining infections. Combining the model results with the disease outcomes (by risk group) and the estimation of the QALY loss (chapter 6) allowed for the estimation of the cost-effectiveness of a targeted vaccination approach compared to strategies aimed at controlling the transmission. The study is the first, and only, real-time transmission and cost-effectiveness analysis evaluating different vaccination strategies during an on-going pandemic.

PART III

Streptococcus pneumoniae

The third part of the thesis is focussed on Streptococcus pneumoniae and the epidemiology and cost-effectiveness of a 7-valent conjugated vaccine (PCV-7). This vaccine which was introduced in April 2006 in the Netherlands [30] and September 2006 in England and Wales [31].

S. pneumoniae is a capsulated gram-positive bacteria which colonizes the nasopharynx. The bacteria behaves in the majority of carriage events as a

commensal bacteria, where carriage is not accompanied by symptoms or disease. However occasionally the bacteria does cause disease. Pneumoccocal disease can be non-invasive, with outcomes including pneumonia and otitis media or invasive with the most severe outcomes including death, meningitis and empyema. The incidence by age is U shaped, with a high incidence among children and elderly.

There are over 90 known serotypes of the bacterium, where each type differs based on the expressed polysaccharide in the capsule. These polysaccharides form the bases of the conjugated vaccine, for PCV-7 the polysaccharides expressed are of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. The conjugate pneumococcal vaccine is a conjugated vaccine, the first developed conjugated vaccine was a vaccine against Hemophilus influenzae type b. The conjugated vaccines are a great achievement in vaccinology as they are the first example of rational vaccine design based on a deep understanding of immunology [32]. The rationale is as follows; one of the characteristics of polysaccharides is that they are poorly presented on the major histocompability complex (MHC), a molecule on antigen presenting cells which activate T-cells, a major component of the adaptive immune system. Conjugation of the polysaccharide with a highly immunogenic protein, such as the tetanus toxoid or CRM-157, enables presentation on the MHC and therefore a T-cell dependent response, leading to relatively long-lasting immunity [33,34], a marked improvement on the plain polysaccharide vaccine. The generated immune response does not only protect against disease but also against carriage of the bacteria [35]. Due to the prevention of carriage the chain of transmission is interrupted leading to herd protection, which is the protection of those who are not vaccinated. The ability to protect the unvaccinated population by only vaccinating children has been an enormous driver in the introduction of the vaccine. A cost-effectiveness analysis suggested that if this additional protection occurred, and was not cancelled by serotype replacement then vaccine introduction would likely be cost-effective, despite the high price of the vaccine [36].

This part of the thesis focuses on the post-introduction evaluation, both in terms of epidemiology and cost-effectiveness. The effect of vaccinating different target groups is evaluated, as are alternative vaccination schedules and the expansion of the vaccine coverage from 7 serotypes to a 10 valent vaccine (PCV-10, including also serotype 1, 5 and 7F) or a 13 valent vaccine (PCV-13; including PCV-10 + the serotypes 3, 6A and 19A).

CHAPTER 8

Aim

Establish the cost-effectiveness of a programme with more replacement than expected.

The cost-effectiveness of a vaccination programmes is dependent on its ability to reduce overall disease burden. There are several factors which can lead to a lower reduction in the disease burden; a first example is a situation in which the

people who you vaccinate do not reflect the people in the clinical trial. For example when only healthy elderly are included and the vaccinated cohort consists for 40% of immune-compromised people, in such circumstances there might be a lower reduction in overall disease burden. A second example is a situation where you base the vaccine efficacy on a correlate of protection, an indirect measure of the effectiveness, which does not hold in real life. For example the vaccine efficacy has been shown to increase the level of antibodies against a certain antigen above a certain threshold, however in real life this antigen is poorly presented or the antibody response, although reaching a certain threshold, is not strong enough to induce protection. A third example might be a situation in which there is an unpredicted lower uptake of the vaccine leading to less herd protection, on its turn leading to a lower reduction in the overall disease burden.

A fourth example, and the example focussed on in this chapter, is replacement disease. Due to the reduction of vaccine related disease it is possible to get an increase in non-vaccine related disease. Bacteria grow in ecological niches where they compete among each other for nutrients and space, or indirectly via the host immune response. Prevention of the growth of one type might lead to others occupying the vacated niche. If the replacing types are disease-causing, then the overall reduction in incidence will be reduced by non-vaccine related pathogens.

In the case of Strep. pneumomiae there are 90 known serotypes, and only 7 of them are included in the original conjugate vaccine, the rest of the serotypes can therefore be considered non-vaccine related. Given that a great number of serotypes are found in carriage it is likely that there is competition between the serotypes, possibly leading to replacement in the case of vaccination. Initially this replacement effect was thought to be minor, because in the United States, where PCV-7 was introduced first, low levels of replacement were observed. However the post-vaccination experience in England and The Netherlands was different, with much higher level of replacement. In this chapter we investigate the impact of the greater than anticipated replacement effect on the cost-effectiveness of PCV7 in the Netherlands. The analyses also focus on the impact of herd protection, reducing the number of doses, and introduction of PCV-10 or PCV-13.

CHAPTER 9

Aim

Describe the post-vaccination carriage of Strep. pneumoniae after introduction of PCV-7 in England and Wales.

To understand the observed replacement trends in IPD we conducted a carriage study in two regions in England (Hertfordshire and Gloucestershire). In a carriage study samples are taken from the mucosal flora in the nasopharynx, the normal environment of the streptococcus pneumoniae, by a long flexible swab. Subsequently

material on the swab is transferred into a medium, which is cultured on a plate to investigate the existence of strep. pneumoniae. The positive samples are serotyped. In our study we included children and adults and the samples were taken in 2009, 3 years after the introduction of the vaccine. Results were compared to the pre-vaccination carriage prevalence in 2001-2002 [37,38], when a longitudinal carriage study was conducted in the same regions.

As the conjugated vaccine is effective against carriage there is an expected decline in the prevalence of vaccine related serotypes. Some interesting questions in this study are: firstly, the overall reduction in carriage, as this will highlight if there is a (vaccine induced) reduction in the transmission of streptococcus pneumoniae. Secondly, the increase in carriage of serotypes not included in the vaccine, which will show the level of serotype replacement and thirdly, the carriage prevalence in relation to the observed serotypes in hospitalised disease. This latter will learn us if the replacing serotypes are more likely to cause disease given a carriage episode (more invasive) compared to the disappearing vaccine serotypes. The invasiveness of serotypes will determine the overall reduction of disease in case the overall carriage of strep. pneumoniae is not altered due to the introduction of the vaccine. When the replacing serotypes are less invasive you will observe a decrease in disease, even when the transmission is not reduced.

In this chapter the outcomes of the carriage study are presented and are placed in the context of the ranked prevalence distribution before and after introduction of PCV-7.

CHAPTER 10

Aim

Obtain the relative risk of developing pneumococcal disease among different risk groups in England.

Similar to the VZV vaccine (chapter 2 to 4) PCV can be used among older age or risk groups. Since 1992 clinical risk groups have been recommended to get the 23-valent pneumococcal polysaccharide (PPV-23) vaccine [39], and since 2003 this recommendation has been extended to all people aged 65 and over [39]. The current identified clinical risk groups are: asplenics, those with chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, diabetes, the immunosuppressed, individuals with cochlear implants and individuals with cerebrospinal fluid leaks [40]. PPV-23 is a non-conjugated vaccine and is therefore less effective in inducing lasting immunity in children. As the overall efficacy of the PPV-23 vaccine is questionable in risk groups [41], the question can be raised if it is better to inoculate these with the conjugated vaccine, given the observed high efficacy against vaccine-types among children [31]. However the benefits of a possible higher vaccine efficacy are possibly offset by the lower serotype coverage (13 serotypes vs 23 serotypes) and a higher price of per dose of PVC-13. To support

this decision our aim was to estimate the extent to which the various clinical risk groups had a higher disease incidence compared to the non-risk population. This necessitated knowledge of the size of the risk groups in the general population and the proportion of IPD in the various risk-groups. To obtain the risk group status of the IPD patients we linked laboratory test results (including serotype information) to hospital diagnostic data. This linkage allowed us to explore the diagnostic codes for each admission, and assign the patient to a risk group if risk group specific codes were present. The absolute size of the different clinical risk-groups in the population was obtained from a large dataset extract from GP databases, including 60% of the English population. Patients were assigned to a risk group on the bases of their health care seeking behaviour in the year the data was extracted.

Quantification of the increased risk of IPD for people in risk groups will inform decision making, and the absolute estimates of the odds will enable us to obtain the cost-effectiveness ratio of a targeted vaccination approach.

This chapter is an example of performing epidemiological analyses using data linkage methods utilizing large electronic databases of routinely collected data, an asset which has become available over the last decade or so.

CHAPTER 11

Aim

Describe the cost-effectiveness of the vaccination of people in risk groups

In chapter 10 the absolute risk of developing disease in clinical risk-groups was estimated, in this chapter we translate this disease risk into disease incidences and predict the cost-effectiveness of a targeted vaccination policy with the 13-valent conjugated vaccine. PCV-13 had replaced PCV-7 in the childhood vaccination programme in England since April 2010. One of the main reasons to introduce the conjugated vaccine among children was its ability to reduce transmission of vaccine types, creating a reduction of disease even in those who are not vaccinated themselves. In this chapter we investigate the impact of this reduction of vaccine-type related disease in (non-vaccinated) clinical-risk groups and the subsequent reduction of the cost-effectiveness of a targeted vaccination policy.

The vaccine efficacy of PCV-13 in clinical risk groups is not known; therefore a part of the study was a formal consultation of an expert panel. Another issue which had to be resolved to obtain sound estimates of the cost-effectiveness was an evidence based estimation of the reduced life expectancy among patient in clinical-risk groups. To do so data from the Royal College of General Practitioners (RCGP) was investigated, obtaining a mortality rate by age for different risk-group and subsequent the shorter life expectancy.

Apart from the above, also an extensive sensitivity analysis on the possible impact of vaccination on non-invasive disease was included. However, although

the cost-effectiveness is very dependent on the projected impact on non-invasive disease the reduced transmission of vaccine-types will also apply. Therefore the overall conclusion of a reduced cost-effectiveness due to herd protection will hold regardless of the level of impact against non-invasive disease endpoints.

CHAPTER 12

Aim

To investigate serotype-specific differences in the clinical presentation and quality of life of IPD in the context of the newly available PCV vaccines (PCV-10 & PCV-13).

Introduction of serotype specific vaccines necessitates serotype specific surveillance and knowledge. To increase the knowledge of disease presentation for the different serotypes we expanded the analysis described of the linked dataset of hospital admission data and laboratory data described in chapter 10. In this chapter we utilize this dataset to document the serotype specific disease presentation, case fatality ratio and subsequently the serotype specific QALY loss. The quality of life combines disease severity and mortality, including the (population based) life expectancy at the moment of death, in one composite number and should therefore document the total health impact of the individual serotypes more accurately.

Knowledge of serotype specific disease outcomes is essential to predict or understand the post-vaccination disease burden. This is because replacing serotypes can result in less (or more) severe disease outcomes, changing the overall impact of the vaccine; for example even with a similar number of hospital admissions the number of death can decline due to a lower case fatality in the replacing serotypes.

In the presented work the different disease outcomes of the various serotypes was put into context of the observed serotype distribution in England in the period July 2009- June 2010 to show the different predicted impact of PCV-10 and PCV-13 on the burden of meningitis, the mortality and the QALY loss. This chapter is one of the most extensive and detailed descriptions of clinical outcomes differentiated by individual serotypes available in the literature.

CHAPTER 13

Aim

To obtain the cost-effectiveness of the introduction of PCV-13 in April 2010, 4 years after the introduction of PCV-7.

There are three parameters driving the overall disease burden caused by the individual serotypes of Strep. pneumoniae, this is; the transmission/fitness of the serotype (studied in chapter 9), the invasiveness (studied in chapter 9), and the disease severity and associated mortality rates (studied in chapter 12), where each serotype has its own score for each of the three parameters. Types with high

transmission & high invasiveness potential will cause most disease, types with a high transmission & low invasive potential or types with a low transmission & high invasive potential will cause a significant disease burden but less so than the first group, serotypes with a low transmission & low invasiveness will be rare in IPD. Depending on the clinical presentation and case fatality rate invading serotypes can become important in the overall QALY loss.

These three serotype specific parameters came together in the estimation of the cost-effectiveness of the introduction of PCV-13 four years after the introduction of PCV-7. The analysis consisted of a dynamic transmission model (developed and published by Y. Choi and S. Flasche at the Health Protection Agency [42]) which was fitted to the pre-PCV7 carriage data and the pre-and post-PCV7 IPD data, differentiated by PCV-7 type disease, PCV-13 type disease and non-vaccine type disease. Based on the predicted number of IPD cases by the transmission model, the number of vaccine doses and the vaccine type specific disease presentations (by age) the cost-effectiveness was estimated.

The dynamic transmission model focussed only on disease trends in invasive disease (pneumonia/bacteraemia/meningitis) and did not investigate the disease trends in non-invasive disease (otitis media/pneumonia). The burden of non-invasive disease caused by Strep. pneumoniae is hard to estimate, as it is unknown which proportion of the recorded disease is caused by the bacteria and subsequently what the contribution was of vaccine types. In this chapter we explore the impact of PCV-7 on non-invasive disease endpoints based on a regression using the post-PCV7 IPD disease trends for vaccine types and non-vaccine types. The inclusion of these non-invasive endpoint in the cost-effectiveness analysis does affect the overall conclusion however the problems with quantifying this possible impact merits caution in the interpretation of the results.

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PART I

VARICELLA ZOSTER

chapter TWO

ESTIMATING THE COST-EFFECTIVENESS OF VACCINATION AGAINST HERPES ZOSTER IN ENGLAND AND WALES

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ABSTRACT

A live-attenuated vaccine against herpes zoster (HZ) has been approved for use, on the basis of a large-scale clinical trial that suggests that the vaccine is safe and efficacious. This study uses a Markov cohort model to estimate whether routine vaccination of the elderly (60+) would be cost-effective, when compared with other uses of health care resources. Vaccine efficacy parameters are estimated by fitting a model to clinical trial data. Estimates of QALY losses due to acute HZ and post-herpetic neuralgia were derived by fitting models to data on the duration of pain by severity and the QoL detriment associated with different severity categories, as reported in a number of different studies. Other parameters (such as cost and incidence estimates) were based on the literature, or UK data sources. The results suggest that vaccination of 65 year olds is likely to be cost-effective (base-case ICER = £20,400 per QALY gained). If the vaccine does offer additional protection against either the severity of disease or the likelihood of developing PHN (as suggested by the clinical trial), then vaccination of all elderly age groups is highly likely to be deemed cost-effective. Vaccination at either 65 or 70 years (depending on assumptions of the vaccine action) is most cost-effective. Including a booster dose at a later age is unlikely to be cost-effective.

INTRODUCTION

Herpes Zoster (shingles, HZ) is a disease with high incidence among the elderly, causing pain and reduced quality of life. Herpes Zoster is a reactivation of the varicella zoster virus (VZV) which causes chickenpox usually during childhood. HZ occurs in all age groups but the highest incidence is in the elderly. The life time risk of HZ is around 25-35 percent [1, 2]. Immunosuppression increases the risk of zoster however the majority of the cases occur in the immunocompetent population.

Herpes Zoster usually starts with local prodomal pain, which lasts for 2-3 days before rash onset. The rash is typically localised and lasts for 3-4 weeks. The most common complication of HZ is post-herpetic neuralgia (PHN), which is persistent pain following acute zoster. Various definitions of PHN occur in the literature, though the most common is pain independent of the rash that persists for 3 months or more after onset [3-8], but 1 month [9], 4 months [10] and 6 months definitions [11, 12] have also been used. The severity of disease varies among patients but HZ and PHN can have a substantial impact on daily living [13-15] due to poorer physical functioning and increased emotional distress. Other complications that can occur as a consequence of HZ are encephalitis, zoster opthalmicus and retinitis. Complications are more common in immunocompromised patients [16].

In 2006 marketing approval was given to Zostavax (Merck&Co in the USA, Sanofi Pasteur MSD in Europe) by the European Medicines Agency (EMEA 2006). Zostavax

is a vaccine consisting of a live attenuated (OKA strain) varicella zoster virus (VZV). The vaccine is a higher dosage of Varivax, the vaccine used to prevent chickenpox in children. Vaccination is thought to boost the immune system by increasing VZV specific T-cells [17, 18]. A large-scale double-blind placebo controlled clinical trial suggested that the vaccine prevents 51% of cases in people aged over 60 years and reduces the severity of disease in those that are affected [5, 19]. However vaccine efficacy appears to decline with age: from an overall efficacy against HZ of 64% when vaccinating at 60-69 years to 38% among those over 70 years of age [5, 19].

Although the clinical trial suggests that the vaccine is safe and effective, it is not clear what the long-term impact of vaccination in the general population will be. Furthermore, vaccination against HZ needs to be compared with other possible uses of health care resources. This paper uses a decision analytical model to assess the effectiveness and cost-effectiveness of routine vaccination of the elderly against HZ in England and Wales.

METHODS

Data sources

GP consultations

Age-specific incidence rates were taken from a number of different GP-based sources: the Royal College of General Practitioners (RCGP) Weekly Returns Service [20], the fourth Morbidity Survey in General Practice (MSGP-4) [21], which included many of the same practices as in the RCGP database, and the General Practice Research Database [22]. See appendix 1 for a more in-depth description. Rates were adjusted for misdiagnoses, which is in the range of 5-13% [6, 7, 23-26]. In the base case the amount of false positive is set at 10% (7.9% - 12.4%, appendix 1).

As the vaccine was licensed for an immuno competent population, the proportion of immuno competent HZ patients was obtained from the MSGP-4, a survey conducted in 1991-1992 and covering a 1% sample of England and Wales [27]. Patients reporting any of the following conditions were considered immunocompromised and thus not eligible for vaccination: cancer (ICD9: 1400-2399), human immunodeficiency virus (HIV) (ICD9: 0420-0449), tuberculosis (ICD9: 011-018) and transplantations (ICD9: 9960-9968) (Merck 2006).

Hospitalisations

Hospitalisation data for England were extracted from the Hospital Episode Statistics (HES) database for the years 2002-2005. For each hospital admission the age, date of admission, date of discharge and the diagnosis at discharge were extracted. Although fourteen diagnostic fields are available in the database, hospitalisations were considered zoster related only if a clinical registration code for HZ and/or PHN (ICD-10: B02 and G053) was present in any of the first three diagnostic fields.

In line with the selection made on GP consultations, patients with an underlying immunosuppressive condition were excluded from the analysis; cancer (ICD10: C0-C9 and D0-D4), human immunodeficiency virus (HIV) (ICD10: B20-B24), tuberculosis (ICD10: A15-A19) and transplantations (ICD10:Y83) [28].

Average annual age-specific hospitalisation rates were derived dividing the number of hospitalisations by the average population for England for the same years. As hospitalisation rates have to represent those cases that are preventable with the vaccine, only admissions that reported HZ as the first diagnosis were considered in the base case. Of these 25.5% reported PHN as a co-diagnosis (HES year 2004-5) and 18.5% had ophthalmic complications (ICD10: H0–H5, HES year 2004-5). In the sensitivity analysis hospitalisation rates were calculated using admissions that reported HZ in any of the first three diagnostic fields. Patients with HZ as the second or third diagnosis report pneumonia and urinary tract infection as the most common main diagnoses. Those conditions are associated with a compromised immune system which may justify the focus on the first diagnostic field.

Deaths

Mortality data were extracted from the Office of National Statistics (2001-2005) database (ONS 2005). Mortality due to herpes zoster is low until the age of 85 (0-0.5 deaths per 100,000 per years), and then it increases to 4.3 per 100,000 per year (average 2001-2005) (Table 1). This corresponds to a case fatality rate of 0.36% in the oldest age group. However due to the pathology of HZ it is probable that many of these deaths are not caused directly by HZ, and they may not be preventable by vaccination. Therefore a scenario without mortality was also considered.

Pain, incidence of PHN and quality-adjusted life-year (QALY) loss

Pain is the most important outcome of HZ, and there is believed to be a direct relation between QALY loss and severity of pain [29]. Severity is often categorised into, no pain, and mild, moderate and severe pain. The last two groups are often

Table 1. Estimated annual age-specific incidence, hospitalisation rate, length of inpatient stay, proportion developing PHN, and case-fatality ratio associated with Herpes Zoster.

Age group	Incidence per 100,000 per year (general)	Proportion hospitalised first diagnosis (first three diagnoses)	Mean number of days in hospital (median)	% CRP after 90 days	CFR
60-64	706	0.8% (1.3%)	9 (4)	9%	0.00%
65-69	791	1.0% (1.7%)	8 (5)	11%	0.00%
70-74	876	1.5% (2.4%	11 (5)	15%	0.01%
75-79	961	2.2% (3.8%)	14 (7)	20%	0.02%
80-84	1046	3.0% (5.2%)	17 (9)	27%	0.06%
85+	1216	4.4% (8.1%)	22 (13)	52%	0.36%

considered clinically relevant pain (CRP) [5, 7, 8, 29-31]. In keeping with the clinical trial [5] CRP is defined here as a pain score of 3 or more on an 11 point pain scale, from 0 = no pain, to 10 = worst pain imaginable. The duration of pain is related to the severity and age of the patient [6]. To estimate the duration of pain by severity and age, and subsequently the QALY loss, a model was fitted to the proportion of patients in any pain or CRP after 90 days of onset. Details of this model are given in appendix 2. The model provides an estimate of the overall QALY loss associated with zoster (by age) when combined with data on the health-related quality of life (QoL) weights associated with mild, moderate and severe pain. The QoL weights used in the analysis are based on studies that report EQ-5D values as recommended by the National Institute for Clinical Excellence (NICE); see appendix 3 for details. It is possible that the QoL detriment associated with a particular pain severity improves over time, as individuals cope with their disease. Alternatively, they may become increasingly affected by it (perhaps becoming more depressed or anxious). To allow for these possibilities, in the sensitivity analysis we assumed that the QoL detriment changes by ± 10 or 20% per year for patients in long-term pain.

Ophthalmic zoster

In 10-20% [1, 4] of cases there is an ophthalmic localisation of the zoster rash. A proportion (~4% of total [32]) of these cases result in long term sequelae. The ophthalmic localisation also leads to an increased chance of long term pain [4]. The additional costs of ophthalmic zoster are incorporated in the GP and hospitalisation costs as found in the GPRD and HES databases. The increased pain is already covered in our pain model, as a proportion of the patients in the original studies would have had ophthalmic zoster (only in [8] were they excluded). Hence, costs and QALYs lost from ophthalmic zoster are included in this analysis, but not identified separately.

Vaccine parameters

The proportion of vaccinees who respond (vaccine take) and the decline in vaccine efficacy with time since vaccination (waning) was estimated by fitting a model to the clinical trial data. The estimated take and waning rates are positively correlated with each other (the higher the take the higher the estimated waning rate), and it is difficult to identify these parameters independently. Hence, in the sensitivity analysis 15 different take and waning scenarios were assumed for each age group (60-64, 65-69, 70-74, 75+). Waning rates were obtained from overall incidence in the first four years after vaccination. Vaccine take was estimated from age-specific data. See appendix 4 for more details. Vaccine coverage was assumed to be 73.5%, based on the average influenza vaccine coverage in 2007/2008 [33].

The results of the clinical trial suggested that the efficacy against the burden of illness (BOI) (defined as the area under a curve of the pain severity (worst pain in last 24 hours marked on an 11-point scale) through time over 182 days after rash onset) and PHN was greater than the efficacy against episodes of herpes zoster,

suggesting that the vaccine reduced the morbidity associated with herpes zoster episodes in vaccinees [19]. This could have been due to a reduction in the pain severity, or the duration of pain, or a combination of both. In addition, it is not clear whether the reduction in BOI was due to a reduction in PHN, and the estimate of vaccine efficacy against BOI may be inflated due to the counting procedure [34]. Further analysis of the data on PHN [35], suggest that there were more cases of PHN in the placebo group in the first year of the trial than in the subsequent years, and that this may have biased the efficacy results for PHN (and therefore also, perhaps BOI). Adjusting for this excess of PHN cases in the first year, then additional efficacy against PHN only reached statistical significance in the 70+ age group [36]. To capture the overall effect of burden of illness (including the effect on reduced incidence of zoster), the QALY loss in the first six months of the modelled vaccinated cohort was adjusted (downwards) to give the overall age-specific efficacy against BOI reported in the clinical trial (see appendix 4). This required adjusting the QALY loss to a greater extent in the older age groups, as the reported efficacy against HZ declined with age, but the reported efficacy against BOI remained relatively high. We also applied a scenario without any additional efficacy (i.e. vaccine only protects against developing in a proportion of vaccinees, but does not reduce the severity of HZ or the likelihood of developing PHN if HZ occurs). Finally, we also modelled a scenario in which there was an additional efficacy against PHN of approximately 40%, as estimated by Brisson and colleagues [36], after adjusting for possible "excess" cases in the placebo group in the first year. These additional effects were only applied in the 70+ age group in our scenario analysis, as they were not significant in other age groups [36].

The clinical trial showed an injection site reaction in ~30% of the cases [28], which was significantly higher than in the placebo group. Because of the short nature of those complaints and the unknown QALY loss that might be related to this side effect, this reaction is neglected in the base case scenario. Its impact is however explored in the sensitivity analysis, where we assumed adverse reactions occur in 30% of cases lasting for two days with a reduction in health-related quality of life of 0.05.

Cost data

Following UK guidance [37] the cost-effectiveness analysis was performed from the health care provider perspective, and thus costs to the patient and wider society were not considered. The exclusion of productivity costs (as recommended by NICE) would not, however, be expected to have a major impact on the cost-effectiveness due to the low participation in the active workforce in the target group. All cost are presented in £2006. Unit costs from previous years were inflated using the Hospital and Community Health Services Pay and Prices Index [38].

The average costs of HZ cases in primary care was based on a study conducted among 25,000 enlisted patients with HZ [22] in the GPRD database. This study

estimated the cost of HZ to be £75.63 (74.68-76.58) per episode. More than 50% of the costs originated from prescribed medications. The average total cost of a PHN case, based on a three month definition, was estimated to be £340.04 (319.23-360,85), which included GP and outpatient visits as well as prescribed medications. Note that this study used data up to March 2006. Recently two further medications have become widely available (lidocaine patch and pregabalin). As these treatments are relatively expensive, we may have underestimated the cost of HZ here. Although an episode of HZ may be a trigger for admission into care homes in elderly and frail patients it is not possible to say in what proportion of patients this may occur, or how long they would have been able to continue with their previous arrangements if the episode did not occur. Hence, we have not attempted to estimate these potential costs.

To estimate the cost of hospitalised cases, daily inpatient costs for minor skin infections (Reference costs 2006; HRG J42 and HRG J41) were used and multiplied by the average age-specific number of days spent in hospital (Table 1). Infection control measures such as isolation, staff exclusion and administration of Varicella Zoster Immuno globulin may be necessary to prevent infection of vulnerable patients in the hospital setting. Wreghitt and colleagues [39] has estimated these costs at £1010 cost per hospitalisation. However, much of these costs are associated with staff exclusion, and since their study was performed routine vaccination of health care workers against varicella has been recommended. Hence, in the base-case we ignore these costs, but include them in the scenario analysis.

Although the private sector price of the vaccine is $162 (£82; single dose) the CDC price is $108 (£55; 10-pack). A price per dose of £55 was therefore used in the base case analysis, as this is likely to reflect the price for bulk purchase by a publicly funded programme. Administration costs were set to £10 based on the cost of a GP nurse consultation [38].

Cost-effectiveness model

Quality adjusted life years gained were the primary outcome of interest and were compared to net costs in the form of incremental cost-effectiveness ratios (ICER). The comparator programme in each case was the no-vaccination option. A scenario with a booster dose was also of interest, the two dose schedule was compared with a one dose strategy. Future costs and health effects were discounted at 3.5% per annum as recommended by NICE [37].

A Markov-cohort-model was set up in Excel (Microsoft, USA). In case of Herpes Zoster a cohort model is sufficient because the indirect effect of vaccination on the force of infection of varicella and cases of zoster is very small. 0Multivariate (probabilistic) sensitivity analyses were performed using @Risk (Palisade, USA), in which parameter sets were randomly drawn from input parameter distributions, assuming that all parameters are independent. As the vaccine efficacy parameters are not independent 15 scenarios (combinations of take and waning) were

Table 2. Vaccine parameters. Estimated vaccine take (%) by age group, for different average durations of vaccine induced immunity (average duration = 1/waning rate).

Age group	Scenarios based on the duration of protection														
	3.6	4.1	4.5	4.8	5.2	5.5	6.1	7.5	9.5	11.4	13.5	16.1	20.7	32.7	100.0
60-64	95%	91%	88%	87%	85%	84%	82%	78%	75%	73%	72%	71%	70%	68%	66%
65-69	92%	87%	85%	83%	82%	81%	79%	75%	73%	71%	69%	68%	67%	65%	63%
70-74	64%	61%	59%	58%	57%	56%	55%	53%	51%	49%	48%	48%	47%	45%	44%
75+	45%	43%	42%	41%	40%	40%	39%	37%	36%	35%	34%	34%	33%	32%	31%
60-69	93%	89%	87%	85%	83%	82%	80%	77%	74%	72%	71%	69%	68%	66%	64%
70+	55%	52%	51%	50%	49%	48%	47%	45%	43%	42%	41%	41%	40%	39%	38%

simulated for each age group (Table 2). Univariate sensitivity analysis was also performed in which individual parameters were varied across the range or 95% CI of their distribution, while all other parameters were held at their base-case level.

Background mortality rates for the general population were used. However, to take account of increasing life expectancy, a projected mortality schedule for 2028 was used in the sensitivity analysis. When assuming a zoster-related mortality, age-specific background quality of life weights, as derived by Kind and colleagues [40], were used to weight the life-years lost.

Table 3. Unit costs of care and treatment parameters.

Description	Costs	Source
GP visit, secondary care and prescribed medication		
HZ case	£75.63	Gauthier et.al. 2008
PHN case	£340.04	Gauthier et.al. 2008
Hospitalisation		
Hospitalisation day, <70 yrs (Minor skin infections <70 – HRG J42)	£187	Reference costs
Hospitalisation day, >69 yrs (Minor skin infections >69 – HRG J41)	£215	Reference costs
Cost per vaccine dose		
Vaccine cost (per dose)	£55	See text
Administration costs	£10	Curtis & Netten 2006
Number of doses	1	

RESULTS

Current burden of disease

The estimated annual number of HZ cases in England and Wales in the immunocompetent population of 60 years and older is 88,650 (95% Credibility Intervals 65,000-113,000), of which 18,200 (13,500-23,300) are estimated to remain in pain after 3 months. There are an estimated 1,750 (1,300-2,200) hospitalisations in the 60+ age group every year, and 55 (54-56) persons are estimated to die, with zoster being recorded as a cause of death (Table 4). The overall cost to the health care system generated by these cases is estimated at £17.3m (£12.9m-£21.8m) annually of which £11.5m (£8.5m-£14.6m) will be GP-related costs and the remaining costs fall on secondary care. Almost 50% of the total costs originate from disease occurring in the very elderly (80+ years), due to the higher incidence and complication rates in these ages.

Table 4. Burden of disease in the immunocompetent population England & Wales (population 2007)

Age group	HZ cases	PHN cases	HZ Deaths	Cases hospital	Total Costs
60-64	18765	1696	1	149	£2,126,063
65-69	16189	1858	1	161	£1,963,856
70-74	15720	2355	1	242	£2,373,168
75-79	14376	2874	3	321	£2,807,137
80-84	11614	3157	7	352	£3,005,354
85+	11987	6270	43	522	£5,066,370
Total	88,652	18,210	55	1,746	£17,341,948

Effectiveness of vaccination

Vaccination of 65 year olds at 73.5% coverage is estimated to reduce the life-time risk of herpes zoster from 15% to 12% (a reduction of 20%, nearly 11,200 cases). This is estimated to reduce the incidence of PHN by about 1,500 cases in the cohort, and reduce the number of hospitalisations by nearly 150. Overall 1000 QALYs are estimated to be gained through vaccination, using the base-case assumptions. Vaccination of 65 year olds is estimated to cost about £23.7m, but result in savings to the health service of around £1.3m over the life-span of the cohort, most of which would occur in primary care. The (discounted) costs saved are only 6% of the vaccine cost. The introduction of the vaccine, would result in a significant increase in the overall proportion of the health budget spent on herpes zoster.

Table 5. Estimated burden of disease in a cohort of vaccinated (at 73.5% coverage) and unvaccinated 65 year olds over their life-time. Cases and hospitalisations are shown undiscounted, and QALYs and costs are shown discounted (at 3.5% per annum) and undiscounted.

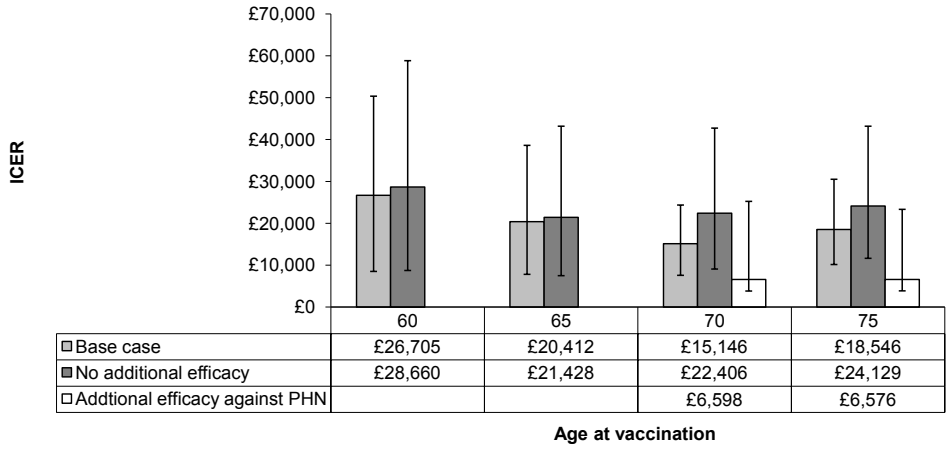
	No vaccination	Vaccination	Difference
Cases HZ	56389	45189	11200
Cases PHN	12856	11351	1514
Hospitalisations	1595	1457	174
QALY lost	6206	5106	1099
QALY lost undiscounted	10128	8785	1343
Vaccine costs (incl. administration costs)	0	£23,763,500	£23,763,500
GP costs	£4,978,000	£3,912,500	-£1,065,000
GP costs (undiscounted)	£7,666,000	£6,418,000	-£1,247,500
Hospitalisation costs	£2,625,000	£2,368,500	-£258,000
Hospitalisation costs (undiscounted)	£476,500	£4,401,500	-£325,000
Overall costs	£7,603,000	£30,044,500	£22,441,500
Overall costs (undiscounted)	£12,392,500	£34,583,500	£22,191,000
Cost per case prevented	£2,004		
Cost per QALY gained	£20,412		
Cost per QALY gained (undiscounted)	£15,455		

Cost-effectiveness of vaccination

The estimated impact of the vaccine on the burden of disease, use of the health care system and mortality is age dependent, and thus the ICER is sensitive to the age at vaccination, particularly if vaccination offers additional protection against PHN in the 70+ year olds (Figure 1). The base-case model with vaccination at 65 years of age results in an ICER of around £20,400, with wide credibility intervals (Figure 1).

The sensitivity of the ICER for the base-case model to changes in the vaccine price is shown in Figure 2. The threshold price for the vaccine is around £80-90 including the additional effect of the vaccine against the burden of disease (at a threshold value per QALY gained of £30,000) excluding this additional effect lowers the price.

The effect of varying other assumptions on the ICER is investigated in Table 6. Here, one parameter at a time is varied keeping all the other ones at their base case values (base-case model is assumed). The results are sensitive to the estimated



	60	65	70	75
Base case	£26,705	£20,412	£15,146	£18,546
No additional efficacy	£28,660	£21,428	£22,406	£24,129
Addtional efficacy against PHN			£6,598	£6,576

Figure 1. Base-case incremental cost-effectiveness ratio (ICER) of vaccination at different ages compared with no vaccination. The 95% credibility interval of ICERs from the multivariate sensitivity analysis is shown. The base-case model (green bars) assumes additional decline in the burden of illness. The second bar shows the ICER when no additional decline in the morbidity or protection against PHN is assumed. The last scenario assumes additional protection in the 70+ age group against PHN (see appendix for details of assumptions). The relevant base-case ICERs are reported under the graph.

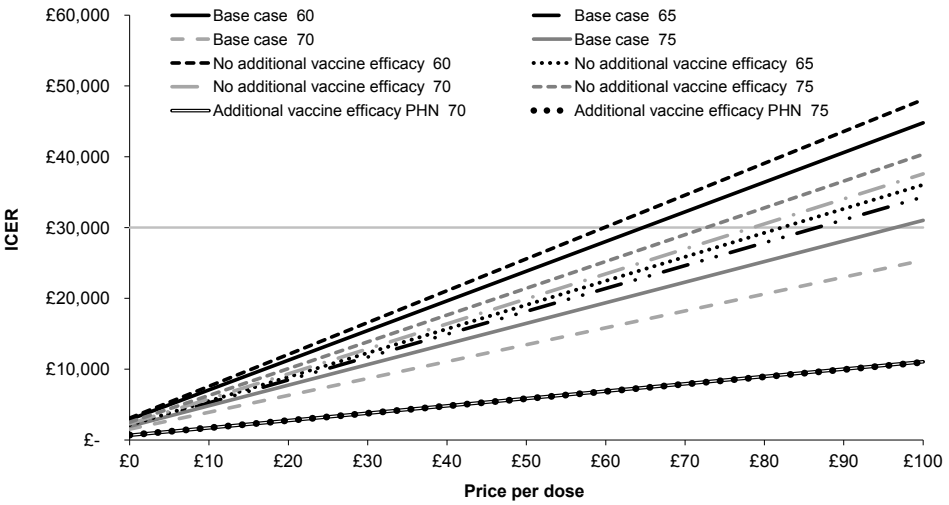


Figure 2. Sensitivity of the ICER to vaccine price under base-case assumptions.

Table 6. Univariate sensitivity analysis. Incremental cost-effectiveness ratio of vaccination at different ages, compared with no vaccination.

	Age at vaccination (yrs)			
Scenario	60	65	70	75
Base case	£ 26,705	£ 20,412	£ 15,146	£ 18,546
Incidence				
Incidence – constant; lower 95% CI	£ 38,900	£ 28,609	£ 20,289	£ 24,282
Incidence – constant; upper 95% CI	£ 20,145	£ 15,695	£ 11,949	£ 14,822
Incidence – slope; lower 95% CI	£ 27,538	£ 21,499	£ 16,326	£ 20,213
Incidence – slope; upper 95% CI	£ 25,870	£ 19,353	£ 14,036	£ 16,985
False positive 7.9%	£ 26,034	£ 19,875	£ 14,730	£ 18,017
False postive 12.4%	£ 27,428	£ 20,950	£ 15,525	£ 18,985
Vaccine efficacy assumptions				
Only an effect against HZ incidence	£ 28,660	£ 21,428	£ 22,406	£ 24,129
100 year protection	£ 6,148	£ 5,660	£ 6,988	£ 9,891
21 year protection	£ 12,185	£ 10,232	£ 10,508	£ 14,473
3.6 years protection	£ 45,578	£ 34,647	£ 20,458	£ 25,482
Additional vaccine efficacy against PHN	NA	NA	£ 6,598	£ 6,576
QALY assumptions				
QALY loss side effect vaccination	£ 29,764	£ 22,017	£ 6,636	£ 6,605
10% increase of QALY loss over time	£ 22,824	£ 17,198	£ 13,239	£ 15,973
20% increase of QALY loss over time	£ 21,286	£ 15,955	£ 12,471	£ 14,963
10% decrease of QALY loss over time	£ 32,011	£ 24,925	£ 17,549	£ 21,876
20% decrease of QALY loss over time	£ 35,001	£ 27,591	£ 18,921	£ 23,933
Severity CRP; lower 95% CI	£ 27,436	£ 20,956	£ 15,538	£ 19,005

Table 6. continued

	Age at vaccination (yrs)			
Scenario	**60**	**65**	**70**	**75**
Duration long term CRP; upper 95% CI	£ 21,588	£ 16,233	£ 12,700	£ 15,327
Duration long term CRP ; lower 95% CI	£ 31,335	£ 24,346	£ 17,286	£ 21,537
QALY loss; lower 95% CI	£ 32,694	£ 24,841	£ 18,165	£ 22,199
QALY loss; upper 95% CI	£ 22,613	£ 17,323	£ 12,952	£ 15,848
b of alfa[i]; lower 95% CI	£ 29,176	£ 22,611	£ 16,861	£ 20,925
b alfa[i]; upper 95% CI	£ 24,385	£ 18,356	£ 13,523	£ 16,313
w[i]; lower 95% CI	£ 26,327	£ 20,143	£ 14,996	£ 18,350
w[i]' upper 95% CI	£ 26,936	£ 20,539	£ 15,172	£ 18,548
Hospitalisation				
First 3 diagnoses hospitalisation	£ 26,543	£ 20,194	£ 14,905	£ 18,140
Cost prevention nosocomial infections	£ 26,558	£ 20,240	£ 14,991	£ 18,333
Mortality scenarios				
Mortality due to HZ	£ 26,505	£ 20,293	£ 15,029	£ 18,311
Background Mortality 2028	£ 25,989	£ 19,674	£ 13,623	£ 16,360
Price				
No administration costs	£ 22,365	£ 17,046	£ 12,641	£ 15,470
price per dose £50	£ 24,522	£ 18,709	£ 13,869	£ 16,967
price per dose £60	£ 28,835	£ 22,034	£ 16,326	£ 19,962
Discounting scenarios				
Discounting; no discounting	£ 19,732	£ 15,414	£ 11,039	£ 14,311
Discounting; cost 6% - effects 1.5%	£ 22,864	£ 17,693	£ 12,858	£ 16,195
Discounting; costs 5% - effects 5%	£ 29,852	£ 22,653	£ 16,993	£ 20,377

incidence of HZ, the QALYs lost due to HZ, the waning rate of vaccine protection, and whether the vaccine also reduces the severity of disease (in the 70+ years). The model is not sensitive to different assumptions about mortality or hospitalisation rates. Adopting a differential discount rate of 6% for costs and 1.5% for health benefits (as recommended by the UK Treasury), improves the cost-effectiveness of vaccination.

The model is sensitive to whether the QoL detriment associated with pain states changes with time (either worsens, or improves).

Booster doses are less cost effective than the first dose, see table 7. The most cost-effective strategy for a two dose schedule is vaccination at 60 and 70, though even this strategy results in ICERs over £40,000 per QALY gained, and are therefore unlikely to be deemed cost-effective.

Table 7. Incremental cost-effectiveness ratio of a booster dose at different ages, compared to one dose. Vertical age at first dose, horizontal age at the second dose.

		Age at 2nd dose		
		65	70	75
Age t1st Dose	60	£48,381	£42,706	£45,393
	65	NA	£70,293	£50,545
	70	NA	NA	£83,986

The average QALY loss from acute zoster and, more importantly, PHN is a key variable, which is difficult to estimate accurately. Figure 3a shows the estimated cost-effectiveness of the model (vaccination at 65 years, no additional efficacy against burden of disease), using QALY loss parameters used in previous cost-effectiveness studies. The average QALY loss per case was estimated to be lower in Pellissier et al., which results in higher ICERs, whereas Edmunds et al. estimated the QALY loss per case to be higher than is estimated here (Figure 3b).

Figure 4 shows the results of the multivariate sensitivity analysis. The figure shows the change in the ICER for the 65 year old programme given 1 standard-deviation increase in each of the parameters (vaccine efficacy is a combination of two parameters, take and waning and done by scenario, therefore a one SD increase from the base-case (Scenario 8) is Scenario 11). The results show that the model results are most sensitive to the vaccine efficacy parameters, as well as the estimated incidence of zoster and parameters that describe the QALY loss from HZ.

The proportion of simulations that would be deemed cost-effective at different threshold values of a QALY gained (cost-effectiveness acceptability curves) is shown in Figure 5. The model suggests that at a maximum willingness to pay for a QALY gained of £30,000 then the probability that vaccination at 65years would be cost-

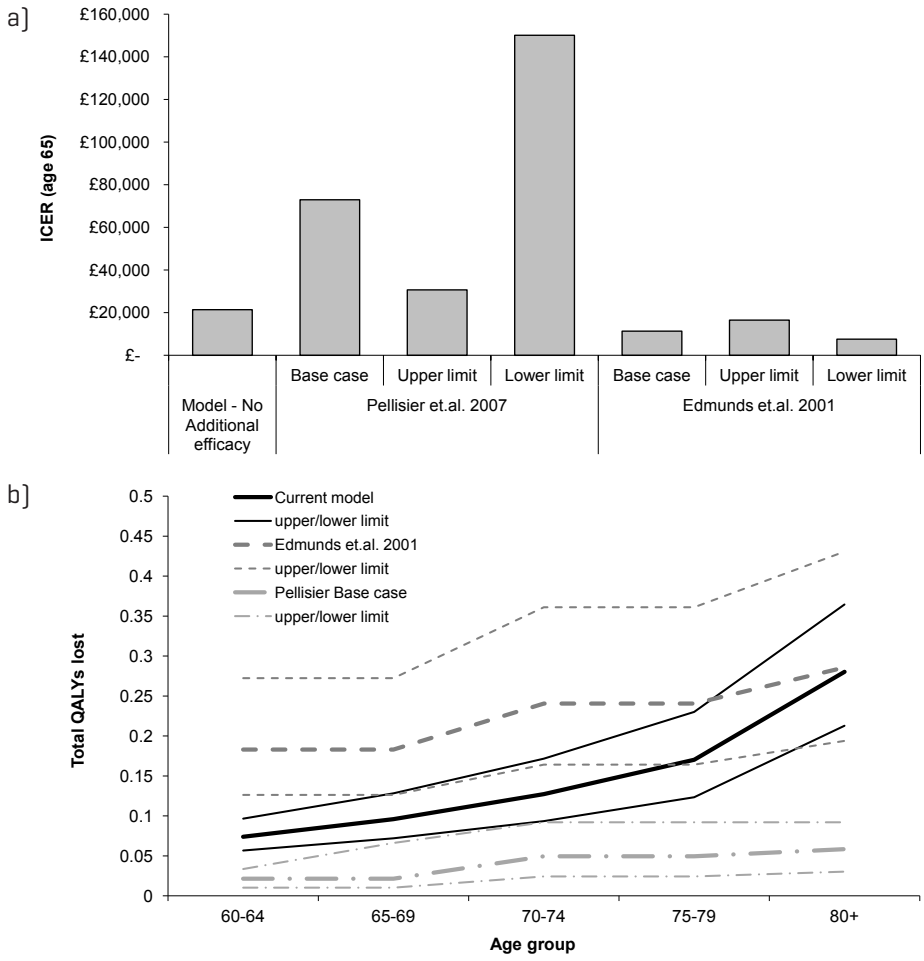


Figure 3. a) Sensitivity of the model to alternative estimates of the average QALY loss per HZ episode (including PHN), and b) a comparison of the estimated QALY loss by age group used in this, and previous cost-effectiveness analyses.

effective is 87%, whereas vaccination at 70 years has a 98% chance of being cost-effective, using our base-case assumptions about vaccine efficacy. If, however, the vaccine does not provide additional protection against PHN, then vaccination of the 70+ age groups is less likely to be cost effective (around 80% of simulations would be deemed cost-effective).

DISCUSSION

In this work a cohort model has been used to assess the cost-effectiveness of zoster vaccination in the elderly. Results from this analysis suggest that the program is

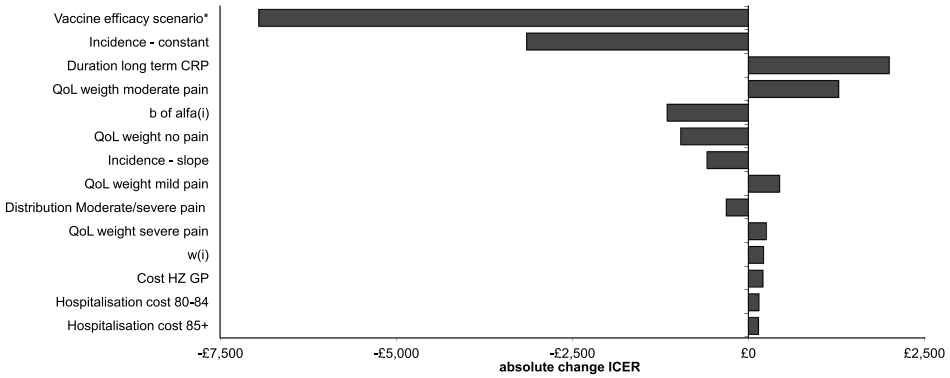


Figure 4. Results of a regression analysis on the multivariate sensitivity analysis. The outcome variable is the ICER for vaccination of 65 year olds, and the input variables the parameter values. The figure shows the predicted (from the regression analysis) change in the ICER following a one standard deviation increase in parameter values from their mean. Only the most influential parameters are shown (more than 1% change).
*vaccine efficacy is based on fifteen scenarios; the presented change is based on scenario 11.

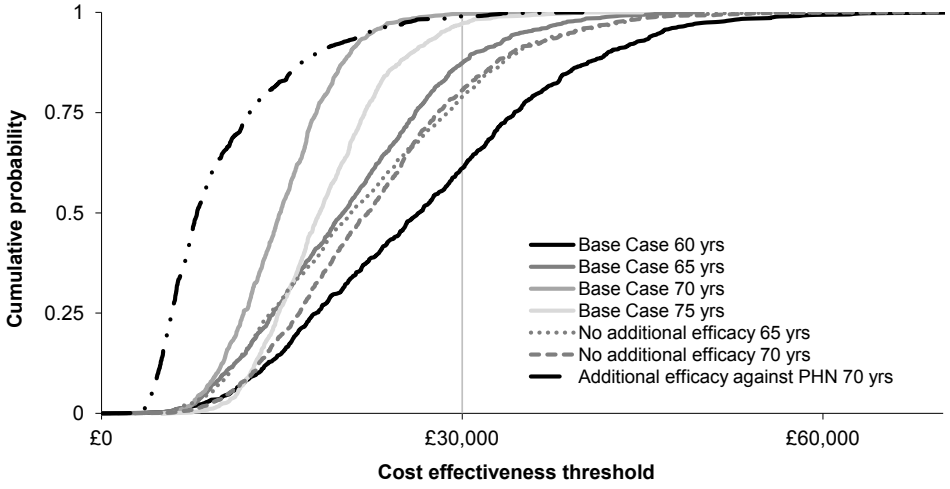


Figure 5. Cost-effectiveness acceptability curves for vaccination at different ages, using the base-case model, a model that assumes that there is an additional effect of vaccination on PHN in the 70+ year age group.

likely to represent a cost-effective intervention for England and Wales, although there is a lot of uncertainty around the duration and range of vaccine induced protection and the QALY loss due to long term pain. The most cost-effective age to vaccinate is 70 years, or 65 years if the vaccine does not offer additional protection against the severity of disease. The ICER does not increase steeply with age, which makes a catch-up campaign possible, although more data is needed on vaccine efficacy in the extreme elderly to make a decision on the maximum age in case of such campaign. Applying a two dose schedule is not likely to be cost-effective. The introduction of the vaccine would, however, not be cost saving, as the savings derived are low in comparison to the vaccine price. Indeed, vaccination would be expected to approximately triple health-care expenditure on HZ. Therefore the major gain of the vaccine is the reduction of the burden of illness.

The conclusions of this study are comparable to previous cost effectiveness studies in the UK, suggesting that vaccination may be cost-effective in a number of scenarios [41, 42]. These previous cost-effectiveness studies were published before the clinical trial, and therefore used speculative vaccine efficacy parameters. Since then the clinical trial has become available as well as more data on the quality of life impact of HZ. Three further cost-effectiveness studies have been published, all of them for the US. Hornberger & Robertus (2006) suggested that it was more cost-effective to vaccinate at younger age, because the higher incidence was offset by lower vaccine efficacy as age increased. They also showed the sensitivity of results to the duration of vaccine efficacy (waning) and concluded that there is too little information about the effect of HZ and PHN on quality of life to be able to accurately assess the cost-effectiveness of vaccination. Moreover the authors point out that the difficulties relate not only to the lack of data but also on the lack of generally accepted definitions. Rothberg and colleagues (2007) compared vaccination of different genders and ages and found that vaccination was less likely to be cost-effective in men (due to a higher incidence in women) and unlikely to be cost-effective in the younger and oldest age groups. Only at 70 years of age (the most cost-effective age group to vaccinate in their model) did base-case cost-effectiveness ratios approach $50,000 per QALY gained. Rothberg et al. did not assume additional protection against PHN, though they did assume that the vaccine reduced the burden of illness in their base-case model. Pellisier and colleagues (2007), estimated that vaccination would be cost-effective under a wide range of scenarios (base-case ICER $28,000 ≈ £14,000 per QALY gained), although they did assume an additional effect against PHN.

Extensive univariate and multivariate sensitivity analyses have been performed to identify key parameters and assumptions and to assess the robustness of the results to variation in these. Two key areas of uncertainty are the burden of disease associated with PHN, and whether the vaccine offers additional protection over and above the protection resulting from a reduced incidence of herpes zoster.

To estimate the burden of disease associated with HZ we fitted a model of pain severity over time (stratified by age) to data from a large number of studies. This provided an estimate of the duration of pain, by severity and age. However, there are few data on long-term pain (few studies were carried our over a long-enough time period and the numbers of patients remaining in those studies is small). The average duration of long term pain used of 2.8 years (95% CI: 1.9-4.3 years) is comparable with the average duration (2.3 years) that was found in a retrospective study in the UK [1]. However a recent study of the GPRD database suggested that the average duration of PHN is much shorter, at 10 months [22], this is however based on care seeking behaviour and not on actual pain levels. Thus the estimate of the mean duration of PHN is very uncertain, and the value adopted for this parameter accounts for much of the difference in average QALY loss per case derived in different studies in the cost-effectiveness literature. Further research in this area would be valuable to help improve decisions regarding the cost-effectiveness of vaccination as well as treatment options for PHN patients.

Vaccine efficacy was estimated from the clinical trial data [5]. However, a number of limitations regarding our parameter estimates should be borne in mind. First there were many exclusion criteria for enrolment into the clinical trial, and the death rate was somewhat lower in trial participants than the average by age (suggesting that participants may have been somewhat healthier than average). Second, the characteristics of the vaccine (i.e. take and waning rates) were estimated by fitting a model to the published clinical trial data. Although it was possible to identify best-fitting parameter estimates, there were many combinations of take and waning that gave a reasonable fit to the data. In particular the 95% confidence interval on the duration of immunity is from 3.6 to life-long immunity. Our best-fitting efficacy parameters were lower than those used in other studies. The only previous study to estimate the waning rate was published by Pellissier and colleagues [43] using data not available in the public domain. Their base-case estimate was life long protection, with a take of 69.8% and a lower bound of the confidence interval of 12 years. Our base-case take was 75% (in 65 year age group) with an average period of protection of 7.6 years (95% CI 3.6 to infinity). One reason for the difference is the apparent use of a lower zoster incidence in the vaccine group in year five compared with the data submitted to FDA (comparing Figure 5 with Table 9-7). An alternative explanation may be the use of a function describing waning by age. Both of these may reduce the apparent effect of waning through time (extending vaccine efficacy). We covered a range of durations from 3.6 years to lifelong immunity in our scenario and sensitivity analysis. The relatively low duration of protection used in the base-case model accounts for the low proportion of zoster cases estimated to be prevented by vaccination of 65 year olds - their life-time risk of zoster is only decreased by about 20% (at 73.5% coverage), because protection will have waned in many individuals before the age of peak incidence. Post-vaccination surveillance

data from countries that have introduced the vaccine would be important to improve our estimates of the duration of protection.

The results of the clinical trial suggest that the vaccine offers greater protection against PHN than it does against herpes zoster, suggesting that those vaccinees that do get zoster are less likely to go on to develop its most serious complication. However, there is debate in the literature about the validity of this finding. Rothberg et al. suggested that much of this effect could be explained by an unusually high number of PHN events in the placebo group in the first year of the trial [35]. Brisson and colleagues [36], performed a similar re-analysis of the trial data, but separated their results by age group. They found that there was a statistically significant additional effect of vaccine against PHN in the 70+ age group, even after adjusting for the "excess" cases in the placebo group in the first year of the trial.

The clinical trial also reported that the "burden of illness" (a measure of the overall number of days spent in pain weighted by their severity) was also significantly reduced in the vaccine group compared to placebo recipients. Some of this difference might be accounted for by the additional protection against PHN, though it seems unlikely that all of this would be, as the estimated efficacy against BOI was significant in all ages. We modelled this by assuming that the QALY loss in vaccinees that did develop zoster, was reduced in the first six months. By changing how much the QALY loss was reduced we could match the efficacy against BOI reported in the clinical trial. Note however, that our estimate of efficacy is not identical to that used in the trial, as we used QALY loss, and the trial pain. Furthermore the measure of BOI has been criticised, as it would tend to overestimate the efficacy [34]. Nevertheless, as efficacy against BOI was one of the primary endpoints in the clinical trial (efficacy against HZ incidence was a secondary endpoint), we included the apparent additional efficacy against severity of illness in "breakthrough" zoster in our base-case.

The introduction of childhood varicella vaccination could increase the incidence of herpes zoster due to a decline in natural boosting [44-46]. As a consequence, HZ vaccination would become more cost-effective. However, the introduction of a HZ vaccination could have an effect on the evaluation of the varicella program. Combined varicella and zoster vaccination programmes should be evaluated using a comprehensive cost effectiveness model.

Vaccination of the elderly against herpes zoster is likely to be cost-effective. Although there is considerable uncertainty in many of the parameters, this finding appears to be reasonably robust. The most cost-effective age to vaccinate appears to be 70 years of age, unless duration of protection exceeds 20 years or the protection is only against HZ incidence. If shingles vaccination is introduced then good quality surveillance data should be collected to evaluate duration of protection whether further changes to the programme may be necessary in the future.

ACKNOWLEDGMENTS

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chapter THREE

ASSESSING THE POTENTIAL EFFECTS AND COST-EFFECTIVENESS OF PROGRAMMATIC HERPES ZOSTER VACCINATION OF ELDERLY IN THE NETHERLANDS

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ABSTRACT

Background

Herpes zoster (HZ) is a painful disease affecting a considerable part of the elderly. Programmatic HZ vaccination of elderly people may considerably reduce HZ morbidity and its related costs, but the extent of these effects is unknown. In this article, the potential effects and cost-effectiveness of programmatic HZ vaccination of elderly in the Netherlands have been assessed according to a framework that was developed to support evidence based decision making regarding inclusion of new vaccines in the Dutch National Immunization Program.

Methods

An analytical framework was used combining a checklist, which structured relevant data on the vaccine, pathogen and disease, and a cost-effectiveness analysis. The cost-effectiveness analysis was performed from a societal perspective, using a Markov-cohort-model. Simultaneous vaccination with influenza was assumed.

Results

Due to the combination of waning immunity after vaccination and a reduced efficacy of vaccination at high ages, the most optimal cost-effectiveness ratio (€21,716 per QALY) for HZ vaccination in the Netherlands was found for 70-year olds. This estimated ratio is just above the socially accepted threshold in the Netherlands of €20,000 per QALY. If additional reduction of postherpetic neuralgia was included, the cost-effectiveness ratio improved (~€10,000 per QALY) but uncertainty for this scenario is high.

Conclusions

Vaccination against HZ at the age of 70 years seems marginally cost-effective in the Netherlands. Due to limited vaccine efficacy a considerable part of the disease burden caused by HZ will remain, even with optimal acceptance of programmatic vaccination.

BACKGROUND

The varicella-zoster virus (VZV) causes varicella (chicken pox) as well as herpes zoster (HZ, shingles).

Varicella is the primary infection, whereas HZ is caused by reactivation of latent VZV in sensory nerve ganglia. HZ is characterized by a painful localized vesicular rash. The most common complication of HZ is postherpetic neuralgia (PHN), a chronic pain condition that can last for months or even years. In contrast to varicella, which is mainly a childhood disease, HZ predominantly affects older adults [1]. Presently, a vaccine to prevent HZ is available [2]. In this article, we present an assessment of the potential effects of programmatic HZ vaccination of elderly in the Netherlands. Fur this purpose we used a framework that was developed to

support evidence based decision making regarding inclusion of new vaccines in the Dutch National Immunization Program (NIP). This framework consists of a checklist that structures all relevant data on vaccine, pathogen and disease [3]. These data, presented in the Background section, are input to a cost-effectiveness analysis that is presented in the Methods and Results section.

Vaccine

Available vaccines and indications

Only one vaccine (ZOSTAVAX®; SP-MSD) has been registered for the prevention of HZ. This live attenuated vaccine is manufactured by the same process as the chicken pox vaccine VARIVAX® but has a higher viral load per dose [2]. The vaccine has been registered in the EU as a single dose vaccine for the prevention of HZ and PHN among people aged 50 years or older.

Vaccine efficacy

Natural protection against HZ may occur by exogenous boosting (due to circulating VZV in the population) or endogenous boosting (through subclinical reactivation of latent VZV). Although the mechanism of latency is not fully understood, there is strong evidence that the risk of developing HZ is linked to a decline in VZV-specific cellmediated immunity (CMI) [1,4]. The functional mechanism of the vaccine is to boost this specific CMI [2].

The efficacy of the vaccine was assessed in a large randomized placebo-controlled trial. There was a reduction of 51.3% in the incidence of HZ, 61.1% in the burden of illness (BOI) and 66.5% in the incidence of PHN [5]. The vaccine appeared less effective in the older age group (70+ years) compared to the younger age group (60-69 years) (Figure 1), indicating that the effect of vaccination is age dependent [5]. The long term efficacy of the vaccine is unknown (mean follow-up duration so far was three years), but the immunity seems to decrease over time after vaccination [2].

Contra-indications and adverse events following vaccination

Since the vaccine consists of live-attenuated virus, it should not be used in immunocompromised people, people with active untreated tuberculosis or in pregnant women [2].

Adverse events at the injection site occurred more frequently in the vaccine group (48.3%) compared to the placebo group (16.6%), but most of them were mild. Furthermore, vaccine-related systemic adverse events occurred more frequently in the vaccine group than in the placebo group (6.3% vs 4.9%) [5].

Factors affecting successful implementation

So far, influenza vaccination is the only generally advised vaccination for elderly in the Netherlands. The general practitioner (GP) invites all people aged 60 years or older annually for this vaccination, which has a high coverage (in 2008/2009 76.9%) [6]. HZ and influenza vaccine given concomitantly are well tolerated [7]. Furthermore, antibody responses were similar compared to sequential vaccination.

A recent study, however, showed that among community-dwelling elderly to whom both influenza and HZ vaccination were offered within an existing influenza vaccination program, only 39% accepted HZ vaccination, whereas 76% accepted influenza vaccination [8]. Determinants of non-compliance with additional HZ vaccination were: perceived lack of recommendation by the GP, unwillingness to comply with the doctor's advice, perception of low risk of contracting HZ, perception of short pain duration of HZ and the opinion that vaccinations weaken one's natural defenses [8]. Other studies also found that a recommendation by the GP is a major determining factor of accepting vaccination in this age group [9,10]. An international survey pointed out that the understanding of the risk of developing HZ, its symptoms, complications and treatment among adults ≥55 years of age is very limited [11]. Moreover, in the United States the lack of patient awareness and physician recommendation were pointed to be barriers to HZ vaccine uptake [10].

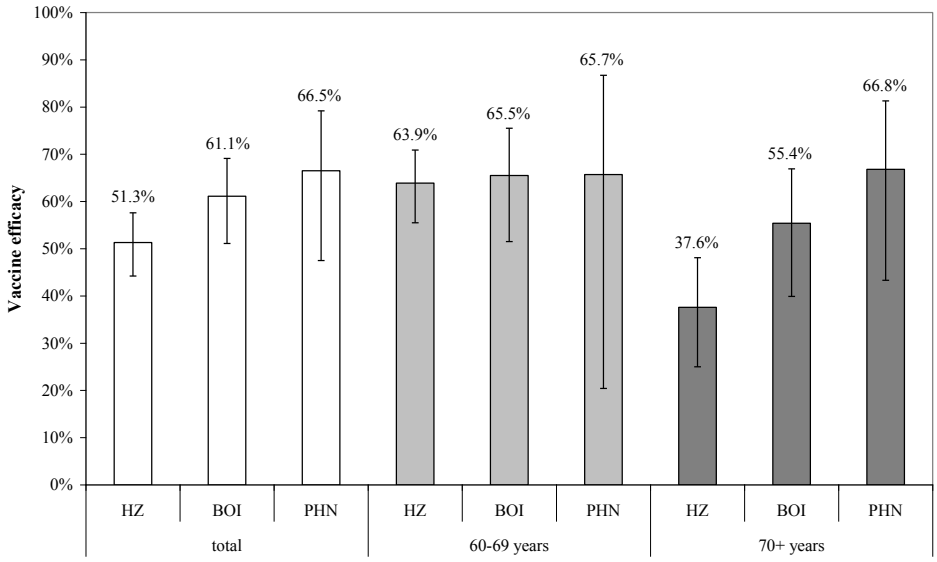


Figure 1. Overview of the vaccine efficacy with respect to the incidence of herpes zoster (HZ), burden of illness (BOI) and incidence of postherpetic neuralgia (PHN) by age-group. (source: Oxman MN, Levin MJ, Johnson GR et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005; 352(22):2271-84).

Herd immunity

The transmission of VZV resulting from patients with HZ is very low in comparison to varicella [1]: therefore no herd immunity effects are to be expected. Reaching a high vaccination coverage is therefore not important, unlike for most other vaccinations. HZ vaccination will only give benefit on individual level.

Pathogen

Pathogenicity

VZV-seroprevalence in the Netherlands approaches 100% from seven years onwards [12]. In HIV-infected persons the risk of HZ and its recurrence is increased (12-17 fold) [1]. Intercurrent infection with viruses that can alter CMI responses (such as Epstein-Barr virus and cytomegalovirus) also influences the risk of developing HZ [4].

Infectiveness and transmissibility

HZ is not transmitted directly; it is a reactivation of VZV that remains latent in sensory nerve ganglia after primary VZV-infection. The herpes lesions are contagious for non-immune persons (until the lesions have crusted) and can lead to varicella [1]. Subclinical reactivation of the VZV virus is possible but the frequency of occurrence is unknown [4]. In immunocompetent individuals, the frequency of recurrent HZ is low (1.7-5.2%) [13].

Antigenic variation

The VZV genome is extremely stable. So far, seven distinct genotypes of the wild-type VZV have been distinguished with a different geographic distribution, but all belong to the same serotype. No evidence for recombination among wild-type VZV-strains has yet been found [14]. Although recombination events could theoretically alter the virulence of circulating VZV strains [15], the impact of such events would probably be very small. Ecological consequences after implementation of vaccination are not expected. VZV is an exclusively human pathogen. Both the vaccine strain and the wild-type VZV establish a latent infection. Furthermore, interaction or competition with other alpha-herpes viruses like HSV-1 and HSV-2 has not been described for VZV [16].

Burden of disease

Risk factors for herpes zoster

It is estimated that 23-30% of the population in Europe will develop HZ during their lifetime; approximately 50% of all people reaching the age of 85 years will have experienced HZ [13]. Prior infection with VZV, either with wild-type or vaccine virus, is a prerequisite for developing HZ. The vaccine virus may have less opportunity to reactivate than does wild-type VZV [4]. The vaccine virus usually does not cause viremia or skin infection, factors that are both likely to enhance the development of HZ [17].

The incidence of HZ increases with age, which is attributed to the natural process of age-related immunosenescence. Furthermore, the incidence is higher among people with immunity attenuating diseases or medication [1,4,18]. Other possible risk factors that have been suggested are physical trauma at the involved dermatome, psychological stress, changes in mental health, depression, white race and intercurrent infection with viruses that can alter CMI responses [1,4,18]. Some studies show also higher incidence rates in women, even after correction for higher average age and health care seeking behavior [18,19]. VZV-infection in utero or shortly after birth has been found to be a risk factor for (childhood) HZ [1,4,18].

PHN is more likely to occur in older HZ patients and in HZ patients with severe pain or rash during the acute phase [4,18,20].

Consequences of herpes zoster

HZ begins with a prodrome, during which abnormal skin sensations and pain of varying severity are the most common symptoms, followed by a vesicular rash. This rash is typically unilateral, does not cross the mid-line, normally involves a single dermatome, is usually accompanied by acute pain and lasts for 7-10 days or longer. PHN, a persistent pain after resolution of the rash, is the most important complication of HZ and can last for several years [1,4]. Therapeutical options for HZ and PHN are scarce. About half of the patients with PHN will benefit from therapy with only partial relief [4]. The quality of life during HZ is influenced by the severity and duration of the acute and chronic pain that can affect physical, psychological, social and functional domains [1,4].

Alternative preventive measures

There are no direct alternatives to prevent HZ. Childhood vaccination against varicella might reduce the HZ incidence on the long term, because the vaccine strain is less likely to cause HZ than the wild-type. However, reduced VZV transmission due to varicella vaccination will diminish exogenous exposure (boosting), which might lead to an increase in the incidence of HZ in the mid-term (the first 30-50 years) [21]. Studies monitoring the incidence of HZ in the US, where universal vaccination against varicella was introduced in 1995, have shown inconsistent findings at this point. Two studies did not show an increase in overall incidence [22,23], whereas three others demonstrated a rise [24-26].

METHODS

Data sources

GP consultations, hospitalizations and deaths

Most HZ patients will consult their GP as it is a painful condition. Age-specific incidence rates for the period 2002-2007 were derived from the Netherlands Information Network of General Practice (LINH) [27]. A correction was made for false positives (10%; 7.9- 12.4%[28]) and immunocompromised people (5%[28]), since both groups will not benefit from vaccination. A linear regression was plotted on the HZ incidence of the separate years 2002-2007.

Hospitalization data (ICD-9 code 053) were taken from the National Medical Register (LMR) for the period 2000-2007. Only admissions with HZ as main diagnosis were included because these admissions represent cases that are preventable by vaccination. The incidence of clinical admissions was rather stable in the period 2000-2007. However, the incidence of admissions for one day decreased from 7.5 per 100,000 in 2002 to 4.0 per 100,000 in 2007 [29]. Therefore, an alternative

scenario was included in which the daytime hospital visits were excluded. The distribution used in the probabilistic sensitivity analysis is listed in Additional file 1.

Mortality data (ICD-10 code B02 and G530) for the period 2000-2007 were derived from Statistics Netherlands (CBS). Only deaths with HZ as primary cause of death were included in the base case scenario. An alternative scenario without prevention of death was also included since it is likely that death is not caused directly by HZ.

Pain, incidence of PHN and quality-adjusted life-year (QALY) loss

The duration of pain by severity and age, and subsequently the QALY loss due to HZ, was estimated by Van Hoek et al [28] and applied to the Dutch situation. For clarity, this does include PHN which was defined as the presence of clinical relevant pain after three months. In the model QALY loss after onset was modeled based on the duration spent in clinical relevant or mild pain [28] instead of using a fixed percentage developing PHN.

Vaccine parameters

We used the vaccine efficacy as estimated by Van Hoek et al [28]. The vaccine efficacy was split into two parameters, a take (initial vaccine efficacy) and waning (reduction of protection over time) and those two parameters were estimated on the data from the initial clinical trial. The base case waning was only 7.5 years and was estimated to be between 3.6 to 100 years, with an age dependent take. In the sensitivity analyses the effects of a longer and shorter duration of protection were calculated. Based on the coverage for influenza vaccination in the Netherlands, we assumed a vaccine coverage of 75%.

The different protection of the vaccine against the three endpoints (Figure 1) as measured in the clinical trial was simulated by three different scenarios. In the scenario based on the reduction of HZ only, the reduction of HZ and subsequent QALY loss was included. In the scenario describing the reduction of BOI, a reduction of QALY loss for the first 6 months in people with disease was included above the reduction in HZ cases (this is because the vaccine reduces disease severity in cases where HZ occurs in spite of vaccination). For the reduction of PHN (only applicable above the age of 70 years) the number of people in clinically relevant pain was decreased by the specific vaccine efficacy [28,30]. If not mentioned otherwise, presented numbers are based on the protection against BOI (base case), the main endpoint in the clinical trial.

Cost data

All costs are presented in 2008 Euros: costs in previous years were deflated with the consumer price index according to CBS. To assess the costs of an average HZ or PHN case, the in depth patient data as collected within the PINE study was used [31]. Patients were considered to suffer from PHN if they had a pain level of at least 25 (on a scale of 0-100) at three months after onset. The cost assumptions that were used in this assessment are described in Additional file 2.

Direct costs of disease

The major costs involved in HZ are the prescription of antivirals and repetitive GP visits for PHN patients. In the PINE study, detailed information on GP consultations, medication and additional use of health services due to HZ was available for the first 6 months of the study (Additional file 2). Based on those findings the average total costs per patient of GP consultations and drug use is €72.05 (€66.90 - €77.20) in case of HZ and €101.10 (€81.72 - €120.70) for PHN based on the first 6 months of the study. Because the duration of PHN can be longer, these costs were doubled: €201.91 (€163.30 - €241.15). Confidence intervals of the mean price (95%) were acquired by bootstrapping.

Indirect costs of disease

Indirect costs were considered for estimated work loss till the age of 65. Data on work loss due to HZ is scarce and the participation in the workforce is not high in the age group 60+. A questionnaire among 65 HZ patients in the UK [32] showed that 29 patients were employed, with an average working loss of 10.1 days (SD of mean 1.82). According to CBS, participation in the work force (in 2006) was only 20.8% in the age group 60-65. The number of hours of labour per week is 32 or 6.4 per day with a payment of €24.10 per hour. With a correction for participation in the workforce this is an average of €32.04 lost per day or €324 for the total work loss for someone in the age group 60-65.

Cost of the vaccine and the vaccination program

Because the HZ vaccine is not yet available in the Netherlands, the Dutch price is unknown. The official retail price of the HZ vaccine in the US is $153.93 or €110 (Pack 10-Vial; January 2009). However, in case of introduction in the NIP, the CDC price of $107.67 or approximately €77 (January 2009) seems more applicable. In the sensitivity analyses the effect of lower vaccine prices was calculated.

Based on experience with the introduction of the pneumococcal vaccine in the Netherlands in 2006, the once-only costs (not included in the cost-effectiveness model) are estimated to be €0.3 million and include costs for education of GPs, developing information material (invitation letter, flyer, publicity campaign, website), adjustment of software for registration and monitoring, and administration. In case of implementing HZ vaccination within the current influenza vaccination program and assuming a vaccination coverage of 75%, the estimated yearly administration costs range from ~ €14.7 million for vaccinating people at the age of 60 to ~€4.9 million for vaccination at the age of 80. This includes compensating vaccination personnel (€4.80 per application, this is half the influenza tariff) and coordination costs (€1.65 per application). In the sensitivity analyses the effect of higher applications costs (€9.60 instead of €4.80 per vaccination) was calculated. Monitoring of adverse events can be included in the already existing passive surveillance system, for which the total costs are estimated to be €0.4 million per year. Vaccine effectiveness,

reflected by the reduction of the incidence of HZ, PHN and related hospitalizations, could be monitored using GP and hospitalization statistics.

Cost-effectiveness model

The cost-effectiveness analysis was performed from a societal perspective. The incremental cost-effectiveness ratio (ICER) was used to compare the quality of adjusted life years gained with the net costs of programmatic HZ vaccination (compared to no-vaccination). The prevented number of cases, costs, QALYs and the Incremental cost-effectiveness ratio (ICER) were calculated at different ages: 60, 65, 70, 75 and 80 years. According to the Dutch guidelines for health technology assessment, future costs and effects of vaccination were discounted with 4% and 1.5%, respectively.

A Markov-cohort-model was set up in Excel (Microsoft, USA) and univariate and probabilistic sensitivity analysis were performed with @Risk (Palisade, USA). The same model was used in a cost-effectiveness model for HZ vaccination in England and Wales [28]. The effect of different assumptions regarding the duration of protection of the vaccine, discount ratio, prevention of death, vaccine price, application costs and hospital day care were investigated in the sensitivity analyses.

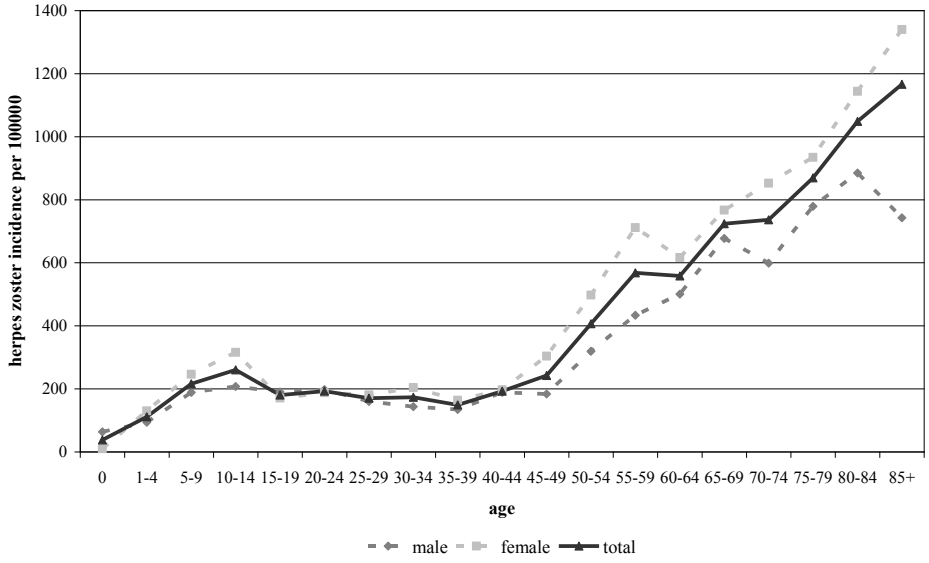


Figure 2. Age-specific average annual incidence of GP-consultations due to herpes zoster per 100000 by sex 2002-2007. (source: Verheij RA, van Dijk CE, Abrahamse H et al. Netherlands Information Network of General Practice (LINH): Facts and figures on GP care in the Netherlands. Utrecht/Nijmegen: NIVEL/WOK, 2008).

RESULTS

Current burden of disease

For the Netherlands, the average annual incidence of HZ based on GP consultations was 332 (range 310-370) per 100000 in the period 2002-2007. The incidence increases with age (Figure 2) [27]. The linear regression that was plotted on the HZ incidence of the separate years 2002-2007 predicted an incidence of 509 (394 - 626) per 100000 at the age of 60 and going up with 22 (17.1 - 27.0) per year.

The average annual incidence of *clinical* hospital admissions due to *main* diagnosis HZ in the period 2000-2007 was 2.3 (range 2.0-2.7) per 100000 (when including *side* diagnosis HZ too, the total incidence was 4.7 (range 4.0-5.1) per 100000). In the same period, another 6.3 (range 4.0-7.5) hospital admissions *for one day* due to *main* diagnosis HZ were registered per 100000. The incidence of hospital admissions also increases with age (Figure 3). In the period 2000-2007 on average 18 deaths (range 13-26) with HZ as primary cause of death were registered annually. Most deaths occurred among people aged 75 years and older (92%).

The burden of disease in the Netherlands is estimated to be at highest in a cohort of 60 year olds (a loss of 3024 QALYs, discounted) and at lowest in a cohort of 80 year olds (a loss of 1060 QALYs, discounted) (Table 1). The ratio of QALY loss per HZ case (discounted), however, increases by age towards a maximum at the age of 80. Therefore the relative burden of disease is the highest at the age of 80. The estimated total costs for HZ for the group 60 year olds are almost €3.5 million per year; this is including an estimated €1.2 million of indirect costs. Although the estimated total costs for the group 80 year olds are lower (€0.8 million per year), the cost per HZ case in this age-group is higher than for 60 year olds (€177.79 versus €128.86) (Table 1).

Effect of vaccination on cases and costs

Most cases (~4300) are prevented by vaccination at the age of 60. This number decreases to ~470 at the age of 80. The prevented number of deaths, however, increases by age at vaccination. From 0.2 prevented deaths by vaccination at 60 towards the maximum of 1.2 prevented deaths at the age of vaccination at 75 (Table 1).

By vaccinating people, costs regarding GP visits, prescription of antivirals and painkillers are prevented as well as hospitalization costs and costs due to work loss. For HZ vaccination the prevented costs are distributed equally between hospital costs and prevented cost generated in the GP practice. Prevented costs will reach a maximum of about €1085146 (or €384658 excluding indirect costs) for vaccinating people at the age of 60. The saved discounted costs, however, are low for each vaccinated person. Per vaccinee between €1.49 and €2.65 (or €6.17 including indirect costs) will be saved. Subsequently a vaccine price higher than this will have to be justified by preventing QALYs.

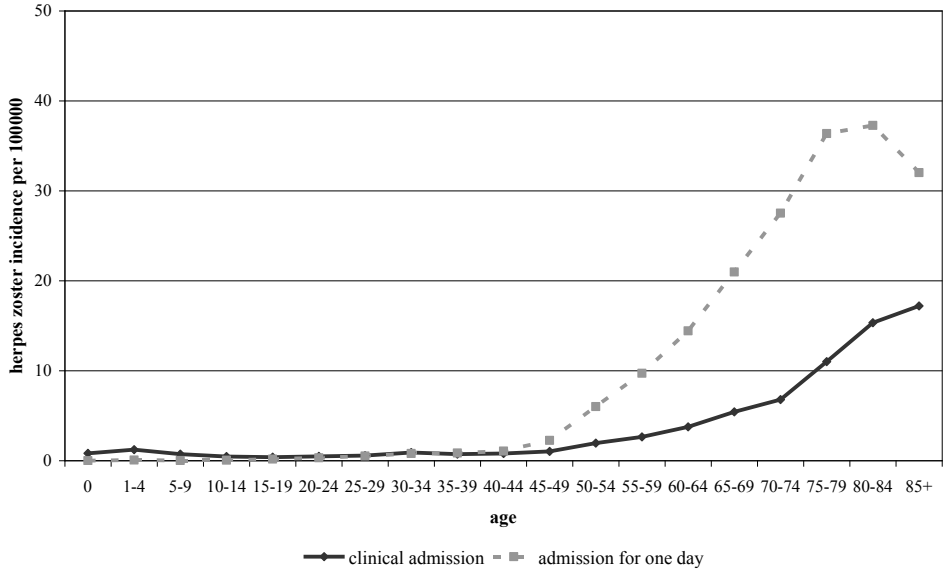


Figure 3. Age-specific average annual incidence of hospital admissions due to main diagnosis herpes zoster per 100000 2000-2007.(source: Prismant. National Medical Registration. Utrecht: Prismant, 2000-2007).

The absolute number of gained QALYs is the highest by vaccination at the age of 60 years with ~353, and the lowest by vaccination at the age of 80 years with a total gained of ~140. However this absolute number must be seen in the context of the number of people who have to be vaccinated to gain those QALYs. The number of people needed to be vaccinated to gain one QALY is a good proxy: the lowest number is 268 at the age of 70 years, the highest 498 at the age of 60 years.

Cost-effectiveness of vaccination

The information on the number of doses, vaccine efficacy, prevented costs and QALYs gained together is expressed in the cost-effectiveness ratio (Figure 4). Using the reduction of BOI as an endpoint the most optimal cost-effectiveness ratio is €21,716 (95% CI: €11,569 - €31,870) for vaccination at the age of 70. The worst ratio is €38,519 (95% CI: €12,176 - €67,158) for vaccination at the age of 60 under the same perspective (indirect costs included) or €40,503 under the healthcare payer perspective (indirect costs excluded). This implies that vaccinating at the age of 70 results in the best value for money.

In the scenario with reduction of HZ cases only the cost-effectiveness ratio increases towards ~€33,500 at the age of 70; using the scenario with reduction of PHN improves the cost-effectiveness to a ratio of ~€10,000. Although the clinical trial showed a higher impact of vaccination on the BOI compared to the incidence of HZ, we

Table 1. Absolute outcome and prevented cases for different ages at vaccination in the base case scenario

	60 years	65 years	70 years	75 years	80 years
Before vaccination:					
Cases HZ	26845	15513	11093	7630	4769
Cases PHN	4639	2936	2351	1857	1370
Hospitalisation	320	205	163	128	89
1 day visit hospital	1102	683	515	363	210
Deaths	30.7	20.9	18.6	17.6	16.5
Direct costs*	€2217577	€1527388	€1306022	€1100313	€847884
Indirect costs*	€1241555	€0	€0	€0	€0
QALYs lost*	3024	2024	1703	1402	1060
After vaccination: (75% coverage)					
Nr. of vaccinees	175925	115943	94354	80712	58724
Vaccination costs**	€14680941	€9675443	€7873841	€6735416	€4900518
Cases HZ	22512	12496	9201	6277	4299
Cases PHN	4222	2581	2071	1603	1257
Hospitalisation	292	178	141	107	81
1 day visit hospital	966	563	426	294	188
Deaths	30.5	20.6	18.1	16.4	15.4
Direct costs*	€1832919	€1219724	€1082777	€902727	€760458
Indirect costs*	€541068	€0	€0	€0	€0
QALYs lost*	2671	1724	1350	1133	921
Prevented:					
Cases HZ	4334	3017	1892	1352	471
Cases PHN	417	355	280	254	113
Hospitalisation	28	27	21	20	9
1 day visit hospital	136	120	89	70	22
Deaths	0.2	0.3	0.5	1.2	1.1
Direct costs*	€384658	€307664	€223245	€197586	€87427
Indirect costs*	€700487	€0	€0	€0	€0
QALYs lost*	353	300	352	269	140

* Costs are discounted with 4% and QALYs with 1.5%
** Vaccination costs are based on a vaccine price of €77, application costs of €4.80 per vaccination and coordination costs of €1.65 per vaccination

want to mention that using BOI or PHN endpoints will be more sensitive towards the decisions made in the way the QALY loss due to HZ is currently modeled/estimated.

According to the sensitivity analyses (Table 2), changing assumptions regarding the discounting rate, vaccine price and duration of protection of the vaccine have the greatest impact on the ratio, especially with a longer duration of protection or a lower vaccine price the costeffectiveness profile improves.

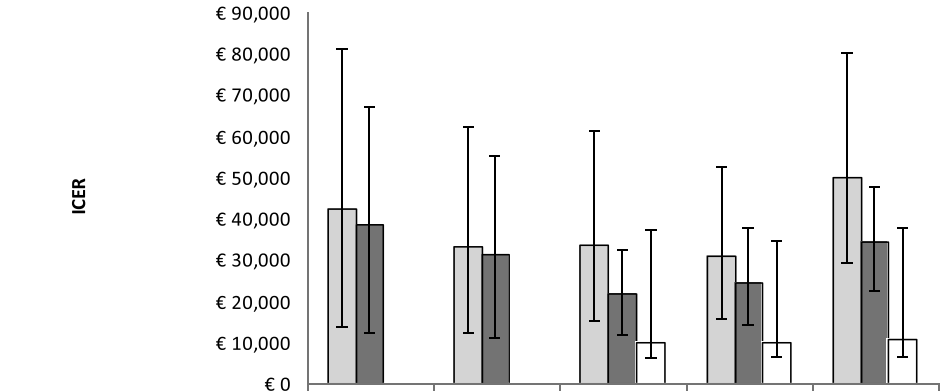
If a diagnostic test to determine immunity against VZV would become available in the future, a more targeted vaccination strategy could be implemented. Furthermore, people with a history of HZ could be excluded to save costs, as HZ does not frequently reoccur.

DISCUSSION

In view of the scarce therapeutic options for HZ and its sequelae the reduction of the risk of this disease by vaccination is an important development. Moreover, the HZ vaccine could be relevant because of the predicted temporary increase in the incidence of HZ after introducing childhood varicella vaccination [21]. HZ vaccination could prevent part of the disease burden of this often painful disease among elderly. However, the number of prevented GP-consultations, hospitalizations and deaths is relatively limited compared to other vaccine preventable diseases. In the decision process it is important to consider that the health gain that could be realized by HZ vaccination is in particular related to the reduction of (long term) pain; the number of life years gained is rather small. Furthermore, a considerable part of the disease burden caused by HZ will still remain despite programmatic vaccination since the vaccine efficacy is suboptimal. The indirect disease burden estimations might increase in future, if the recently reported increased risk of stroke after HZ is being confirmed in future research [33]. The relative low efficacy and the lack of knowledge on protection of the vaccine on the long term might be a problem for general acceptation of vaccination against HZ.

Offering HZ vaccination in combination with influenza could be a promising option. However, a previous Dutch study showed that the acceptance of HZ vaccination given simultaneously with influenza vaccination was only 39%, i.e. considerably lower compared to the vaccination coverage for influenza (76%) [8]. Insight into the degree of acceptance by the public is important, especially in the light of the recent experiences in the Netherlands with objection to introduction of the vaccine against human papillomavirus (HPV).

It will be difficult to make a decision on the target group for HZ vaccination: the HZ incidence increases whereas the vaccine efficacy decreases with age. Based on the cost-effectiveness analysis (base case scenario), vaccinating at the age of 70 years would be the best option. However, the value of €21,716 lies just above the socially accepted threshold in the Netherlands of €20,000 per QALY. This implies that the cost-effectiveness profile is marginal, although this is not the first evaluation



	60	65	70	75	80
Based on reduction of HZ	€ 42,151	€ 33,099	€ 33,454	€ 30,701	€ 50,105
Based on reduction of BOI (base case)	€ 38,519	€ 31,228	€ 21,716	€ 24,336	€ 34,449
Based on reduction HZ and PHN			€ 9,861	€ 9,959	€ 10,552

Age at vaccination

Figure 4. Incremental cost-effectiveness ratio (ICER) for different scenarios and ages; indirect costs are included (loss of working hours,only relevant for vaccination at 60 years of age). The base case (dark grey) is including a lower QALY loss in the first 6 months of HZ among vaccinees, in the 'without additional effect' (light grey) this is not included. Error bars represent 95% confidence intervals and under the bars the relevant cost-effectiveness ratios are shown.

criterion for introduction of a new vaccine [34]. The scenario with additional reduction of PHN improves the cost-effectiveness to a ratio of ~€10.000. However, this scenario has some major limitations. First, the definition of PHN as used in the clinical trial does not necessarily concern pain on the long term. Second, the effectiveness of the vaccine against PHN is not straightforward (extra effectiveness only above the age of 70 years) and has a high uncertainty. If the duration of protection turns out to be longer, the vaccination could be given at an earlier age which might improve the cost-effectiveness of the vaccine. Research on new vaccines with a higher vaccine efficacy, in particular at older age, is recommended.

There are several other estimations of the costeffectiveness of HZ vaccination [28,35-39]. Most of those cost-effectiveness studies apply for the USA [35-37] and Canada [38,39] and one for the UK [28]. Because of differences between countries in health care costs and health care seeking behavior, direct comparisons are hard to make. Also, the assumptions regarding the vaccine price were different: $150 (€107) instead of the €77 assumed in this analysis (which is based on the lower price CDC pays for its vaccine). Nevertheless the majority of studies conclude that vaccination against HZ is costeffective in their health care system, in contradiction with this study where it is marginally cost-effective. This difference can be

mainly attributed to the differences in the threshold value used by the countries. Internationally the threshold of €20,000 per QALY as used in the Netherlands is the lowest among the countries where a costeffectiveness study was done. Moreover, the incidence among the elderly seems to be slightly lower in the Netherlands. Whether this is due to a slightly lower reportage in the Dutch general practice, due to uptake of patients in nursing homes (that are not included in the Dutch reporting system) or due to other factors is unknown.

Table 2. Cost-effectiveness ratio under different circumstances and at different ages of vaccination

	60 years*	65 years	70 year	75 years	80 years
Base case	€38519	€31228	€21716	€24336	€34449
No prevention of death	€38901	€31489	€21910	€25020	€35930
No daytime visits hospital	€38540	€31251	€21731	€24351	€34458
No discounting	€33305	€27482	€18827	€21688	€31285
Discounting 3.5%/3.5%	€45313	€36210	€25647	€27874	€38725
Vaccine price €60 per dose	€30045	€24658	€17163	€19228	€27304
Vaccine price €50 per dose	€25061	€20793	€14485	€16224	€23100
Application costs €9.60**	€40911	€33083	€23002	€25778	€36466
Duration protection 4.8 years***	€61247	€48828	€27817	€32449	€42428
Duration protection 16.1 years***	€16954	€15031	€14030	€16013	€25953

* indirect costs included (loss of working hours, only relevant for vaccination at 60 years of age)
** full influenza tariff (instead of half the influenza tariff €4.80, that was used in the base case)
*** based on van Hoek AJ, Gay N, Melegaro A, Opstelten W, Edmunds WJ. Estimating the cost effectiveness of vaccination against herpes zoster in England and Wales. Vaccine 2009; 27(9):1454-67.

CONCLUSION

In conclusion, programmatic vaccination could reduce the burden of disease due to HZ considerably but is estimated to be marginally cost-effective even at the economically most attractive option, i.e. vaccination at the age of 70 years simultaneously with influenza vaccination. A final judgment on the cost-effectiveness will depend on price negotiations with the different parties involved. Even with vaccination at levels comparable to influenza vaccination, less than half of the disease burden caused by HZ will be prevented by vaccination, due to the relative low efficacy of the vaccine. It would be a challenge to reach high acceptance of vaccination despite the occurrence of HZ among vaccinees; involvement of the GP is essential.

While for many childhood vaccinations in addition to individual protection, indirect protection by herd immunity is offered, this does not hold for HZ. Making

the public aware of the existence of a HZ vaccine (with its current limitations) that could be obtained individually is necessary, irrespective of the decision whether or not to implement programmatic vaccination.

ADDITIONAL MATERIAL

The additional material can be found at: http://www.biomedcentral.com/1472-6963/10/237

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AUTHOR'S CONTRIBUTION

EAvL* drafted the manuscript, AJvH* performed the cost-effectiveness analysis and drafted the manuscript regarding this component. WO critically revised the manuscript. HJB initiated the design of the manuscript and helped to draft the manuscript. HEdM designed the vaccination evaluation framework and critically revised the manuscript. All authors read and approved the final manuscript.
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chapter FOUR

MODELLING THE IMPACT OF A COMBINED VARICELLA AND ZOSTER VACCINATION PROGRAMME ON THE EPIDEMIOLOGY OF VARICELLA ZOSTER VIRUS IN ENGLAND

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SUMMARY

This study updates previous work on modeling the incidence of varicella and Herpes Zoster (HZ) following the introduction of childhood vaccination. The updated model includes new data on age-specific contact patterns, as well as data on the efficacy of zoster vaccination in the elderly and allows for HZ among vaccinees. The current study also looks at two-dose varicella childhood programmes, and assesses the combined impact of varicella vaccination in childhood and zoster vaccination of the elderly. The results suggest that a two-dose schedule is likely to reduce the incidence of varicella to very low levels, provided first dose coverage is around 90% and second dose coverage is in excess of 70%. Single dose varicella vaccination programmes are expected to result in large numbers of breakthrough cases. Childhood vaccination is expected to increase the incidence of zoster for more than 40 years after introduction of the programme, the magnitude of this increase being influenced primarily by the duration of boosting following exposure to the varicella zoster virus. Though this increase in zoster incidence can be partly offset by vaccination of the elderly, the effectiveness of this combined strategy is limited, as much of the increase occurs in those adults too young to be vaccinated. Childhood vaccination at intermediate levels of coverage (70% and 60% for first and second dose coverage respectively) is expected to lead to an increase in adult varicella. At high coverage (90% and 80% coverage) this is unlikely to be the case. These results will be used to inform a cost-effectiveness analysis of combined varicella and zoster vaccination programmes.

BACKGROUND

In 1995 childhood vaccination against varicella (chickenpox) was introduced in the US [1-3]. However there is an ongoing debate about the potential negative effect of childhood varicella vaccination on the incidence of Herpes Zoster (HZ) and varicella in adults [4-7]. Herpes Zoster is a reactivation of the same virus (Varicella Zoster Virus, VZV) that causes varicella on initial infection [8]. Following primary infection the virus remains latent in the dorsal root ganglia. Reactivation of the virus is suppressed by cell-mediated immunity, which can be boosted by exposure to a varicella case [9,10]. With the introduction of childhood vaccination this exogenous boosting would be expected to decrease due to the reduction of varicella incidence, which may lead to an increase of HZ [9,11,12]. With the licensure of a vaccine to prevent HZ [13,14] , any increase in HZ following childhood vaccination could be offset (at least in part) by vaccination of the elderly (60+ years) against Herpes Zoster. There are other concerns with varicella vaccination, which include the potential increase in adult varicella (which tends to be more serious than childhood infection) that may occur following mass childhood vaccination [11,15,16], and concerns regarding the efficacy of a single dose of the vaccine at preventing varicella [17-19]. This latter

concern has lead to recommendations for two-dose policies in childhood [3,20], which has an obvious impact on the economic attractiveness of the programme.

Several studies have explored the effectiveness and cost-effectiveness of different varicella vaccination programmes in the UK and around the world [4,21-24]. However, to our knowledge no previous models have looked at a combined strategy of vaccination in childhood and of the elderly. Furthermore, previous modeling work has concentrated on single-dose varicella vaccination programmes [11,12,15,16]. Many of the indirect effects (such as an increase of adult varicella or HZ) depend on estimates of the rate of transmission across age groups. Previous analyses had to assume the relevant contact rates, as little relevant quantitative information was available at the time. However we update previous models [9,11,25] by using UK contact patterns collected as part of a European project (POLYMOD) [26]). In this paper we describe the estimated impact of one and two-dose varicella vaccination strategies, either alone or in combination with vaccination of the elderly against Herpes Zoster. The described epidemiological impact will constitute the basis for an economic evaluation of these strategies

METHODS

Model structure

To assess the impact of combined varicella and zoster vaccination programmes, a transmission dynamic model based on that of Brisson and colleagues [11] was adapted. The model consists on a set of ordinary differential equations and incorporates realistic age-structure (RAS) and age-specific mortality rates for England and Wales (Office for National Statistics). A stable population of 48 million people is considered, with 621,300 individuals born (=number of live births in E&W in 2003) every year on the 31st of December. The mortality of individuals in the oldest age group (95+ year old) is calculated separately so that the age distribution remains constant over time. Both varicella and zoster vaccination programmes are incorporated in the model as discrete events at the end of each year, when individuals age.

The model structure is illustrated in the flow diagram in Figure 1, which describes the natural history of VZV with and without varicella and/or zoster vaccination. People are initially protected by maternal antibodies, become susceptible to varicella, can be infected with varicella, develop disease and become immune to varicella. After a certain time (average period of natural protection = $1/\delta$) people become susceptible to zoster. In this state, they can either progress to zoster, or they can be boosted by an infectious case, rendering them (temporarily) protected against developing zoster. Therefore within the model infectious people can do two things – infect susceptible people or boost zoster susceptible persons. In case of vaccination against zoster, individuals pass into the vaccine protected

compartment. These people become zoster-susceptible again over time (average period of vaccine protection = $1/\delta_v$). When natural protection is assumed to be longer than vaccine-induced protection, vaccinated individuals are not moved from the immune compartment into the vaccination compartment because in that case vaccination will reduce their time protected.

Vaccinated individuals are tracked separately because of the difference of infectiousness and severity of breakthrough cases. In the model described by Brisson *et.al.* [11] individuals who had been immunised against varicella were not able to develop zoster. In the current model this possibility is allowed for, as studies suggest that vaccinees can, in fact, develop HZ, though it appears that they may do so at a somewhat lower rate [27-29]. In the new structure it is possible to distinguish between HZ among vaccinees after breakthrough or after vaccination only, because in the latter zoster will be caused by vaccine virus instead of wild type.

Varicella vaccination

Vaccination with varicella vaccine is assumed to result in three different outcomes. First, a proportion of individuals (p) suffer an initial vaccine failure and remain susceptible. Second, a proportion of individuals who respond initially (1-p) are protected from varicella infection ((1-p)*T; in which T is the proportion of vaccine responders who are protected). Third, a proportion of individuals respond, but they are liable to be infected (i.e. become a breakthrough case) if they are exposed. This proportion is therefore ((1-p)(1-T)). Those in the vaccine immune class (V Immune) can lose protection over time and pass into the vaccinated susceptible class (V Susceptible) at a rate (w). If individuals receive a second dose of varicella vaccine, the responders (T_{Vii}) move on to a vaccine protected class (VP 2nd dose) and when they lose protection pass into the vaccinated susceptible class (V Susceptible) at a rate (w_{ii}). Those who do not respond to the second dose remain in whatever compartment they were already in.

Zoster vaccination

Zoster vaccination is given irrespective of a history of varicella. Those who are still susceptible for varicella are handled as if they are vaccinated against varicella and moved to the varicella vaccinated arm of the model, this because the Zoster vaccine is a high dose version of the Varicella vaccine. Within the model it is assumed that individuals can experience only one episode of zoster throughout their life, vaccination was thus not effective among individuals in the zoster infected or immune compartments (ZI and ZR) because that will mean they become susceptible to zoster again.

Mixing patterns

Data on the contact patterns among individuals of different ages were collected as part of the POLYMOD project [25] and were used to parameterize the mixing patterns

assumed in the model. A general base-case Who-Acquired-Infection-from-Whom (WAIFW) matrix (β-*matrix*) was derived from a contact matrix based on the UK study population (all contacts) combined with an age-specific transmission parameter (*q*) following the methodology originally developed by Wallinga and colleagues [30]. The β-*matrix* influences the steady state disease incidence, which is assumed to reflect the cumulative proportion of individuals with serological evidence of infection by age. Therefore information about contacts is combined with information about the disease incidence to find a best-fitting value of *q*. In this case the *q* is fitted in such way that the resulting age-specific force of infection based on the resulting β-*matrix* fits observed seroprevalence (<20years of age) [31] and varicella incidence (20> years of age) [32]. To fit the data three different values for *q* where estimated, for the age 0-3, 4-21 and 22+, under the assumption of differential susceptibility to infection by age-group. Fifty thousand different contact matrices were obtained by bootstrapping the individual contact data. For each of the matrices the transmission parameters were fitted, and the best fitting matrix was used as the base case scenario. In the sensitivity analyses a set of 1000 different β-*matrices* were obtained by rejection sampling. For each contact matrix 750 different sets of *q* where sampled, by varying *q* as a percentage of the most optimal *q* for that given matrix. In the rejection sampling process only contact matrices were used with at least 1% probability based on their most optimal transmission parameter, this to improve the speed of the process. Of the obtained possible matrices a subset of 1000 matrices where randomly selected to use in the sensitivity analyses.

Reactivation rate

In the model the β-*matrix* influences the steady state varicella incidence, and the incidence of herpes zoster is determined by the reactivation rate. This reactivation rate is fitted to the zoster incidence data given the β-*matrix* and the assumption about the duration of protection acquired by boosting. In the sensitivity analyses for each of the 1000 iterations the reactivation rate was refitted based on the different β-*matrix* and assumption about the duration of protection. Age-specific zoster reactivation rates $\rho(a)$ (see Brisson *et.al.* [9] for formula used) were fitted by maximum likelihood to the age specific zoster incidence as found in the 4th Morbidity Survey in the General Practice [31].

Biological parameters

For varicella the duration of the infectious period was assumed to be 7 days after a latent period of 14 days [11]. The infectious period for Zoster is also assumed to be 7 days.

Efficacy of varicella vaccine

In this paper we reviewed the two dose schedule of vaccine Varivax (Merck/SPMSD). Unfortunately only one trial is available investigating the efficacy of a two dose

schedule [33], this trial has several short-comings. Firstly the number of plaque forming units of the vaccine used in the trial was higher than the licensed version; 1350 plaque forming units in the licensed vaccine compared to a minimum of 2900 in the trial. Secondly the age distribution was wide (4-12 years), and each age group face a different force of infection making it hard to extrapolate to the effectiveness of vaccination at 1 year old. Thirdly the presented results include the years 1996 and onwards, in those years widespread vaccination was in place in the US. Due to the dramatic change in force of infection caused by the vaccination program those years should be dropped from the analysis. However because no other trial data was available we have used this data.

Values for take (T) and waning (W) were fitted with a simple model by maximum likelihood (Figure A1-1), assuming that the force of infection (λ) = 0.2 per year, and the rate of flow to zoster susceptible (π) = 1/20 per year. To reduce the number of parameters describing vaccine efficacy we assumed that the susceptibility of vaccinated individuals to become infected (parameter *b*, Figure 1) is the same as non-vaccinated people (hence takes a value of 100%). Vaccinated people are as likely as non-vaccinated people to become boosted when they come into contact with a varicella case (described by parameter *k* – assumed value of 100%). For the sensitivity analysis 1000 sets of take (T) and waning (W) were obtained by rejection sampling.

Zoster vaccine efficacy

Parameters describing vaccine take and waning associated with HZ vaccine were estimated by fitting a model (figure A1-2) to the zoster vaccine trial [14]. The vaccine efficacy is age dependent but the available data is not detailed enough to estimate age specific take and waning rates. Therefore a previously estimated duration of protection was assumed and subsequently the take was fitted [34] (Appendix 1). The base-line proportion of people who are immune and protected was based on the placebo group in the clinical trial. For the sensitivity analyses 1000 sets of take and waning combinations were obtained.

The probability of developing zoster after vaccination was set so that the incidence will be lower in vaccinated people. Two parameters describe this process π and χ (Figure 1). π describes the rate at which individuals in the vaccine protected class become susceptible to boosting (or development of zoster), and χ describes the reduction in the probability of developing zoster by age given that an individual is susceptible to boosting, but has been vaccinated with varicella vaccine. As the data are simply reports of the reduction in zoster incidence in vaccinees compared to non-vaccinees, it is not possible to identify these two parameters independently. Thus π was set to be equal to 0.05 (based on Brisson's base-case estimates for the duration of a boost from a wild-type infection [11]), and χ was estimated to give the required long-term reduction in the incidence of zoster. Furthermore as these studies generally do not distinguish whether zoster cases in vaccinees are caused by

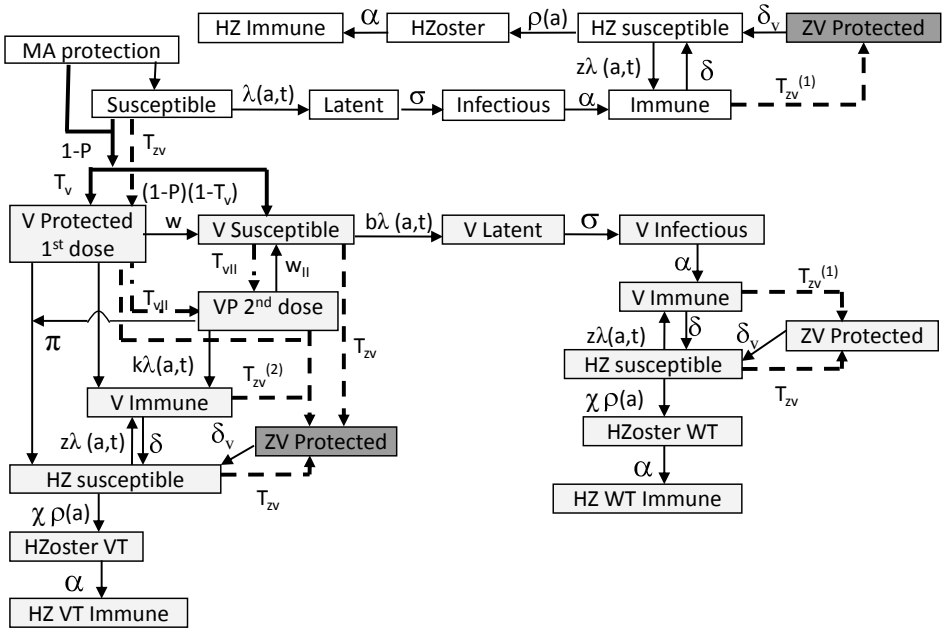

Figure 1. Flow diagram of the model structure.(bold lines are vaccination flows), WT= wild type virus, VT = Vaccine type, MA = Maternal antibody, V = vaccinated, P =initial vaccine failure, T_v =Take first vaccine dose varicella, T_{vII} =Take second vaccine dose varicella, σ =Duration infectious period, α =Duration of infectious period ρ[a] =Reactivation rate, π=Progression rate from vaccine protected to zoster susceptible, λ =force of infection, K=probability to be boosted after contact when you are vaccine protected, χ=Change in zoster reactivation rate in varicella vaccines, Z=probability to be boosted after contact when you are zoster susceptible, s=Duration of latency (rate to become infectious), W =Waning rate first dose, W_{II}=Waning second dose, b =susceptibility of vaccinated individuals. (1) In case of $\delta > \delta_v$ people will remain in the immune compartment although they are vaccinated against HZ. (2) In case of $\pi > \delta_v$ people will remain in the immune compartment although they are vaccinated against HZ

the vaccine strain or wild-type infection the rate of development of zoster in these two groups was set to be equal. In the base case scenario χ was set in such way that among the vaccinees the zoster incidence will be 10% of that of zoster before vaccination, assuming no background boosting (Appendix 2). This percentage is varied between 0 and 100% in the sensitivity analysis (with such distribution that 50% is below 10% and 50% above the 10%).

VZV was assumed to be at endemic equilibrium prior to vaccine introduction, and the model was run for 100 years after the start of the vaccine programme. The model was programmed in Berkeley Madonna 8.3.14.

Vaccination policies

The following vaccination strategies were considered in the model simulations:

- single dose childhood programme (1 year of age)
- two-dose childhood programme (1 and 3 years of age)
- single dose adult vaccination programme against HZ (70 years of age [35])
- combined programme of two varicella doses in childhood and 1 dose adult vaccination against HZ.

The base-case coverage was assumed to be 90% for the first varicella dose, and 80% for the second varicella dose. Only those who receive the first dose, get a second dose (that is there is assumed to be no catch-up of unvaccinated individuals at 3 years of age). The base-case age at which HZ vaccine is given (70 years) was based partly on the results of an economic analysis [34], and partly on the basis of guidance from the JCVI subcommittee [35]. The base-case coverage for the elderly vaccination is assumed to be 70%. In the sensitivity analysis the impact of vaccination coverage was investigated using lower coverage rates. The duration of protection due to contact with wild type virus or zoster vaccine was elucidated looking to the extreme scenarios as possible in the parameterization.

RESULTS

Comparison to epidemiological data, and estimation of force of infection

Figure 2 compares the best-fitting model fits with the age-specific seroprevalence data [31], age specific incidence of varicella GP consultations [32] and the age specific incidence of herpes zoster [32]. Although the model describes infection and not GP visits 100% reporting was assumed for varicella above the age of 20 years and for Herpes Zoster in all age groups. The estimated force of infection with associated 95% credibility intervals is shown in Figure 2d. As the figures show, a good fit was obtained.

Dynamics of varicella and zoster post vaccination

Figure 3 shows predicted impact of alternative vaccination programmes on the incidence of varicella (a) and Herpes Zoster (b) over time. The model predicts that a single dose of varicella vaccine is likely to result in substantial numbers of breakthrough varicella cases in the long-run with an incidence around 330 (190-447) per 100,000 per year. On the other hand, vaccinating infants at such high levels of coverage with a two dose schedule is expected to result in a large reduction of varicella in both the short and long-term. However, there is predicted to be an increase in Herpes Zoster incidence for about 40-60 years after varicella vaccination. The incidence of zoster is expected to increase by up to , 20% (12-36%) to almost

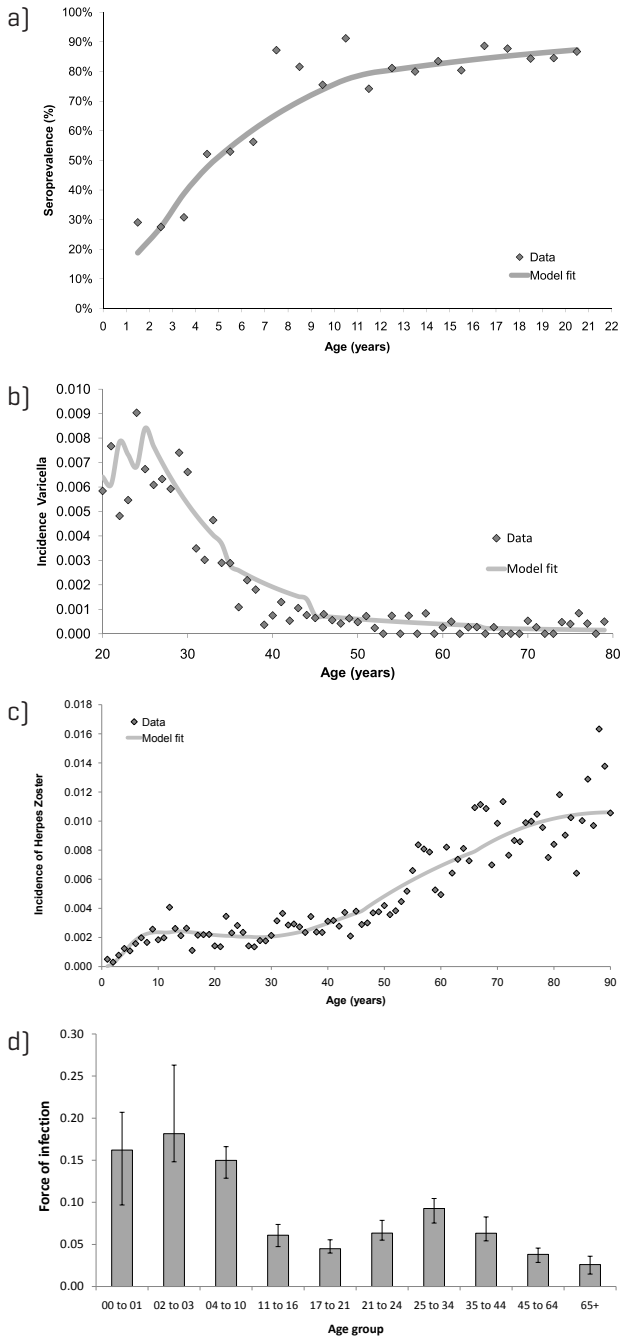

Figure 2. Best-fit model (line) compared to data (points): a) is the fit to seroprevalence data; b) is the fit to the varicella GP consultations and c) is the fit to the zoster incidence (both of the latter are from MSGP4). The resulting best-fitting force of infection estimates and associated 95% credibility intervals are shown in c).

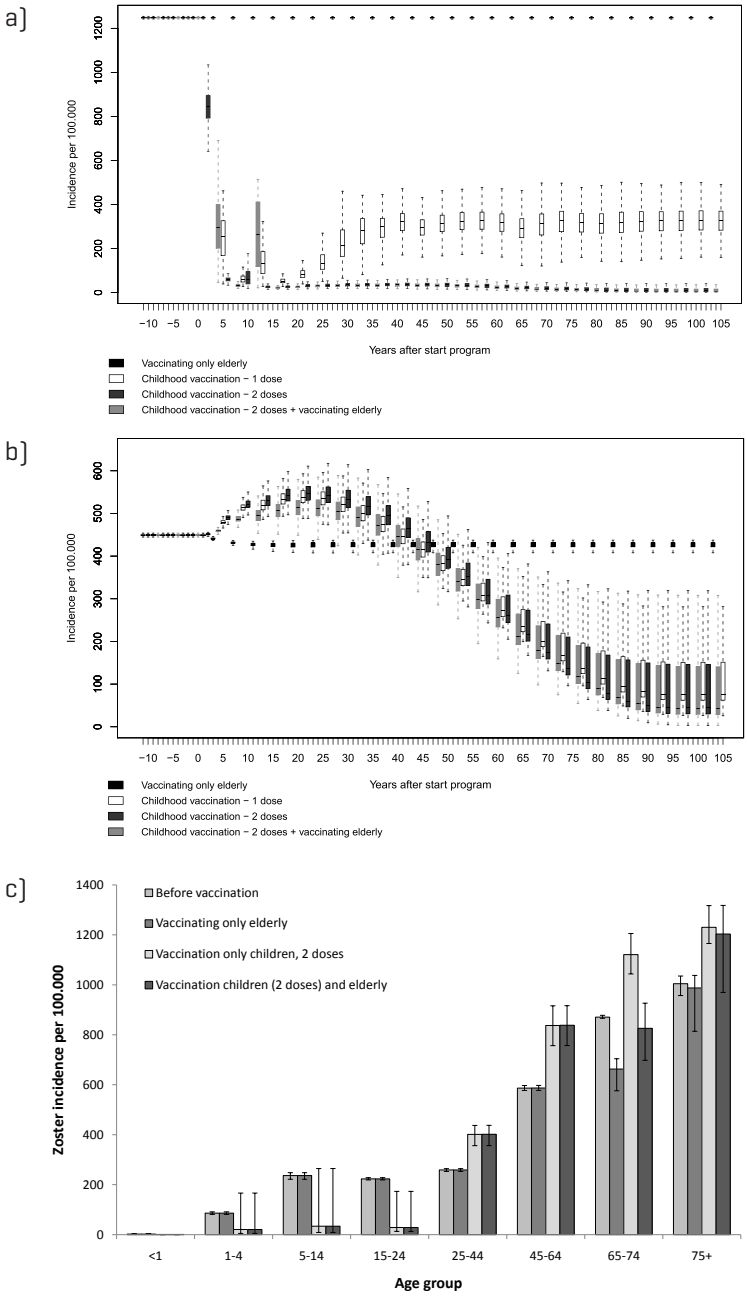

Figure 3. Model results on the incidence of varicella (a) and Herpes Zoster (b). The boxes show the inter-quartile range the whiskers 10-90% of the range of results generated by the model. The different shading represent different programmes: black boxes elderly vaccination only (70% coverage); white 1 dose infant varicella (90% coverage); dark grey two-dose infant vaccination (90% first dose, and 80% second dose coverage); and light grey combined infant and elderly programme. The age-specific incidence of herpes zoster 25 years after vaccine introduction is shown in c).

Table 1. Model parameters

MODEL PARAMETERS	Mean value (CI)	Source
Biological parameters		
Duration of maternal protection (months) (12/ε	6	Assumed
Duration of latent period (days) (365/σ)	14	[11]
Duration of infectious period (days) (365/α)	7	[11]
Duration of immunity to zoster after varicella infection (years) (1/δ)	20	[11]
Proportion of effective varicella contacts that boosts against zoster (*z*)	100%	[11]
Varicella vaccine efficacy parameters		
Rate of varicella acquisition of vaccines compared to non vaccines (b)	100%	Assumed
Proportion of temporarily protected individuals who become immune due to contact with varicella (k)	100%	Assumed
Rate at which temporarily protected individuals become susceptible to Herpes Zoster (1/year) (π)	0.05	Duration of protection of natural boosting.
Rate of varicella infectiousness of vaccines compared to non-vaccinees (m)	50%	
Coverage varicella: first dose	90%	
Coverage varicella: second dose	80%	
Change in the reactivation rate χ	0.052 (0.021 – 0.793)	See Appendix 2
Zoster vaccine efficacy parameters		
Percent of individuals who become temporarily protected after zoster vaccination by age at vaccination	FOI_{65+}=0.0179, 1/ δ_v=7.5	See Appendix 1
59-64	91%	
65-69	81%	
70-74	58%	
75-79	50%	
80-84	21%	
85+	9%	
Coverage level	70%	
	First dose	**Second dose**
Percent of individuals for which vaccine fails completely (P)	4%	
Percent of individuals who become temporarily protected after vaccination (T)	100% (93%-100%)	100% (97%-100%)
Rate at which temporarily protected individuals become susceptible to varicella (1/year) (W)	0.04 (0.067-0.015)	0.013(0.026-0.005)

620 per 100,000 per year. With only vaccination against Herpes Zoster there is no reduction in the incidence of Varicella and a modest reduction in the incidence of Herpes Zoster. In case of a combined programme there is estimated to be a large reduction of varicella but still an increase of Herpes Zoster, although to a lesser extent than only childhood vaccination, a median increase of 10% (5.6%-25%). This is because a large increase in zoster incidence occurs in middle-aged adults, i.e. adults who are too young to be vaccinated by a programme targeted at the elderly (70 years) (see Figure 2c). There is considerable uncertainty with regards estimates of the impact of varicella vaccination on the incidence of HZ, in both the medium and long-term.

Figure 4 shows the sensitivity of these results to vaccine coverage, using the base case strategy and base-case model parameters. As expected, the incidence of varicella is more sensitive to first-dose coverage than second dose coverage. The short-and medium term incidence of zoster is not sensitive to variation in infant coverage levels (only with very low coverage is there a difference, not shown), as breakthrough infections are assumed to be less infectious than natural cases. The long-run incidence of zoster is affected by varicella first dose coverage, as vaccinees are assumed to be less likely to subsequently develop zoster than those who are infected by the wild virus.

The sensitivity of the model results towards duration of protection after a contact with a varicella case or zoster vaccination is presented in figure 5 assuming a two dose varicella vaccination programme is combined with vaccination of the elderly against HZ. Only the base case and the two extreme combinations of the possibilities are presented. As expected assumptions regarding the duration of boosting from natural infection or vaccination of the elderly have little impact on varicella incidence. However, they do influence the expected change in the incidence of zoster post varicella vaccination. When there is a short natural protection and an extremely long protection from the zoster vaccine there is expected to be almost no increase in HZ. In the case of very long protection due to a natural boosting and very short protection from vaccination of the elderly, there will be a more dramatic increase in the zoster incidence.

Changes in the long-run incidence of adult varicella (among those aged 15 and over) are shown in Figure 6, for a two-dose vaccination strategy aimed at children. Coverage was lowered from 90% first dose and 80% second dose to 50% and 40% coverage for the first and second dose respectively. It can be seen that at high levels of two-dose coverage the model predicts that a decrease in adult cases is likely, whereas at the lower level of coverage, especially below 70% an increase in adult disease, with an increasing contribution of natural varicella in the overall varicella burden after vaccination.

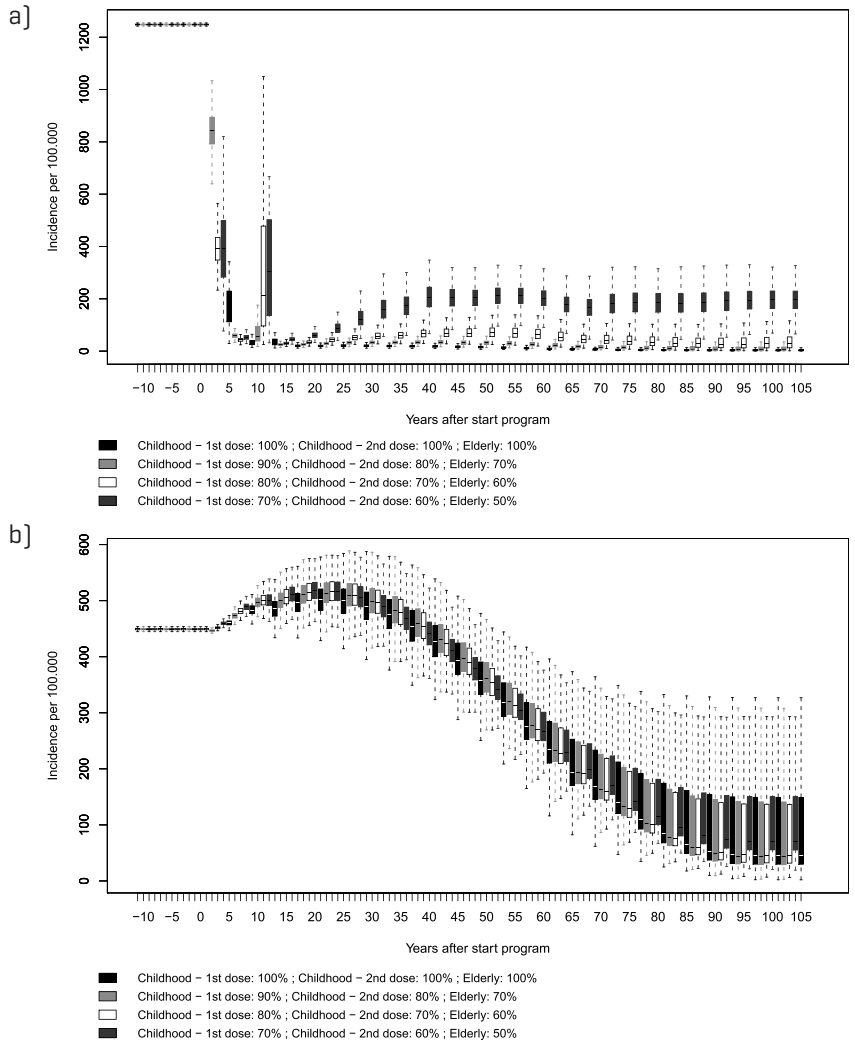

Figure 4. Sensitivity of base-case model results to different levels of first and second dose coverage. The overall incidence of varicella and zoster is shown.

DISCUSSION

We present an updated analysis of the possible impact of varicella and/or zoster vaccination on the incidence of varicella and zoster. A number of changes have been incorporated into this model compared to previous work [11]. The most important of which is the use of data on observed age-specific contact patterns from a population-based survey [26] and subsequent uncertainty in the contact rates. The incorporation of these data, necessitates the re-estimation of zoster reactivation

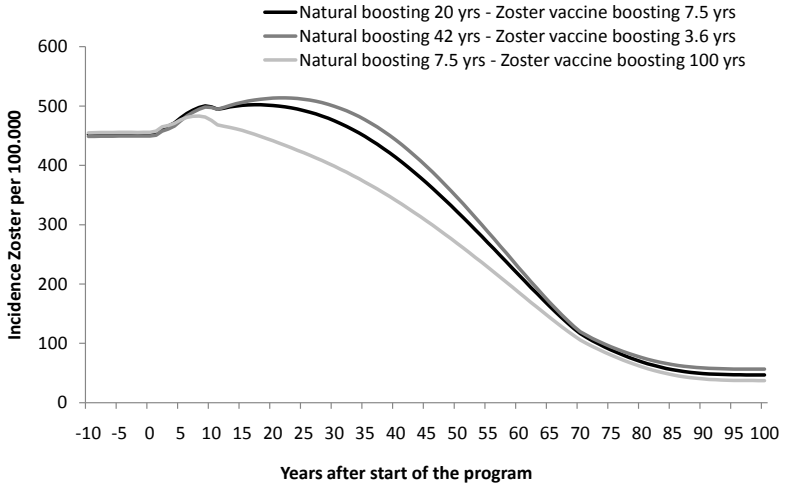

Figure 5. Incidence of zoster for different durations of natural boosting and vaccine protection. From the different combinations of the two durations only the base case and the two extremes are shown.

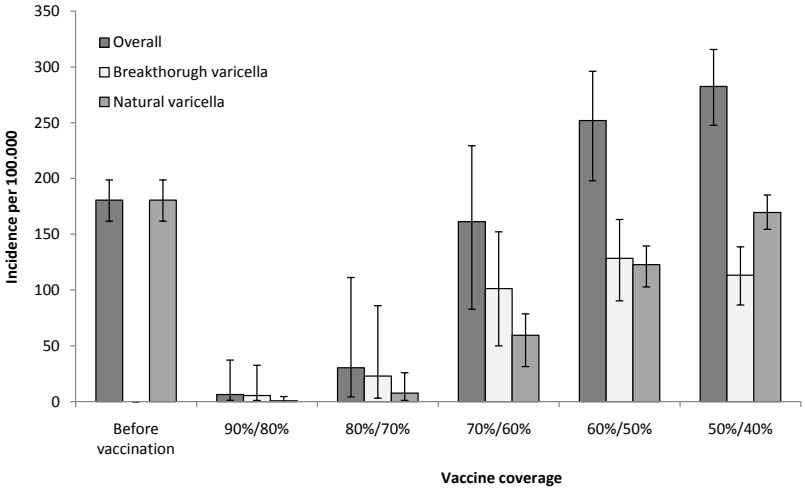

Figure 6. The post-vaccination equilibrium (at 100 years) annual incidence of varicella in adults age 15 and above by levels of coverage (2 dose combined policy). The height of the bar is the median of 1000 simulations, and the error bars represent 2.5 and 97.5 percentiles.

rates, with updated information on the force of infection in adults due to contact with children. Importantly, the model now also includes a two-dose schedule and vaccination of the elderly to reduce the incidence of zoster (the parameters describing this being based on analyses of a double-blind placebo controlled trial of

the zoster vaccine). The updated model also allows for vaccinees to develop zoster, though at a reduced rate compared to those experiencing natural protection. The average duration of boosting against zoster (exogenous boosting) following exposure to VZV remains an uncertain and influential parameter. As can been seen in figure 3 the joint uncertainty in the contact rates, duration of natural protection and other epidemiological parameters lead to wide confidence intervals, meaning that the presented outcomes are more disease trends, since individual outcomes are dependent on a spectrum of parameter values.

The results of the model with regards a one-dose policy are similar to those published by Brisson et al. [11,16] That is, vaccination of infants at achievable levels of coverage in the UK (around 90%) is likely to result in a rapid decline in incidence of varicella, followed by a period of low incidence (for perhaps a decade), which may be followed by a series of epidemics, before the system finally settles around a new level of incidence which is considerably lower (i.e. reduced by about 75%) than in the pre-vaccine era. Breakthrough varicella makes up a substantive portion of these cases. No increase in adult varicella is expected with our base-case parameters. However, if lower coverage is achieved (<70%) than an increase in varicella among adults is expected in the long run. Our results for the varicella only schedules are comparable with the recent publications by Karhunen et.al. [23] and Gao et.al. [24], and Brisson et.al. [4]. None of these publications incorporate zoster vaccination on top of varicella vaccination in a combined schedule.

Two-dose routine vaccination at the coverage levels that may be achievable in the UK (90% and 80% for the first and second dose respectively), is expected to result in very low incidences of varicella among all age groups in the long-run and may even lead to elimination of the virus. However, the magnitude of this reduction is dependent on our assumptions on the efficacy of the second dose of vaccine, for which there is little good data. As with the one-dose strategy, vaccination of young children is expected to result in an increase in zoster in the medium term. This increase in incidence can be partly attenuated by routine vaccination of the elderly. The long-run incidence of HZ following vaccination of children is highly uncertain, as this depends on the likelihood of vaccinees developing zoster, either via the vaccine strain, or from wild-type breakthrough infection. The data on this are scarce, and no consistent pattern has emerged. Most, but not all, studies have suggested that the incidence of zoster in vaccinees is likely to be reduced [25,28], but exact quantification of this risk is difficult [28, 29].

As with all models the findings are reliant on the reasonableness of the assumptions made and the values of the parameters. We estimated the force of infection of varicella for people above the age of 20 based on the incidence of GP notifications. This is not ideal because there is a possibility varicella was misdiagnosed as Herpes Zoster or vice versa. More data on the actual force of infection in adults would be welcome since the changes in Zoster and adult varicella

incidence after vaccination depends on this. A key assumption with regards zoster epidemiology is the degree and duration of boosting that results from exposure to the virus. We used Brisson et al.'s best fitting estimates in our base-case model (an average duration of boost of 20 years). In this estimation the duration of boosting was identical for all ages. Brisson et.al. [4] have shown that an age dependent duration of boosting can decrease the relation between varicella and zoster, leading to a smaller increase of zoster after vaccination. By fitting models to the data from the large-scale clinical trial of the zoster vaccine [14], van Hoek et al. [34] estimated that the average duration of vaccine-induced protection may be significantly shorter than Brisson et al.'s estimates (best fitting estimates are in the range of 3.6-100 years). The shorter the duration of boost, the smaller the increase in zoster following childhood varicella vaccination (Figure 5). It is therefore possible that the base-case results overestimate the post-vaccination increase in zoster. Even using Brisson et al.'s estimates of the duration of boost, our estimates of the increase of zoster following varicella vaccination are lower than those of Brisson et al. [11, 16]. This is because we re-estimated the force of infection in adults using the POLYMOD contact survey, which resulted in a revision of our estimates of the risk of reactivation. Although the data on the incidence of HZ in the US are limited and contradictory, the evidence suggests that the incidence is probably increasing (four of the five published studies reports an increase in HZ [36-40]), though whether this is attributable to varicella vaccination, or some other factors (like increased use of corticosteroids) is less clear. Further surveillance data on zoster (accompanied by good varicella coverage and incidence data) is clearly needed.

We used Kuter et al.'s data to re-estimate the vaccine efficacy parameters [33]. A number of these, particularly those concerned with breakthrough varicella, are uncertain. However, since a two-dose schedule would be expected to reduce the number of breakthrough cases to low levels, and it is likely that two-dose schedules will be adopted, then this uncertainty does not significantly affect findings.

This study updates previous work [11,16] on the impact of vaccination on the incidence of both varicella and zoster. The results suggest that a single-dose policy may result in significant numbers of breakthrough cases, a pattern which has been observed in the US [17]. A two-dose schedule is likely to lead to a low incidence of varicella, provided coverage is maintained at around 90% for the first dose. An increase in zoster incidence is still expected following varicella vaccination in childhood, and this increase can only be partly ameliorated by introduction of zoster vaccination in the elderly.

APPENDICES

The appendices can be found at: http://www.sciencedirect.com/science/article/pii/S0264410X11000764

CONTRIBUTION

AJvH involved in coding, parameterization, model run and writing up, AM programming the model in Berkeley Madonna and initial validation and writing up, EZ assisted on bootstrap of the contact matrices, JE supervision, model structure and majority of the writing up, NG involved in methodology, parameterization, model structure and supervision. All authors agreed with the final draft.

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chapter FIVE

THE COST-EFFECTIVENESS OF VARICELLA AND COMBINED VARICELLA AND HERPES ZOSTER VACCINATION PROGRAMMES IN THE UNITED KINGDOM

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ABSTRACT

Background

Despite the existence of varicella vaccine, many developed countries have not introduced it into their national schedules, partly because of concerns about whether herpes zoster (HZ, shingles) will increase due to a lack of exogenous boosting. The magnitude of any increase in zoster that might occur is dependent on rates at which adults and children mix - something that has only recently been quantified - and could be reduced by simultaneously vaccinating older individuals against shingles. This study is the first to assess the cost-effectiveness of combined varicella and zoster vaccination options and compare this to alternative programmes.

Methods and Findings

The cost-effectiveness of various options for the use of varicella-zoster virus (VZV) containing vaccines was explored using a transmission dynamic model. Underlying contact rates are estimated from a contemporary survey of social mixing patterns, and uncertainty in these derived from bootstrapping the original sample. The model was calibrated to UK data on varicella and zoster incidence. Other parameters were taken from the literature. UK guidance on perspective and discount rates were followed. The results of the incremental cost-effectiveness analysis suggest that a combined policy is cost-effective. However, the cost-effectiveness of this policy (and indeed the childhood two-dose policy) is influenced by projected benefits that accrue many decades (80-100 years or more) after the start of vaccination. If the programme is evaluated over shorter time frames, then it would be unlikely to be deemed cost-effective, and may result in declines in population health, due to a projected rise in the incidence of HZ. The findings are also sensitive to a number of parameters that are inaccurately quantified, such as the risk of HZ in varicella vaccine responders.

Conclusions

Policy makers should be aware of the potential negative benefits in the first 30-40 years after introduction of a childhood varicella vaccine. This can only be partly mitigated by the introduction of a herpes zoster vaccine. They have to decide how they value the potential benefits beyond this time to consider childhood vaccination cost effective.

INTRODUCTION

Varicella vaccination was introduced into the United States in the mid 1990s (1-3). However, other countries have been slower to introduce varicella prevention programmes, partly as a result of concerns that infant vaccination may increase the occurrence of adult varicella (which tends to be more serious) (4,5), or may increase the incidence of herpes zoster (6-9), and partly because data from the

clinical trials [10] and subsequent surveillance [3,11,12] suggest that vaccination may not provide solid, lasting protection for many vaccinees. Previous modelling and economic analyses [e.g. [13]] have addressed some, or all of these concerns [see [14] and [15] for reviews], and shown that an increase in herpes zoster [in particular] can have a profound effect on the estimated cost-effectiveness of infant varicella vaccination [13]. Since these studies were published further data have become available from the US on the impact of childhood vaccination on the incidence of varicella in different age groups [16,17], as well as the incidence on zoster [18-21] . Furthermore, data are now available on underlying patterns of mixing [22], which should lead to a more accurate estimate of the impact of vaccination of one age group on the incidence of infection and disease in other age groups. In addition, two-dose strategies are now recommended for varicella vaccination to counter the high rates of breakthrough infection [3]. Finally, a vaccine is now available against herpes zoster [HZ, shingles] [23,24], raising the possibility that combined strategies of varicella vaccination of children and zoster vaccination of the elderly are possible. The current study updates previous analyses [13], takes into account new data, and is the first to evaluate combined strategies, as well as a two-dose childhood programme.

There are three basic uses of these two vaccines:

- Childhood varicella vaccination alone
- Varicella vaccination in children and HZ vaccination of the elderly [the vaccine is licensed for use in those aged 60 years and above].
- Herpes zoster vaccination of the elderly alone.

In this paper we investigate the incremental cost effectiveness of these different strategies, and compare them to no vaccination. Further details of the strategy of vaccination of the elderly are given in van Hoek et al. [25]. As the Advisory Committee on Immunization Practices [ACIP] no longer recommend varicella vaccination be given as a single dose [3] we do not consider a single dose varicella schedule here.

To investigate the cost effectiveness of these programmes a dynamic transmission model [26] was set up and combined with a cost effectiveness model. Within this combination it was possible to investigate for the first time the joint uncertainty in assumptions and parameters regarding the transmission model as well as uncertainty in economic parameters. This approach allowed us to include uncertainty around the contact patterns, which has not been previously integrated fully in economic analyses of vaccination programmes, as it has not been previously possible to quantify this uncertainty accurately.

METHODS

The cost-effectiveness of different VZV vaccination programmes were assessed, from the perspective of the National Health Service [NHS], as recommended by the

National Institute of Health and Clinical Excellence (NICE) (27) in the UK. All costs are presented in GB£2007. Unit costs from previous years were inflated to this year using the Hospital and Community Services Pay and Prices Index (28).

An age-structured transmission dynamic model of varicella and zoster was developed and used in the economic analysis. The model is based on that of Brisson and colleagues (5), updated to include two-dose strategies and HZ vaccination. It was parameterised via an updated review of the literature, and secondary data analyses. The model structure and results are given elsewhere (26). The model uses contemporary data on age-related contact patterns (22). Cost-effectiveness was assessed by projecting the outcome of vaccination from the dynamic infectious disease model on the number of cases of both varicella and HZ and subsequent loss of Quality Adjusted Life Years (QALY) associated with these diseases and costs to the NHS. To be able to investigate both the uncertainty in the transmission parameters and economic parameters the economic parameters were directly integrated into the dynamic model. This means that the number of cases were discounted over time (after introduction of the vaccine) and multiplied by the cost and QALY loss per case. To calculate the cost and QALY loss per case by age group, a decision analytic model was set up in Excel that estimated the cost per case by projecting the number of general practice (GP) visits, treatment costs and hospitalisations and associated QALY losses. Within this model distributions were attached to the different inputs and a set of 1000 different parameter combination were generated to feed into the transmission model. Distributions in Excel were generated with @Risk 5.0 (Palisade, USA).

Sensitivity analysis was done by running the infectious disease model with economic parameters with 1000 different datasets for cost and QALY loss but also for disease characteristics as the duration of acquired immunity due to boosting, contact patterns and vaccine efficacy. Each simulation resulting in a unique cost per QALY gained for that specific run.

Varicella-related parameters

The infectious disease model simulates the number of infectious cases and not GP visits or hospitalisations, therefore an adjustment must be made for the probability that an infectious person will seek medical care. This was done by comparing the incidence of infection by age as generated by the transmission dynamic model (which itself is parameterised by comparing to serological data) with the age-specific incidence of GP attendance. GP visits due to varicella were estimated based on the database of the Royal College of General Practitioners Weekly Returns Service (29) over the time period 2004-2007. From this database the number of GP visits per case was estimated. See table 1 for the outcomes.

Hospitalisation was expressed as admissions per varicella infection and is based on the number of varicella cases as found in the Hospital Episode Statistics database (HES – 2000-2005, which covers all NHS admissions in England) (ICD-10 code B01

in first 3 diagnostic fields), divided by the modelled incidence of varicella, see table 1. Information about the average duration of hospitalisation by age was obtained from the same source. The cost of hospitalisation was estimated by multiplying the number of days in the hospital with the average cost of an inpatient day. For children under the age of 15 years a cost of £475 (code PA18 reference costs, www.ic.nhs.uk) per day was used, for children and adults of 15 years and above a daily cost of £340 (code WA06Y reference costs) was assumed, as shown in table 2. Additional costs may be associated with infection control measures. These have been estimated to be £865.1 per case (30), and were added to each inpatient episode.

To protect risk groups such as immunocompromised patients, pregnant women and neonates varicella zoster immune globulin (VZIG) is provided. Treatment with VZIG costs £280. In 2007 6813 vials were distributed within the UK of which 5514 were for pregnant women and neonates and 1299 for other risk groups. The vials for pregnant women were distributed according to data of the Office of National Statistics (ONS) about the mothers' age in case of a live birth, the remaining vials (apart from neonates) were evenly distributed over all age groups as presented in table 1.

Mortality due to varicella by age was extracted from ONS for 2005. There were 20 deaths, 16 of which were in adults.

The QALY loss per case of varicella was obtained from Brisson and Edmunds (13) and is based on the HUI2 questionnaire that was distributed among parents of young children within GP practices. Due to the questionnaire used in the study data collection might have been biased towards more severe disease presentation (>50 spots), therefore a correction was made based on the observed distribution of patients with less than 50 spots and more than 50 spots (31). Patients with less than 50 spots were believed to have only 25% (triangular distribution between 5% and 50%) of the QALY loss compared to patients with more than 50 spots. See the supplementary data online for more information.

Varicella vaccination parameters for the 2 doses were estimated by fitting a model to data from a clinical trial as presented by Kuter et al.(32) The values for vaccine take and waning are based on a clinical trial with an average of 2900 – 9000 plaque forming units (pfu's), which is slightly above those used in the licensed varicella vaccines (minimal 1350pfu), see reference (26) for the parameter values used. The first dose is assumed to be given at 1 year of age, and the second at 3 years of age. It is assumed that these would be given as a combined preparation with MMR vaccine, and so the administration costs would be negligible. In the base-case we assume that the coverage will be 90% for a first dose, and 80% for the second dose, and that there is no catch-up of unvaccinated individuals at the second opportunity. These coverage levels are optimistic at the moment, as coverage has fallen due to concerns over the safety of the MMR vaccine in the UK, but as the coverage is assumed to remain constant through time, we are implicitly assuming that the MMR coverage (and therefore VZV coverage) will return to levels

Table 1. Proportion consulting GPs and estimated hospitalisation rate, with duration of stay and administration of VZIg for varicella and the estimated hospitalization rate and duration of stay for Herpes zoster (for distributions see the online supplement).

	Percentage patients who visits the GP (model projections)	GP visits per case (RCGP 2004-2007)	Hospitalisation rate (HES 2000-2005)	Hospitalisation duration (days) (HES 2000-2005)	% patients with VZIG treatment (HPA 2007)	Hospitalisation rate (HES 2002-2005)	Number of days in the hospital (HES 2002-2005)
<1	41.0%	1.40	1.4%	1.5	0.5%	55%	1.5
1-4y	40.7%	1.41	0.6%	1.8	0.0%	3%	1.6
5-14y	20.3%	1.50	0.2%	2.5	0.1%	0%	1.1
15-24	16.6%	1.69	0.4%	2.7	4.2%	0%	3.9
25-44	10.8%	1.66	1.0%	4.4	8.5%	0%	4.7
45-60	43.4%	1.81	1.9%	7.7	4.9%	1%	5.1
60-64	43.4%	1.81	1.9%	7.7	4.9%	1%	9.3
65-69	28.8%	1.69	4.8%	9.3	15.9%	1%	8.2
70-74	28.8%	1.69	4.8%	9.3	15.9%	1%	10.8
75-79	36.9%	1.73	8.3%	14.3	48.9%	2%	13.9
80-85	36.9%	1.73	8.3%	14.3	48.9%	3%	17.1
85+	36.9%	1.73	8.3%	14.3	48.9%	5%	22.3

Table 2. Costs and QALY loss due to Varicella and Herpes zoster

		Parameter values	Source
Varicella			
QALY loss			
Natural varicella	< 15 years	0.0027	[13,31] *See online supplement*
	> 15 years	0.0038	[31,41] *See online supplement*
Breakthough varicella	< 15 years	0.0014	[13,31] *See online supplement*
	> 15 years	0.0019	[31,41] *See online supplement*
Costs			
Cost GP consultation		£50	[28]
Treatment costs per GP consultation		£ 2.78	[9]
Cost per inpatient day age	< 15	£475	[42] Non elective inpatient day 2006-2007 Minor infection PA18 (most used reference cost in children)
age	>15	£340	[42] Non elective inpatient day 2006-2007 Other viral illness WA06Y (most used reference cost in adults and elderly)
Average treatment cost hospitalisation		£ 865.1	[30]
Costs per VZIG vial		£ 280	Cost as obtained from the Immunisation Department, HPA
Herpes zoster			
QALY loss			
The QALY loss is age dependent			See reference [25]
For example at age:	20	0.022	
	40	0.032	
	60	0.067	
	80	0.201	
Costs			
Cost GP consultation (incl. treatment)		£ 75.63	[33]
Cost treatment postherpetic neuralgia		£ 340.04	[33]
Cost Inpatient day age	<69	£195.2	[42] Minor skin infections <70 – HRG J42]
age	>70	£224.4	[42] Minor skin infections >69 – HRG J41]

seen previously. However, in acknowledgement that this may not be the case, we also vary the coverage as part of the sensitivity analysis.

In the base-case, each dose of varicella vaccine is assumed to cost £31, based on the price that the Centers for Disease Control and Prevention pay for a publically funded VZV vaccination in the US.

Zoster-related parameters

Estimates of the age-specific costs and QALY losses associated with HZ in the UK are described by van Hoek et al. [25] but are also presented in table 1, 2 and the online supplement. The average costs of treating zoster cases (including the costs of treating post-herpetic neuralgia (PHN) were taken from a retrospective analysis of the UK General Practice Research Database [33]. As for varicella the details about hospitalisation and associated cost was obtained from the HES database (HES 2002-2005, ICD-10 code B02, G053 in the first three diagnostic fields).

The QALY loss due to HZ was estimated by estimating the severity and duration of pain by age with subsequent QALY loss and fully described by van Hoek et al. [25].

Parameters describing vaccine take and waning associated with HZ vaccine were estimated by fitting a model to the data from the Shingles Prevention Study [24]. The published data is not detailed enough to estimate age specific take and waning rates. Therefore a duration of protection was assumed and the take was then fitted [25]. This resulted in a number of parameter sets for take and waning, which also varied by age group. For the sensitivity analyses 1000 sets of take and waning combinations were used. Note that the clinical trial [24] has as primary endpoints, the burden of illness (BOI) associated with zoster (a measure of days spent in pain) and the incidence of PHN, and as a secondary endpoint protection against an episode of HZ. Analysis of these data suggest that the vaccine may have had an additional effect on severity of disease (BOI and PHN), over and above the prevention of HZ (that is, some of the cases that occurred, may have had less severe disease). However, in this analysis, we have simply assumed that the vaccine protects against HZ (and therefore those episodes of PHN associated with this). That is, we may have underestimated the (cost-) effectiveness of the HZ vaccination programme (see [25] for details). In the base-case we assume a 70% coverage of zoster vaccine using a single dose. We determine the optimum age to vaccinate and then use that in the remainder of the paper. In the base-case combined programme we assume that zoster vaccination is not switched off, though in the sensitivity analysis we show a scenario where vaccination of the elderly is terminated when the vaccinated cohorts become old enough to receive the zoster vaccine.

It was assumed that individuals who had responded to the vaccine would be less likely to develop zoster than individuals infected by the wild-type virus. This is based on a summary of the evidence provided by Gershon et al.[34] and Civen et al. [35]. Gershon et al. provide a review, of studies in both healthy and immunocompromised

children. The findings from the different studies are highly heterogeneous, though overall, most studies suggest a lower incidence of zoster in those who were vaccinated compared to those who are naturally infected. This is confirmed by Civen et al. [35] who estimated that the incidence of zoster was 4 to 12 times lower in vaccinated children. It should be noted, however, that in the long term post-vaccination equilibrium (almost) everybody is vaccinated with two doses of varicella vaccine, and where there is a very low transmission of wild type virus, due to this low disease transmission there is almost no exogenous boosting and (all) people only carry the vaccine virus. In short; a situation which will be different to any situation currently available to study. Given the uncertainties in the literature and the uncertainty with the interpretation of this literature we assume here, that in the base-case the incidence of zoster in vaccine responders will be 10% of those infected naturally. This percentage is varied between 0 and 100% in the sensitivity analysis (using a triangular distribution the mass of which is 50% below 10% and 50% above 10%).

The base case cost of the zoster vaccine is assumed to be £55, with an addition £10 for administration costs (based on the costs of a nurse consultation) [25].

The parameters used in the cost effectiveness analyses are given in Tables 1-6. Further details of the distributions used in the sensitivity analysis are given in the online supplement (for varicella related parameters) and in [25] for HZ-related parameters.

Sensitivity analysis of uncertain parameters

To assess how influential each uncertain input parameter is on the cost-effectiveness of vaccination, parameter specific coefficients of determination (R^2) are estimated [36]. The R^2 measures how much of the variance in the outcome (incremental costs and QALY's) is explained by a linear relation with that input parameter. For the contact matrix (analysed as a group of 100 beta coefficients since it is a 10 by 10 matrix) a single R^2 is obtained, as these parameters are interdependent because they are estimated using a single model and dataset. For the same reason, a single R^2 is obtained for the 2 parameters describing vaccine efficacy, i.e. take and waning, and for parameter delta (δ) and chi (χ). A full description of the parameters used in the model can be found in reference [26]. Assumptions of linearity and normality of residuals for these regression analyses are checked. Analyses were performed in SAS 9.1. Analysis is done for the base-case scenario of the combined strategy of vaccination of children against varicella and the elderly against zoster.

Discounting and time horizons

Future costs and benefits are discounted to account for time preferences and the opportunity costs of capital investments. In the base-case discount rates of 3.5% per annum are applied to both benefits and costs, as recommended by NICE [27]. In the case of varicella vaccination there is a possibility that the incidence of HZ will rise in the short to medium term, and then decline. As the incidence of HZ may be much

lower among vaccinees a large decrease in the HZ incidence might be expected once the whole population becomes vaccinated (after about 80 years) (see Figure 1). After this period there is estimated to be a low incidence of varicella and zoster. For this reason, results are sensitive to the time horizon and discount rates. Previous authors have used cut offs of 80 years (13). In this paper as a base-case we use an infinitive time horizon, in the following way. At 100 years after vaccination has been introduced, when a new steady state has been achieved (Figure 1), the number of cases in that year are handled as a perpetuity and discounted to year 0. Because this has strong effects on the cost effectiveness of the program over all, cost effectiveness profiles are shown after 50, 80 and 99 years after start of the program. In addition, the sensitivity of the results to variation in the discount rates is also shown.

RESULTS

Impact of the programmes on VZV incidence over time

Figure 1 provides estimates of the impact of the different vaccination programmes over time: a two dose infant policy (90% and 80% coverage); a two dose policy with vaccination of the elderly (70% coverage); and vaccination of the elderly alone. It can be seen that a two-dose strategy, is expected to result in a large reduction in incidence of varicella, which is not affected by whether zoster vaccination is included as well. A one dose strategy results in far smaller reductions in the incidence of varicella in the long run, though many of these cases are expected to be breakthrough varicella cases (not shown). Infant vaccination is expected to increase the incidence of zoster in the medium term (up to 30-50 years after vaccination), and this is only partly offset by vaccination of the elderly, as the estimated duration of protection is rather short, and the largest increase in zoster incidence is expected to occur in adults too young to be vaccinated.

Vaccination of the elderly against HZ

We first investigated what was the optimum age to vaccinate the elderly against HZ. Figure 2 shows the results of this analysis. It can be seen that there is little difference in the estimated cost-effectiveness of vaccination over the age range 65-75 years. However, using our base-case assumptions for vaccine efficacy (that there is no additional effect over and above the protection against HZ) then vaccination at 75 years is marginally more cost-effective than the other ages. Therefore in further analyses, vaccination of the elderly is assumed to be given at this age.

Impact of different vaccination programmes on VZV-related costs and QALYs lost

Table 3 gives the estimated discounted cases, costs and QALYs lost after vaccine introduction for each of the programmes. Over an infinite time horizon, and

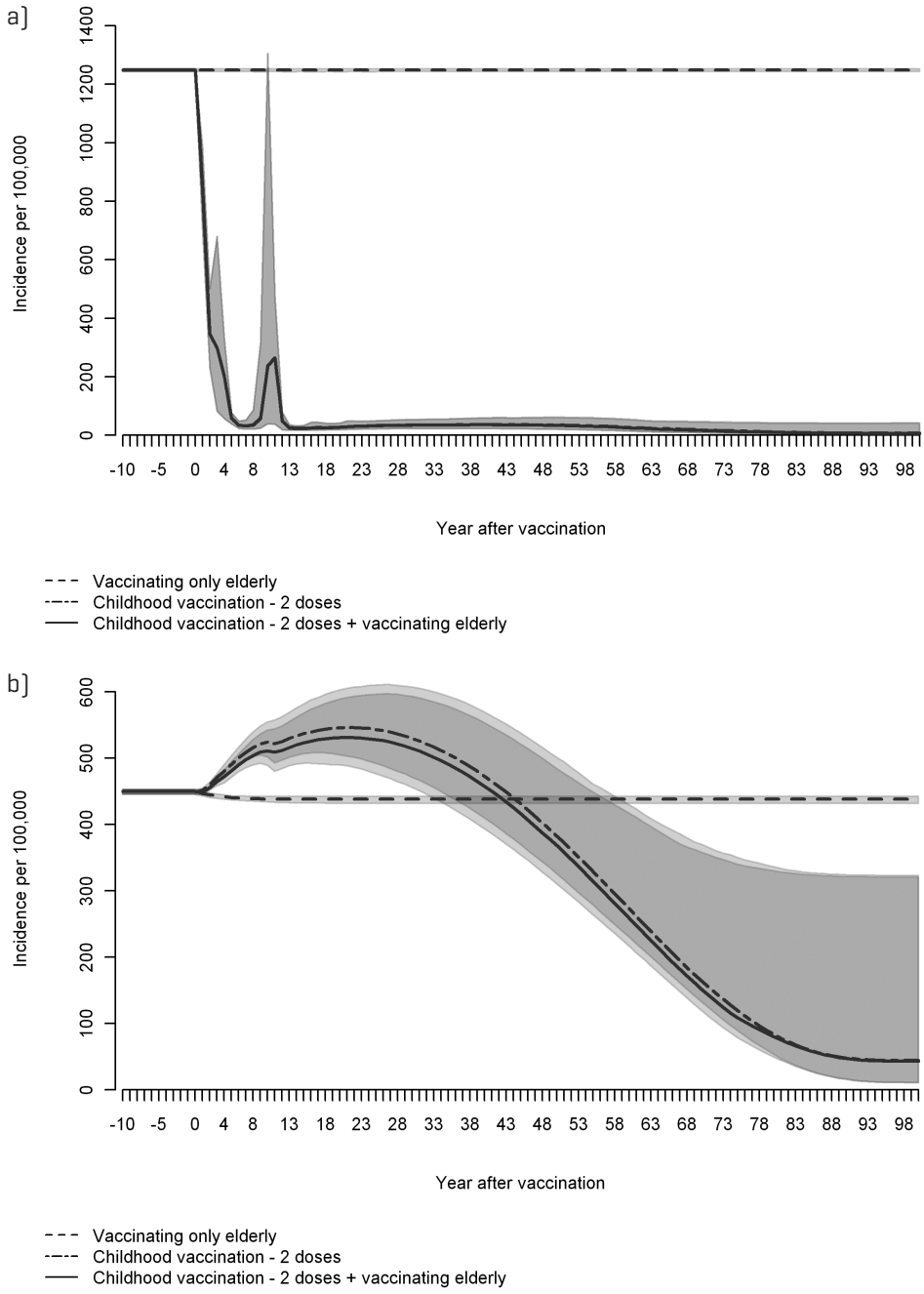

Figure 1. The estimated incidence of varicella (a) and herpes zoster (b) over time, following vaccine introduction, for each of the base-case programmes. The shaded area contains 95% of the model simulations.

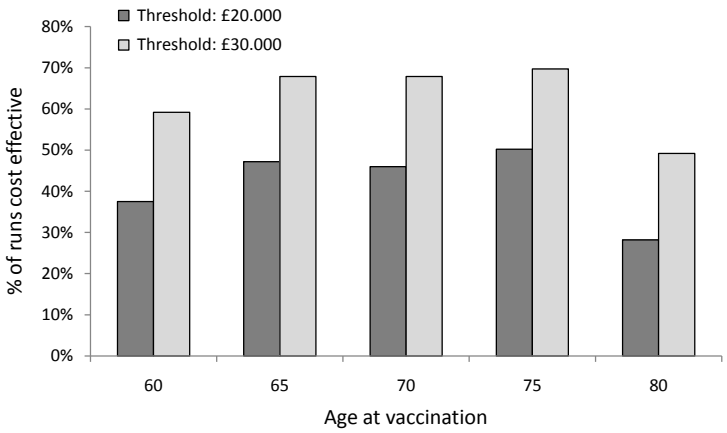

Figure 2. The cost-effectiveness of vaccination of the elderly against herpes zoster at different ages. The height of the bars is represents for each age group the percentage of 1,000 simulations which results in a cost effectiveness ratio below the threshold. Base-case model assumed.

discounted at 3.5% per annum, then the two-dose programme costs less than vaccination of the elderly (at the base-case prices of £62 per varicella course, and £65 per zoster course).

The change in the costs and change in QALYs arising from each of the programmes when compared with the "no vaccination" alternative are shown in Figure 3. It is clear from this figure, that there is large variation in the estimated benefits derived from the two-dose programme, with a significant proportion of simulations resulting in QALYs lost (points on the left-hand side of the figure). The estimated impact of vaccination of the elderly against HZ has much lower variance (the points are more clustered in the cost-effectiveness plane). The combined programme is clearly much more costly than its two component programmes, and as with the two-dose strategy is highly variable in effectiveness. This high variability is mainly due to the uncertainty about the probability of developing zoster among the vaccinated, the duration of protection from a boosting event, and the contact patterns (table 5).

Cost-effectiveness of the different vaccination programmes

The cost-effectiveness of the different strategies as compared to the no vaccination alternative, and an incremental analysis are shown in Table 4 a and b. The model suggests that the optimum strategy is the two-dose policy with vaccination of the elderly. However, this strategy should, nevertheless be viewed with some caution, as some simulations (1%) result in QALYs lost (i.e. losses to the population health), and significant extra health care expenditure (see figure 3).

Table 3. The median discounted (at 3.5% per annum) cases and costs for the different programmes, using the infinite time horizon.

Programme	Cases varicella	Cases Zoster	Treatment costs Varicella	Treatment costs Zoster	QALYs Varicella	QALYs Zoster	Doses Varicella vaccine	Doses Zoster vaccine	Total vaccination costs	Total net vaccination costs*
No vaccine	17,348,450	6,243,080	£661,348,000	£883,975,500	60,385	588,332	0	0	0	0
2 dose	1,924,280	6,237,320	£75,483,600	£917,885,500	7,763	630,188	29,970,200	0	£929,076,000	£379,299,500
Elderly	17,344,450	6,105,380	£658,633,000	£851,420,000	60220	562299	0	8278300	£538,090,000	£506,663,000
Elderly + 2 dose	1,913,445	6,080,215	£74,348,050	£882,094,500	7661	601433	29970200	8278300	£1,467,170,000	£875,540,500

*Costs are the costs of vaccination minus the treatment costs averted.

Table 4. The proportion of simulations with a cost per QALY gained below £20,000 or £30,000 for the base-case discount rate (infinite time horizon), and for the situation with differential discounting of health benefits (1.5%) and costs (3.5%). Table a) gives the cost per QALY gained of the different base-case programmes compared with no vaccination, and b) gives the incremental cost per QALY gained of the alternatives, where the alternatives are ranked by net cost and the incremental benefits and incremental costs of the next alternative are given.

	Costs 3.5% / Effects 3.5%		Costs 3.5% / Effects 1.5%	
Discounting	% below £20,000	% below £30,000	% below £20,000	% below £30,000
2 dose	41%	50%	100%	100%
Elderly	49%	96%	100%	100%
2 dose + elderly	50%	70%	100%	100%

b)

Discounting	Costs 3.5% / Effects 3.5%		Costs 3.5% / Effects 1.5%	
From 2 dose to:	% below £20,000	% below £30,000	% below £20,000	% below £30,000
Elderly	61%	64%	1%	1%
2 dose + elderly	70%	99%	100%	100%

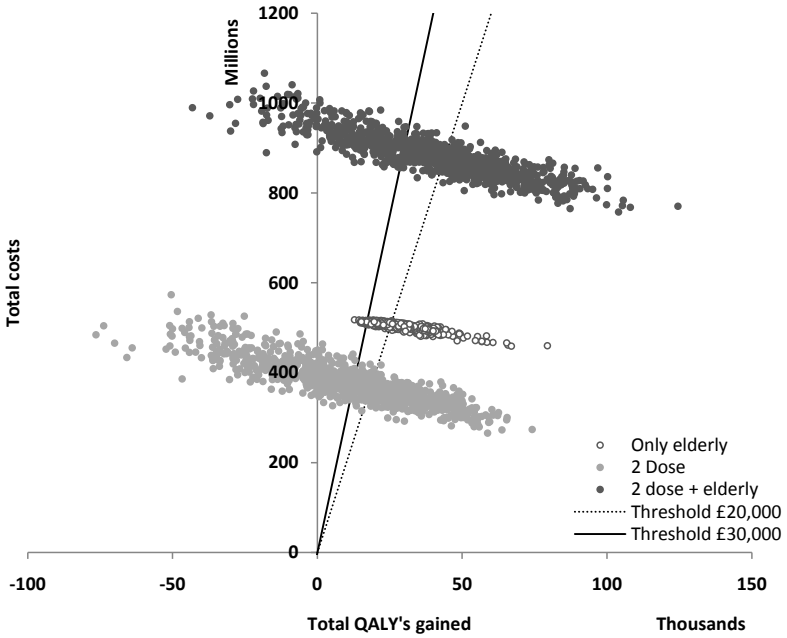

Figure 3. The estimated change in costs (vertical axis) and QALYs (horizontal), of the two-dose infant programme (light grey points), one dose elderly vaccination (white points) and the combined programme (dark grey). All programmes are compared to the no vaccination alternative. Each point represents a model simulation (there are 1000 for each strategy). An infinite time horizon is assumed, with 3.5% per annum discount rates for both benefits and costs. Base-case levels of coverage are assumed. Vaccination of the elderly is assumed to occur at 75 years, as this is the most cost-effective age to vaccinate. For reference the two lines represent a cost per QALY gained ratio of £30,000 (heavy line) and £20,000 (light line).

Sensitivity to discount rate and time frame - Table 4 a and b also shows how sensitive these findings are to the discount rate. Using a lower rate of discount for health gains, results in the childhood programmes appearing more cost-effective in the long run (virtually all of the simulations resulting in a cost-per QALY gained of below £20,000). That is, benefits occurring 60+ years after vaccination (when the incidence of both zoster and varicella is very low under the two-dose or combined policies) are even more influential on the results. Over shorter time frames, adopting a lower discount rate will result in the two-dose or combined policies appearing less cost-effective, and the overall QALY loss can be negative over shorter time periods (not shown).

The effect of the time frame of analysis is explored in more detail in Figure 4. It is clear from this figure that vaccination would not be deemed cost-effective for many years after implementation (even after about 100 years the median is above the £20-30,000 per QALY gained). Before this period the combined programme would

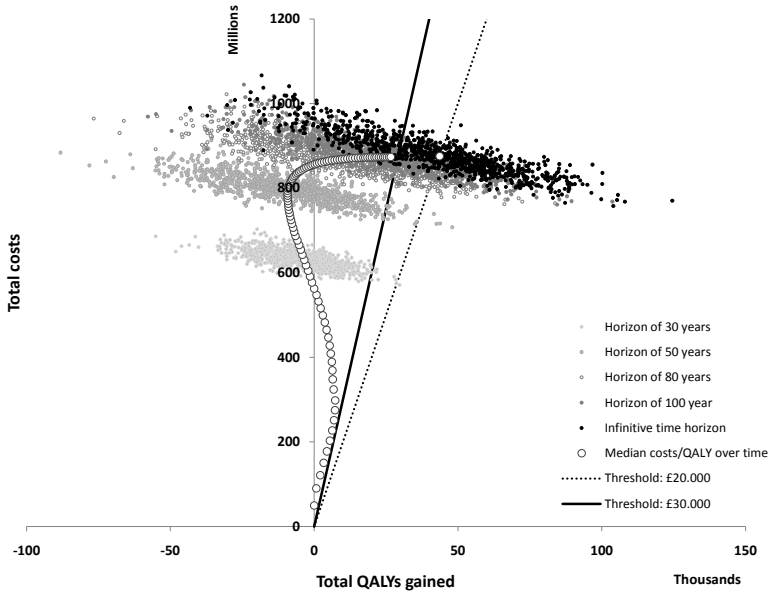

Figure 4. The estimated change in costs and benefits of the combined vaccination programme compared with no vaccination over different time frames of analysis (time since programme implantation). A 3.5% discount rate for benefits and costs is used.

be unlikely to be deemed cost-effective, and for 30-50 years has a high probability of being not effective (i.e. many points lie to the left of the vertical axis, implying QALY losses). That is, with an infinite time horizon benefits accruing many decades (even centuries) into the future are very influential on the overall assessment of the cost-effectiveness of varicella (or a combined) programme.

Sensitivity to coverage - The cost effectiveness of the combined programme is not very sensitive to coverage, over the range of coverage levels explored (Figure 5). The level of vaccine coverage in both the children and elderly is a major driver of the overall costs of the programme (vertical shifts in the cloud of points in Figure 5), and affects the benefits (horizontal shifts), but does so in roughly equally. Lowering the coverage improves the cost effectiveness marginally due to a lower increase in HZ post-vaccination.

The supplementary information provides a sensitivity analysis on the price per dose and changes in the probability of developing zoster in vaccinees.

DISCUSSION

Although there have been a large number of economic analyses of varicella vaccination (14,15), only a small number of previous cost-utility analyses has taken into account the possible impact of varicella vaccination on the incidence of HZ. These updated analyses are more favourable to chickenpox vaccination

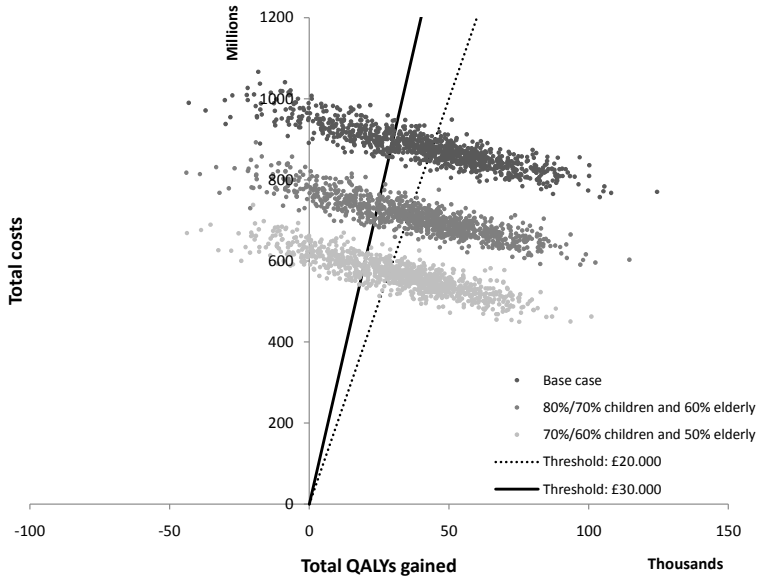

Figure 5. The estimated impact of changes in coverage on the cost-effectiveness of the combined programme (as in Fig 4 change in costs compared to the no vaccination scenario is shown on the vertical axis, and change in QALYs on the horizontal axis).

Table 5. Proportion (R^2) of total variance in the incremental costs and incremental QALY's explained by each (group) of the input parameters. Only the (group of) input parameters that explain 1% or more of the variance of incremental costs and/or QALY's are shown. Chi is the zoster reactivation rate in varicella vaccinees compared to people who are not vaccinated against varicella, delta represents the duration of boosting after exposure. R^2 of the linear model with all input parameters (main effects only) are 0.92 and 0.87 for incremental costs and incremental QALY's respectively, indicating the models approximate well the relationship between input parameters and incremental costs and incremental QALY's. Residuals are normally distributed (Shapiro-Wilk normality test, W>0.95).

Parameter (groups)	Incremental costs	Incremental QALYs
Chi and delta	0.62	0.47
Contact patterns	0.28	0.29
Zoster vaccine take and waning	0.04	0.11
Other parameters (group)	<0.01	<0.01

than previous analyses concluded (13), due to a combination of factors. The most important are that the time frame of analysis has been extended and the increase in zoster following varicella vaccination is expected to be somewhat less than previous modelling work suggested (13). These issues are addressed in turn, below.

The results are very sensitive to the time-frame of analysis. Childhood varicella vaccination evaluated over 30 or 50 years post-vaccination are unlikely to be cost-

effective. However, programmes evaluated over a longer time frame are increasingly likely to be cost-effective. That is, benefits occurring 60 years or more after infant vaccination is initiated are very influential on the results (even when discounted). This is the period when the incidence of HZ is expected to decline, as the vaccinated cohorts pass into the age groups when they are at greatest risk of developing zoster. The model assumes that individuals who respond to the varicella vaccine are less likely to develop zoster than those naturally infected. The data on this is scarce, and as our findings are sensitive to this the results should be viewed with considerable caution. That is, the conclusions are influenced by a parameter value for which there is very little quantitative support, and depend on very long time-frames of analyses (time frames over which it is not realistic to conclude that other aspects of VZV epidemiology and economics would remain stable).

The increase in zoster that is expected after vaccination is less than was estimated by Brisson and colleagues (5,6,9,13). This results from an updated estimation of the force of infection in adults (derived from the analysis of contact patterns), which then necessitated a re-estimation of the reactivation rate. There remains considerable uncertainty regarding these parameters, which influences strongly the results. and continued surveillance of HZ in countries that have introduced the vaccine should, given time, help to improve our quantitative understanding of these processes. Leung et al. have shown that there has been an increase in hospitalisation for HZ in the US in the years after vaccination (37). Unfortunately there is no good baseline data available, hence it is not possible to attribute this increase with any certainty to vaccination practice. In addition there does not seem to be a striking difference between states with a low and high vaccine uptake, although the absolute difference in vaccination coverage is not presented, and a substantial difference is needed before an effect might become apparent (37). On the other hand, Leung have also shown that the incidence of zoster in adults living with children is lower than in those who do not (as has been shown in the UK(5)), added suggesting that exposure to varicella does indeed reduce the risk of zoster. In addition, this gap in incidence between those living with/out children has been decreasing (37); as would be expected if, as children became vaccinated, the influence of living with children (and being boosted) disappears. Overall, although the pattern of increase in zoster in the US is consistent with a boosting hypothesis, no definitive proof can ever be derived from such associations.

The current study also looked at a two-dose strategy and combined strategies of vaccination of children against varicella and the elderly against zoster. The results suggested that a combined policy may be cost-effective, though there are a number of caveats attached to this statement (see above). Terminating zoster vaccination when the cohorts who have had varicella vaccine become old enough to receive zoster vaccine is slightly more cost-effective. This is because the varicella vaccinated cohorts are assumed to be less likely to develop zoster. If such a combined

strategy were to be employed there should be ample opportunity to accurately estimate the rate of acquisition of zoster in vaccinees, before considering when (or if) HZ vaccination can be terminated.

The Shingles Prevention Study (a large placebo controlled trial of HZ vaccination) took as its primary endpoints the burden of illness associated with HZ (a measure of days spent in pain weighted by the severity of that pain) and prevention of PHN (24). Prevention of HZ was a secondary endpoint. The efficacy against these BOI and PHN was higher than that against HZ, suggesting that the vaccine may have an effect over and above prevention of shingles. However the burden of illness was measured as a reduction in days of pain, which does not have to correspond with a reduction in QALY loss. We ignored these potential additional effects in our analyses, and so we may have underestimated the benefit of the HZ vaccine. The inclusion of these additional effects alters the optimum age at HZ vaccination as the severity of HZ increases with age, and the additional effects also appear to be age dependent (see (25) for further details). Based on the assumption of an exponential decline our most likely duration of protection of HZ vaccination was 7.5 years (3.6 – 100 years) (25) which is shorter than previous estimates (38), due to different model assumptions (39). A longer duration of protection will lower the optimal age of HZ vaccination. Thus, the optimal age of HZ vaccination is not as clear as seems apparent here.

The transmission model assumed a stationary population, with constant mortality and birth rates over time. This is, perhaps, an oversimplification, as the elderly population, in particular, is expected to increase in size (40). Indeed, the over 85s are expected to more than double in size over the next 20 years (from 1.3 million to 3.3 million). As the risk of zoster increases exponentially with age we would expect the crude incidence to increase over time due to population aging. Modelling these changes would complicate the interpretation of the zoster incidence trends shown here. In addition allowing a variable demographic structure would necessitate constant re-evaluation of contact rates, as there would be a different number of individuals by age group. Incorporating these changes into the model would be a major undertaking, especially for the fitting procedures, and we have therefore chosen to ignore them. It should, however, be borne in mind that an increase in the incidence of zoster would, other things being equal, render vaccination against zoster more cost-effective than is shown here.

One of the strengths of this paper is in how it has handled uncertainty. To our knowledge no previous economic analysis of any vaccination programme has incorporated uncertainty in the underlying epidemiology (including contact patterns) as well as uncertainty in the economic and health outcome parameters. The existence of the contact pattern data allowed us not only to quantify the relevant average contact patterns between and within age groups, but also a measure of the statistical uncertainty in this. This parameter uncertainty was found to be, given the base-case scenario, one of the most influential on the expected impact of the vaccination

programs. Hence, quantifying this uncertainty, and propagating it through the epidemiological and then economic analysis, is a key methodological advance.

The fact that the time-frame of analysis and discount rate chosen are so influential is very problematic for decision-making. Over the time-frames modelled here (including an infinite time frame) huge changes in society are likely to result, as are enormous technological changes and changes to the health service. Model results are also likely to be inaccurate over such time frames. Decision-makers need to be aware of this, and that an infant vaccination programme may not be cost-effective for many decades following vaccination, when judging whether childhood varicella vaccination should be adopted.

APPENDICES

Appendices are online available at: http://www.sciencedirect.com/science/article/pii/S0264410X11017932

CONTRIBUTIONS

AJvH programming the model, parameterisation and writing up, AM programming, model structure and methodology, NG methodology and model structure, JB was responsible for developing and executing the sensitivity analysis, JE was responsible for the overall design, supervision, vaccination scenarios, parameterisation and writing up.

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PART II

INFLUENZA

chapter SIX

THE IMPACT OF PANDEMIC INFLUENZA H1N1 ON HEALTH-RELATED QUALITY OF LIFE: A PROSPECTIVE POPULATION-BASED STUDY

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ABSTRACT

Background

While the H1N1v influenza pandemic in 2009 was clinically mild, with a low case-fatality rate, the overall disease burden measured in quality-adjusted life years (QALY) lost has not been estimated. Such a measure would allow comparison with other diseases and assessment of the cost-effectiveness of pandemic control measures.

Methods and findings

Cases of H1N1v confirmed by polymerase chain reaction (PCR) and PCR negative cases with similar influenza-like illness (ILI controls) in 7 regions of England were sent two questionnaires, one within a week of symptom onset and one two weeks later, requesting information on duration of illness, work loss and antiviral use together with EQ-5D questionnaires. Results were compared with those for seasonal influenza from a systematic literature review. A total QALY loss for the 2009 pandemic in England was calculated based on the estimated total clinical cases and reported deaths. A total of 655 questionnaires were sent and 296 (45%) returned. Symptoms and average illness duration were similar between confirmed cases and ILI controls (8.8 days and 8.7 days respectively). Days off work were greater for cases than ILI controls (7.3 and 4.9 days respectively, p=0.003). The quality-adjusted life days lost was 2.92 for confirmed cases and 2.74 for ILI controls, with a reduction in QALY loss after prompt use of antivirals in confirmed cases. The overall QALY loss in the pandemic was estimated at 28,126 QALYs (22,267 discounted) 40% of which was due to deaths (24% with discounting).

Conclusion

Given the global public health significance of influenza, it is remarkable that no previous prospective study of the QALY loss of influenza using standardised and well validated methods has been performed. Although the QALY loss was minor for individual patients, the estimated total burden of influenza over the pandemic was substantial when compared to other infectious diseases.

INTRODUCTION

Influenza severity is usually characterised by the case-fatality rate (CFR). There are major problems with this measure as the denominator (the number of cases) is difficult to ascertain, resulting in widely varying estimates for the same viral strain (1) Using the CFR to characterise severity ignores the burden of disease in the vast majority of individuals who have symptomatic influenza (possibly severe) but do not die. Many millions of individuals were infected with the pandemic strain of influenza A H1N1v in 2009, and it is likely that many more will be infected by related strains in the coming years. In order to help evaluate the overall impact of the 2009

H1N1v pandemic on the health of populations it is necessary to measure the burden associated with non-fatal as well as fatal cases. One simple way to measure the impact would be to use a measure that combines morbidity and mortality in a single unit. Quality Adjusted Life Years (QALYs) are a commonly used metric that has this property. The EQ-5D is a generic preference-based instrument designed to measure the health related quality of life (QoL or QALY-weight) of any disease state. Using this instrument allows quantification of the severity of H1N1v on a comparable and standardised scale. It enables rational decisions to be made about interventions in future waves of H1N1v by comparing, for instance, the cost per QALY gained from such interventions with nationally accepted norms. In addition, it gives more in depth understanding of the impact of influenza on different aspects of well being.

The health-related quality of life detriment from a population-based sample of confirmed H1N1v patients was prospectively measured and compared to controls who were investigated because they had influenza like illness (ILI), but were not laboratory confirmed as H1N1v. The aims were: 1) to quantify the burden of H1N1v for individual patients and investigate factors, such as age and treatment with antivirals, that may affect this; 2) compare the severity of the 2009 strain to other infections that cause ILI and previous estimates of the severity of influenza from a systematic literature review; and 3) to estimate the overall burden attributed to H1N1v in the population. The findings can then be used to inform effectiveness and cost-effectiveness analyses on policy decisions related to the control of future waves of this (or related) viruses.

METHODS

Prospective study of severity of H1N1v

The EQ-5D is a combination of a questionnaire and a valuation technique. The tool values health-related quality of life in five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. For each dimension there are three levels: no problems, some problems and severe problems. The overall health status is also measured using the visual analogue scale (VAS). The power of the EQ-5D is that it makes it possible to convert an outcome for each dimension of this scale into a quality of life score. It is recommended by the National Institute for Clinical Excellence for use in cost-effectiveness analyses in the UK (2). During the early stages of the 2009 pandemic PCR confirmed cases of influenza A H1N1v and a control group of PCR negative cases of ILI were identified. The PCR test used was validated and has a good specificity and a sensitivity of 95.4% (3). During this time (weeks 27/28 2009) the containment phase of the response to the pandemic was still in place in England and all cases of influenza were being actively traced and centrally registered on a single database (Fluzone), irrespective of risk status, age group, complications, etc. Demographic, clinical, and epidemiological information was recorded on each case, including name, age, address, date of onset, and

whether the case had been confirmed as H1N1v, tested and confirmed as not being H1N1v (discarded), or was awaiting test confirmation. The database was updated daily. Cases found to be negative for H1N1v (ILI controls) were not investigated further, and so their aetiological causes are unknown. From this database patients who had confirmed H1N1v and those who had ILI but had tested negative for H1N1v, who had a date of onset within 1 week of the (then) current date were contacted by post and asked to take part in the survey. During the period of the study, two regions of England (London and the West Midlands) stopped investigating every case. To avoid biasing the results of the survey, we excluded cases from these regions.

The Fluzone database was checked daily during the recruitment period (weeks 27 and 28 2009) for new cases of ILI with recent onset (i.e. onset within 1 week of the day on which the database was checked) who were not resident in London or West Midlands. These were then contacted and asked to participate. The covering letter explained the study and contained instructions for completing the survey. The questionnaire asked for age, sex, presence of pre-disposing conditions (diabetes, asthma or other chronic respiratory disease, chronic heart, kidney or liver disease, long-term neurological disease, or immuno-suppression), attendance at hospital, date of onset of symptoms, whether antivirals were being taken, and if so when they were first taken, and a checklist documenting their symptoms on the day of the survey and on their worst day of illness. In addition, they were asked to fill in the two copies of the EQ-5D, one for the worst day of their illness and one for the day they filled in the questionnaire. A second questionnaire was sent out two weeks after the first, which requested information on the total duration of symptoms, and absenteeism from work or school. Respondents were also asked to fill in another EQ-5D questionnaire on that day to obtain a base line score for their health-related quality of life. In case there was no response from the first mailing a reminder was sent out, containing both questionnaires. Non-responders to the second questionnaire were not followed up. Patients could fill in the questionnaires by post or on-line (they were provided with a secure login to enable this).

Children (<16 years) were sent a child version of the EQ-5D (4) and questions were altered somewhat (e.g. absence from school instead of work). A separate question on the work loss of the parents due to disease in the child was added. In the covering letter (addressed to the guardian) it was suggested that older children fill in the survey themselves (with the assistance of the parent/guardian) and that for younger ones the parent/guardian fill out the survey on their behalf. Copies of the questionnaires and cover letters are available from the authors on request.

Enquiry to the NHS Research Ethics Committee indicated that ethics approval for this study was not required, since collection of QoL information from patients is part of the routine surveillance activities of the Health Protection Agency (HPA).

Only individuals with an ILI should have been investigated for H1N1v but to be certain, we asked respondents whether they had fever plus at least one other

respiratory symptom on their worst day of illness. In the statistical analysis, only cases and control participants who recorded that they had symptoms consistent with an ILI were included. Differences between the two groups (confirmed cases and ILI controls) were tested having corrected for multiple comparisons using the Šidák correction (an exact version of the Bonferroni correction). For the QALY analysis we only included patients for whom a complete set of data was available to calculate the QALY loss; this is an onset and end date, as well as quality of life weights for the worst day and the date of onset. The overall QALY loss was estimated to be the area denoted by the triangle with vertices being the background quality of life weight at onset date, the quality of life weight at the worst day and the time since onset of the worst day, and the background quality of life weight at the recovery date. Attribution of risk factors to the QALY score was investigated by linear regression. In the regression QALY scores were logged to take account of the skew in the original data. Statistical analysis was performed with R version 2.11.0.

Systematic literature review

To compare our results with previous estimates of the quality of life detriment due to influenza we performed a literature review. Pubmed was searched for the terms 'influenza' and 'quality-adjusted life year', 'QALY', 'QALD' or 'EQ-5D'. The abstracts of all identified papers were reviewed, and original articles (not reviews) published in English were retained.

Overall disease burden

To estimate the overall disease burden in England for the 2009 H1N1v pandemic, we focussed on the number of cases presenting with fever and those who died. The estimated number of people presenting with ILI (fever + respiratory symptom) was based on the estimated number of infections. To obtain the latter the estimated total number of clinical cases (5) in the first and second waves in England was multiplied by a factor 10. This factor is based on a comparison of the estimated clinical cases and seroprevalence after the first wave in England (6). Although it might be justified to use a higher multiplication factor for the second wave based on mortality and other surveillance data (5; 7), the same multiplier was used for the whole period and can therefore be seen as a conservative approach. To obtain the estimated number of infected persons presenting with ILI, the number of infections was multiplied by the proportion of infections presenting with fever (27%) as estimated from an intensive household follow up during the initial stages of the 2009 pandemic (8). The total burden expressed in QALYs was a multiplication of the QALY loss obtained in this study by the number of infections presenting with ILI, plus the QALY loss for fatal cases. The QALY loss for fatal cases was estimated as the average life-expectancy corrected for the expected quality of life in those years (9). This assumes that each recorded death was actually caused by H1N1v, that there was no under-reporting of deaths, and that

despite most deaths being in risk groups, the average life-expectancy was lost per death. The base-line estimate assumed no discounting of future life-expectancy. Discounting at 3.5% (2) was also used in the sensitivity analysis.

RESULTS

Prospective study of severity of H1N1v

A total of 655 patients met the inclusion criteria and were sent a questionnaire, of whom 390 were confirmed cases and 265 were ILI controls. We received 287 responses, of which 269 reported ILI and were included in the analysis, 186 from confirmed cases and 83 from ILI controls. The response rate was significantly higher in the confirmed H1N1v group (48% vs 31% p<0.001). This difference was slightly larger in children (55% vs 31%).

The demographic composition of the two groups was similar (Table 1). Although there was a slightly higher fraction of the control group that was in a risk group (25% vs 19%) this was not significant. The hospitalisation rate was 8-9% in both groups. This high level of hospitalisation may represent heightened concern at the outset of the epidemic. Antiviral use was higher among the confirmed cases (although this was not significant after adjusting for multiple comparisons). The proportion of cases receiving antivirals within 2 days of onset was similar between the two groups.

Table 1. Background characteristic of patients.

	Confirmed H1N1v ILI cases	ILI controls (non-H1N1v ILI cases)
Ill (fever+1 other symptom)	186 (96%)	83 (89%)
Of those with ILI		
Adults	115 (62%)	58 (70%)
Children	71 (38%)	25 (30%)
Risk group	36 (19%)	21 (25%)
Hospital admission	16 (9%)	7 (8%)
Antivirals	132 (71%)	44 (53%) p=0.0065*
Antivirals within 2 days after onset (day0&1&2)	65 (35%)	26 (31%)

* not significant when corrected for multiple comparisons

The symptoms recorded by both groups were similar (Table 2). The only significant difference was that the confirmed H1N1v cases recorded more occurrences of cough (90% vs 64%, p<0.001). The duration of symptoms was not known for everybody due to non-respondents to the second questionnaire. Nevertheless, the duration

was similar for the two groups (average duration of 8.8 and 8.7 days respectively for the confirmed and control group). The duration of time off work was 7.3 days for the confirmed cases and 4.9 for the ILI controls: a significant difference using the Welch two sided t-test (p=0.003). The worst day of disease appeared shortly after onset of the symptoms for both groups, however for the control group the worst day was slightly later (median 2 days) after onset than for the confirmed cases (median 1 day after onset) (Table 2).

Table 2. Symptoms reported by patients.

Symptoms	Confirmed H1N1v ILI cases	ILI controls (non- H1N1v ILI cases)
Sore throat	152 (82%)	68 (82%)
Cough	167 (90%)	53 (64%) p>0.001
Headache	160 (86%)	69 (83%)
Tiredness	176 (95%)	77 (93%)
Chills	142 (76%)	49 (59%) p= 0.006*
Loss of appetite	147 (79%)	62 (75%)
Muscle pain	128 (69%)	54 (65%)
Joint pain	99 (53%)	51 (61%)
Nausea	87 (47%)	38 (46%)
Diarrhoea	46 (25%)	28 (34%)
Conjunctivitis	53 (28%)	18 (22%)
Average duration of symptoms (min-max)	8.8 (1 – 28) n=133	8.7 (2-32) n=56
Worst day (median, mean, modus)	1, 1.64 ,day 1	2, 2.18, day 1
time off work information available	82 (44%)	39 (47%)
Average time off work (min-max)	7.3 (1-28)	4.9 (1-21) p = 0.003

* not significant when corrected for multiple comparisons

All five of the dimensions measured in the EQ-5D were affected by ILI, in both groups of patients, though usual activities and pain/discomfort were the most affected (Table 3). Only about 5% of patients said that they had no problems with pain or discomfort on the worst day of illness, and 2% (8%) said they had no problems with usual activities on the worst day of their illness in the confirmed (control) groups.

The overall quality of life weight for the worst day was 0.29 for the confirmed cases and 0.34 for the ILI controls (Table 4). After the symptoms had gone the quality of life weights were 0.96 and 0.97 respectively. Based on the VAS scale the QALY weight was 90 (on scale 0-100) for the background and 30 for the worst day.

Table 3. Impact on the 5 dimensions as measured in the EQ5D

	No problems		Some problems		Severe problems	
	H1N1v	ILI controls	H1N1v	ILI controls	H1N1v	ILI controls
Background						
Self care	125 (98%)	51 (96%)	1 (1%)	2 (4%)	1 (1%)	0 (0%)
Mobility	122 (96%)	52 (98%)	4 (3%)	1 (2%)	1 (1%)	0 (0%)
Usual activities	115 (90%)	50(94%)	11(9%)	3 (6%)	1 (1%)	0 (0%)
Pain/discomfort	118 (93%)	50(94%)	8 (6%)	3 (6%)	1 (1%)	0 (0%)
Anxiety / Depression	123 (97%)	50(94%)	4 (3%)	3 (6%)	0 (0%)	0 (0%)
Worst day						
Self care	83 (46%)	38 (48%)	57 (31%)	28(35%)	41(23%)	13(16%)
Mobility	31(17%)	17 (20%)	72 (39%)	34 (41%)	81 (44%)	32 (39%)
Usual activities	3 (2%)	7 (8%)	53 (29%)	25 (30%)	126 (69%)	51 (61%)
Pain/discomfort	8 (4%)	4 (5%)	111 (60%)	48 (59%)	65 (35%)	30 (37%)
Anxiety / Depression	82 (45%)	30(37%)	57 (31%)	37 (46%)	43 (24%)	14 (17%)

The comparable values for the ILI controls were similar, 89 and 30 respectively. Complete information to calculate an overall QALY loss was only available for 114 of the 186 (61%) confirmed cases and 46 (55%) of the 83 control ILI cases. The final QALY loss due to the whole period of disease was 0.0075 for the confirmed cases and 0.008 for the cases in the control group, i.e. 2.7 and 2.9 Quality Adjusted Life Days (QALDs), respectively.

In multivariable linear regression only antiviral use (within 48 hours) was associated with the number of QALDs lost, and only in confirmed H1N1v cases (p= 0.084). Prompt antiviral use was found to reduce the number of QALDs lost by 50% (22%-110% CI 95%). No other factor (including age, sex, presence of risk-factors, whether hospitalised, whether the case was confirmed H1N1v or not) was significantly associated with the number of QALDs lost.

Systematic literature review

Sixty-one articles were found, 10 of which were reviews and discarded. A further 10 studies only estimated life years lost, two papers described different diseases, a further two were not published in English, leaving 36 studies mentioning the burden of influenza or ILI. However, none of the reviewed papers was specifically dedicated to the burden of disease, but gave values for this as part of a cost effectiveness study. A number of papers present the same data from the clinical trials of the antiviral zanamivir but with different analyses. Overall we were only able to identify

Table 4. Impact of ILI on health related quality of life for confirmed and control patients.

	Confirmed H1N1v ILI cases	ILI controls (non-H1N1v ILI cases)
EQ-5D Background (min-max,median)	0.96 (0.15-1,1)	0.97 (0.5-1,1)
EQ-5D Worst day (min-max,median)	0.29 (-0.073-1,0.24)	0.34 (-0.073-1,0.24)
VAS Background (min-max,median)	90 (20-100,95)	89 (55-100, 90)
VAS Worst day (min-max,median)	30 (0-100,25)	30 (5-80,30)
Overall QALY loss (min-max,median)	0.0075 (0-0.027,0.006)	0.008 (0-0.044,0.006)
Overall QALD loss (min-max,median)	2.74 (0-9.84, 2.18)	2.92 (0-16.2, 2.12)

four original sources of information on the burden of disease due to ILI as measured in QALYs, including the trial data as one source, see table 5 for an overview.

The first original source of data is a study by Griffin et.al (10) in which 21 working adults were asked to fill an EQ-5D questionnaire within 3 months of onset of ILI, and 8 GPs were asked to do the same. The study reported relatively low QALY weights for ILI with values below zero (corresponding to a state worse than death) being recorded. The weights were, however, applied to a very short duration of illness which was measured separately on a different group of patients (2.48 days). Hence the overall loss was estimated at 2.19 QALDs. The second source of data is the clinical trials of zanamivir, reported by O'Brien et al.(11) In the zanamivir trials almost 640 patients with ILI were asked within 48 hrs of onset of disease to value their health on a scale between 0 and 10 every day for 21 days. Since this is not a QALY scale, several separate analyses have been performed on the same data to map the disease-specific scale onto a QALY scale. In addition, since these data have mostly been used in cost-effectiveness studies of the use of antivirals, no figures for overall QALY loss due to ILI have been published, only the difference in QALY loss due to ILI in patients with and without antivirals (11-14). Only two studies (15; 16) use these data to estimate the overall QALY loss: the first uses a separate estimation of the background quality of life weight based on population estimates and the second a separate estimation of the duration of illness. The final estimates differ by up to 6-fold. The QALD lost estimated by Siddiqui et al. (16) is 1.68 for complicated influenza and 1.57 for non-complicated, non-influenza ILI whereas the QALD loss calculated by Sander et al. (15). is 5.33 for 0-19yrs, 6.35 for 20-64yrs and 10.69 in over 65s. A third potential source of QALY loss data is a study in which 15 randomly selected working age patients and health care workers (17) were asked to fill in the HUI-3 questionnaire based on their recollection of their most recent episode of ILI. The results were used to estimate a quality of life weight of 0.25 for an individual with ILI. Unfortunately, the duration that someone is in this state was not determined and so no QALY loss due to an episode of ILI can be easily calculated from these data. The

Table 5. Overview of different published estimates of QALDs lost due to ILI, for sources which presented data or interpretation of that data.

Study	QALY weight Worst day/ disease	Background QALY weight	Duration of disease (days)	QALD loss	Sample size	Method	Focus group	Age group
[Griffin, Perry, & Fleming, 2001]	-0.066	0.817	2.48	2.19*	21	EQ-5D	Patients (within 3 months after onset)	18+
[Griffin, Perry, & Fleming, 2001]	-0.263	0.72	2.48	2.45*	8	EQ-5D	GPs	Unknown
[O'Brien, Goeree, Blackhouse, Smieja, & Loeb, 2003]	Changed by day	Not reported	Not reported	Not reported	920 in placebo (639 with influenza	Likert score transferred to VAS	ILI patients (clinical trails antivirals GSK)	18-64
[Turner et al., 2003]	Changed by day	Not reported	Not reported	Not reported	See O'Brien at al	Converted the Likert scores into VAS scores converted those into time-trade off scores	ILI patients (clinical trails antivirals GSK)	18-64
[Rothberg, Bellantonio, & Rose, 2003]	0.25	1	Not reported	Not reported	15	HUI-3	Patients	Working adults
[Prosser et al., 2006]	Not reported	Not reported	Not reported	1.83	Not reported	Time trade off	Parents of children	Children
[Siddiqui & Edmunds, 2008]	VAS scores as presented by O'Brien et.al	0.85	Not reported	1.68 for influenza ILI 1.57 for non-influenza ILI	See O'Brien et.al.	VAS scores substracted from the baseline	ILI patients	18-64
[Sander et al., 2010]	QALY scores as presented by Turner et.al.	Not reported	Not reported	5.33 (0-19yrs) 6.35 (20-64yrs) 10.69 (65+)	See O'Brien et.al	Uses published QALY weights and combines this with unpublished disease duration	ILI patients	18-64

fourth source of data is a study by Prosser et al in which parents were asked how much time they were willing to trade off their own life to prevent ILI in their children, which resulted in a value of 1.825 QALDs lost per ILI case.

Total burden of disease pandemic

Given the estimated QALY loss in this study the overall burden of the 2009 H1N1v pandemic in England was around 27,070 QALYs (21,211 discounted). This is because almost a 7.8 million people were estimated to be infected with the novel virus over the course of the two waves of disease. Of these, around 2.1 million were estimated to have experienced fever and there were 337 deaths (5). Mortality accounted for 41% (25% with discounting) of the QALY loss attributable to H1N1v.

DISCUSSION

Given the global public health significance of influenza, it is remarkable how few studies have tried to quantify the morbidity and mortality impact in QALYs of this ubiquitous disease. In addition, as our systematic review reveals, the studies that have been performed often have considerable methodological limitations. For instance, two of the studies were small and retrospective (10; 17), two studies collected data from proxies (such as GPs) in addition to or instead of patients (10; 18), and the studies based on the zanamivir trial did not use standardised instrument and only estimated the difference in QALYs lost when on antivirals (11) . Finally, many of the studies did not estimate the duration of illness, and no previous study explicitly mentions their assumptions about the shape of the QALY loss (e.g. rectangular or triangular). This study is the only prospective population-based study of the health-relative quality of life impact of confirmed influenza and influenza-like illness that uses a standardised and well-validated instrument (the EQ-5D). The study shows that the overall QALY loss for confirmed H1N1v and other non-H1N1v influenza-like-illness was similar, at around 2.8 QALDs per patient. The study also confirmed that the range of symptoms and the severity of illness appeared similar in the two groups of patients, with the vast majority of patients reporting some problems with usual activities and pain and discomfort when they were ill with influenza or ILI. Only the prompt use of antivirals was significantly associated with a reduction in the QALDs lost, and only in the confirmed cases. Although deaths from H1N1v were comparatively rare, our study suggests that the overall burden of illness was considerable with more than 28,000 QALYs lost over the two waves of infection in England. This compares with an estimated QALY loss per year of 18,000 for chickenpox and shingles combined (19) and 97,000 for type 1 diabetes (20). However compared to a high mortality disease such as coronary heart disease which has an estimated annual burden of 8.2 million QALYs lost (20), it is relatively small.

The main strength of the study was that it was a population-based prospective controlled study. The study was carried out during a period when every case seeking

health care actively was investigated, with follow-up of all confirmed cases and their contacts. Therefore it should be as representative a study as is likely to be possible. Indeed, during the period of the study the two regions that were most heavily affected at the beginning of the epidemic (London and the West Midlands) stopped investigating every possible case, and so we excluded data from these regions to prevent bias. Nevertheless the possibility remains that more severe cases were more likely to come to the attention of medical authorities. In addition, although the overall response rate was good for a postal survey (>40%), there is always the possibility that more severely affected patients were more likely to return the questionnaire. Most patients probably knew their status (i.e. whether they were a confirmed H1N1v case or not), which may have led to the differential response between confirmed and other ILI cases. Hence, although every effort was made to reduce bias, there remains the possibility that the average loss estimated here is an overestimate of the true QALY loss per case.

The total burden of influenza in the population is probably underestimated, however, as we do not include the QALY loss from atypical cases i.e. those without fever. Only patients with ILI were investigated and their data recorded on the Fluzone database. Thus patients with milder symptoms – particularly those lacking fever – were not followed up. Carat et al. (20) suggest that about one half of influenza patients with respiratory symptoms do not develop fever. These individuals probably have a lower QALY loss than febrile cases. Indeed, of the 18 individuals who reported not having fever, 7 responded to both questionnaires, with an average loss of 1.2 QALDs per case. Little weight should be put on these numbers as the study was not designed to ascertain the burden of non-febrile acute respiratory illness, and the sample is small. However, as there may have been large numbers of patients without fever their contribution to the overall burden may have been significant. A preliminary literature review for QALY loss for acute respiratory illness revealed no papers, and so this remains an area for further study.

Our findings suggest that prompt use of antivirals reduces the number of QALDs lost. There are (to our knowledge) no other data on the effect of antivirals on health related quality of life of H1N1v patients. Our findings confirm the results from clinical trials on seasonal influenza (11), and are also in accordance with virological data, which seem to suggest that antivirals reduce viral load in H1N1v infected patients (21). Other factors, such as age, were not significantly associated with severity as measured by QALDs lost, which also seemed to confirm the findings of virological studies of H1N1v (21)

This study provides important baseline information on the severity of H1N1v and other influenza-like-illnesses that can be used to judge the overall impact of these diseases on the health of populations. This will facilitate rational decision-making regarding the control of influenza over the coming seasons.

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CONTRIBUTION

AJvH, MJ, EM and WJE designed the study and questionnaires. AJvH was leading on the logistics of the study, performed the data analysis and literature review. AU was responsible for the database. WJE and AJvH drafted the paper and AU, MJ and EM gave comments.

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chapter SEVEN

VACCINATION AGAINST PANDEMIC INFLUENZA A/H1N1V IN ENGLAND: A REAL-TIME ECONOMIC EVALUATION

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ABSTRACT

Decisions on how to mitigate an evolving pandemic are technically challenging. We present a real time assessment of the effectiveness and cost-effectiveness of alternative influenza A/H1N1v vaccination strategies. A transmission dynamic model was fitted to the estimated number of cases in real-time, and used to generate plausible autumn scenarios under different vaccination options. The proportion of these cases by age and risk group leading to primary care consultations, National Pandemic Flu Service consultations, emergency attendances, hospitalisations, intensive care and death was then estimated using existing data from the pandemic. The real-time model suggests that the epidemic will peak in early November, with the peak height being similar in magnitude to the summer wave. Vaccination of the high risk groups is estimated to prevent about 45 deaths (80% credibility interval 26-67), and save around 2,900 QALYs (80% credibility interval 1,600-4,500). Such a programme is very likely to be cost-effective if the cost of vaccine purchase itself is treated as a sunk cost. Extending vaccination to low-risk individuals is expected to result in more modest gains in deaths and QALYs averted. Extending vaccination to school-age children would be the most cost-effective extension. The early availability of vaccines is crucial in determining the impact of such extensions. There have been a considerable number of cases of H1N1v in England, and so the benefits of vaccination to mitigate the ongoing autumn wave are limited. However, certain groups appear to be at significantly higher risk of complications and deaths, and so it appears both effective and cost-effective to vaccinate them. The United Kingdom was the first country to have a major epidemic in Europe. In countries where the epidemic is not so far advanced vaccination of children may be cost-effective. Similar, detailed, real-time modelling and economic studies could help to clarify the situation.

INTRODUCTION

In March 2009, an outbreak of a novel strain of influenza A/H1N1 (hereafter H1N1v) linked to swine influenza was detected in Mexico. By 12 June 2009, the infection had shown sustained human-to-human transmission across the world, leading the World Health Organization to declare an influenza pandemic. The first wave of the outbreak of H1N1v in the United Kingdom (UK) appeared to peak around 25 July 2009, but cases began to increase again in September.

Vaccines specific to pandemic influenza have been successfully developed. The UK has a contract with two vaccine manufacturers (GlaxoSmithKline and Baxter) to procure H1N1v vaccines. On 7 August 2009, the Joint Committee on Vaccination and Immunisation (JCVI) recommended that high-risk individuals be prioritised for vaccination[1]. These individuals consist of everyone in the current seasonal influenza vaccine clinical at-risk groups (those with chronic respiratory, heart,

kidney, liver neurological disease, diabetes, and immunosuppression), excluding the low-risk elderly but including pregnant women and household contacts of immunocompromised individuals. The vaccination programme was rolled out on 21 October 2009, with primary care surgeries receiving the vaccine in the following week [2]. The UK has ordered sufficient doses to cover the entire population, so there is the opportunity to extend these recommendations to lower risk individuals. However, the extent of vaccination is restricted by other considerations including the timeliness of the arrival of vaccine doses, the cost of distribution and likely vaccine uptake among different population groups.

Decisions about extending vaccination to low-risk individuals depend partly on the epidemiological impact and cost-effectiveness of such options. Here we describe how we fit an epidemic model to the estimated number of cases in real-time to predict the impact and cost-effectiveness of a range of vaccination options.

METHODS

Epidemiological modelling

An age-and risk-group structured deterministic transmission dynamic model was used to estimate the impact of vaccination. The model has a modified SEIR structure, meaning that it has compartments for individuals who are susceptible to being infected by H1N1v (S), latently infected (E), infectious (I), and recovered (R). The population is also split into three risk groups – those in a seasonal influenza risk group, pregnant women, and those who are not in a risk group, with random mixing (within an age group) between the groups. The size of these groups is 8.6 million, 0.5 million and 42.3 million respectively. Population data were obtained from the Office for National Statistics (ONS) estimate from England mid 2008 and estimates of the size of each risk group provided by the Department of Health, England (Peter Grove, personal communication).

At the onset of the widespread epidemic (1 June) a small fraction of individuals in each age class were assumed to be infectious, and the remainder susceptible. However, older individuals were assumed to have a lower susceptibility, based on results from recent sero-epidemiological analyses [33]. An individual who became infected in the model was assumed to have natural immunity to further infections of H1N1v throughout the time course of the model (12 months). In addition, a fraction of individuals who were vaccinated were assumed to respond and become immune to infection and therefore disease, while non-responders remained susceptible to infection and disease. Vaccination was assumed to begin in the autumn of 2009 and be spread out over a number of weeks. Protection was assumed to occur on average 2 weeks after vaccination (see Appendix 1 for details). The model population was subdivided into seven age groups: under 1 year, 1-4 years, 5-14 years, 15-24 years, 25-44 years, 45-64 years and over 64 years.

In order to estimate plausible epidemiological scenarios for a second wave, the model was fitted using maximum likelihood to central estimates from the Health Protection Agency (HPA) of the weekly number of H1N1v cases from 1st June to 18th October 2009[3]. Key parameters (the initial reproduction number, latent and infectious periods) were sampled from uniform distributions which were wide enough to encompass the range of values suggested in analyses of the initial influenza epidemic[4] (see Appendix 1 for details). Those combinations of parameters that gave an acceptable fit to the observed data were retained and used to simulate the future incidence of infection and disease with different vaccination programmes in place.

The rates at which individuals from different age groups came into contact with each other was based on the reported frequency of close contacts by UK respondents in the recent POLYMOD study of epidemiologically relevant contact patterns[5]. The method of Hens et al.[6] was used to take into account uncertainty in contact patterns. Two sets of contact patterns were used: one for term-time and one during summer holidays when schools are closed. School holidays were assumed to start 46 to 52 days after June 1[7]. Each of these model realisations were compared to the 20 weeks of data by minimising the Poisson deviance between the number of cases each week reported by the HPA, and the model estimate of this. The best-fitting 1% of the realisations were retained to simulate the effect of vaccination. Every vaccination programme evaluated was implemented on each of the retained (i.e. best fitting) realisations to generate an estimate of the expected impact of vaccination, including epidemiological uncertainty.

A significant fraction of influenza infections are subclinical, or do not result in typical febrile symptoms. Thus, there are likely to have been more influenza infections over the summer and early autumn than the estimate of clinical cases by the HPA predict, requiring the data to be re-scaled to take account of this. The epidemic has grown more slowly in the autumn than occurred in the summer, suggesting that a significant fraction of individuals were infected in the early wave. By rescaling the estimated cases by different factors and comparing the model fits (including the fit to the autumn growth rate) it is possible to estimate by how much the weekly number of clinical cases underestimates the number of infections (see Appendix 1). A multiplication factor of 10 gives a good overall fit to the data, though multipliers of 7.5 and 12.5 were used in the sensitivity analysis. To check the validity of the multiplication factor and selected model runs, we compared the proportion of children who were infected during the first wave with sero-incidence data collected by the HPA [33], using samples taken in September (a sufficient time after the first wave to allow for a delay in seroconversion). The clearest signal in the sero-incidence data is an increase in the proportion of children under 15 years old who were seropositive between baseline and the first wave, and this corresponded well with our model predictions (see Appendix 1).

Figure 1(a, c, d) show the predicted size of the first and second waves, using different multiplication factors. In each case, the model predicts that the peak height of the autumn wave will be similar in size to the summer wave (though, on average, if a high multiplication factor is assumed, then a lower second wave results). The epidemic is expected to peak in the first two weeks of November 2009, and epidemic activity is expected to cease around January 2010. Figure 1(b) shows the results of the model validation exercise. The model was fitted to data on 27 September, and the resulting model projections (blue shaded area) are compared with the HPA's estimated weekly numbers. The pink shaded area shows a similar comparison using data up to 18 October. It can be seen that the model gives accurate short-term projections. For instance, using data up to the end of September the model accurately predicts the height and timing of the peak, 6 weeks later. The uncertainty around the projections is narrowed as more data become available. The good description of the subsequent epidemic suggests that the model provides a sound basis for projecting forward over the forthcoming weeks.

Economic modelling

Following the guidelines used by the National Institute of Health and Clinical Excellence (NICE) [8], the reference case was a cost-utility analysis performed from the perspective of the health care provider (the NHS) and lifetime time horizon, with future benefits and costs discounted at 3.5% per annum. The burden of disease due to the number of infections predicted by the epidemiological model was estimated, and a proportion of them assumed to result in clinical symptoms. Each clinical case was associated with an age- and risk-group specific risk of a general practitioner (GP) consultation (either telephone or clinic), National Pandemic Flu Service (NPFS) consultation (either telephone or internet), antiviral delivery, hospitalisation, intensive care and death. Each of these health care or clinical endpoints was then associated with a cost to the health service and quality of life detriment. The cost-effectiveness of different vaccination options was then estimated by calculating a net incremental discounted cost per quality adjusted life year (QALY) gained. This incorporated the discounted cost of each option (cost of vaccine programme minus treatment costs saved) as well as the number of discounted QALYs gained as a result of averting cases of H1N1v.

All costs are expressed in 2008 prices, and were assumed to occur in the current financial year, although benefits from deaths averted that occurred in future years were discounted at the recommended rate. Unit costs taken from previous years were inflated to £2008 using the Hospital and Community Services Pay and Prices Index[9].

Estimate of health outcomes and health service utilisation

Symptomatic cases

The clinical definition of ILI is a report of fever and at least one other influenza-related symptom. A review of volunteer challenge studies found that 37% of individuals infected

with influenza A/H1N1 had fever[10], so this was assumed to be the proportion of H1N1v cases with symptoms. Thus 37% of infections (on average) are assumed to result in clinical cases that may then incur costs, and incur a health (QALY) loss.

Calls to the National Pandemic Flu Service (NPFS)

The NPFS is a telephone and internet service that was launched on 23 July 2009 to allow people in England with ILI to obtain antivirals without visiting their GP[11]. The number of assigned unique numbers for receipt of antivirals (equivalent to a prescription) by age up to 29 September 2009 was multiplied by the age-specific proportion positive, using data from 3 August – 26 September. Cases were distributed according to risk groups, using the data available from two separate weeks (23-30 July, and 23-29 September), giving the estimated number of antivirals distributed for H1N1v. Dividing this by the model estimate of the number of symptomatic cases gave the proportion of cases that received antivirals via NPFS. We attributed antiviral prescriptions to a telephone or internet consultation using data from the NPFS.

GP calls and consultations

FluSurvey (www.flusurvey.org.uk) [12] is an internet-based cohort in which participants report the occurrence of respiratory symptoms, as well as contact with health service and usage of medication. The number of cases of influenza-like illness (ILI) reported in FluSurvey was extracted. A respondent was assumed to have ILI if he or she reported a fever and at least one other influenza-related symptom (blocked/runny nose, cough, sore throat, headache, muscle/joint pain, chest pain, stomach ache, diarrhoea, nausea, chills, weakness or eye irritation). The age and risk group dependent ratio of cases reporting calls or office consultations to GPs to total cases was calculated. Between 8 May and 18 September there were 1551 cases recorded in FluSurvey resulting in 476 calls and 145 consultations.

Uncertainty around parameters governing the proportion of cases requiring calls to the NPFS, calls to a GP, GP office visits, hospitalisations and intensive care treatment was estimated by sampling from binomial distributions representing the number of cases among all individuals reporting ILI (for the FluSurvey database) or confirmed pandemic influenza (for the Regional Microbiology Network (RMN) database). This was multiplied by similar binomial samples representing uncertainty in the age and risk group breakdown of cases.

Hospitalisations

The age-specific hospitalisation rate was estimated using information collected by the Regional Influenza Centre via the FluZone database during the containment phase of the epidemic. Out of the 7,564 people with confirmed swine flu 129 were hospitalised. Risk-group specific rates were estimated using the distribution of hospitalised cases in a study of laboratory-confirmed pandemic influenza cases admitted to hospitals, reported through the Regional Microbiology Network (RMN). Data were available for 456 patients of whom 203 were in a risk group. Empirical

distributions were used for sampling since the long tail made fitting to standard parameterised distributions (gamma or lognormal) difficult. Distributions were adjusted for age and risk group according to the ratios in the data set. The proportions of risk group and non-risk group patients admitted to intensive care, paediatric intensive care and intensive treatment units were also recorded. No cases were recorded as being admitted to high dependency units.

Deaths

The case fatality ratio was estimated using two methods. Firstly, we used the likely number of deaths due to H1N1v in two Southern Hemisphere countries (Australia and New Zealand), where the pandemic wave is believed to be largely ended [13]. Data from other Southern Hemisphere countries were not used since they were either extremely small (French Polynesia, New Caledonia) or were in different income levels from the UK as defined by the World Bank. This number was then inflated by the ratio of the population size to the size of the UK population, and divided by the total number of H1N1v cases predicted by real-time modelling. Secondly, the cumulative number of confirmed deaths due to pandemic influenza on 16 September was divided by the estimate of the cumulative number of symptomatic pandemic influenza cases on 16 September[3]. As a form of sensitivity analysis, the ratio was recalculated after assuming that deaths occurred several weeks after the case was assumed to have occurred, as highlighted in a previous estimate of the case-fatality ratio of H1N1v [14]. Four scenarios (instantaneous deaths, one week after case, two weeks after case, and three weeks after case) gave very similar case fatality due to the slow rate of growth in cumulative cases after mid-August. The mean of the three estimates (one each using Australian, New Zealand and UK data) was thus obtained. The overall rate was then combined with a risk- and age-group dependent multiplier which was calculated using data from 59 of the 66 reported deaths with risk-group information. The estimated mortality rate was assumed to have a normally distributed error term, with standard error calculated from the three estimates used to estimate the mean. Uncertainty around age and risk group information was estimated from sampled binomial distributions representing the number of individuals in particular groups among the 59 reported deaths with risk group information.

The differential life-expectancy for those in influenza-risk groups was calculated from the MSGP4 survey of 500,000 individuals in general practices in England and Wales[15], using a previous analysis used to estimate the benefit of pneumococcal vaccination[16]. This assumes that those who did not consult over the period of the study (1 year) for any of the risk conditions were not in the risk group, and that the relative mortality risk has not changed since 1991-2 (even though overall life expectancy has improved). The resulting age-group specific relative risk (compared to the general population) was multiplied by the current (2008) age-specific risk of death to calculate the age- and risk-group specific life-expectancy. Pregnant women were assumed to have the same life-expectancy as the low risk group. The age- and risk-group specific discounted

life-expectancy was used to estimate the (discounted) life-years lost per case. Life-expectancy was assumed to be higher for those in the low-risk group.

QALY loss

To estimate the health related quality of life loss from non-fatal cases of H1N1v, we contacted individuals with confirmed H1N1v infection in the first and second week of June. These individuals were identified using an electronic reporting system of suspected H1N1v cases, which contained information on all detected and confirmed, rejected and presumed cases outside London and the West Midlands for the first two and a half months of the pandemic (the survey was not conducted among individuals from London and the West Midlands)[17]. Only cases that had occurred in the previous eight days were sent the questionnaire, to minimise recall bias. Confirmed H1N1 cases and controls (investigated for ILI, but found not to have H1N1v) were sent a questionnaire about their age, pre-existing risk conditions and the symptoms of their recent illness. In addition they were asked to complete the EQ-5D questionnaire (a generic health status instrument) [18] for the worst day of illness and for the day of receipt of the questionnaire. They were followed up two weeks later to obtain base-line data (i.e. their health status after recovery), as well as data on the duration of symptoms. Children (11 years or over) received a child-friendly version of the questionnaire (using slightly modified language). Parents or guardians were asked to fill out the questionnaire on behalf of younger children. A total of 647 questionnaires were sent out and 288 (45%) returned. The results suggested that the mean QALY loss per episode in children was 0.0074 (SD = 0.00085) and 0.0082 (SD = 0.00081) in adults. Although the differences were not significant we used these differential age-based QALY losses in the later analysis. A QALY loss of 0.008 is equivalent to losing 2.9 days of full health. We assumed that this QALY loss described cases not requiring hospital treatment. For hospitalised cases we assumed a QALY loss 2.17 times greater, based on the ratio of QALY loss between hospitalised and uncomplicated influenza cases used in a previous economic evaluation of interventions during an influenza pandemic [19].

Costs

Unit costs of a clinic and telephone consultations, hospitalisations, stays on intensive care and antivirals were taken from standard or published sources. The cost of an NPFS telephone consultation was assumed to be equal to that of an NHS Direct consultation [20]. Internet based consultations are assumed to be free (that is the sunk costs of setting up the NPFS website are ignored). In the base case, the cost of the vaccines is also assumed to be sunk. This is because the vaccines were ordered at the start of the pandemic and the cost of the vaccines cannot be readily recovered. Delivery costs of £5.25 per dose are assumed [21]. Transport and other costs are assumed to be small, and are ignored. The costs of the vaccine are varied in the sensitivity analysis. Unit costs and their sources are given in Table 1.

Vaccination assumptions

In the base case, a two dose strategy for children under 10 years old and one dose for all others was assumed, based on advice by the Joint Committee on Vaccination and Immunisation (JCVI)[21]. The efficacy of Pandemrix® (the main H1N1v vaccine used in the United Kingdom) against clinical endpoints has yet to be determined, although it short-term safety and immunogenicity has been established in clinical trials [23]. Seasonal influenza vaccines have been found to have a clinical efficacy of over 70% [24], and Pandemrix®, whose trials have demonstrated very good serological responses in adults, may be expected to have better clinical efficacy due to its novel adjuvant. Hence we investigated two scenarios for clinical efficacy in individuals 10 years and over: a base case scenario with single dose clinical efficacy of 70%, and a more optimistic scenario with efficacy of 85%. For children under 10 years old, only half the usual adult dose is given, so we assumed 35% efficacy after a first dose and 70% after a second dose (or 42.5% and 85% for the optimistic scenario). We also investigated the possibility that a single half-dose of vaccine in these children would provide the same efficacy as in older individuals (70% or 85%). In these scenarios, it was assumed that these children would only be given a single vaccine dose. Vaccine uptake was assumed to be 70% in risk groups and 40% in other groups.

The schedule over which doses are expected to be procured puts constraints on the vaccination programmes that can be implemented over the autumn. It was assumed that high risk groups are vaccinated first (as decided by the JCVI in August[1]), and that the first dose of the vaccine is delivered between Oct 26 and Nov 8 [2]. Children under 10 years old were assumed to receive the vaccine 3 weeks after the first dose. We then explored the possibility of extending vaccination to low risk groups in any of four age categories (6 months – 4 year olds, 5-14 year olds, 6 months – 14 year olds and 65+ year olds). In the base case, it was assumed that vaccination of low risk groups would begin on Nov 16, that it would take two weeks for the first dose to be given and that children under 10 years would receive the second dose after 3 weeks. We also explored the effect of delays in vaccinating the low risk groups.

Since there are likely to be large operational constraints to vaccinating significant numbers of individuals in a very short space of time, we assume that these strategies are mutually exclusive: that is, vaccination can be extended to one of these low-risk groups. We ignore policies involving vaccination of low-risk adults aged 15 – 64 years old, since they would have to wait until the epidemic was largely over (see later) before sufficient doses would be available to start vaccinating.

Sensitivity analyses

Parametric sensitivity analyses were conducted in order to quantify the impact of uncertainty around parameters governing the incidence of different levels of severity of illness, costs and quality of life weights. These were sampled across the distributions given in Table 1. For each of the 600 accepted realisations from

Table 1. List of parameters used in the model as well as distributions representing uncertainty around them used in sensitivity analysis.

Parameter	Estimate	Uncertainty distribution	Source
Vaccation parameters			
Days between vaccination and vaccine protection	14	Triangular on [7,21]	Assumption
Incidence and risk estimates			
Proportion of infected cases with symptoms	0.37	Triangular on [0.25, 0.51]	Review of volunteer studies[10]
Proportion of ILI cases calling GP			FluSurvey [12]
Low risk 0-14 years	0.35	Bootstrap sample from binomial (np=26, n=74)	
Low risk 15-64 years	0.29	Bootstrap sample from binomial (np=285, n=969)	
Low risk 65+ years	0.28	Bootstrap sample from binomial (np=30, n=107)	
High risk 0-14 years	0.13	Bootstrap sample from binomial (np=2, n=16)	
High risk 15-64 years	0.36	Bootstrap sample from binomial (np=124, n=343)	
High risk 65+ years	0.22	Bootstrap sample from binomial (np=9, n=42)	
Proportion of ILI cases visiting GP			FluSurvey [12]
Low risk 0-14 years	0.11	Bootstrap sample from binomial (np=8, n=74)	
Low risk 15-64 years	0.08	Bootstrap sample from binomial (np=74, n=969)	
Low risk 65+ years	0.06	Bootstrap sample from binomial (np=7, n=107)	
High risk 0-14 years	0.12	Bootstrap sample from binomial (np=2, n=16)	
High risk 15-64 years	0.13	Bootstrap sample from binomial (np=45, n=343)	
High risk 65+ years	0.21	Bootstrap sample from binomial (np=9, n=42)	
Proportion of ILI cases calling NPFS			NPFs[11]
Low risk 0-14 years	0.12	Data-derived; 95% interval [0.09,0.17]	
Low risk 15-24 years	0.16	Data-derived; 95% interval [0.11,0.22]	
Low risk 25-44 years	0.11	Data-derived; 95% interval [0.08,0.16]	
Low risk 45-64 years	0.07	Data-derived; 95% interval [0.04,0.10]	
Low risk 65+ years	0.02	Data-derived; 95% interval [0.00,0.07]	
High risk 0-14 years	0.26	Data-derived; 95% interval [0.18,0.36]	
High risk 15-24 years	0.09	Data-derived; 95% interval [0.06,0.12]	
High risk 25-44 years	0.07	Data-derived; 95% interval [0.05,0.09]	
High risk 45-64 years	0.11	Data-derived; 95% interval [0.07,0.16]	
High risk 65+ years	0.01	Data-derived; 95% interval [0.00,0.04]	

Table 1. continued

Parameter	Estimate	Uncertainty distribution	Source
Proportion of ILI cases calling NPFS			NPFS [11]
<1 years	0.32	Bootstrap sample from binomial (np=682, n=2134)	
1-4 years	0.65	Bootstrap sample from binomial (np=13970, n=21642)	
5-14 years	0.64	Bootstrap sample from binomial (np=30734, n=48116)	
15-24 years	0.53	Bootstrap sample from binomial (np=47620, n=89207)	
25-44 years	0.50	Bootstrap sample from binomial (np=72162, n=143619)	
45-64 years	0.59	Bootstrap sample from binomial (np=36380, n=61344)	
65+ years	0.80	Bootstrap sample from binomial (np=10522, n=13088)	
Proportion of ILI cases admitted to hospital			RMN, FluZone
Low risk 0-4 years	41.8 per 1000	Bootstrap sample from binomial (np=64, n=82) * binomial (np=21, n=414)	
Low risk 5-14 years	5.6 per 1000	Bootstrap sample from binomial (np=55, n=91) * binomial (np=31, n=3514)	
Low risk 15-64 years	11.5 per 1000	Bootstrap sample from binomial (np=132, n=260) * binomial (np=69, n=3585)	
Low risk 65+ years	24.4 per 1000	Bootstrap sample from binomial (np=2, n=23) * binomial (np=8, n=51)	
High risk 0-4 years	214.4 per 1000	Bootstrap sample from binomial (np=18, n=82) * binomial (np=21, n=414)	
High risk 5-14 years	67.1 per 1000	Bootstrap sample from binomial (np=36, n=91) * binomial (np=31, n=3514)	
Proportion of hospitalised cases requiring intensive care			
Low risk	41.4 per 1000	Bootstrap sample from binomial (np=6, n=145)	
High risk	70.0 per 1000	Bootstrap sample from binomial (np=7, n=100)	
Case fatality ratio	0.112 per 1000	Normal (μ=0.112/1000, σ=0.0121/1000)	Pandemic influenza death register, Southern Hemisphere countries[13]

Table 1. continued

Parameter	Estimate	Uncertainty distribution	Source
Proportion of deaths by age and risk group			Pandemic influenza death register
Low risk 0-14 years	0.039	Bootstrap sample from binomial (np=2, n=51)	
Low risk 15-64 years	0.098	Bootstrap sample from binomial (np=5, n=51)	
Low risk 65+ years	0.020	Bootstrap sample from binomial (np=1, n=51)	
High risk 0-14 years	0.20	Bootstrap sample from binomial (np=10, n=51)	
High risk 15-64 years	0.67	Bootstrap sample from binomial (np=34, n=51)	
High risk 65+ years	0.14	Bootstrap sample from binomial (np=7, n=51)	
Costs			
GP telephone consultation	£22	None	Costs of Health and Social Care [9]
GP clinic consultation	£37	Lognormal (normal μ 37, normal σ 8.4)	
NPFS call	£17		Harris et al. [20]
Antiviral (oseltamivir) course including delivery	£16		British National Formulary [32]
Hospital admission	£840	Lognormal (normal μ 839, normal σ 192.1)	
Intensive care (0-14 years)	£1600	Triangular (vertices 1197, 1680, 1900)	NHS Reference costs [18]
Intensive care (15-65 years)	£1400	Triangular (vertices 1192, 1410, 1607)	NHS Reference costs [18]
Vaccine (per dose)	£10	None	Assumption
Vaccine delivery costs	£5.25	None	Department of Health [21]
Utilities			
QALY loss for non-hospitalised children	0.0074	Normal (μ 0.0074, σ 0.00085)	EQ-5D study
QALY loss or non-hospitalised adults	0.0082	Normal (μ 0.0082, σ 0.0018)	EQ-5D study
QALY loss for hospitalised children	0.016	Normal (μ 0.016, σ 0.00082)	Siddiqui and Edmunds [19]
QALY loss for hospitalised adults	0.018	Normal (μ 0.018, σ 0.0018)	Siddiqui and Edmunds [19]

the epidemic model 20 simulations were produced, sampling randomly over the parameter space in the economic model, to give a total of 12,000 samples. Hence the sensitivity analyses incorporated uncertainty in both epidemiological and economic parameters. The number of simulations preformed represented a compromise between computational effort and validity of findings. The results of the base-case model were checked using a larger sample (120,000 simulations) and were found to be very similar to those shown (data available on request).

Regression analysis was used to assess the key drivers of the cost-effectiveness results. Variables that were found to be multicollinear with other variables were excluded. The influence of each non-multicollinear variable on cost-effectiveness was shown as a tornado graph. A net benefit approach was used by assuming that the marginal societal willingness to pay for a QALY gained was £20,000. This approach was taken to ensure that the error terms were well behaved.

RESULTS

Figure 1(e) shows the estimated impact of the different vaccination programmes on number of infections during the second wave of the H1N1 epidemic. The impact of vaccination is attenuated by the fact that vaccination can only occur late in the epidemic. Table 2 shows the estimated number of cases and deaths prevented, QALYs gained and treatment costs averted for the different vaccination strategies, compared with the no vaccination alternative. Vaccination of the high risk groups is estimated to avert about 45 deaths (80% credibility interval 26-67), and save 2,910 QALYs (80% credibility interval 1,579-4,471). Extending vaccination from the risk groups to low-risk individuals is estimated to have a modest impact on deaths averted as few deaths occur in the low risk individuals, and vaccination is assumed to start later in these groups. The impact on cases is greater, particularly if vaccination is extended to low-risk school children.

Figure 2 shows the range of values for the incremental cost-effectiveness ratios for the different strategies across all realisations of the model. Each realisation of the model is a single set of model parameter values sampled over the entire distribution of possible values that they can take. The horizontal lines represent £20,000 and £30,000 per QALY gained, the thresholds used by the National Institute for Health and Clinical Excellence as a guide to determine if a policy is cost-effective[25]. Hence realisations below the two thresholds are likely to be deemed cost-effective, realisations above the thresholds are unlikely to be deemed cost-effective, and there is less certainty about decisions regarding realisations located between both thresholds.

The largest incremental benefit is obtained by vaccinating risk groups compared to not vaccinating anybody. Such a strategy is also very likely to be cost-effective, since most model realisations lie below the £20,000 per QALY gained threshold. Extending vaccination to low risk groups as well is relatively less costly than vaccinating high risk

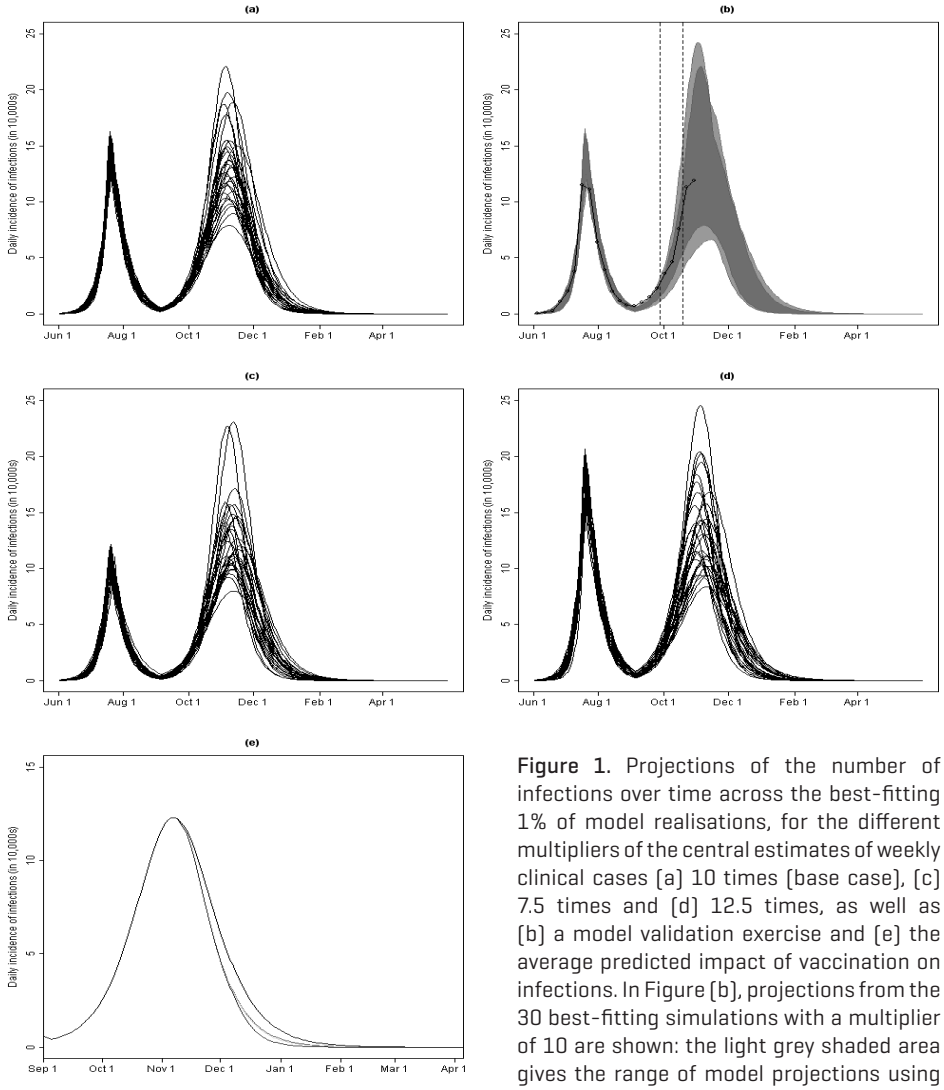

Figure 1. Projections of the number of infections over time across the best-fitting 1% of model realisations, for the different multipliers of the central estimates of weekly clinical cases (a) 10 times (base case), (c) 7.5 times and (d) 12.5 times, as well as (b) a model validation exercise and (e) the average predicted impact of vaccination on infections. In Figure (b), projections from the 30 best-fitting simulations with a multiplier of 10 are shown: the light grey shaded area gives the range of model projections using data up to 27 September (first vertical line), the dark grey shaded area gives the range of projections using data up to 18 October (second vertical line). The estimated number of infections (rescaled HPA weekly estimates) is shown as points joined by a line. Note that data up to 1st November are shown. In Figure (e) the black curve shows the course of the epidemic without vaccination, red with vaccination of high risk individuals, green with vaccination of risk groups and 0.5 – 4 year olds, while blue shows vaccination of risk groups of 5 – 14 year olds.

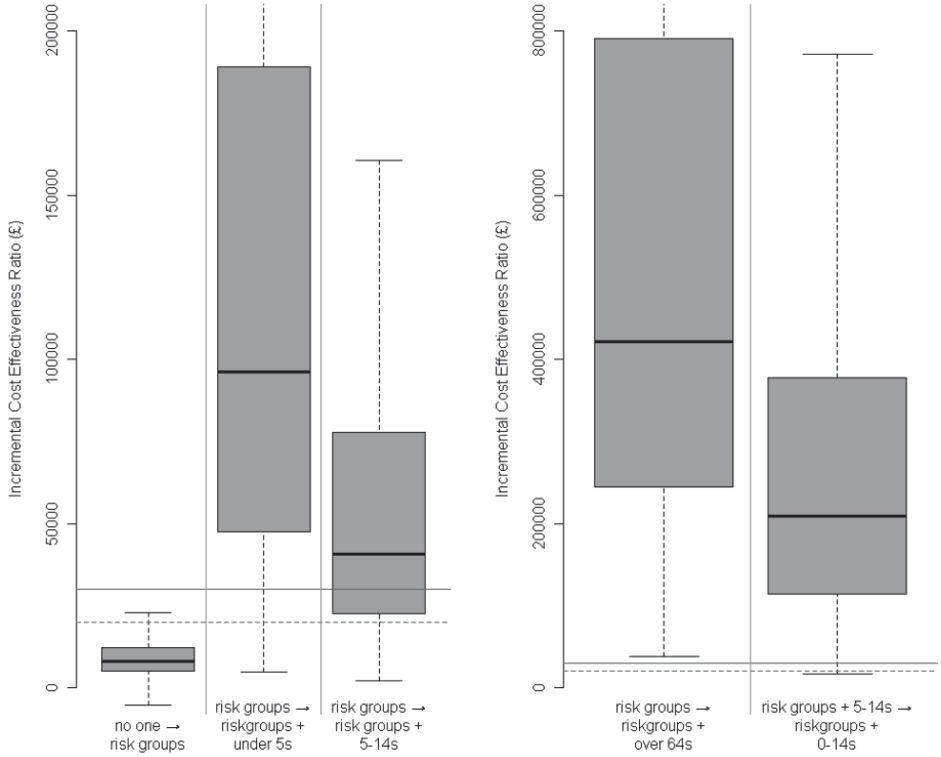

Figure 2. Incremental cost-effectiveness ratio of the base case model across different realisations of the model, assuming £5.25 administration costs per dose of vaccine. Vaccination high risk individuals only is compared to no vaccination, while low risk group vaccination strategies are compared to vaccinating risk groups only. Horizontal dotted and straight lines respectively show the £20,000 and £30,000 per QALY thresholds used by NICE for decision making. Note the change in scale on the right-hand panel.

groups, partly because uptake among these groups is assumed to be lower. However, such strategies also achieve lower incremental benefits, and are less likely to be cost-effective. Of the strategies involving extending vaccination beyond high risk individuals, extending vaccination to the low-risk adults over 64 years appears least likely to be cost-effective. Vaccinating either 0-4 year olds or 5-14 year olds appears to be more cost-effective than vaccinating older adults, with vaccinating 5-14 year olds having a more attractive cost-effectiveness profile. Choosing to vaccinate all children under 15 year old would prevent more cases than vaccinating 5-14 year olds only, but would be less cost-effective because many of the 0-4 year olds would be protected due to herd immunity as a consequence of vaccinating older children.

Table 3 shows the effect of varying key assumptions in the model around the size of the epidemic, effectiveness of vaccination, speed of vaccine roll-out and likely vaccine uptake. The proportion of model realisations that are cost-effective are shown for two

Table 2. The estimated number of cases and deaths prevented, QALYs gained and treatment costs averted for the different strategies, instead of no vaccination, for base case assumptions†.

Groups to vaccinate	Only risk groups	Risk groups & 0-4 year olds	Risk groups & 5-14 year olds	Risk groups & 65+ year olds	Risk groups & 0-14 year olds	Risk groups & 0-14 & 65+ year olds
Number of cases prevented						
Mean	452,990	486,532	558,168	458,954	573,355	576,503
Median	422,175	448,900	511,930	427,119	524,127	526,817
10th centile	234,274	243,375	267,800	236,046	272,628	273,636
90th centile	710,252	777,693	908,364	721,682	938,357	944,056
Number of deaths prevented						
Mean	45	46	48	45	48	49
Median	43	44	46	43	46	46
10th centile	26	26	27	26	27	27
90th centile	67	68	72	67	73	73
Number of hospital admissions prevented						
Mean	10,386	10,808	11,398	10,460	11,604	11,645
Median	9,569	9,927	10,456	9,629	10,631	10,662
10th centile	5,225	5,349	5,565	5,246	5,627	5,640
90th centile	16,547	17,377	18,430	16,688	18,830	18,911
Total QALYs saved						
Mean	2,910	3,065	3,396	2,938	3,466	3,481
Median	2,733	2,855	3,147	2,757	3,202	3,215
10th centile	1,579	1,619	1,732	1,587	1,753	1,757
90th centile	4,471	4,779	5,380	4,526	5,517	5,546
Treatment costs avoided (£m)						
Mean	13.4	14.0	15.1	13.5	15.4	15.5
Median	12.3	12.8	13.8	12.4	14.0	14.1
10th centile	6.7	6.9	7.2	6.7	7.3	7.3
90th centile	21.5	22.7	24.7	21.7	25.2	25.3

†Vaccine efficacy of 70% after 1 dose in ≥10s and 2 doses in <10s, vaccine efficacy of 35% after 1 dose in <10s, no vaccine purchase costs (administration cost of £5.25 only), 70% vaccine coverage in high risk groups, 40% vaccine coverage in low risk groups and vaccination of low risk groups beginning on Nov 16.

Table 3. Proportion of model realisations that indicate that either (i) vaccinating risk groups or (ii) extending vaccination from risk groups to low risk 5-14 year old children, is likely to be cost-effective, when model assumptions are altered.

	Proportion of model realisations deemed cost-effective			
	No one → Risk groups		Risk groups → Risk groups + 5-14s	
Threshold (£ per QALY gained)	£20,000	£30,000	£20,000	£30,000
Base case†	93%	98%	20%	37%
Vaccinating low risk groups begins on Nov 23 (1 week delay)	93%	99%	7%	16%
Vaccinating low risk groups begins on Nov 30 (2 week delay)	93%	99%	2%	6%
Vaccinating low risk groups begins on Dec 7 (3 week delay)	93%	99%	0%	2%
Vaccinating low risk groups begins on Dec 14 (4 week delay)	93%	98%	0%	0%
50% vaccine coverage in high risk groups	81%	94%	31%	48%
20% vaccine coverage in low risk groups	93%	98%	5%	15%
Vaccine efficacy of 85% after 1 dose in ≥10s, 2 doses in <10s	96%	100%	18%	34%
Vaccine efficacy of 70% after 1 dose in all (no second dose given)	95%	99%	45%	61%
Vaccine efficacy of 85% after 1 dose in all (no second dose given)	95%	99%	41%	57%
Cost of vaccine £10 per dose + £5.25 administration cost	15%	43%	0%	1%
Lower first wave incidence	96%	100%	34%	51%
Higher first wave incidence	91%	98%	19%	35%

strategies. The first is vaccination of high risk groups only compared to no vaccination. The table shows that vaccinating high-risk individuals remains almost certain to be cost-effective across most changes in assumptions. Only if vaccine cost is not treated as a sunk cost is the cost-effectiveness profile of this strategy affected. Even so, with an assumed cost per vaccine dose of £10 (seasonal influenza vaccines cost about £6 per dose), vaccinating risk groups may still be cost-effective at a threshold of £30,000 per QALYs gained. Since this strategy is almost always cost-effective, we also show the cost-effectiveness of extending vaccination to the next most cost-effective group to vaccinate. This is always low-risk children from 5 to 14. This strategy is more sensitive to model assumptions. In particular, delays in the programme by just a few weeks are likely to cause a large part of the benefit of vaccination to be lost, and hence the

strategy to be deemed not cost-effective. Extending vaccination from this group to children under 5 or adults over 64 is highly unlikely to be cost effective across all the scenarios considered (not shown in the table).

Figure 3 is a tornado diagram that shows the most influential parameters driving the cost-effectiveness of vaccinating high risk individuals, as well as the effect of varying them across their likely range. The most influential parameter is the overall size of the epidemic without vaccination (which is a measure of the uncertainty within the epidemiological model). Other key parameters for cost-effectiveness are the QALY loss per case, hospitalisation rates and costs, and case-fatality ratios.

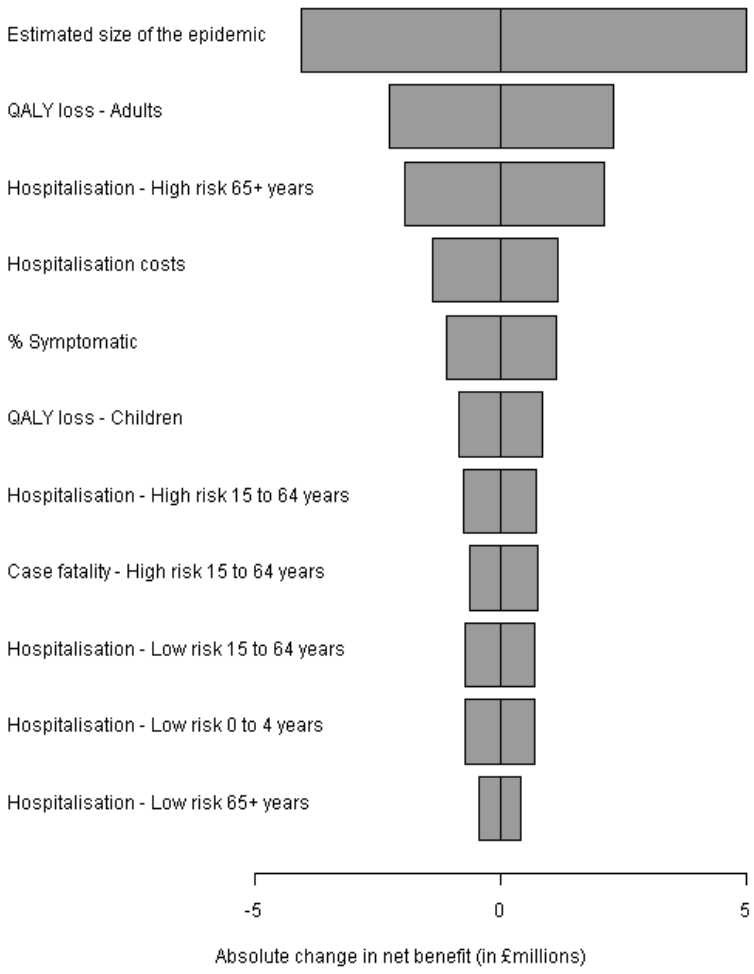

Figure 3. Tornado diagram showing the influence of the most important parameters on the incremental cost-effectiveness ratio of vaccinating high-risk groups. Each bar shows the change in the ratio from its baseline figure of £19,600 when each variable is varied between its 25% and 75% endpoints.

DISCUSSION

The model suggests that a significant fraction of individuals were infected in the first wave of the epidemic, and that the peak height of the autumn wave is likely to be similar to that observed in summer (subsequent data confirmed this model prediction, see Appendix 2). As the risk of serious consequences following infection is much higher in the risk groups, it appears that vaccinating these groups is likely to be effective at reducing deaths and cost-effective, when compared to widely used norms. Extending vaccination to low-risk groups is likely to be much less effective at reducing deaths and QALYs lost, partly because of the lower risk in these individuals, and partly because the programmes must start later in the epidemic, to allow for stocks of vaccine to become available. Furthermore, the effect and cost-effectiveness of such an extension is highly dependent on its timing.

The main strength of the paper is that the epidemiological model is fitted to the data, well describing the particular double-peaked epidemic observed in England. This represents a significant advance over previous assessments of H1N1v vaccination policy [e.g. 26,27], as the model is specifically fitted to the emerging epidemic data in real-time, which should greatly improve the validity of the projections and findings. As the model well describes the unfolding epidemic, it provides a sound basis for estimating future infections as well as an assessment of the uncertainty around these predictions. We have combined this information with economic and health outcome data (including a bespoke study of the impact of H1N1v on health-related quality of life) to estimate the potential impact and cost-effectiveness of vaccination options. Importantly, our key finding that vaccination of the high risk groups is probably both effective and cost-effective, is robust to uncertainty in epidemiological, outcome and economic parameters.

The model used was relatively simple. The model was a deterministic mass-action type transmission dynamic model with no spatial structure assumed. The model had to be transmission dynamic in nature in order to assess the impact of vaccinating the key transmitters (children) and compare this to other strategies (such as vaccinating the elderly or risk groups). It was also clearly necessary to structure the model by age and risk group. No further stratifications were necessary to evaluate the policy options, and it was thus the simplest model that could be chosen. Its simplicity enabled the model to be fitted in real-time. Fitting a stochastic, individual based model, for instance, would have been far more computational demanding, with no additional benefit for policy evaluation.

The model provides an estimate of the underlying number of individuals infected in the population and how this changed over time. By comparing this with the estimated case numbers we could derive a multiplication factor (which we estimated to be 10 times). This is partly because we are comparing estimated infections (some of which would be subclinical) with estimated clinical cases. It is possible that this factor could

have changed over time. However, in order to estimate changes in this factor, it would have been necessary to have data on changing health seeking behaviours and/or changes in the sero-incidence over time. These data were not available in sufficiently large samples sizes to infer whether this ratio was changing over time. A constant ratio also fitted the data very well (figure 1), and was therefore used.

One weakness is the lack of information on key parameters surrounding vaccination. For example, vaccine efficacy data used for licensing were based on H5N1 strains instead of H1N1v strains, and only provided immunogenicity rather than efficacy endpoints. Clinical trials of actual H1N1v vaccines are underway, but again these will only provide immunogenicity endpoints in the short term. Consequently we based our assumptions about vaccine efficacy on experience with seasonal influenza vaccines. It is quite possible that H1N1v vaccines will have better efficacy than this. If this is the case, scenario analyses suggest that vaccinating low-risk children will be substantially more cost-effective than our base case indicates. In addition, it is possible that the vaccines will have differential impacts against infection and clinical disease. In the absence of any data on the action of the vaccine, we have taken the simplest assumptions – that it provides complete protection in those that respond.

There is also considerable uncertainty in the level of vaccine uptake in different age and risk groups. We assumed that 70% of the risk groups would accept vaccination, on the basis of a targeted vaccination programme being aimed at them early in the second wave of the epidemic. There is no experience of vaccinating low-risk groups routinely in the UK (except for the low-risk elderly), and recent attitudinal surveys in other countries suggest that uptake is likely to be low in these groups[27;28]. It is unavoidable that there will be these gaps in our knowledge, since we are evaluating new vaccines aimed at a novel infection, and no similar vaccination programme has been attempted in the past. In the time since submission of this paper, it seems that the coverage in the high risk group has been lower than anticipated here, and it has taken longer to vaccinate them. The impact on the incidence of disease will therefore be lower than anticipated here (see Appendix 2 for an updated analysis) and the cost-effectiveness of the high risk strategy will be lower than is presented in the results.

Lastly, there is uncertainty about the long-term benefit of vaccination. We have assumed that benefits of vaccination only last for the duration of pandemic (assumed to be from June 1 2009 to May 31 2010). However, it is likely that H1N1v will be one of the circulating seasonal strains in 2010 [30], albeit with some antigenic drift, and it is possible that the adjuvanted vaccine will provide some degree of protection a year or more after vaccination [31]. If this is the case, then the benefit of vaccinating even in December 2009 would be greater than our model currently suggests

Vaccinating school children is the most cost-effective option after vaccination of high-risk individuals. Such an option is far more cost-effective if the vaccines can be made available by mid-November, but by mid-December would have little effect and is almost certainly not cost-effective. Such a rapid roll out of sufficient doses

of vaccine may be difficult for operational reasons, since such an extension can only begin when high risk individuals have been vaccinated. This suggests that vaccine uptake in high risk groups needs to be closely monitored. Once this appears to have saturated, making any remaining doses available to low risk groups as promptly as possible could be beneficial. Such a move would benefit high risk groups as well, since they would be indirectly protected through herd immunity.

Decisions on how to control a novel infection in a rapidly evolving situation necessarily have to be made on the basis of incomplete information. In particular, the long manufacturing lead-time means that decisions about ordering vaccines had to be made before detailed information on the severity of this strain were available. As information has become available decisions about how to use this stockpile can be refined. Mathematical and economic models are well suited to this task as they synthesise information from different sources and provide projections under different scenarios. The modelling work presented here has highlighted that England had a much larger epidemic in the summer than was previously thought, and that the second wave will be of a similar size. This means that vaccination of children and other low-risk groups during the latter part of the autumn is likely to have a modest impact. This is not necessarily the case elsewhere, where the epidemic is not so far advanced. Similar, detailed, real-time modelling and economic studies could help to clarify the situation in other countries.

APPENDICES

The appendices can be found at: http://www.sciencedirect.com/science/article/pii/S0264410X10000320

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PART III

STREPTOCOCCUS PNEUMONIAE

chapter EIGHT

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 [1]. 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 [1]. 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 the PCV7 replacing pneumococcal serotypes eliminated by the vaccine (replacement disease) [2-4].

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 [5-10]. Both the four dose (3+1) vaccine schedule and the reduced three dose (2+1) schedule, as implemented in Norway and the UK [11,12], 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 [12-15]. 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 [12,13,15].

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 [9,16]. 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).

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 [17,18]. The case–fatality rate for meningitis and bacteraemia without focus in children was estimated to be 9% (Table 1)[16], which is in line with the international literature [7,10,19]. Invasive pneumonia and bacteraemia with focus were assumed not to result in death in children [16]. 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 [9]. 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 [16]. Baseline risks for non–invasive pneumonia requiring hospital admission and for non–invasive pneumonia and acute otitis media treated in general practitioner surgeries 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)[20]. This value seems to be a conservative estimate if one takes into

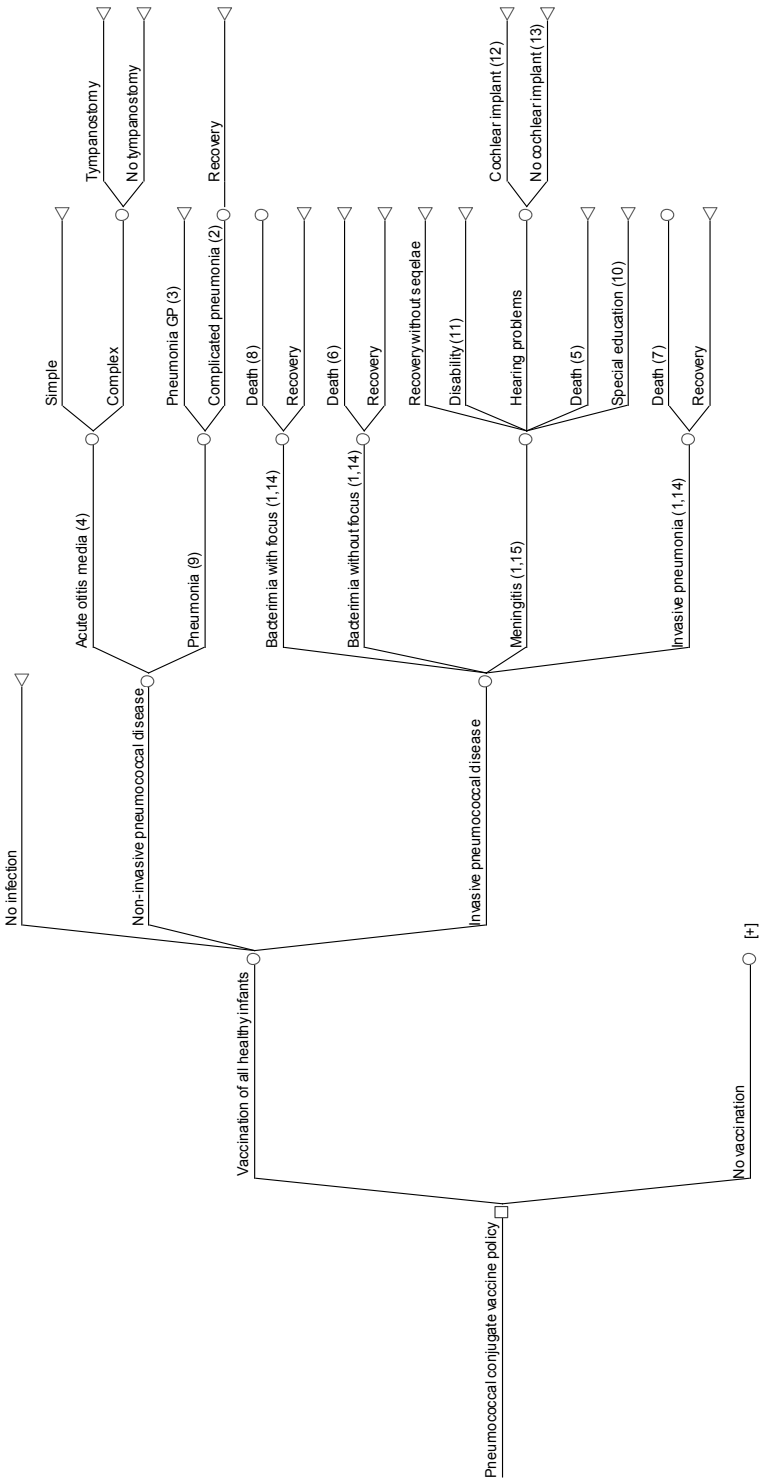

Figure 1. Decision tree used in conjunction with the cohort of 180,000 newborns. Numbers between brackets correspond to probabilities which are shown in Table 1. The "No vaccination" arm is a clone of the "Vaccination of all healthy infants" arm [as represented by the + sign; risk differ between both arms].

Table 1.= Parameters used in the economic model.

	Mean or range	Distribution	Nodes in Figure 1	References
Vaccine Efficacy				
Invasive pneumnococcal disease (all vaccine serotypes)	97.4%	Lognormal (SD 0.044)	1	20
Community–acquired pneumonia (Hospitalized)	11.1%	Lognormal (SD 0.082)	2	21
Community–acquired pneumonia (general practitioner)	6.0%	Lognormal (SD 0.032)	3	21
Acute otitis media	7.0%	Lognormal (SD 0.011)	4	22
Case–fatality ratio (birth cohort)				
Meningitis	9%	Beta (3,32)	5	18
Pneumonia	0%	N/A	N/A	18
Bacteraemia with focus	0%	N/A	N/A	18
Bacteraemia without focus	9%	Beta (2,21)	6	18
Respiratory infections	0%	N/A	N/A	Assumed
Case–fatality ratio (5 years and older)				
Meningitis	9%–92%	Beta (age dependent)	5	18
Pneumonia	0%–29%	Beta (age dependent)	7	18
Bacteraemia with focus	0%–33%	Beta (age dependent)	8	18
Bacteraemia without focus	9%–67%	Beta (age dependent)	6	18
Respiratory infections	0%	N/A	N/A	Assumed
Direct costs (€)				
Cost of hospital admission[a]	1,091–27,318	Triangular (age dependent)	1	18,23
Community–acquired pneumonia	26–2,614	Triangular (severity dependent)	9	16,23,24
Acute otitis media	17–381	Triangular (severity dependent)	4	16,23,24
Special education (annual costs)	9,798–16,962	Triangular (age dependent)	10	16
Institutional care (annual costs)	39,583	Triangular (29,687 ;39,583;49,478)	11	23
Cochlear implantation	56,633	Triangular (0; 0.004; 0.01)	12	25
Indirect costs in (€)				
Invasive pneumnococcal disease[b]	0–974	Triangular (severity dependent)	1	18,23

Table 1. continued

	Mean or range	Distribution	Nodes in Figure 1	References
Non–invasive pneumonia (hospitalized)[c]	0–2529	Triangular (severity dependent)	1	18,23
Non–invasive pneumonia (general practitioner)[b]	115–315	Triangular (severity dependent)	9	16,23
Acute otitis media[b]	58–23	Triangular (severity dependent)	4	16,23
Total QALY detriment				
Disability[c]	0.53	Beta (estimated)	11	26
bilateral hearing loss (first year)[c]	0.45	Beta (estimated)	12	7,27
Bilateral hearing loss cochlear device[c]	0.18	Beta (estimated)	12	7,27
All other hearing loss[d]	0.09	Beta (estimated)	13	26
Hospitalized bacteraemia[d]	0.0079	Beta (estimated)	14	7,28
Hospitalized meningitis	0.0232	Beta (estimated)	15	7,28
Hospitalized community–acquired pneumonia[e]	0.006	Triangular (0.001 ,0.006,0.01)	2	7
Community–acquired pneumonia treated at the general practitioner[e]	0.004	Triangular (0, 0.004,0.01)	3	7
Acute otitis media[e]	0.005	Triangular (0, 0.005,0.01)	4	7
Other parameters				
Increase in non–vaccine serotype invasive pneumococcal disease[f]	100%	Triangular (50%, 100%, 150%)	N/A	12,29[f]
Net–indirect effect for PCV10 and PCV13[g]	10%	Triangular (0%, 10%, 30%)	N/A	Assumed[g]
Discount rate health effects	1.5%	N/A	N/A	30
Discount rate costs	4%	N/A	N/A	30

[a] Based on the average duration hospitalization (both IC and general hospitalisation days) and corresponding unit costs[23]. See also Appendix Table A.2 for age specific hospitalisation costs
[D] 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.
[c] Per year.
[d] Same QALY decrement was assumed for invasive pneumonia, bacteraemia with another focus and bacteraemia without a focus.
[e] Per case.
[r] See also Appendix B Indirect effects in the analysed birth cohort.
[g] See also Appendix C. Indirect effects for those aged 5 years and older.
PCV7/10/13= 7/10/13–valent pneumococcal conjugated vaccine

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 [11,21]. Protection against invasive disease was thus estimated to last for five years in the base case analysis [21,31]. Furthermore, in randomised controlled settings, the vaccine was shown to be effective against non–invasive pneumonia and otitis media in children [21,22,32]. For non–invasive pneumonia, efficacy of pneumococcal vaccination seems to increase with diagnostic certainty [21].

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 [21].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 [21]. In two randomised studies, PCV7 was found to prevent 6.4% to 7.0% of all cases of acute otitis media [21,21,33]. 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 [22]. 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 [18,32,34].

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)[12,13]. 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 [12,13]. See Appendix 2 for a more in depth description of the assumptions for our estimation of indirect effects in the birth cohort.

Table 2. Base case 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 PCV–7, PCV–10, and PCV–13

	PCV7	PCV10	PCV13
Serotypes covered	4,6B, 9V, 14, 18C, 19F, 23F	+ 1, 5, 7F	+ 3, 6A, 19A
Increase in invasive pneumococcal disease 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 invasive pneumococcal disease 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.
[d] 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. The potential maximum was defined as full reduction of invasive pneumococcal disease cases due to vaccine serotype in the absence of any replacement. Lower percentages can be defined as a combination of decrease in vaccine serotype and increases in non–vaccine serotype invasive pneumococcal disease.
PCV7/10/13= 7/10/13–valent pneumococcal conjugated vaccine

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 [21,22,32]. 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 [12]. In this respect, net indirect effects are defined as cases of invasive disease averted by herd protection minus invasive cases of replacement disease.

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 [13,18]. 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 [34]. 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 [30].

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 [35,36], 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 [9,16]. 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)[16]. 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)[37].

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).

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.

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

Table 3. Base–case analysis results for the analysed Dutch birth cohort. The Table shows: cases, direct costs and savings, life years, QALYs, direct and indirect cost savings (related to production losses) specified for acute otitis media, community–acquired pneumonia, and invasive pneumococcal disease (between brackets the additional invasive pneumococcal disease cases, QALYs, LY, and costs are shown related to net–indirect effects for those aged 5 years and older)[a].

	acute otitis media	Non–invasive pneuminia	invasive pneumnococcal disease	Invasive pneumococcal disease related to net indirect effects for individuals aged 5 years or older[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 (€ *1000), 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 (€ *1000; direct effects)					
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 PCV–7, no net indirect effects were included into the model for individuals aged5 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

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

	PCV7 € Per QALY	PCV10 € Per QALY	PCV13 € Per 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)	NA[b]	€ 41,106	€ 31,250
Excluding herd effects in the analysed birth cohort for invasive invasive pneumnococcal disease[c]	€ 129,069	€ 57,770	€ 55,055
Including herd effects in the analysed birth cohort for non–invasive pneumnococcal disease[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.
[D] 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.[38]
[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. [39]
QALY= quality adjusted life years; PCV7/10/13= 7/10/13–valent pneumococcal conjugated vaccine; NA= Not applicable

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 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.

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 [11,35,36,40], 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

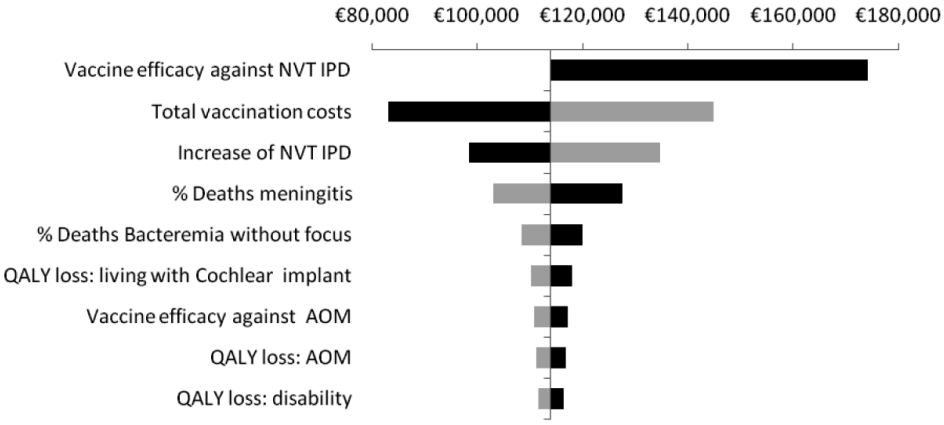

Figure 2. Sensitivity analysis assumptions on base case cost–effectiveness ratio (PCV7). Parameters were changed with 25%. Black bars show the incremental cost–effectiveness ratio for a 25% decrease for the parameter varied, while the grey bars show the incremental cost–effectiveness ratio for a 25% increase the parameters (note that this was not possible for the vaccine efficacy). IPD= invasive pneumococcal disease; AOM = acute otitis media; PCV7= 7–valent pneumococcal conjugated vaccine.

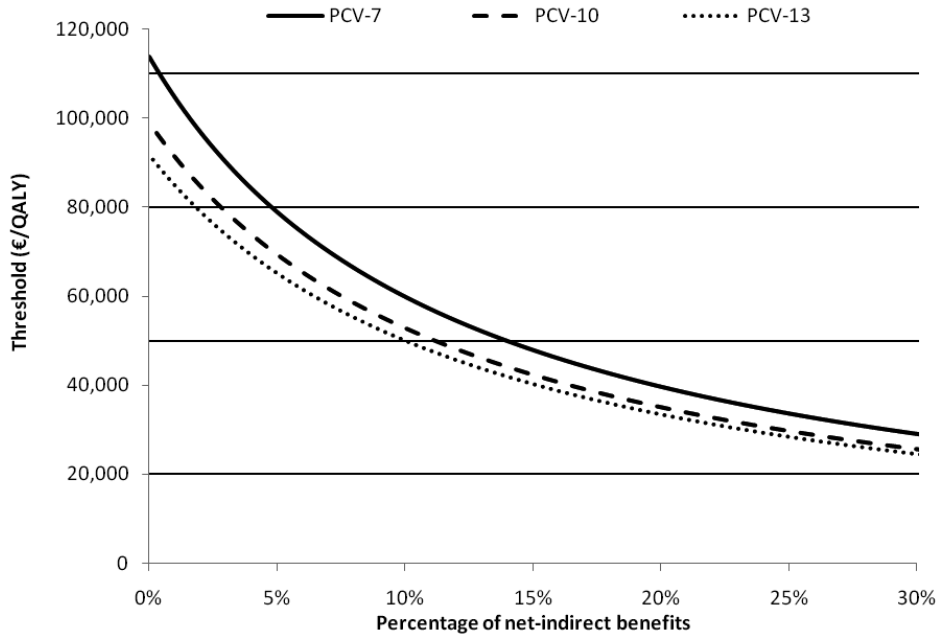

Figure 3. The effect on cost effectiveness ratios of varying the level of net indirect effect of vaccination for individuals aged 5 years or older. The horizontal dashed line shows the threshold at €50,000 per QALY. PCV7/10/13= 7/10/13–valent pneumococcal conjugated vaccine, QALY= quality adjusted life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

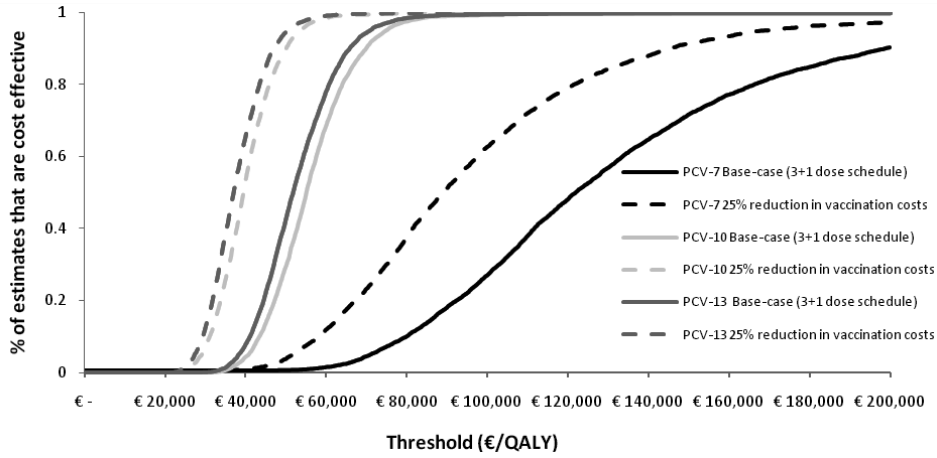

Figure 4. Cost effectiveness acceptability curves for base case vaccination schedules and for alternative scenarios for PCV7, PCV10, and PCV13. Black lines indicate acceptability curves for PCV7, grey lines for PCV10 and red lines for PCV13. PCV7/10/13= 7/10/13–valent pneumococcal conjugated vaccine

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 [12,13]. 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 [18]. 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 [12,13,18]. 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 [12]. 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 [12,13,15]. 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 [41]. 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 [42]. 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 [18,43]. 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 [43].

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 Streptococcus 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 [2-4].

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 [18]. 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 [6-10,16,19,44]. 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 [9,16].

Several recently published cost effectiveness studies included net vaccine benefits for unvaccinated adults and elderly people in their base case analysis [6,8-10,44]. These studies reported vaccination to be cost saving [6,10] or at least cost effective [8,9,44]. 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 [7,16,19]. 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 [7,16,19].

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 [45], or with other vaccines that have not yet been implemented in a national programme in the Netherlands, such as hepatitis B [46] and Varicella [47].

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 years13. 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.

APPENDICES

The appendices can be found at:
http://www.bmj.com/content/suppl/2010/06/02/bmj.c2509.DC1

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COMPETING INTEREST

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.

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chapter NINE

EFFECT OF PNEUMOCOCCAL CONJUGATE VACCINATION ON SEROTYPE-SPECIFIC CARRIAGE AND INVASIVE DISEASE IN ENGLAND: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background

We investigated the effect of the 7-valent pneumococcal conjugate vaccine (PCV7) programme in England on serotype-specific carriage and invasive disease to help understand its role in serotype replacement and predict the impact of higher valency vaccines.

Methods and findings

Nasopharyngeal swabs were taken from children,5 y old and family members (n=400) 2y after introduction of PCV7 into routine immunization programs. Proportions carrying Streptococcus pneumoniae and serotype distribution among carried isolates were compared with a similar population prior to PCV7 introduction. Serotype-specific case:carrier ratios (CCRs) were estimated using national data on invasive disease. In vaccinated children and their contacts vaccine-type (VT) carriage decreased, but was offset by an increase in non-VT carriage, with no significant overall change in carriage prevalence, odds ratio 1.06 (95% confidence interval 0.76–1.49). The lower CCRs of the replacing serotypes resulted in a net reduction in invasive disease in children. The additional serotypes covered by higher valency vaccines had low carriage but high disease prevalence. Serotype 11C emerged as predominant in carriage but caused no invasive disease whereas 8, 12F, and 22F emerged in disease but had very low carriage prevalence.

Conclusion

Because the additional serotypes included in PCV10/13 have high CCRs but low carriage prevalence, vaccinating against them is likely to significantly reduce invasive disease with less risk of serotype replacement. However, a few serotypes with high CCRs could mitigate the benefits of higher valency vaccines. Assessment of the effect of PCV on carriage as well as invasive disease should be part of enhanced surveillance activities for PCVs.

INTRODUCTION

Streptococcus pneumoniae is a bacterium that frequently colonises the human nasopharynx. Apart from disease outcomes such as sinusitis, otitis media, and community-acquired pneumonia, which result from direct spread from the nasopharynx, the pneumococcus can invade the bloodstream and cause septicaemia, meningitis, and invasive pneumonia. Most carriage episodes, however, do not result in either local or systemic disease. It is believed that the propensity to cause invasive disease in healthy individuals—termed invasiveness—is largely determined by the characteristics of the pneumococcus' polysaccharide capsule, although the explicit underlying mechanisms are yet to be identified [1,2]. On the

basis of the immune response to differences in capsular polysaccharide structure, more than 90 serotypes causing invasive disease have been described [3].

A pneumococcal conjugate vaccine (PCV7) that induces anticapsular antibodies against the seven serotypes, which at that time were responsible for most of the pneumococcal invasive disease in the United States (US), was introduced into the US childhood immunisation schedule in 2000 and the majority of the developed world subsequently. Since PCV7 is protective against invasive pneumococcal disease (IPD) [4] and carriage [5,6], the assumption of protection of the unvaccinated against vaccine type (VT) IPD through herd immunity played a major role in evaluating the likely impact and cost-effectiveness of vaccination [7]. Prevention of VT carriage, however, creates a potential ecological niche in the nasopharynx for previously less prevalent serotypes to emerge (replacement).

The extent to which the benefits of herd immunity will be offset by serotype replacement is hard to predict [8] and may vary by country depending on local factors such as differences in serotype distribution before vaccination and the population demography. Hence, there is a need for enhanced surveillance to evaluate the effect of vaccination in different epidemiological settings. Most surveillance systems focus on IPD and have shown large reductions in the numbers of VT cases in the targeted age groups, irrespective of vaccine schedule [9–11]. However, differences were observed in the indirect effect (i.e., the degree of induced herd immunity and the level of non–vaccine-type [NVT] replacement), the reasons for which remain unclear but may include vaccine coverage, time since introduction of PCV, and sensitivity of the reporting system [12].

Monitoring disease outcomes provides little insight into the underlying mechanisms that determine herd immunity and serotype replacement. For this, carriage data are essential. Carriage studies in children from Massachusetts and Norway suggest full replacement of pneumococcus in carriage after PCV7 introduction [13,14]. The implications of changes in serotypespecific carriage prevalence for expression as IPD will, however, depend on the invasiveness of individual serotypes, which is reflected by the case:carrier ratio (CCR). Invasiveness has only been studied in one of these settings and was restricted to children [15,16]. Improving our understanding of this relationship, largely determined by the invasiveness potential of the replacing NVT organisms, is essential to understanding the effect of PCV7 in different epidemiological settings.

In September 2006, PCV7 was introduced into the immunisation schedule in the United Kingdom as a 2/4/13-month routine schedule with a catch-up for children up to 2 y of age. Information on carriage in England prior to PCV7 introduction is available from a longitudinal study conducted in 2001/2002 in index children and their household members. We report here the results of a cross-sectional carriage study conducted in a demographically similar population in 2008/2009. We compare our post-PCV7 findings with the pre-PCV7 baseline both for carriage and IPD to help understand the serotype-specific effects of PCV7 on both carriage and IPD and use

this analysis to predict the potential impact of higher valency conjugate vaccines on herd immunity and replacement disease.

METHODS

Study population

Children born since 4 September 2004 and thus eligible for routine or catch-up PCV were recruited along with family members from general practices in Hertfordshire and Gloucestershire. Exclusion criteria were: moderate to severe disability, cerebral palsy, neurological disorders affecting swallowing, ear, nose, and throat disorders affecting the anatomy of the ear, or immunosuppression. The NHS National Research Ethics Service approved the study protocol. Written informed consent was obtained from adult study participants and from a parent/ guardian of study children prior to enrolment. Information was collected on participants' age, gender, household size, number of smokers in household, recent antibiotic treatment, hours in daycare and PCV7 vaccination history.

To compare to prevaccination carriage in England, we used the results from a longitudinal study carried out in 2001/2002 in families attending the same general practices in Hertfordshire in which swabs were taken each month over a 10-mo period [17]. At that time, serotype 6C could not be distinguished from 6A, but in 2009, 19 of the 122 serotype 6As from the earlier study were randomly retested, six of which were found to be 6C. We have assumed that this proportion (32%) holds for the rest of the 6A carriage isolates from the 2001/2002 study.

Specimen collection and testing

Nasopharyngeal swabs (calcium-alginate) were taken between April 2008 and November 2009 by trained nurses and placed directly in STGG broth. Samples collected at Hertfordshire were sent by same day courier to the Respiratory and Systemic Infection Laboratory at the Centre for Infections (RSIL). They were stored overnight in at 2–8uC and frozen the next morning at 280uC. Samples collected at Gloucestershire were stored locally at the Gloucester Vaccine Evaluation Unit at 280uC and transferred to RSIL in batches on dry ice. On receipt the batches were stored at 280uC. The sample then was thawed, vortexed, and 50 ml STGG broth was placed onto each of Columbia blood agar plate (HPA media services) with optochin disc (MAST) and Streptococcus- selective Columbia blood agar plate (HPA media services) and streaked out. The plates were incubated overnight at 35uC with 5% CO2. Any colonies resembling pneumococcus were subjected to normal identification methods and serotyped using the standard laboratory protocol [18].

Statistical analysis

Descriptive data analysis was performed in R 2.11.0 and Generalized Estimating Equations (GEEs) models were analysed with STATA 10.1. Exact binomial 95%

confidence intervals (CIs) were obtained for carriage rates in 2008/2009 by age group (<5, 5–20,.20 y). To account for longitudinal design in the 2001/2002 study, we computed these carriage rates using a GEE model with exchangeable correlation structure. To determine the significance of changes in carriage for individual serotypes between 2001/2002 and 2008/2009, a Fisher exact test was used because of small numbers. When comparing overall carriage as well as vaccine and NVT carriage between periods, this comparison took account of the longitudinal design of the 2001/2002 along with other covariates by using a GEE model with exchangeable correlation structure and factors for study period, age in years, gender, whether the household has a smoker, and the number of children and adults in the household. For comparability with previously reported changes in carriage, the data were stratified into two age groups (<5 and ≥5 y).

For calculating the CCR the numbers of each serotype were extracted from the national surveillance database for England and Wales [19] for the epidemiological years 2001/2002 and 2008/ 2009 and related to data from the carriage studies conducted in the same years (Table S1). CCRs were calculated using serotypespecific carriage prevalence as denominator. Ages younger than 60 y were combined in both the IPD and carriage datasets. 95% CIs were calculated on the basis of the 95% CIs of the serotypespecific carriage prevalence assuming the national incidence data on IPD to be complete and not based on a population sample [19]. For serotypes with estimates in both datasets, Spearman's rank test was used to estimate the correlation of our estimates and those obtained by Sleeman and colleagues from a paediatric pre-PCV7 carriage dataset in one region of England corrected for duration of carriage [20].

Simpson's index for diversity was calculated to assess the change in diversity in the bacterial population following vaccination [21]. Ranked serotype distribution was compared to the prevaccination distribution and CIs were obtained using the methods described by Hanage and colleagues [22]. To ensure that only a single isolate per carriage episode was included we excluded consecutive swabs with the same serotype (this included swabs of more than one sample interval apart if the individual was not sampled in between) in the 2001/2002 study on the assumption that it was carriage persisting from the previous month.

RESULTS

400 individuals were enrolled between 24 April 2008 and 9 November 2009. One participant withdrew before being swabbed and in 17 individuals swabbing had to be aborted early; these 18 participants were excluded from further analyses. The demographic features of the remaining 382 participants were similar to the participants in the 2001/2002 study, apart from the proportion of households with at least one smoker, which was lower in the more recent study (Table 1). Of 180 children eligible for catch-up or infant vaccination only four were unvaccinated.

Table 1. Overview of numbers of participants recruited, their demographic features and household (HH) structures in the 2001/02 and 2008/09 carriage studies.

	2001/02	2008/09
# Participants	488	382
# Swabs taken	3868	382
# Participants <5 years (%)	180 (37)	192 (50)
# Participants 5-20 years (%)	71 (15)	57 (15)
# Participants 20+ years (%)	237 (49)	133 (35)
# Proportion female	53.0%	56.4%
# HH	121	146
Median HH size (range)	4 (2-7)	4 (3-7)
Median # adults in HH (range)	2 (1-5)	2 (1-5)
Median # children in HH (range)	1 (1-3)	2 (1-4)
Proportion of smoke free HH	66.9%	81.0%

A pneumococcus was grown from 127 of the 382 (33.2%) swabs and a serotype determined in 123 (97%). The most prevalent serotypes were 19A (10), 23B (9), 11C (8), 15B (8), 21 (8), and 6C (8). Compared to prevaccination levels, we found a significant reduction in carriage of VTs 6B, 14, 19F, 23F, and 6A. For the remaining PCV7 types no carriage episodes of serotypes 4 and 9V were found postvaccination, but prevaccination levels were too low to detect any significant change. VT 18C was identified in three out of 382 (0.79%) swabs in 2008/2009 and in 25 out of 3,868 (0.64%) in the 2001/2002 study. NVTs 33F, 7F, 10A, 34, 15B, 31, 21, 3, 19A, 15C, and 23A significantly increased (p,0.05) in carriage with odds of 40.9, 30.8, 20.4, 20.3, 16.5, 10.2, 8.2, 6.2, 4.5, 3.6, and 3.6, respectively. A significant increase was also found in serotypes 23B, 11C, 11B, 24F, and 33A, which were only detected in the postvaccination study.

The proportion of swabs with VT and NVT serotypes according to age group in both studies is shown in Table 2. The odds ratio of VT and NVT carriage postvaccination compared to prevaccination using the GEE with binary outcome was estimated to be 0.07 95% CI (0.03–0.16) and 4.40 95% CI (3.06–6.33), respectively, with, no significant effect on overall carriage: 1.06 95% CI (0.76–1.49) (Table 3). When applying the same models to individuals younger than 5 y only, we found similar patterns. In individuals aged 5 y or older, we detected evidence for herd immunity and full serotype replacement as well (odds ratio [OR] 0.31 95% CI (0.04–2.49), 5.16 95% CI (1.95–13.66), respectively), although the reduction in VT carriage was not significant.

Simpson's index of diversity for the 2001/2002 samples was 0.908 95% CI (0.899–0.917); children: 0.891 95% CI (0.878– 0.904) and adults: 0.936 95% CI (0.926–0.947).

Table 2. Number of positive VT, NVT and All (including non-typeable) carriage isolates in 2008/09. [+]The proportion for 2001/02 was calculated accounting for multiple testing of the participants.

		NVT	VT	ALL
<5 years	Cases 08/09 (n=192)	87	7	98
	Proportion 08/09	45.3% (38.5-52.6)	3.6% (1.0-6.2)	51.0% (43.8-58.3)
	Proportion 01/02[+]	15.3% (12.7-18.3)	31.9% (28.1-36.1)	48.4% (44.1-52.7)
5-20 years	Cases 08/09 (n=57)	15	0	16
	Proportion 08/09	26.3% (15.8-38.6)	0% (0-6.4)	28.1% (17.5-40.4)
	Proportion 01/02[+]	9.1% (6.3-12.8)	9.9% (7.3-13.3)	20.6% (16.1-26.1)
>20 years	Cases 08/09 (n=133)	10	3	13
	Proportion 08/09	7.5% (3-12)	2.3% (0-5.3)	9.8% (5.3-15)
	Proportion 01/02[+]	3.3% (2.4-4.8)	4.1% (3.0-5.5)	7.6% (6.2-9.5)
All	Cases 08/09 (n=382)	112	10	127
	Proportion 08/09	29.3% (24.9-34)	2.6% (1-4.5)	31.9% (27.2-36.6)
	Proportion 01/02[+]	8.5% (7.2-9.9)	15.2% (13.2-17.4)	24.4% (21.9-27.1)

Table 3. Odds ratios for comparing 2001/02 to 2008/09 carriage using GEE.

	<5	>5	ALL
VT	0.06 (0.03-0.16) abg ***	0.31 (0.04-2.49) a***	0.07 (0.03-0.16) aeg ***, b**
NVT	4.25 (2.81-6.43) c*,g***	5.16 (1.95-13.66) ag**	4.40 (3.06-6.33) ag***, bc*
ALL	1.03 (0.70-1.51) ab***,e*	2.46 (1.04-5.83) a***, g*	1.06 (0.76-1.49) ab***,e**

Key for significant fixed effects: a (age), b (antibiotic treatment), c(smoking), d (gender), e (adults in household), f (children in household), g (study period). Significance codes: 0.05 ≥ * > 0.01 ≥ ** > 0.001 ≥ ***

It increased significantly in the 2008/2009 samples to: 0.961 95% CI (0.953– 0.969); children: 0.960 95% CI (0.949–0.971) and adults: 0.955 95% CI (0.928–0.982). Furthermore, the ranked frequency distribution of the serotypes, while similar in the prevaccination era in both children and adults in our study compared to children in Massachusetts, changed to become more distinct after vaccination (Figure 1).

Prior to its introduction, PCV7 included types responsible for similar proportions of carriage episodes (62.2%) and disease (55.9%). In 2008/2009 the additional types covered by higher valency vaccines were more prevalent in IPD than carriage, particularly the additional three in PCV10, which comprised 32.6% of IPD but only 4.7% of carried isolates (Table 4).

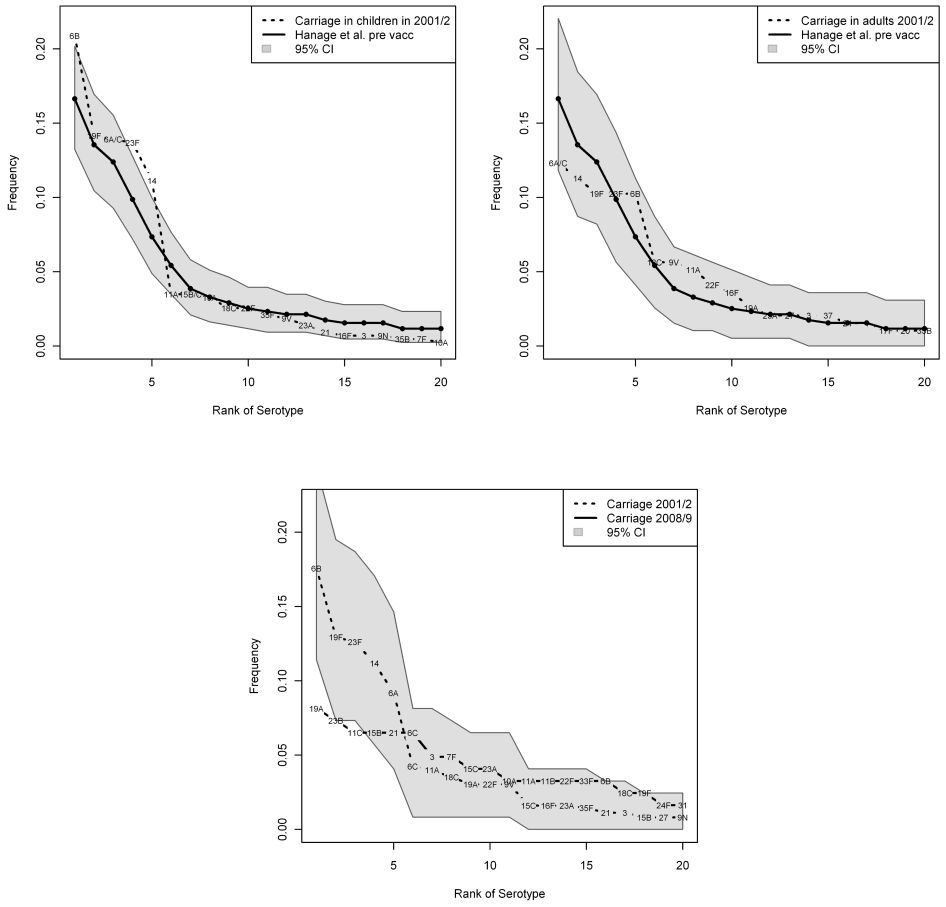

Figure 1. Top: Comparison in ranked-serotype distribution prior to vaccination in children in Massachusetts to our findings in children (left) and adults (right). For comparison with the findings with Hanage and colleagues, we aggregate 6A and 6C to 6A/C and 15B and 15C to 15B/C. Bottom: Changes in ranked serotype distribution in overall carriage in our findings from 2001/2002 to 2008/2009.

Table 4. Carriage prevalence and IPD incidence in those aged less than 60 years caused by serotypes included in PCV7, in PCV10 and not in PCV7, in PCV13 and not in PCV10 and the remaining serotypes.

	2008/09			2001/02		
	Carriage (%)		% in IPD	Carriage (%)		% in IPD
PCV7	11	(8.7)	15.2	605	(62.2)	55.9
+PCV10	6	(4.7)	32.6	2	(0.2)	10.2
+PCV13	18	(14.2)	15.8	155	(15.9)	8.9
Rest	92	(72.4)	36.4	210	(21.7)	25.0

The ranking of carried serotypes by frequency of detection in the post-PCV7 dataset and their associated CCRs as estimated from our 2008/2009 carriage prevalence data are shown in Figure 2. CCR estimates were highly correlated (p,0.001, r = 0.72) to those from Sleeman and colleagues estimated from carriage incidence [20] and allow to distinguish the more from the less invasive serotypes. From the 15 most prevalent serotypes in carriage in 2008/2009 19A, 3, 7F, and 22F stand out with a generally higher CCR. Despite their high incidence in invasive disease serotypes 1, 8, 12F, 4, and 14 (1.14, 0.58, 0.25, 0.22, 0.14 cases per 100,000 population, respectively, in under 60 y olds in 2008/2009) were not detected in carriage. On the other hand, despite being found in 2008/2009 carriage serotypes, 11C, 16A, 17A, 28F, and 33A were not found in 2008/2009 IPD at all and only caused 0, 1, 0, 1, and 0 cases, respectively, of invasive disease out of over 13,000 isolates serotyped between July 2006 and June 2009.

DISCUSSION

Our study documents the changes in carried pneumococci following the introduction of PCV7 in England and relates these to concomitant changes in disease in order to assess the invasiveness potential of the serotypes now predominating carriage. This knowledge is essential for understanding replacement pneumococcal disease and provides insight into the likely population impact of higher valency vaccines. As reported elsewhere [13,14], we found a major reduction in VT carriage in vaccinated children under 5 y, but no overall change in carriage prevalence due to replacement with NVTs. In contrast, there was an overall reduction in IPD in this age group, illustrating that the outcome of the PCV programme as expressed in IPD is determined by the invasiveness potential of the individual NVTs emerging in carriage. Overall carriage prevalence in older unvaccinated siblings and parents was somewhat higher post-PCV7 as found in parents of 2 y olds in a vaccine trial with a 2-dose or a 2+1-dose schedule in the Netherlands [23]. This finding was due to a large increase in NVT and a smaller nonsignificant reduction in VT carriage. However, IPD in these older age groups has not shown an overall increase in the UK [24], indicative of the lower overall invasiveness of the replacing NVTs.

Our study shows that PCV7 provided protection against serotypes that were highly prevalent in both disease and carriage in the UK. The additional serotypes covered by PCV10 and PCV13 are now responsible for a large proportion of invasive disease but were found relatively rarely in carriage (Table 4). While further replacement in pneumococcal carriage is likely to occur after introduction of these higher valency vaccines, our findings suggest that since most of the potential replacement types identified have lower CCRs they will cause less invasive disease. However, serotypes like 22F and especially the ones not found in carriage but present in IPD (e.g., serotype 8 and 12F) could reduce the overall benefits of higher valency vaccines. Interestingly, the three additional serotypes covered by PCV10

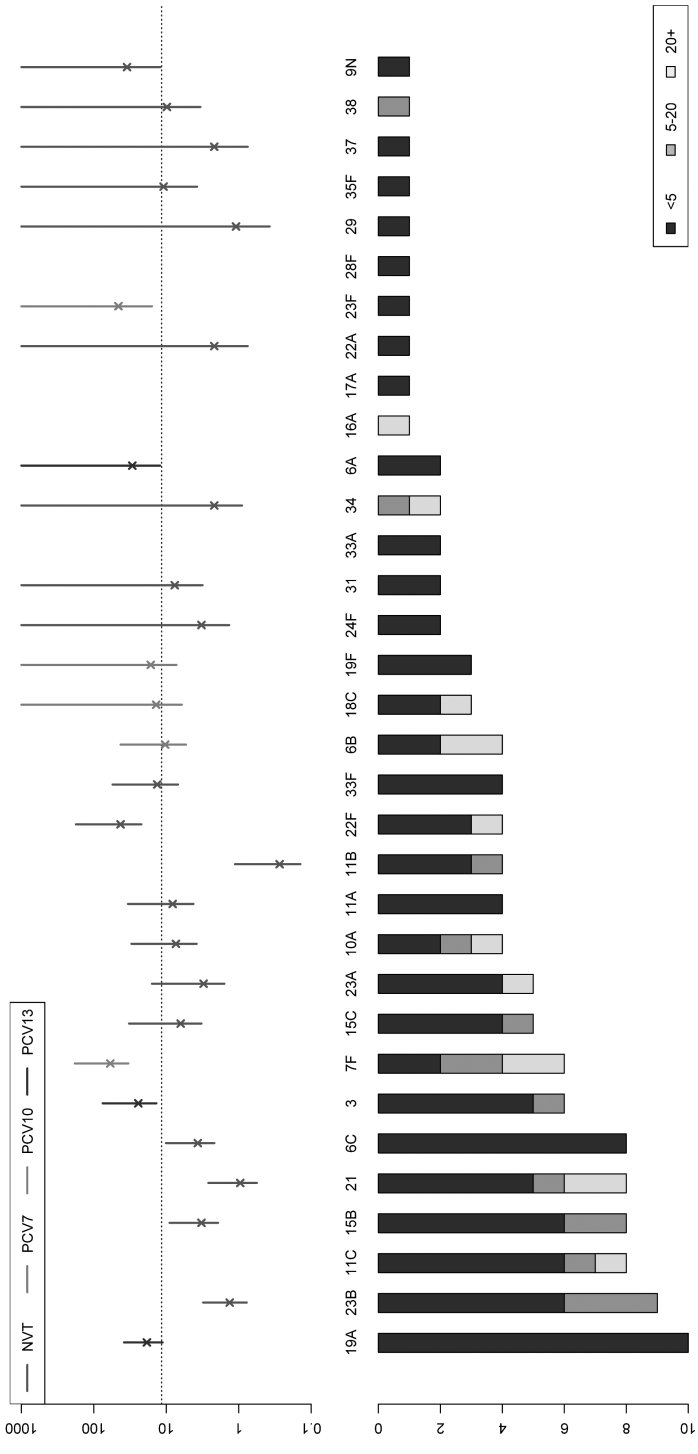

Figure 2. Age-stratified serotype distribution in carriage in 2008/2009 (below, Table S2) and CCR estimated from 2008/2009 carriage and IPD data (above, Table S1). The colour code for the CCR represents that the corresponding serotype is included in PCV7 (green), PCV10 (light blue), PCV13 (dark blue), or is a NVT (red). The dotted line corresponds to the mean CCR for these types. Serotypes 11C, 33A, 16A, 17A, and 28F, although detected in carriage were not found among disease isolates in 2008/2009.

had a very low carriage prevalence accounting for ,5% of the carried serotypes in 2008/ 2009 but.30%of IPD cases, whereas the further three serotypes in PCV13 are more similar to the PCV7 serotypes, being similarly prevalent in carriage and disease. While changing to PCV10 has therefore less potential to prevent IPD than PCV13, it may cause fewer perturbations in the nasopharyngeal pneumococcal population. Comparative carriage studies in countries using PCV10 with those using PCV13, or with different PCV coverage of prevalent serotypes before introduction, would be informative to help understand the carriage dynamics underlying serotype replacement. These studies would ideally be repeated cross-sectional studies to monitor alterations in carriage prevalence, which could be linked to changes in serotype-specific IPD in the same population. The latter requires the continued microbiological investigation of suspected cases of invasive disease, including those in fully vaccinated children, in order to document the serotype-specific changes in IPD associated with vaccine-induced changes in carriage.

The diversity of the pneumococcal carriage population in the absence of any external pressure is thought to be relatively stable [22]. If this population is challenged by vaccination with a reduction in the dominance of a few highly prevalent types, the diversity increases and the population takes time to return to the previous level of diversity. Hanage and colleagues suggested methods of assessing these changes: Simpson's index of diversity and the concept of a typical distribution for the ranked frequency of the serotypes [22]. Applying these to our prevaccination carriage data, we see similar diversity in children and slightly higher diversity in adults, although the significance of this difference was not consistent between both methods. However, we found an increase in overall diversity in 2008/2009 as well as in children and in adults (although not significant in adults), consistent with the PCV7-induced changes in the bacterial population still evolving at that time. Evidence for this can also be found in the ongoing changes in non-PCV7 IPD in 2009/2010, prior to introduction of PCV13. These show a continuing increase in the six additional serotypes covered by PCV13 but a decrease in non-PCV13 serotypes in children under 2 y compared with 2008/ 209 [25]. With the introduction of PCV13 in the UK in March 2010 [26], it will not be possible to evaluate further the longer term impact of PCV7 on carriage and IPD, but it is important to note that PCV7 may continue to have an effect and therefore not all future changes will necessarily be attributable to PCV13.

Recently developed molecular serotyping methods found up to nine times higher proportions of multiple carriage than detectable with standard WHO culturing methods [27]. Using the WHO method we identified one (0.26%) multiple carriage episode in 2008/2009 and four (0.10%) in 2001/2002. Undetected episodes of multiple carriage would result in over estimation of CCRs. However, direct comparison of molecular and conventional serotyping methods have so far only been performed on specimens from developing countries where carriage prevalence is very high [28,29]. In such settings, molecular methods might reveal more multiple carriage

episodes than in countries such as England where carriage prevalence is lower. Furthermore, there is some evidence that detecting multiple serotype carriage is likely to primarily uncover carriage episodes of serotypes previously found to be less prevalent [30]. Therefore we believe that the potential bias introduced by the WHO standard culturing methods would have little impact on our inferences from the CCR, because we focus on the serotypes more common in carriage.

Our study has some limitations. First, the earlier study had a longitudinal design while the recent study was cross-sectional. However, we accounted for multiple testing of individuals in the earlier study as well as differences in age distribution within the age groups, gender, exposure to smoke, and household size by using a GEE, which is designed to fit the parameters of a generalised linear model in the presence of unknown correlation. Second, owing to the lack of power of serotype-specific carriage data in adults, we pooled data of children and adults to derive the CCR, despite different age distributions in the samples for IPD and carriage. Previously reported CCR estimates for children and adults in England and Wales [19] using the carriage data from the earlier study are highly correlated (Figure S1), supporting our use of pooled carriage data from children and adults in the later study. Third, secular changes in serotype distribution in IPD can occur in the absence of vaccination [31], which may be due to alterations in carriage prevalence. With the cross-sectional design of the 2008/ 2009 study, we were not able to account for these. However, in England the only major secular change in the serotypes causing IPD observed over the last decade has been in serotype 1, which was not detected in either our pre- or post-PCV7 carriage studies. Fourth, invasion is thought to follow shortly after acquisition of carriage rather than being a constant risk throughout the duration of carriage [32]. Thus, a further potential limitation of our study is that we estimate CCRs using carriage prevalence rather than the incidence of new carriage episodes, the latter being derived using prevalence and carriage duration. Few data on serotype-specific duration of carriage are published, and for the serotypes newly emerging after introduction of PCV7, no information is available. Therefore, we used carriage prevalence to get an estimate of the CCRs. Where information on CCRs estimated using carriage incidence was available [20], we found a high correlation with our estimates. Furthermore, our estimates for the CCRs were consistent with those derived from 2001/2002 carriage and IPD (unpublished data), showing that this measure is stable over time. Hence we are confident that our estimates of the CCR can distinguish serotypes with lower invasiveness from those with higher invasiveness.

In conclusion, our study illustrates the value of generating carriage data in parallel with IPD surveillance data to help understand the serotype-specific changes in IPD observed in different epidemiological settings and predict the effect of higher valency vaccines. We provide evidence that the incremental benefit on IPD of the recent switch from PCV7 to PCV13 in the UK, while likely to be substantial, may be somewhat offset by increases in serotypes 8, 12F, and 22F. Such emerging

serotypes with high CCRs are potential candidates for inclusion in future conjugate vaccines. More research to elucidate the serotypespecific capsular properties [2,33] or other factors associated with carriage and invasiveness is needed in order to understand better the likely impact of future conjugate vaccines.

SUPPLEMENTARY MATERIAL

The supplementary material can be found at: http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001017

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AUTHOR CONTRIBUTIONS

Analyzed the data: SF NA. Wrote the first draft: SF AJVH EM. Wrote the manuscript: SF AJVH LS PW CS RG EM. ICMJE criteria for authorship read and met: SF AJVH LS PW CS RG EM NA. Agree with the results and conclusions: SF AJVH LS PW CS RG EM NA. Designed the study: AJVH NA EM. Oversaw the field work: LS. Database design and study data management: PW. Culture and serotyping: CS RG.

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chapter TEN

THE EFFECT OF UNDERLYING CLINICAL CONDITIONS ON THE RISK OF DEVELOPING INVASIVE PNEUMOCOCCAL DISEASE AMONG HOSPITALISED PATIENTS IN ENGLAND

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ABSTRACT

Objective

To inform national policy making on the use of the 13-valent pneumococcal vaccine among risk groups we estimated the increased risk of invasive pneumococcal disease (IPD) outcomes among clinical risk groups. Three years of post 7 valent pneumococcal conjugate vaccine (PCV7) data was included to investigate the herd protection effects.

Methods

Over 22,000 IPD patients in England (March 2002-March 2009 - aged 2 and over) were linked to their hospitalisation records. The prevalence of risk factors in these patients was compared to the prevalence of risk factors in the general population.

Results

There was an increased odds of hospitalisation (Odds ratio (OR) 11.7 2-15 years; 7.6 16-64; 2.7 65+) and death (OR 2.4 2-15 years, 3.9 16-64, 1.2 65+) from IPD among risk group. The most important risk factors that predict IPD are chronic liver disease, immunosuppression, and chronic respiratory diseases. Herd protection effects due to introduction of the 7-valent vaccine were identical in both patient groups as shown by the similar decline in the proportion of IPD caused by PCV7 serotypes in risk and non risk groups.

Conclusions

There is a marked increased risk of IPD among those with certain clinical conditions, suggesting potential benefit from a targeted vaccination approach. However, the indirect protection from conjugate vaccination of children suggests PCV vaccination of high risk groups may not provide substantial additional benefit once herd immunity takes effect.

INTRODUCTION

Development of evidence-based guidelines for the prevention of infectious disease by vaccination requires an understanding of the population groups most likely to become infected or to have severe disease or worse outcomes. Identification of high-risk groups allows a selective vaccination programme to be employed, as exemplified by the targeting of vaccination in the recent H1N1 (2009) pandemic to the most vulnerable [1,2]. The 23 valent pneumococcal polysaccharide (PPV23) vaccine has been recommended in the UK since 1992 [3] for prevention of invasive pneumococcal disease (IPD) in those with various clinical conditions considered to be at increased risk of IPD [4] though uptake has been low [3]. There is however limited evidence on the magnitude of the increased risk for these various

clinical groups by age compared with the general population. Moreover, there is little information on the degree and duration of protection from PPV23 in these targeted high-risk groups [5,6]. Pneumococcal conjugate vaccines (PCVs) that are more immunogenic than PPV23 may provide a better alternative for protection of high-risk patients [7-9]. However, they are more costly [10] and cover a lower proportion of the serotypes causing IPD than PPV23.

To help evaluate the potential utility of offering the 10-valent (PCV10) or 13-valent (PCV13) conjugate vaccine to individuals in high-risk groups, we identified patients with IPD admitted to hospital in England and compared the prevalence of risk factors in this group with that in the general population. Among the hospitalised patients with IPD we compare the case-fatality ratio and the serotype distribution before and after the introduction of PCV-7 in September 2006 and the coverage that would be achieved with higher valency vaccines for patients with high risk conditions compared to those without.

METHODS

Ascertainment of risk factors in the general population

Information on the prevalence of clinical risk factors in the general population was estimated from a Department of Health (DH) survey of the uptake of PPV23 using data extracted from 55.6% of the general practices in England, together covering 60% of the population [11-13]. Risk groups recommended for PPV23 vaccination in the Green Book (Immunisation Against Infectious Disease) [4] were identified from the diagnostic codes [14] used to record clinical conditions and medication in the electronic patient records of GP Practices. The clinical groups as extracted from the GP records are listed in table 1. Patients with any of the clinical conditions comprise the "One or more risk factors" group in Table 2. The total number of patients registered in the participating practices and the number of patients with one of the risk group diagnostic codes by individual risk and age group were extracted (age groups 2-15, 16-64 and 65 years and over). The total estimated number of people in England by risk- and age group was extrapolated based on total population estimates [15].

There are three groups that are in the Green Book risk group definitions but, due to the way the data are recorded at the GP are not included in the group with one or more risk factors. These are asthma patients on continuous or repeated steroids who have no other chronic respiratory disease code; other patients on steroids who have no other immunosuppression code; and patients with recently diagnosed malignancies (who are assumed to be receiving chemotherapy) who have no other risk factors. Those three risk groups are not included in this analysis. The number of individuals with no underlying risk factors was derived from the difference in number between the total population in the PPV23 uptake data extract and those flagged as having one or more risks.

Ascertainment of risk factors for hospitalised IPD cases

Risk factor information for hospitalised patients with IPD was obtained by linking the national dataset of laboratory confirmed IPD cases in England and Wales held by the Health Protection Agency (HPA) [16,17] with an extract from the Hospital Episode Statistics (HES) database. A laboratory confirmed case of IPD is defined as identification by culture of S.pneumoniae or (more rarely) antigen detection or polymerase chain reaction (PCR), in a normally sterile site. Identification of the same invasive serotype in the same individual within 30 days was regarded as the same episode. The national IPD data set covers all patients with IPD diagnosed by a laboratory in England and Wales. The HES data set contains clinical information on all patients in National Health Service (NHS) hospitals in England [18], this includes fifteen diagnostic fields in which the primary diagnosis and other clinical conditions of the patient are specified using the tenth revision of the International Classification of Disease coding system (ICD-10). As the HES data set is too large to use in the linkage all hospital admissions with an ICD-10 code indicating possible acute pneumococcal disease (listed in online appendix table 1) in any diagnostic field were extracted from HES between April 2002–March 2009. Linkage was based on NHS number or postcode, date of birth and sex. Underlying clinical conditions were identified using an ICD-10 code list mapped to the READ codes used in the PPV23 uptake survey (see online appendix table 2) to make sure we compared like with like. Because of the lack of medication codes in HES and the inability to identify patients with a recently diagnosed malignancy it was not possible to identify patients on steroids or chemotherapy. Patients with IPD in these groups and with no other risk group code are therefore included in the "no risk" group in line with the way patients are grouped in the PPV23 uptake survey. When multiple episodes in the HES database could be linked to a case in the national IPD dataset (based on an admission date between one week before to one month after the specimen date), diagnostic codes for all linked episodes were used. Deaths recorded in the HES dataset were considered to be related to the IPD episode if occurring within 30 days after the specimen date and were used to derive case fatality rates (CFRs) by risk group. Disease possibly related to alcoholism was assigned using ICD-10 codes from Harboe et al [19]. Linkage of the IPD and HES datasets and subsequent analysis was done in R version 2.12.0.

Statistical Analysis

The risk of being hospitalised with IPD if in a risk group compared with the risk of being hospitalised if not in any risk group was estimated by comparing the odds of being in a risk group in hospitalised IPD cases with the odds of being in a risk group in the general population (PPV23 uptake survey data). The odds ratios will approximate relative risks because IPD is a rare event. Odds ratios are calculated with 95% confidence intervals (Wald method). Although presented results are based

on the whole study period (2002-2009), outcomes were checked for significant changes before and after PCV-7 vaccination which started in September 2006.

To be able to compare the IPD in each risk group over the different age groups we estimated the incidence of IPD in the HES year April 2008 to March 2009. Incidence in specific risk groups was derived from the annual incidence for those without risk factors (estimated based on the total laboratory confirmed cases in England multiplied by the percentage of patients without risk factors divided by the mid-2008 population in England) multiplied by the odds ratio for each risk group as measured over the whole study period (2002-2009).

Comparison of mortality between those with and without underlying conditions was based on comparing the odds of death among hospitalised cases in the risk-group to the odds of death among hospitalised cases in the non-risk group.

Sensitivity analysis

To test the robustness of the results we performed a sensitivity analysis with pneumococcal labelled disease (ICD10 codes A403, B953, G001, J13 and M001) in the unmatched HES dataset. The results of the sensitivity analysis are presented in the online appendix, table 3. This sensitivity analysis showed that the odds ratios for various risk groups in the unmatched HES cases with pneumococcal code was similar to that in the HES cases that could be linked to an IPD record.

Table 1. Description of the risk groups

Asplenia/splenic dysfunction	Includes conditions such as homozygous sickle cell disease and coeliac syndrome that may lead to splenic dysfunction
Chronic Respiratory Disease	Includes chronic obstructive pulmonary disease (COPD) and chronic bronchitis, emphysema1
Chronic Heart Disease	Includes ischaemic heart disease requiring treatment, congenital heart disease, hypertension with cardiac complications, and chronic heart failure
Chronic Kidney Disease	Includes nephrotic syndrome, chronic kidney failure and kidney transplantation
Chronic Liver Disease	Includes cirrhosis, biliary atresia and chronic hepatitis
Diabetes	Includes diabetes mellitus requiring insulin or oral hypoglycaemic drugs but excludes diabetes that is diet controlled
Immunosuppression	Includes those who are immunocompromised by disease, such as HIV or leukaemia, asplenia or splenic disfunction
Cochlear Implants	Includes individuals with cochlear implants
Cerebrospinal Fluid Leaks	Includes individuals with cerebrospinal fluid leaks, following trauma or brain surgery

1 For our analysis patients with Asthma were excluded as explained in the text.

RESULTS

Prevalence of risk factors in the general population

The largest risk group in England are those with chronic heart disease, with just over 3 million patients (table 2); patients with cochlear implants was the smallest with around 3,500 patients. Overall, 13% of the general population had one or more risk factors, and 45% in those aged 65 years and over. Of the total patients in a risk group, 59% were aged 65 years and over.

Table 2. Absolute estimated number of people in risk groups as defined in the 2009 PPV23 uptake survey of registered GP patients in England, extrapolated to the population of England in 2009

Age group	2-15 years	16-64 years	65+ years	Total (2+)
Total cohort	8,373,700	33,671,300	8,434,300	50,479,300
One or more Risk factors 1	147,804 (1.8%)	2,484,329 (7.4%)	3,780,552 (44.8%)	6,412,685 (12.7%)
Asplenia/splenic dysfunction	15,418 (0.2%)	131,115 (0.4%)	49,750 (0.6%)	196,283 (0.4%)
Chronic Respiratory Disease	9,900 (0.1%)	291,953 (0.9%)	609,889 (7.2%)	911,742 (1.8%)
Chronic Heart Disease	76,817 (0.9%)	915,590 (2.7%)	2,122,437 (25.2%)	3,114,844 (6.2%)
Chronic Kidney Disease	18,554 (0.2%)	333,658 (1.0%)	1,489,390 (17.7%)	1,841,602 (3.6%)
Chronic Liver Disease	2,008 (>0.0%)	102,364 (0.3%)	36,472 (0.4%)	140,844 (0.3%)
Diabetes	15,729 (0.2%)	801,642 (2.4%)	842,319 (10.0%)	1,659,690 (3.3%)
Immunosuppression2	28,044 (0.3%)	308,803 (0.9%)	194,188 (2.3%)	531,035 (1.1%)
HIV Infection	393 (>0.00%)	11,098 (0.03%)	497 (0.01%)	11,988 (0.02%)
Bone Marrow Transplant3	598 (0.01%)	5,708 (0.02%)	965 (0.01%)	7,271 (0.01%)
Cochlear Implants	1478 (0.02%)	1,501 (>0.00%)	605 (0.01%)	3,584 (0.01%)
Cerebrospinal Fluid Leaks	2,621 (0.03%)	11,344 (0.03%)	2,844 (0.03%)	16,809 (0.03%)

1 Does not include those with asthma on steroids, other steroid users, and those with recently diagnosed malignancy.
2 This includes Patients with HIV Infection, Asplenia, or dysfunction of the spleen, malignancies affecting the immune system and Bone Marrow Transplants.
3 Bone marrow transplantation on or after 1/4/2003.

Linkage success

Of the 38,055 patients aged over 2 years in the national IPD data set in the study period, 22,298 (59%) could be linked to a HES admission in the same time period. The numbers of linked cases by age group were 1,507 aged 2-15, 9,577 aged 16-64 and 11,214 aged 65 years and over. The proportion linking increased over time, from 48% in April 2002 to March 2003 to 65% in 2008/09, which is attributed to better data completion in the fields used for linkage in the IPD dataset. No linked IPD/HES records were found for patients with cochlear implants, bone marrow transplants or cerebrospinal fluid leaks, precluding further analysis in these groups.

Risk of IPD by clinical condition and age group

Of the 22,298 patients with a linked record, 11,541 (52%) had ICD diagnostic codes indicating a risk group. The effect of having an underlying clinical condition on the risk of hospital admission for IPD was most marked in children aged 2 to 15 years, with nearly a 12 fold increase (11,7; 95% CI 10.2-13.3) in IPD in those with any of the specified conditions compared to those without (Table 3). For adults aged 16-64 years there was a 7.6 (7.3%-7.9%) fold increase and for 65+ year olds a 2.7 (2.6-2.8) fold increase. The overall IPD incidence per 100,000 in the HES year April 2008 to March 2009 was 4.8 in 2-15 yrs olds, 8.3 in 16-64 year olds and 56.7 in 65+ yrs olds. The annual incidence was substantially higher for those in a risk group; incidence in the immuncompromised and chronic liver disease groups were particularly high at around 100 per 100,000 for all age groups.

Among children aged 2-15 years, immunosuppression resulted in the highest risk with an odds ratio of 41 (35-48), increasing to 100.8 (44.7-227.2) in those with HIV. The second most important risk group in children is liver disease with an odds ratio of around 30 (15.3-57.2). Diabetes and heart disease are the least strongly related to IPD among children with an odds ratio of 3.8 (2-7.3) and 4.1 (3.1-5.5%) respectively albeit still elevated above no risk children.

In the age group 16 to 64 years, liver disease had the highest risk, with an odds ratio of 33.3 (30.7-36.1); of the 652 patients identified with chronic liver disease 477 (73%) were linked to alcoholism. The second most important risk group is immunosuppression (odds ratio 17.1 (16.0-18.3), and 61.2 (51.3-72.9) for those with HIV) and respiratory disease (16.8; 15.7-18). The risk group with the lowest odds ratio among this age group is asplenia and/or dysfunction of the spleen.

Among those aged 65 years and over the highest risk was among those with immunosuppression with an odds ratio of 11.7 (11-12.4). Among the elderly the risk group asplenics and kidney disease had odds ratios below one.

Risk of a fatal outcome by clinical condition and age group

The CFRs for those with and without underlying clinical risk conditions, and the odds of dying if in a risk group are shown in Table 4. The overall CFR increased markedly

Table 3. The observed number of cases, the odds ratio comparing the risk group to the non-risk group, and the estimated annual incidence of IPD per 100,000 in 2008/9

	2-15 years			16-64 years			65+ years		
Age group	n	Odds ratio	Incidence	n	Odds ratio	Incidence	n	Odds ratio	Incidence
No risk group	1246	1	3.9	5971	1	5.2	3542	1	17.9
One or more risk factors	261	11.7 (10.2-13.3)	46 (40-52)	3612	7.6 (7.3-7.9)	39 (38-41)	7672	2.7 (2.6-2.8)	48 (47-50)
Asplenia/splenic dysfunction	11	4.7 (2.6-8.5)	19 (10-34)	57	2.3 (1.8-3.0)	12 (9-15)	25	0.7 (0.5-1.0)	13 (9-18)
Chronic Respiratory Disease	19	12.7 (8.1-20.0)	50 (32-79)	938	16.8 (15.7-18.0)	91 (81-93)	2364	5.1 (4.8-5.4)	91 (86-97)
Chronic Heart Disease	48	4.1 (3.1-5.5)	16 (12-22)	1213	6.9 (6.5-7.4)	36 (34-38)	4841	3.0 (2.9-3.1)	54 (52-55)
Chronic Kidney Disease	33	11.7 (8.3-16.6)	46 (33-65)	417	6.5 (5.9-7.2)	34 (30-37)	971	0.9 (0.8-0.9)	16 (14-16)
Chronic Liver Disease	9	29.6 (15.3-57.2)	117 (60-226)	652	33.3 (30.7-36.1)	172 (158-186)	199	7.2 (6.2-8.3)	129 (111-149)
Diabetes	9	3.8 (2.0-7.3)	15 (8-29)	703	4.6 (4.2-5.0)	24 (22-26)	1495	2.3 (2.2-2.5)	41 (39-45)
Immunosuppression	174	41.0 (35.0-48.0)	162 (138-189)	1011	17.1 (16.0-18.3)	88 (82-94)	1728	11.7 (11.0-12.4)	209 (197-222)
HIV Infection	6	100.8 (44.7-227.2)	398 (176-896)	130	61.2 (51.3-72.9)	316 (264-376)	2	5.3 (1.3-21.3)	95 (23-381)

Table 4. Case fatality ratio (CFR) by age and risk group, and the odds ratio of a fatal outcome for those in risk groups with compared with IPD cases with no underlying clinical conditions

	2-15 years		16-64 years		65+ years	
Age group	**CFR**	**Odds ratio**	**CFR**	**Odds ratio**	**CFR**	**Odds ratio**
Overall	2.2% (1.6%-3.1%)	-	10.2% (9.7%-10.9%)	-	31.5% (30.9% - 32.6%)	-
No Risk group	1.8% (1.2%-2.7%)	1	5.4% (4.9%-6.1%)	1	29.1% (27.6%-30.6%)	1
One or more risk factors	4.2% (2.4%-7.4%)	2.5 (1.2-5.1)	18.2% (17.0%-19.5%)	3.9 (3.4-4.4)	33.0% (32.0%-34.1%)	1.2 (1.1-1.3)
Asplenia	27.3% (9.8%-56.6%)	20.9 (5.2-84.0)	10.5% (4.9%-21.1%)	2.0 (0.9-4.8)	12.0% (4.2%-30.0%)	0.3 (0.1-1.1)
Chronic Respiratory Disease	10.5% (2.9%-31.4)	6.6 (1.4-30.0)	18.3% (16.0%-20.9%)	3.9 (3.2-4.8)	32.9% (31.0%-34.8%)	1.2 (1.1-1.3)
Chronic Heart Disease	10.4% (4.5%-22.2%)	6.5 (2.3-17.9)	19.7% (17.6%-22.0%)	4.3 (3.6-5.1)	36.2% (34.8%-37.5%)	1.4 (1.3-1.5)
Chronic Kidney Disease	3.0% (0.2%-15.3%)	1.7 (0.2-13.3)	26.1% (22.2%-30.6)	6.2 (4.8-7.9)	44.0% (40.9%-47.1%)	1.9 (1.7-2.2)
Chronic Liver Disease	11.1% (0.6%-43.5%)	7.0 (0.8-58.0)	37.1% (33.5%-40.9%)	10.3 (8.4-12.5)	53.3% (46.3%-60.1%)	2.8 (2.1-3.7)
Diabetes	0% (0%-29.9%)	-	15.4% (12.9%-18.2%)	3.2 (2.5-4.0)	29.0% (26.7%-31.3%)	1.0 (0.9-1.1)
Immunosuppression	3.5% (1.6%-7.3%)	2.0 (0.8-5.0)	15.4% (13.3%-17.8%)	3.2 (2.6-3.9)	29.9% (27.8%-32.1%)	1.0 (0.9-1.2)
HIV Infection	0%	-	8.5% (4.8%-14.5%)	1.6 (0.9-3.0)	0% (0%-65.8%)	-

with age from 2.2% (1.6%-3.1%) in children to 31.5% (30.9%-32.6%) in those aged 65+ years. Within each age group, CFRs were higher for those with than those without underlying clinical conditions, with odds ratio 2.5 (1.2-5.1) in children, 3.9 (3.4-4.4) in 16 to 64 year olds and 1.2 (1.1-1.3) in the 65+ age group. The highest CFR (53.3%) was among patients with liver disease aged 65 years and over, and the lowest (1.8%; 1.2%-2.7%) among non-risk group children (apart from the diabetes and HIV groups in which no deaths were observed due to low numbers). The greatest risk of death was in asplenic patients compared to non- risk group children (odds ratio of 20.9; 5.2-84).

Effect of PCV7 on serotype distribution

Table 5 shows the proportion of IPD by year caused by the serotypes covered by PCV7 in patients over 16 years of age with and without risk factors. Consistent with the indirect (herd protection) effect of the PCV7 vaccination programme on older age groups 16, there was a progressive reduction in PCV7 serotypes which was similar in those with and without risk factors. In 2008/9, PCV10 would cover 36% (34%-38%) and PCV13 61% (58%-63%) of the remaining IPD in those in a risk group and the extra 10 serotypes in PPV23 but not in PCV13, would cover an additional 22%. The comparable proportions for those not in a risk group were 47% (44%-50%), 64% (62%-67%) and 27% respectively.

Table 5. The overall percentage of patients in a risk group by HES year (April to March) in patients aged 16 years and above, and the percentage coverage for different valency vaccines for those with and without risk factors.

	2005-2006	2006-2007	2007-2008	2008-2009
Overall percentage in a Risk group	56% (54%-58%)	54% (52%-56%)	57% (55%-58%)	58% (57%-60%)
23-valent: Non-risk	95% (93%-96%)	92% (90%-94%)	93% (92%-94%)	91% (89%-92%)
23-valent: Risk group	90% (88%-92%)	87% (86%-89%)	86% (85%-88%)	83% (82%-85%)
13-valent: Non-risk	76% (73%-79%)	77% (74%-79%)	72% (70%-75%)	64% (62%-67%)
13-valent: Risk group	73% (70%-75%)	71% (68%-73%)	66% (64%-68%)	61% (58%-63%)
10-valent: Non-risk	66% (63%-69%)	65% (62%-68%)	60% (57%-63%)	47% (44%-50%)
10-valent: Risk group	57% (54%-60%)	53% (50%-56%)	46% (44%-48%)	36% (34%-38%)
7-valent: Non-risk	40% (37%-43%)	38% (35%-41%)	31% (28%-33%)	19% (17%-21%)
7-valent: Risk group	45% (42%-48%)	41% (38%-44%)	32% (30%-35%)	21% (19%-23%)

Since the overall proportions of IPD cases in a risk group was similar before and after the introduction of PCV7, the overall reduction in IPD incidence post-PCV7 as estimated by Miller et al 17 is likely to be similar in risk and non risk groups.

DISCUSSION

Our study confirms the elevated risk of IPD in those with underlying clinical conditions for whom PPV23 vaccination is currently recommended. Both the incidence of infection and the case fatality rate are increased, especially among the immunocompromised, and those with chronic respiratory conditions or liver disease. A high proportion of the liver disease in adults (73%) was alcohol related, suggesting that life style rather than hepatic problems per se may have been implicated in the increased risk of IPD. However, risk in children with liver disease were similarly elevated. The relative low odds ratios in those with asplenia/splenic dysfunction may reflect the current policy of actively advocating immunisation and antimicrobial prophylaxis in this particular high-risk group. The effect of being in a risk group was less marked in those aged 65 years and over in whom the incidence of IPD rises sharply even in those without any predisposing conditions.

While there are a number of studies that have described the prevalence of clinical risk factors in patients with IPD, there is a paucity of data that allows quantification of the risk in terms of absolute incidence or incidence relative to that in healthy individuals. Klemets et al linked 4,365 patients with IPD in Finland with other health registries to estimate the incidence of IPD in patients aged 18+ years with various clinical conditions [20]. Among immunocompromised patients, IPD incidence varied from 33.4 to 547.2 per 100,000, broadly similar to the range we found; rates were lower in immunocompetent patients with diabetes mellitus, chronic pulmonary disease and cardiac failure, ranging from 12.0–47.1 per 100,000). However, there were no comparisons with those without such risk factors, no age stratification and no information on infecting serotype. In a case control study among children (< 18 years) in Denmark those with haematological malignancy and chronic renal disease were at particularly increased risk of IPD (52.1 and 14.4 higher respectively) broadly similar to elevated risk we found [21]. In the United States, a case control study in children aged under 5 years with IPD confirmed the greatly elevated risk for those with immunosuppression and showed that PCV7 vaccination was effective in reducing the excess risk [22].

A selective PPV23 vaccination programme targeted at those in high-risk groups was in place during our study period and by 2009 had achieved an uptake of around 12% among 2-15 year olds, 34% among 16-64 year olds and 68% among those aged 65 years and over (personal communication F. Begum, DH/HPA). The lower odds ratios for risk group patients aged 65+ years compared with younger age groups is unlikely to reflect their higher coverage with PPV23 than in other age groups, as the coverage in 65+ year olds without risk factors was similar following the extension of the PPV23

programme to all those aged 65+ years between 2003 and 2005. The proportion of disease caused by the serotypes included in PPV23 is slightly lower for the risk group patients, which might suggest a small vaccine effect. However, this difference is mainly caused by the greater contribution of serotype 1 to IPD in the non-risk group. Serotype 1 is highly invasive with a propensity to cause disease in otherwise healthy individuals, whereas serotypes with a low invasiveness potential ie prevalent in carriage but rare in disease [23], act more like opportunistic pathogens for those with underlying risk factors [24]. Those less invasive, opportunistic serotypes are less likely to be indentified for inclusion in higher valency vaccines, which is consistent with somewhat lower coverage observed among the high risk groups.

Even if the PPV23 programme targeted at high-risk individuals has reduced their risk of IPD, the incidence of disease in these groups is still greatly elevated with a disproportionately high case fatality rate, especially among children and younger adults. Immunocompromised patients, especially those that are infected with HIV, are at particularly high-risk of IPD and it is in these groups that conjugate vaccines may offer an immunological advantage [7]. However, there was a reduction in IPD caused by the serotypes covered by PCV7, indicating a herd protection effect, which was similar in those with and without risk factors. Any direct benefit of vaccinating high-risk adults with PCV10 or PCV13 which covered 36% and 61% respectively of the serotypes causing IPD in high-risk adults in 2008/9, will therefore diminish over time as these additional serotypes become eliminated from the population. PPV23 offered additional serotype coverage of 22% in 2008/9 for those in high-risk groups. The incidence of IPD caused by the 10 serotypes only in PPV23 may increase in the future depending on the extent of serotype replacement associated with PCV10 or 13 and whether the replacing serotypes are covered by PPV23.

Our study has a number of limitations. Firstly, we relied on different data sets to identify the proportion of IPD cases and the general population with risk factors. For the IPD cases we relied on relevant clinical conditions being recorded in one of the discharge diagnosis fields which may be more incomplete than in the GP records which were used for the denominator population. Failure to identify IPD cases in high-risk patients with their consequent inclusion in the "no risk" group would result in underestimation of the odds ratio. Similarly, inclusion of patients on steroids or with recent malignancies in the "no risk" denominator for the general population will tend to reduce odds ratios. Our estimates are therefore likely to be conservative. Secondly, non-matching HES admissions with specific pneumococcal codes were not included in the main analysis. Sensitivity analysis using only pneumococcal ICD codes revealed similar odds ratios (online appendix table 3) suggesting no major bias as a result of the incomplete matching of IPD cases with HES admissions. Thirdly, there were no HES codes that allowed the identification of asthmatic or other patients on steroids or those a recently diagnosed malignancy who are likely to be immunosuppressed from chemotherapy, precluding any estimates of the risk of IPD in these specific patient

groups. For those on chemotherapy, it seems reasonable to assume that their risk is similar to that of other immunosuppressed patients – an assumption that is supported, at least in children, by the Danish and US case control studies [21, 22]. Other studies have reported a doubling of the risk of IPD in asthma patients, with the highest rates in those with more severe disease requiring medication or frequent hospital admission [25, 26]. A fourth limitation of our study is that the prevalence of risk factors in the general population was based on data obtained in 2009 whereas the risk factor data for IPD cases was an average over the period 2002 to 2009. A few groups showed a minimum two fold change in odds ratios over time, for example, HIV patients who showed a change in odds ratio from 176.9 (72.7-430.4) between 2002-2005 to 32.02 (4.5-228.0) between 2006-2009. This may be associated with the increasing use of highly active anti-retroviral therapy, which reduces the risk of IPD, though it remains around 10 fold higher in treated HIV patients than in the general population as shown in a recent HPA study [27]. In that study, which linked IPD cases with the national HIV database, the risk of IPD in HIV positive adults aged 15-44 years was found to be around 50 times higher than in the general population. These elevated risks are close to the 61.2 odds ratio found in our study by an independent method. Finally we did not investigate the risk associated with having more than one co-morbidity, which is the situation for some patients. The odds ratios shown for individual risk conditions may therefore be elevated by the existence of associated co-morbidities.

It has been suggested that part of the increased risk of IPD in patients with underlying disease may be the result of a lower threshold for hospital admission of such patients rather than just a greater incidence or severity of disease [28]. This is supported by the Danish study that showed that patients with chronic conditions that required frequent hospital visits were also at increased risk of admission for an episode of IPD [21]. Even if part of the elevated risk is due to a greater propensity to investigate and admit patients with underlying conditions, the resultant health care costs associated with the admission are nevertheless the same, irrespective of the reason for admission. Moreover, the outcome of infection, as measured by the case fatality rate, was higher in patients with underlying conditions.

In conclusion, our study has shown a marked increased risk of IPD and of a fatal outcome in patients with various clinical conditions. It provides an evidence base for the targeted vaccination approach with PPV23 adopted by many countries, or if an age based vaccination approach is adopted, that evaluating the coverage among risk groups is key. Quantification of the increased risk allows an assessment of the cost effectiveness of offering the potentially more effective conjugate vaccines to these high-risk individuals. However, any such assessment needs to take account of likely future changes resulting from the introduction of PCV10 or 13 vaccination programmes for children on the pneumococcal serotypes causing IPD in the general population and in high-risk groups, as our study shows that the herd protection benefits from PCV occur similarly in high risk and healthy individuals.

APPENDICES AND ONLINE MATERIAL

The appendices and online material can be found at: http://www.sciencedirect.com/science/article/pii/S0163445312000473

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CONFLICT OF INTEREST

AJvH, no conflict; NA, no conflict; PAW, no conflict; JS, no conflict; PG, no conflict; RG, has received assistance to attend scientific meetings from Wyeth (Pfizer) and GlaxoSmithKline, and his laboratory has received research funding from Wyeth (Pfizer) and GlaxoSmithKline; EM, no conflict.

ETHICAL APPROVAL

The Health Protection Agency has approval under PIAG Section 60 of the Health and Social Care Act 2001(now subsumed into the National Information Governance Board for Health and Social Care with Section 60, now Section 251 of the NHS Act 2006) to process confidential patient information for the purposes of monitoring the efficacy and safety of vaccination programmes.

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chapter ELEVEN

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 using the 13 valent pneumococcal conjugate vaccine. 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 invasive pneumococcal disease due to chronic kidney disease; splenic dysfunction; HIV infection; a compromised immune system; chronic heart, liver, or respiratory disease; or diabetes. Main outcome measures Costs, gains in life years and quality adjusted life years (QALYs), and incremental cost effectiveness ratios.

Results

Increasing indirect protection resulting from the vaccination programme of infants using the 13 valent pneumococcal conjugate vaccine 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 incremental cost effectiveness ratio 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 13 valent pneumococcal conjugate vaccination 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 13 valent pneumococcal conjugate vaccine 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 and related mortality [1]. To prevent disease among these high risk groups many countries recommend vaccination with the 23 valent polysaccharide vaccine, 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 [2,3]. The use of conjugated pneumococcal vaccines could potentially overcome the limitations of the 23 valent polysaccharide vaccine. In children the seven valent pneumococcal conjugate vaccine has been shown to be highly effective in preventing invasive pneumococcal disease caused by vaccine related serotypes [4]. 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 [3]. The limited data on efficacy that are available suggest that pneumococcal conjugate vaccines are effective in preventing invasive pneumococcal disease (and possibly pneumonia) in adults and children infected with HIV, a group in whom the 23 valent polysaccharide vaccine is ineffective [5,6]. 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 seven valent pneumococcal conjugate vaccine in the infant immunisation programme led to a dramatic decline in incidence of invasive pneumococcal disease due to vaccine serotypes in all age groups (including those in risk groups)[7]. However, these decreases were partly offset by a simultaneous increase in disease caused by non-vaccine serotypes, reducing the impact on overall invasive pneumococcal disease [8].

In the infant programme in the United Kingdom, as elsewhere, the seven valent pneumococcal conjugate vaccine has recently been replaced by the 13 valent pneumococcal conjugate vaccine. 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 seven valent pneumococcal conjugate vaccine 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 the 13 valent pneumococcal conjugate vaccine 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 the 13 valent pneumococcal conjugate vaccine, taking into account that herd benefits of the current infant 13 valent pneumococcal conjugate vaccine 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 the 13 valent pneumococcal conjugate vaccine on top of the current risk based vaccination programme with the 23 valent polysaccharide vaccine. This was done because the existing programme with the 23 valent polysaccharide vaccine is likely be continued despite the potential introduction of a risk based programme using the 13 valent pneumococcal conjugate vaccine. In addition our risk estimates for pneumococcal disease were estimated in the current situation in which a risk based programme using the 23 valent polysaccharide vaccine is already in place (albeit with a low uptake of vaccination).

As infants are already vaccinated with the 13 valent pneumococcal conjugate vaccine, 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 the 13 valent pneumococcal conjugate vaccine. Groups included in this analysis were based on a recent study among patients admitted to hospital in England with culture confirmed invasive pneumococcal disease, which compared the prevalence of clinical risk factors in the general population with that in patients admitted to hospital with invasive pneumococcal disease [7]. 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 invasive pneumococcal disease laboratory held at the Health Protection Agency [7].

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 [7].

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 invasive pneumococcal disease over the full lifetime of the participants in each cohort—that is, until death or 100 years.

Incidence of invasive pneumococcal disease 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 invasive pneumococcal disease 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) [8]. These incidences were subsequently used to estimate the incidence of invasive pneumococcal disease 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 invasive pneumococcal disease [7]. From the same databases we estimated the age specific share of meningitis and empyema to the total invasive pneumococcal disease 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 invasive pneumococcal disease from this same study [7].

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 [9]. 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 the 13 valent pneumococcal conjugate vaccine on non-bacteraemic pneumococcal pneumonia in the base case we looked at the impact of the seven valent pneumococcal conjugate vaccine 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 in supplementary file) as used for invasive pneumococcal disease, 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 the seven valent pneumococcal conjugate vaccine, whereas the incidence in high risk children of the same age was not significantly reduced (see appendix 1 in supplementary file). 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 [10,11]. 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 invasive pneumococcal disease.

Indirect effects

In virtually all countries the introduction of the seven valent pneumococcal conjugate vaccine was followed by a large reduction in invasive pneumococcal disease 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 invasive pneumococcal disease due to non-vaccine serotypes [4]. This was also the case in the United Kingdom in which the seven valent pneumococcal conjugate vaccine 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 [8]. In April 2010, the 13 valent pneumococcal conjugate vaccine replaced the seven valent vaccine in the infant vaccination programme.

To predict the future decrease in invasive pneumococcal disease due to vaccine serotypes in unvaccinated age groups, we divided the serotypes into those covered by the seven valent vaccine and those included in the 13 valent vaccine but not in the seven valent pneumococcal conjugate vaccine. 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 the seven valent vaccine. 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 invasive pneumococcal disease due to the vaccine serotypes (see appendix 2 in supplementary file).

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 the 13 valent vaccine—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 the seven valent vaccine after the introduction of the routine infant vaccination programme using the seven valent pneumococcal conjugate vaccine in 2006 [7]. The only difference was that we delayed the herd effects for the six additional serotypes in the 13 valent vaccine by one year as the introduction of the vaccination programme using the 13 valent

pneumococcal conjugate vaccine 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 vaccination programme using the 13 valent pneumococcal conjugate vaccine [12]. Furthermore, in the Netherlands, where the vaccination programme using the seven valent pneumococcal conjugate vaccine was launched without a catch-up, herd effects were not observed in the first year after implementation in contrast with the United Kingdom [13].

We did not include serotype replacement effect in the model as we assumed that it would not affect the incremental cost effectiveness ratio because changes in invasive pneumococcal disease 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 the seven valent vaccine 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 [3]. Data on the efficacy of the 13 valent pneumococcal conjugate vaccine is limited [12]; 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 [14] (see appendix 3 in supplementary file 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 [15]. The objectives of the elicitation were to estimate the efficacy of the 13 valent pneumococcal conjugate vaccine (against invasive pneumococcal disease 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 the 13 valent pneumococcal conjugate vaccine seems to be ineffective against invasive pneumococcal disease caused by this serotype [16]. 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 in the supplementary file. Briefly, we asked five members of the Pneumococcal Subcommittee of the Joint Committee on Vaccination and Immunisation to give an estimate for the efficacy of the 13 valent pneumococcal conjugate vaccine in risk groups based on the available efficacy data for the seven valent pneumococcal conjugate vaccine and immunogenicity data for both the seven valent and the 13 valent pneumococcal conjugate vaccines. We used the estimates to create distributions for vaccine effectiveness using the Sheffield elicitation framework [15]. 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 [17,18], 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 in supplementary file). We also calculated the mortality for non-risk groups and validated these against life tables from the Office for National Statistics [19]. In addition to life years gained we also calculated QALYs gained by vaccination. For patients admitted to hospital for invasive pneumococcal disease, we used losses in QALYs of 0.0079 per case for bacteraemia and 0.0232 per case for meningitis [20]. We assumed that non-bacteraemic pneumococcal pneumonia resulted in a QALY loss of 0.006 per case [21]. 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 [22] (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 [23]. 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 invasive pneumococcal disease. 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 invasive pneumococcal disease episode was the main cause for admission to hospital—defined as those patients who had a primary diagnostic code related to an invasive pneumococcal disease code (see appendix 6 in supplementary file). Table 1 displays the costs and probabilities related to invasive pneumococcal disease. 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 [24].

The total cost per dose of 13 valent pneumococcal conjugate vaccine was estimated at £56.61, consisting of the price of the vaccine (£49.10) and administration costs (£7.51).

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 incremental cost effectiveness ratio.

In specific scenario analyses we explored the impact of changes in vaccine efficacy, vaccine waning, delaying the herd effect of the infant vaccination programme using the 13 valent pneumococcal conjugate vaccine, 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 invasive pneumococcal disease 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 incremental cost effectiveness ratio 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 [25]. In the analyses we compared the possible impact of vaccination using the 13 valent pneumococcal conjugate vaccine 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 the 23 valent polysaccharide vaccine[26]; however, uptake of the vaccine is relatively low, especially in those aged less than 65 years (see appendix 7 in supplementary file) [7]. We assumed that the 13 valent pneumococcal conjugate vaccine, would be used in addition to the 23 valent polysaccharide vaccine.

Finally, we assumed that the uptake of the 13 valent pneumococcal conjugate vaccine 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 [27] and that vaccination with the 13 valent pneumococcal conjugate vaccine would be offered irrespective of previous vaccination with the 23 valent polysaccharide vaccine.

RESULTS

Incidence of invasive pneumococcal disease, vaccine efficacy, indirect effects, and life expectancy

Among high risk groups the highest incidence of invasive pneumococcal disease was in young people infected with HIV and the lowest in those with chronic heart disease, diabetes, or splenic dysfunction (see appendix 8 in supplementary file for estimated incidence of invasive pneumococcal disease 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 invasive pneumococcal disease. Appendix 2 in the supplementary file presents the Poisson regression for invasive pneumococcal disease due to vaccine serotypes after the introduction of the seven valent pneumococcal conjugate vaccine. Finally, appendix 5 in the supplementary file 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 vaccination programme using the 13 valent pneumococcal conjugate vaccine, the model predicts that from 2012-13 to 2020-21 about 1333 cases of invasive pneumococcal disease due to vaccine serotypes would occur in people at high risk (table 2). This corresponds to a total loss of about 5900 life years or 6200 QALYs (undiscounted). The herd impact of the infant vaccination programme using the 13 valent pneumococcal conjugate vaccine is large; preventing an additional 6200 invasive pneumococcal disease cases due to vaccine serotypes corresponding to an additional 30 400 QALYs lost compared with a continuing infant vaccination programme using the seven valent pneumococcal conjugate vaccine.

Impact on budgets

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%

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	[7], see methods
Case fatality ratio†	Age and risk group dependent†	β	[7], 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]	[9]
Mild hearing loss	0.21	β [mean 0.21 SE 0.02]	[9]
Seizures and hydrocephalus	0.07	β [mean 0.07 SE 0.02]	[9]

Table 1. continued

Variables	Expected value	Distribution	Reference
Spasticity or paresis	0.09	β (mean 0.09 SE 0.01)	[9]
Cranial nerve palsy	0.12	β (mean 0.12 SE 0.04)	[9]
Quality adjusted life year losses			
Hospital admission for meningitis	0.023	β (mean 0.023 SE 0.031)	[21], [20]
Hospital admission for bacteraemia¶	0.0079	β (mean 0.079 SE 0.083)	[21]
Hospital admission for non–bacteraemic pneumonia	0.006	Normal (mean 0.006 SD 0.0015)	[21],[20]
Quality of life weights			
Deafness	0.81	β (mean 0.81 SE 0. 028)	[22]
Mild hearing loss	0.91	β (mean 0.91 SE 0.015)	[22]
Seizures	0.83	β (mean 0.83 SE 0.015)	[22]
Hydrocephalus	0.62	β (mean 0.62 SE 0.021)	[22]
Spasticity or paresis	0.67	β (mean 0.67 SE 0.023)	[22]
Cranial nerve palsy	0.67	β (mean 0.67 SE 0.023)	[22]
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)	[24]
In subsequent years	203	Log normal (mean 8.7 SD 0.4)	[24]
Outpatient follow–up for meningitis	382	Log normal (mean 5.2 SD 0.4)	[24]

Table 1. continued

Variables	Expected value	Distribution	Reference
Cost of PCV13	49.10	Fixed	[42]
Administration costs	7.51	Fixed	[42]
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	25

*Odds ratio of IPD comparing risk groups to non–risk groups. Specific odds ratios can be found in Van Hoek et al.[7]
†Age specific case fatality ratios can be found in Van Hoek et al.[7]
‡After single dose during first year of vaccination. Efficacy estimates do not apply for serotype 3 (see method section) [16]. 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.

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.

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

	Assumed uptake*		
Risk group	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 ≥65 years [27]. 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 ≥65 years). See Appendix 7.

uptake) and the impact assuming the same annual coverage as for the 23 valent polysaccharide vaccine (see appendix 7 in supplementary file). If coverage is no higher than that achieved by the 23 valent vaccine, then the impact on budgets would be much reduced, as this programme only achieves poor levels of uptake.

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,25 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 incremental cost effectiveness ratio of £61,200 per QALY gained. Vaccinating all other at risk groups would not be considered cost effective, with an incremental cost effectiveness ratio 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 (incremental cost effectiveness ratio of ≤£30,000 per QALY). Figure 1 shows the impact of time on the incremental cost effectiveness ratio for the years 2009-10 up to 2015-16.

Sensitivity analyses

Table 4 shows the impact on the incremental cost effectiveness ratio of assuming an overall impact on non-bacteraemic pneumonia. If included, even vaccinating the whole group at increased risk of invasive pneumococcal disease might be considered cost effective, with an incremental cost effectiveness ratio 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.

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 incremental cost effectiveness ratios. 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. Other important factors were the price of the vaccine, the risk and age group specific incidence, and the case fatality ratio. Also, the scenario

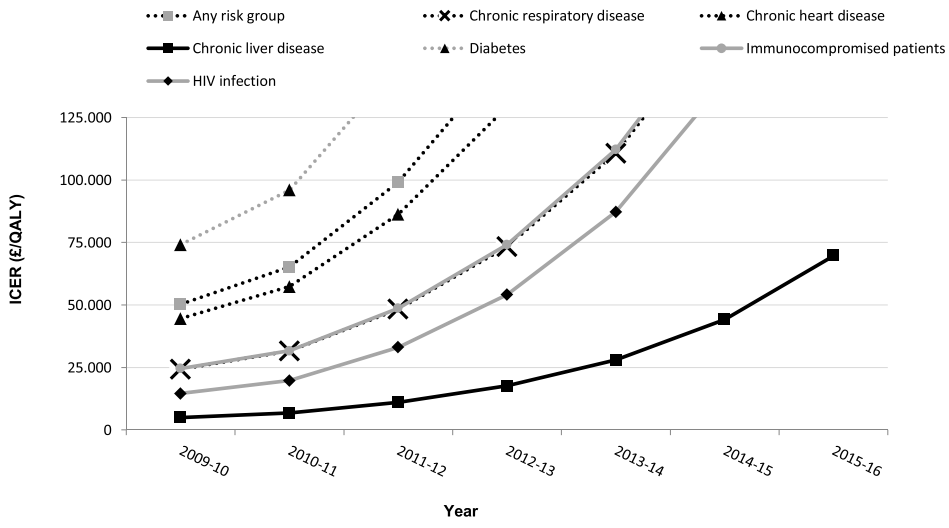


Figure 1. Impact of time on incremental cost effectiveness ratio. QALY=quality adjusted life year

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

	ICER (£/QALY)	
Risk group	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.

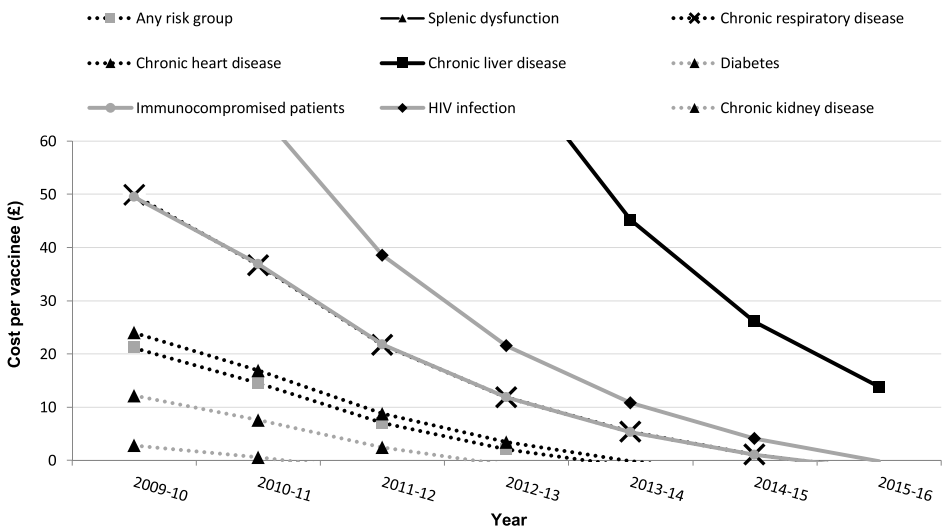


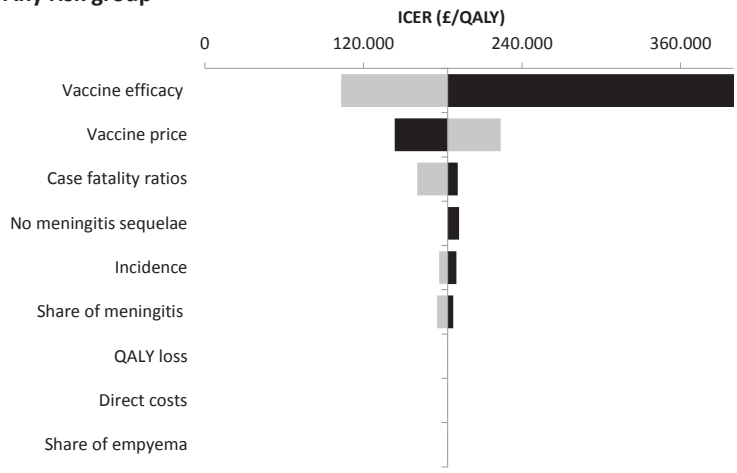
Figure 2. Maximum costs per vaccinee (including costs of vaccine and administration) to consider risk group vaccination cost effective (incremental cost effectiveness ratio of ≤£30 000 per quality adjusted life year)

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.

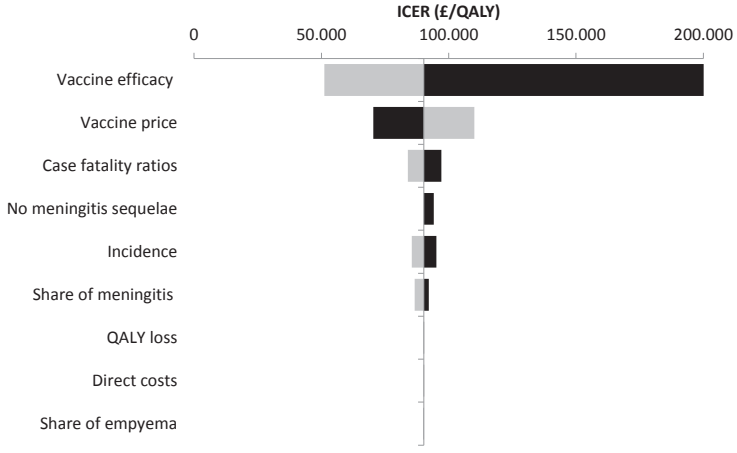
Variables	Any risk group	Chronic respiratory disease	Chronic liver disease	Immunocompromised	HIV infected
Base case	183,680	90,243	20,324	90,720	61,239
No herd effects due to any serotypes in PCV13 *	37,687	18,061	2848	20,059	10,059
No herd effects due to six additional serotypes in PCV13 †	46,903	22,715	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.

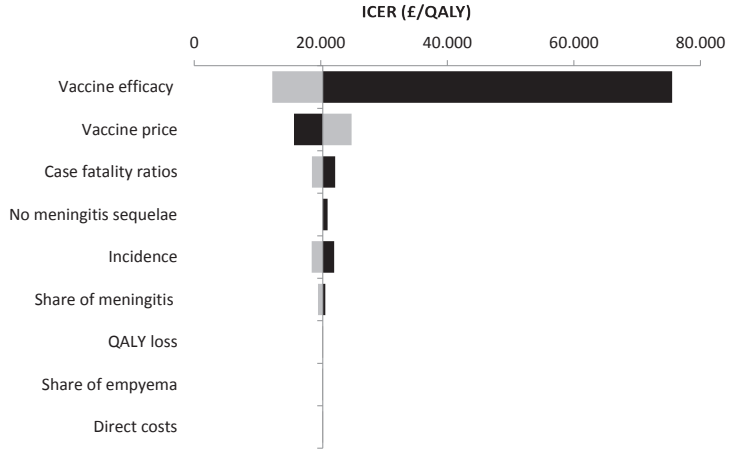
a) **Any risk group**



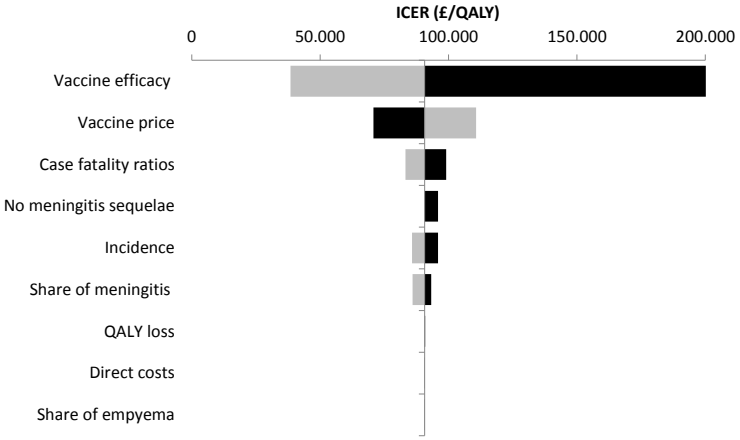
b) **Chronic respiratory disease**



c) **Chronic liver disease**



d) **Immunocompromised patients**



e) **HIV infection**

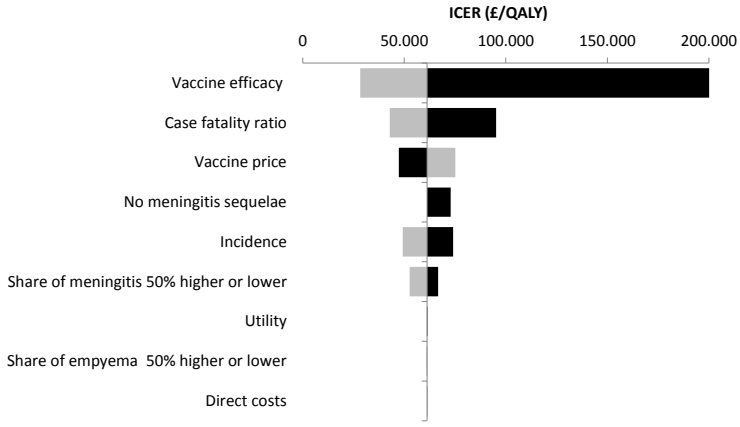


Figure 3. Univariate sensitivity analysis for any at risk group. Variables were changed over their 5% and 95% quantiles, with exception of share of meningitis and empyema, which were varied by 50%. Incidence was altered by varying odds of invasive pneumococcal disease in those with risk factors compared 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. QALY=quality adjusted life year

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 incremental cost effectiveness ratio 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.

DISCUSSION

Although the herd effects of the infant vaccination programme using the 13 valent pneumococcal conjugate vaccine will in time indirectly protect people at high risk, the burden of preventable pneumococcal disease will remain high during the first years after the introduction of the vaccination programme. Vaccinating all groups at high risk of invasive pneumococcal disease with the 13 valent pneumococcal conjugate

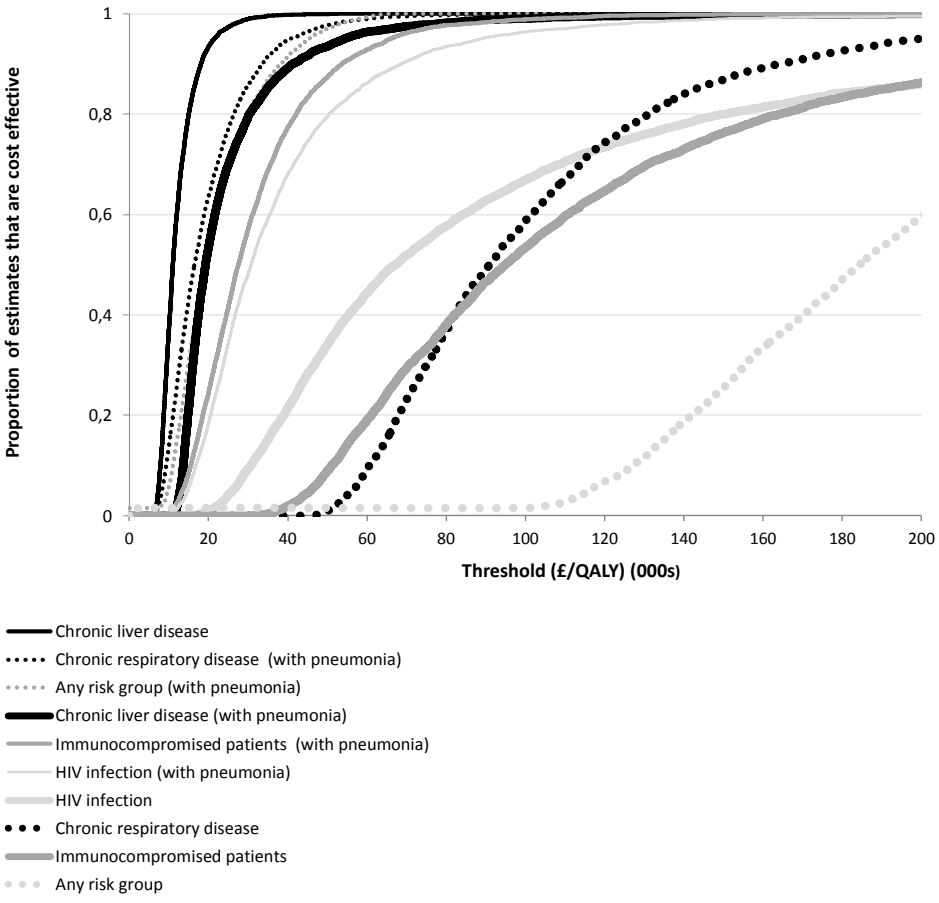


Figure 4. Results of probabilistic sensitivity analysis.

vaccine 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 the 13 valent pneumococcal conjugate vaccine 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 [28] 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 the 13 valent pneumococcal conjugate vaccine. 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 [18,29]. 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 seven valent pneumococcal conjugate vaccine. Nevertheless, the herd effect for the six additional serotypes in the 13 valent pneumococcal conjugate vaccine might be different from those in the seven valent vaccine owing to differences in carriage, transmissibility, and the potential to cause disease [30,31]. 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 invasive pneumococcal disease due to serotypes in the seven valent pneumococcal conjugate vaccine.7 However, as the less invasive serotypes primarily affect people at high risk and the additional serotypes included in the 13 valent pneumococcal conjugate vaccine are the more invasive, people at high risk might benefit less from herd effects compared with healthy people [32]. 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 invasive pneumococcal disease 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 seven valent pneumococcal conjugate vaccine, 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 [33,34]. We do, however, also note that the effect of being in an at risk group on increasing the risk of invasive pneumococcal disease is more noticeable in children than in adults [7], which might mean that our assumption of lack of a direct effect of the 13 valent pneumococcal conjugate vaccine on non-bacteraemic pneumonia in adults may be conservative [5], yet consistent with the BMJ guidelines for economic evaluations [7,35]

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 invasive pneumococcal disease 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 incremental cost effectiveness ratios. 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 [36]. This caused a noticeable increase in invasive pneumococcal disease in the age groups with the highest incidence of H1N1 infection [36], and, given the overlap between the risk groups for influenza and invasive pneumococcal disease, selective vaccination of high risk groups with the 13 valent pneumococcal conjugate vaccine might help mitigate the effects of future increases in such viral infections.

Comparison with other studies

This is the first cost effectiveness analysis of the 13 valent pneumococcal conjugate vaccine focusing specifically on people at increased risk for invasive pneumococcal disease. As far as we know, two other studies have focused on the cost effectiveness of vaccinating non-infant populations [33,34]. A main difference is that these studies focused on older adults (>50 years [34] and 65 [33] years), 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 in unlikely to be considered cost effective. The main driver for this difference is that in the base case analysis we assumed that the 13 valent pneumococcal conjugate vaccine would not have an overall impact on non-bacteraemic pneumonia. This difference was further driven by the assumption that vaccine would not be effective against serotype 3, as early data from England and Wales suggests that this component of the 13 valent vaccine does not seem to provide direct protection to vaccinated people [16]. 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 invasive pneumococcal disease 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 [8].

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 the 13 valent pneumococcal conjugate vaccine programme based on risk group 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 the seven valent pneumococcal conjugate vaccine with the 13 valent vaccine, herd effects are likely to decrease the burden of preventable pneumococcal disease over time rendering any additional preventive efforts less cost effective. If the 13 valent vaccine 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 the 13 valent vaccine 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 [28]. 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 vaccination programme using the 13 valent pneumococcal conjugate vaccine 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 [37]. 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 the 13 valent pneumococcal conjugate vaccine around the same time and have a similar uptake of vaccination. Some European countries are, however, already recommending the 13 valent pneumococcal conjugate vaccine for at risk groups or adults. For example, in Austria and Greece the 13 valent pneumococcal conjugate vaccine is recommended for those aged 50 and older [38,39], whereas in France, parts of Germany, and Italy the vaccine is being recommended for (specific) risk groups [40,41].

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 vaccination programme using the 13 valent pneumococcal conjugate vaccine.

APPENDICES AND SUPPLEMENTARY MATERIAL

The appendices and supplementary material can be found at: http://www.bmj.com/content/345/bmj.e6879?view=long&pmid=23103369

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CONTRIBUTORS

JE and EM designed the study. MHR, AJvH, and JE designed the computer model and carried out the computer simulations and analysis. MH, AJvH, and CT carried out the data analyses under the supervision of EM and JE. DF was responsible for the analysis of the Royal College of General Practitioners data that provided the survival curves by risk groups. MHR, EM, and JE drafted the manuscript. All authors commented on drafts of the manuscript and contributed to the final version. MHR and JE are guarantors of the study.

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chapter TWELVE

EFFECT OF SEROTYPE ON FOCUS AND MORTALITY OF INVASIVE PNEUMOCOCCAL DISEASE; COVERAGE OF DIFFERENT VACCINES AND INSIGHT INTO NON-VACCINE SEROTYPES

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ABSTRACT

Background

Differences in pathogenicity between pneumococcal serotypes are important when assessing the potential benefit of different valency vaccines. We investigated the effect of serotype on clinical presentation, outcome and quality of life lost from invasive pneumococcal disease (IPD) in the context of the 7, 10 and 13 valent pneumococcal conjugate vaccines (PCV7, PCV10, PCV13).

Method

Serotyped IPD cases in England were linked to the national dataset of hospital admissions for April 2002 to March 2011. Based on patients' diagnostic codes and vital status at the end of the admission, disease focus (meningitis, empyema, sepsis or respiratory disease) and case fatality rates by serotype and age group (5, 5-64 and 65 years and over) were obtained. Using these data the quality adjusted life years (QALY) lost from the IPD remaining when use of PCV7 stopped in 2010 was estimated for the serotypes covered by higher valency vaccines.

Results

The linked dataset contained 23,688 cases with information on diagnosis, mortality and serotype. There were significant differences between serotypes in the propensity to cause meningitis, death and QALY loss in each of the investigated age groups. As a result, vaccines' coverage of disease burden differed by endpoint. For example, in children under 5 years in 2009/10, PCV10 covered 39% of meningitis, 19% of deaths and 28% of the QALY loss of attributable to IPD, whereas the respective percentages for PCV13 were 65%, 67% and 66%. The highest QALY loss per serotype in this age group was for 6A. Non-PCV serotypes causing the highest QALY loss were 22F and 33F in < 5 year olds and 31 in older individuals.

Conclusion

Marked differences exist between serotypes in clinical presentation and outcome which should be considered when evaluating the potential impact of higher valency vaccines on overall disease burden and associated QALY loss.

INTRODUCTION

Streptococcus pneumoniae is a commonly carried bacterium that causes both invasive and non-invasive disease. There are 90+ known serotypes of S. pneumoniae, each characterised by the molecular structure of its polysaccharide capsule [1]. Since capsular differences between serotypes have been linked to such properties as carriage prevalence [2,3], propensity to cause invasive disease [4,5,2], and case fatality [6–8], each serotype could theoretically be regarded as a separate

pathogen [4]. Differences in the pathogenicity and thus clinical impact of different serotypes are important from a public health perspective because available vaccines are serotype-specific, and only target a small subset of the known serotypes. Introduction of the first pneumococcal conjugate vaccine that protected against seven of the most common serotypes in developed countries (PCV7) had a profound effect on serotype-specific carriage prevalence and caused replacement of vaccine types by serotypes not included in the vaccine [9,3,10,11]. The overall impact of this change in carriage prevalence on pneumococcal-attributable morbidity and mortality is dependent on the inherent pathogenicity of the replacing serotypes compared with the previously predominant vaccine types.

To evaluate the potential benefit of introducing higher valency conjugate vaccines, as well as assessing the potential impact of previously uncommon and less studied emerging serotypes, it is important to have information on the invasiveness potential and clinical impact of different serotypes. The latter would ideally include disease focus (eg meningitis, empyema or sepsis), risk of long term sequelae and life years lost as a result of the infection. Expression of the serotype-specific clinical impact in terms of quality of life endpoints would incorporate these multiple facets of disease burden and provide a measure to use in cost-utility evaluations of different intervention strategies, for example, replacing of PCV7 by newer 10 valent (PCV10), 13 valent (PCV13) or higher valency conjugate vaccines.

The aim of this study was to investigate serotype-specific differences in clinical presentation of IPD and impact on quality of life in the context of the newly available PCV vaccines and the existing 23 valent polysaccharide vaccine (PPV23) which, although covering a higher number of serotypes, is poorly immunogenic in children and largely used in risk groups and the elderly. The Health Protection Agency holds one of the largest datasets of invasive pneumococcal disease (IPD) in the world [12] with an annual total of nearly 5000 cases in England and Wales serotyped in recent years. This national dataset has been used to monitor vaccine effects such as herd immunity and serotype replacement after the introduction of PCV7 in 2006 as a 2+1 infant programme [11] and has provided an early indication of the direct effect of PCV13 introduced in April 2010 [13]. Its availability provides a unique opportunity to document the effect on clinical presentation and quality of life of the different serotypes causing IPD over a nine year period spanning the introduction of PPV23 for all 65+ year olds, and the universal infant PCV7 and PCV13 vaccination programmes.

METHODS

Construction of the dataset

Microbiology laboratories in England and Wales voluntarily report electronically all clinically significant pneumococcal isolates (obtained by culturing or DNA based methods) to the Health Protection Agency (HPA) [11] and are actively requested to

refer these isolates to the Respiratory and Systemic Infection Laboratory (RSIL) for serotyping. Isolates referred to RSIL are confirmed as pneumococci and serotyped with antisera (Statens Serum Institut, Copenhagen) using standard methods. IPD reports with the same serotype within 30 days in the same individual are regarded as the same episode. As the clinical detail routinely available for IPD cases in the national dataset is limited, more comprehensive information on disease focus and outcome by serotype was obtained by linking the laboratory confirmed IPD cases in England (excluding IPD cases from Wales) with the dataset of hospital episode statistics (HES; Copyright © 2012, Re-used with the permission of The Health and Social Care Information Centre. All rights reserved) which is only available for England (10), using National Health Service (NHS) number or a full match on date of birth, sex and postcode. In HES, information on the duration, diagnoses (coded according to the International Classification of Disease series 10, ICD10), operative procedures and deaths during admission are recorded. All admissions with a code specific for IPD, or disease presentations which are likely to be related to acute pneumococcal disease were extracted from the HES database for the administrative years April 2002 to March 2011. The list of ICD10 codes used in the extraction can be found in the Supplementary Material S1. Hospital admissions which were on-going the week before and up to a month after the date of the positive culture were included in the analysis. Linkage and subsequent analysis was performed in R 2.12.0 (www.R-project.org).

Classification of disease focus and impact on quality of life

Disease focus was established using the clinical classifications published by the Healthcare Cost and Utilization Project [14] with some minor adjustments; convulsions (ICD-10 "R56") were included in the meningitis classification, empyema was included as a separate condition based on ICD-10 code "J86" and the different respiratory classifications (pneumonia, lower and upper respiratory tract infections) were grouped into one broad respiratory disease category (excluding empyema). Categorisation was based on all ICD-10 diagnosis codes for an admission rather than just the primary diagnosis, thus highlighting the most important focus of the pneumococcal-related infection. Where patients had multiple pneumococcal related diagnoses the most severe was chosen in the order; meningitis, empyema, sepsis, respiratory disease and other. For the serotype-specific analyses only serotypes isolated from at least 50 episodes of IPD were included. Cases for which only the serogroup was known, and cases serotyped as 6A but not tested for 6C were excluded from the analysis.

Mortality was based on the discharge information within HES. Only deaths within 30 days of the culture date were regarded as pneumococcal-attributable. As serotype distribution, disease presentation, and mortality varies between age-groups, data are presented for the age groups 0-4 years, 5-64 and 65+ years.

To compare the loss in quality adjusted life years (QALYs) by serotype an average QALY loss per case of 0.0079 was assumed for hospitalisation with a non-meningitis

focus [15], 0.023 QALY loss for hospitalisation due to meningitis [15] with a further 0.255 QALY loss for each remaining life year applied to the 31.7% of meningitis cases expected to have long term sequelae [16]. Empyema is severe in the acute phase [17], and in absence of a published QALY loss estimates for empyema, the QALY loss for meningitis was applied. No QALY loss from sequelae of empyema was included as the long term outcome is good [17]. For fatal cases, we used one QALY for each lost life year as expected by the gender specific life expectancy which is based on the 2010 mortality rates for England [18]. When conducting economic analyses future disease burden is normally discounted to reflect a time preference, therefore we added a discount rate of 3.5% per annum, as recommended by the National Institute for Health and Clinical Excellence (NICE) [19].

Statistical analysis

To assess differences between serotypes we calculated the odds ratio of developing meningitis and death for a given serotype compared to serotype 14. This is because serotype 14 had the greatest number of samples, and has previously been used as a reference for intra-serotype comparisons [7]. To correct for potential confounding due to age (years), gender, socio-economic factors, co-morbidities, study year and alcoholism we used a binomial logistic regression for meningitis and mortality. Due to the bimodal distribution of the QALY loss we show a p-value based on the difference of 1000 bootstrap samples for the mean of the given serotype and serotype 14 (this approach precluded correction based on potential confounders). For all tests the (adjusted) p-values are presented in the paper and the obtained odds are included in the Supplementary Material S1. Socio-economic deprivation was based on the rank in the deprivation index, as published by the Department for Communities and Local Government in the UK [20]. This index is assigned to a small geographical area (lower super output area) and related to the postcode of the patient at the time of admission as recorded in HES. The deprivation index is not updated every year so to reduce the effect of changes of deprivation over time we divided the rank into quartiles, as it is less likely that a neighbourhood will change so extensively that it moves over quartiles. Co-morbidities were scored based on the Charlson index, where the included conditions were crossed mapped with ICD-10 codes [21]. In the analysis the Charlson index was sub-grouped into "no-comorbidities", "Charlson score 1-2" and "3 and above". As alcoholism is not a part of the Charlson index patients were identified for alcohol related problems based on the codes used by Harboe et al [6].

To assess the precision of the estimates, binomial confidence intervals are presented for mortality and the 2.5% and 97.5% percentiles of 1000 bootstrap samples for the mean QALY loss.

To investigate the proportion of IPD (and its various disease outcomes) that was possibly preventable by the different pneumococcal vaccines (PCV7, PCV10, PCV13 and PPV23) at the time PCV13 was introduced in April 2010, the number of cases by

age group and clinical endpoint was estimated for each serotype. This was achieved by multiplying the serotype specific percentage with meningitis, the case fatality rate (CFR) or QALY loss as measured over the full period with the absolute serotype distribution in the period April 2009 to March 2010. In this calculation the serotypes with less than 50 cases were included.

RESULTS

Linkage success

The linkage was increasingly successful over the years, with 50% of IPD cases linked to a HES admission in 2002/2003 rising to 76% in 2010/2011, resulting in a total of 33,196 linked cases over the nine year period from England. Of these, 23,688 (71%) had information on ICD-10 diagnoses, mortality and infecting serotype (2,605, 10,389 and 10,694 for the age groups <5,5-65 and 65 and over). The matched cases had a similar serotype and age distribution to the unmatched cases, suggesting that there were no major biases with respect to these variables as a result of the incomplete linkage (see figure S-1 and S-2 in the Supplementary Material S1).

For the under 5 year olds there was a total of 51 different serotypes in the matched dataset; however many did not achieve the pre-specified minimum of 50 cases leaving only 14 serotypes (comprising 86% of the cases) for analysis. Among 5-64 year old patients, 67 different serotypes were identified, with only 26 (comprising 96% of the cases) having enough cases for individual analysis. Among the 65 years and over, 62 different serotypes were recorded, with 29 (comprising 97% of the cases) having enough for individual analysis.

Serotype- specific disease focus

Within each age group, the clinical presentation differed significantly between serotypes, even after correcting for co-morbidities and socio-economic factors, see Figure 1 and the Supplementary Material S1. Among children under 5 years, serotype 18C was the most likely to cause meningitis, with 52% of the patients presenting with this outcome, followed by 19F (46%) and 6B (45%). All three serotypes were significantly more likely to cause meningitis compared to serotype 14 (31%). The non-PCV serotypes, 22F and 33F, had a percentage with meningitis of 37% and 40% respectively. The lowest proportion of meningitis cases was among serotypes 1 (10%), 3 (14%) and 19A (24%), although only serotype 1 and 3 were significantly different from serotype 14. The serotypes causing a low burden of meningitis had a relatively high percentage of children presenting with empyema; serotype 3 (45%), 1 (37%) and 19A (17%) showed the highest proportions with empyema whereas only 0-3% of the serotypes associated with meningitis (6A, 19F, 18C 22F and 33F) caused empyema. The percentage of IPD resulting in meningitis was lower in the age group 5-64 years than in the under 5 year olds (10% vs 33%). Compared to

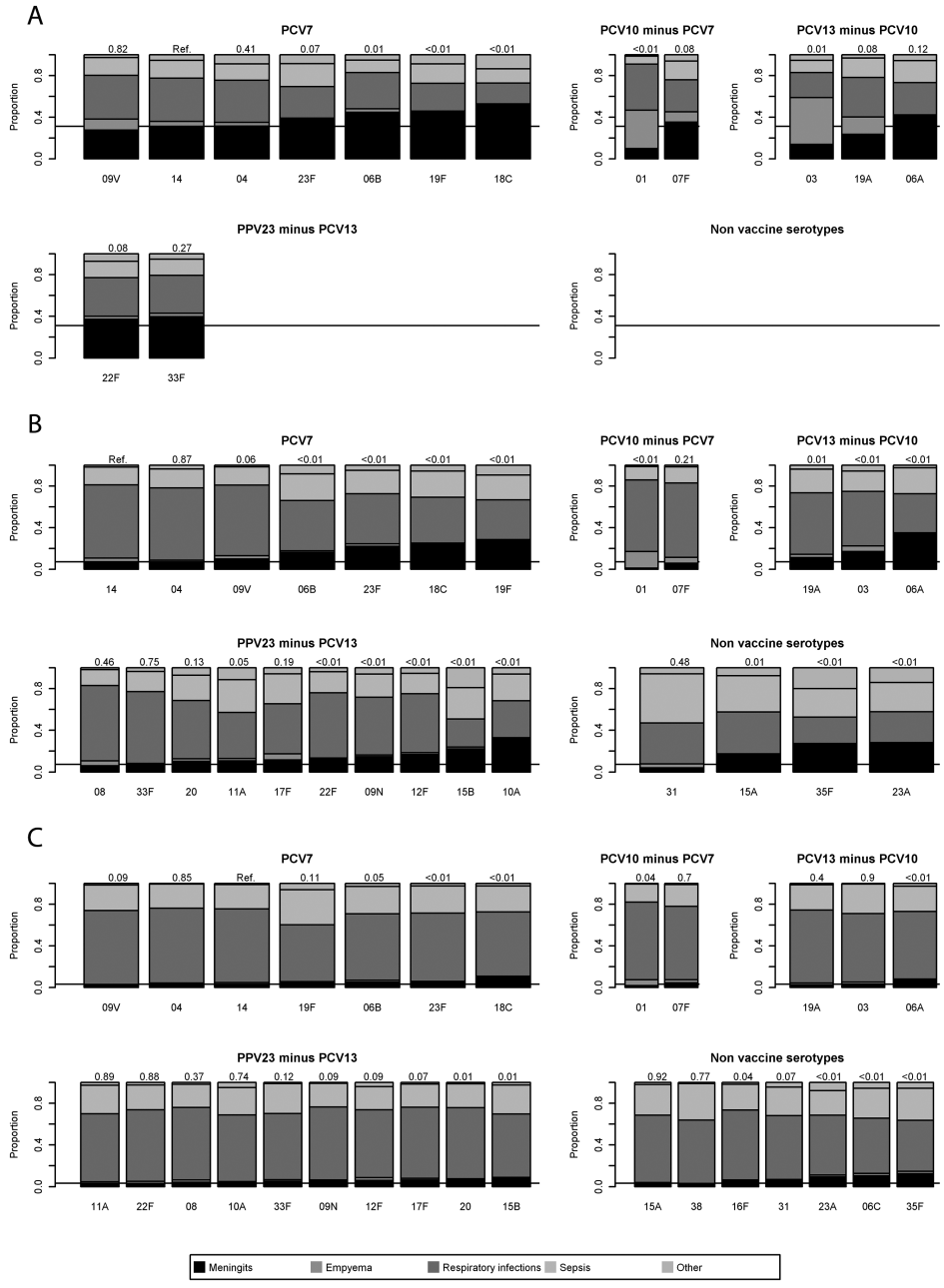

Figure 1. The distribution of disease focus (meningitis, Empyema, respiratory diseases, sepsis and other) per serotype grouped by vaccine type and age group. The line shows the absolute percentage of patients with meningitis for serotype 14, which was used as reference in the logistic regression. The p-values of this regression are shown above each bar. When there are no serotypes with ≥50 cases an empty plot is shown. a)Under 5 years, b) 5-64 years, c) 65 years and over

serotype 14 (7% with meningitis in this age group), serotypes 6A (34%), 10A (32%), and 23A (28%) were significantly more likely to cause meningitis, as were 6B, 19F, 18C, 35F and 15B. Serotype 1 rarely caused meningitis (1%), followed by 31 (4%) and 7F (6%). Again serotype 1 was linked to empyema, with 16% of cases having this presentation, followed by 7F (6%). Serotypes more likely to cause meningitis rarely caused empyema - 6A (1%), 10A (1%) and 23A (0%).

For the age group 65 years and over few cases presented with meningitis or empyema. The serotypes most likely to cause meningitis were 35F (13%), 6C (10%) and 18C (10%). For empyema, serotype 1 showed the strongest association (6%) followed by 7F and 12F (both 3%).

In the regression analysis, having no co-morbidity was significantly associated with a higher probability of developing meningitis in the patients above 5 years of age (odds 1.88 and 2.51 respectively). The other confounders were not significantly associated with meningitis and/or no trends by year or socio-economic factors were identified. Disease focus over time (results not shown) was stable.

Serotype-specific mortality

The case fatality among under 5 year olds was low (overall 3%). The serotype with the highest case fatality rate was 6A with 7%, followed by 19F with 5%, and 9V and serotype 3 (5%) (see Figure 2 and the Supplementary Material S1). Serotype 4 (0%) had the lowest case fatality rate followed by serotypes 1, 7F and 6B each with 1%. However, none of these case fatality rates differed significantly from serotype 14 (3%). Non PCV types 22F (3%) and 33F (3%) had an average mortality.

Among the age group 5-64, (overall CFR 10%) serotypes 31 (33%), 11A (30%) and 19F (21%) had the highest case fatality rates; serotypes 1 (3%), 7F (4%) and 8 (6%) had the lowest rates. Serotype 3, 19F, 19A, 6A, 9N, 11A and 31 (the last 3 serotypes are not included in any current conjugated vaccine), were all significant higher compared to serotype 14 (8%), only serotype 1 was significantly lower.

Patients aged 65 years and over had the highest case fatality rate (overall 30%). Serotypes most likely to be associated with a fatal outcome were 19F (41%), 31 (40%), and 3 (39%), all significantly different from serotype 14 (29%). The lowest case fatality rates were for serotypes 1 (17%), 7F (20%) and 12F (21%), all three significantly lower than serotype 14.

Confounders associated with mortality in all age groups were meningitis (p value: <0.01; <0.01; 0.03 for the age groups <5, 5-64 and 65+ years respectively), and co-morbidities (p values: 0.06; <0.01, <0.01 respectively). Among the age group 5-64 years there was a decline in mortality over time (reducing the odds to 0.6 in 2010-2011 compared to 2002-2003) and a declining risk of mortality by declining social-economic deprivation (an odds of 0.7 in the least deprived status compared to the most deprived). These trends were not observed for the other age groups.

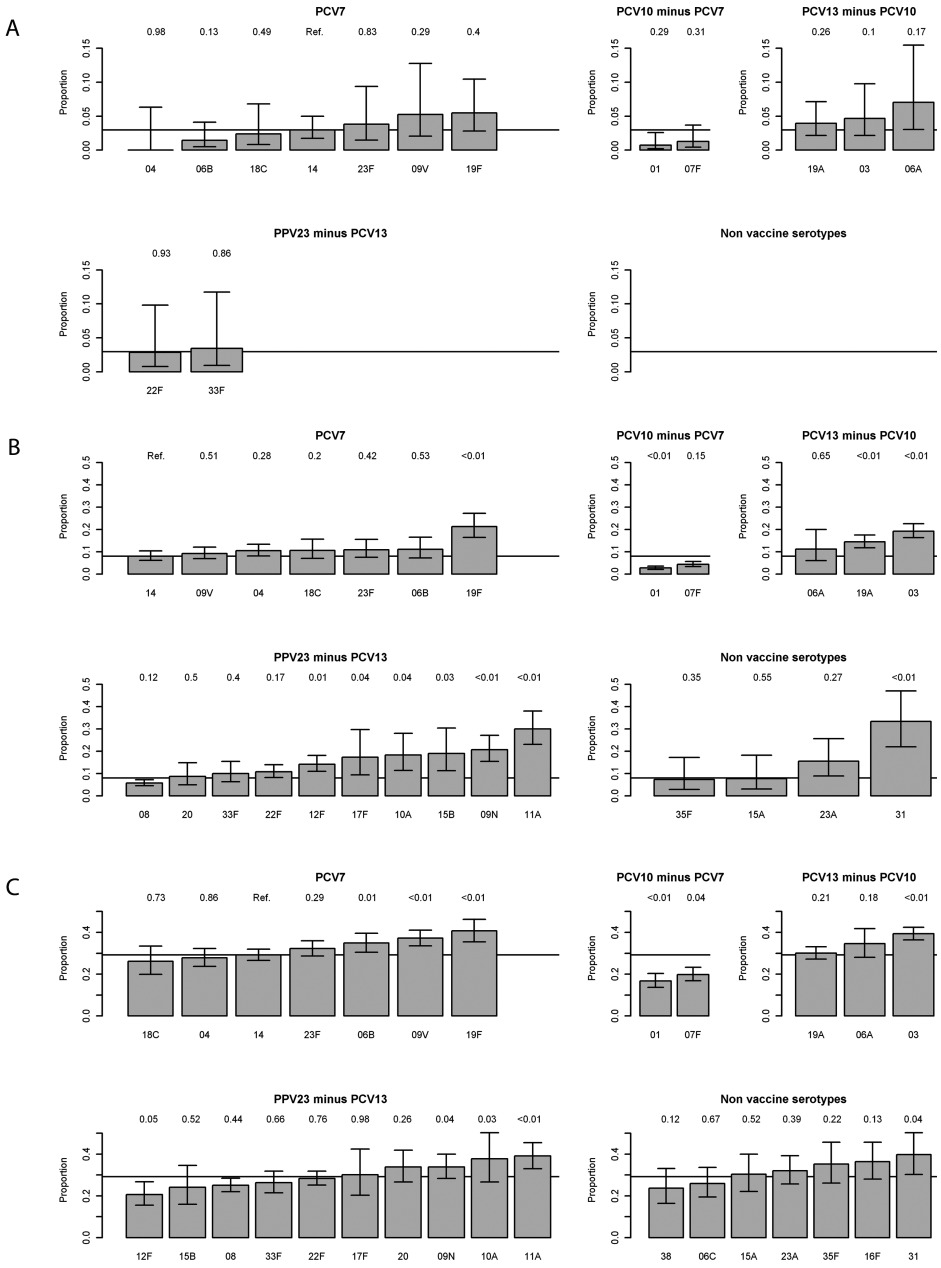

Figure 2. Serotype-specific differences in mortality between serotypes. The line shows the absolute case fatality rate for serotype 14, which was used as reference in the logistic regression. The p-values of this regression are shown above each bar. The whiskers show the 95% confidence intervals based on a binomial distribution. When there are no serotypes with ≥50 cases an empty plot is shown. a) Under 5 years, b) 5-64 years, c) 65+ years

QALY loss by serotype

The lowest overall QALY loss per serotype among children under 5 years was serotype 1 (0.43 per case) followed by 4 (0.71) and 7F (1.15). The highest QALY loss was among serotypes 6A (2.86). 19F (2.53) and 9V (2.05). Serotype 22F scored 1.62 and 33F 1.83 (see Figure 3 and the Supplementary Material S1for more detail). Within the age group 5-64 years the difference between the low and high burden of disease serotypes was more marked. The serotypes causing the highest QALY loss were 31 (6.34), 11A (5.82) and 19F (4.34). Serotype 1, 7F and 8 had the lowest QALY loss 0.57, 0.95 and 1.17 respectively.

Among the 65 years and over the differences between serotypes in QALY loss per case declined again, with serotypes 1 (1.38), 38 (1.42), and 7F (1.52) at the low end of the spectrum and 19F (3.09), 31 (2.95) and 3 (2.93) on the high end.

We performed a sensitivity analysis (results not shown) because a significant decrease of mortality was observed for 5-64 years over the period. We adjusted the QALY loss for each death before July 2006 by replacing it by p*(QALY loss for death) + (1-p)*(multiplication with the odds for mortality in the second half of the period (July 2006 onwards) and adding the QALY loss for meningitis) where p was the adjusted odds ratio of mortality after July 2006 compared to before July 2006 by age. Doing so resulted in slightly lower QALY losses, and only minor changes in the ranking of serotypes.

Burden of IPD potentially preventable by different valency vaccines in England before PCV13 introduction

The contribution of the vaccine-specific serotypes to the overall burden of IPD in England changed over the study period, largely due to the impact of PCV7 on serotype distribution. For 2009/2010, the last administrative year before PCV13 introduction, the contribution of the different vaccine-specific serotype groupings to the overall burden of IPD and its associated QALY loss are shown in Table 1 by age group. For children under 5 years, the cumulative coverage for PCV10 was 41% for all IPD, 39% for meningitis and 19% for mortality, and 28% for the total QALYs lost. For PCV13 the coverages were 75%, 65%, 67% and 66% respectively for the same outcomes. PCV13 therefore covered 1.8 times more IPD cases compared to PCV10, 1.6 times more meningitis, 3.5 times more mortality, and 2.4 times the total QALYs lost. For patients 5-64 years, PCV13 covered 1.4 times more cases of IPD, 2 times more cases of meningitis, 2.2 times more cases of mortality and 2.1 times as much QALY loss as PCV10. Among the 65 years and over, PCV13 covered 2.2 times more IPD cases compared to PCV 10, 2.0 times more meningitis cases, 2.6 times more fatal cases and 2.5 times the number of QALYs lost.

Deaths and life years lost due to IPD, England 2009/2010

In 2009/2010 there were 5,719 cases of IPD confirmed by culture or polymerase chain reaction in the England IPD dataset. Based on the age-specific serotype distribution

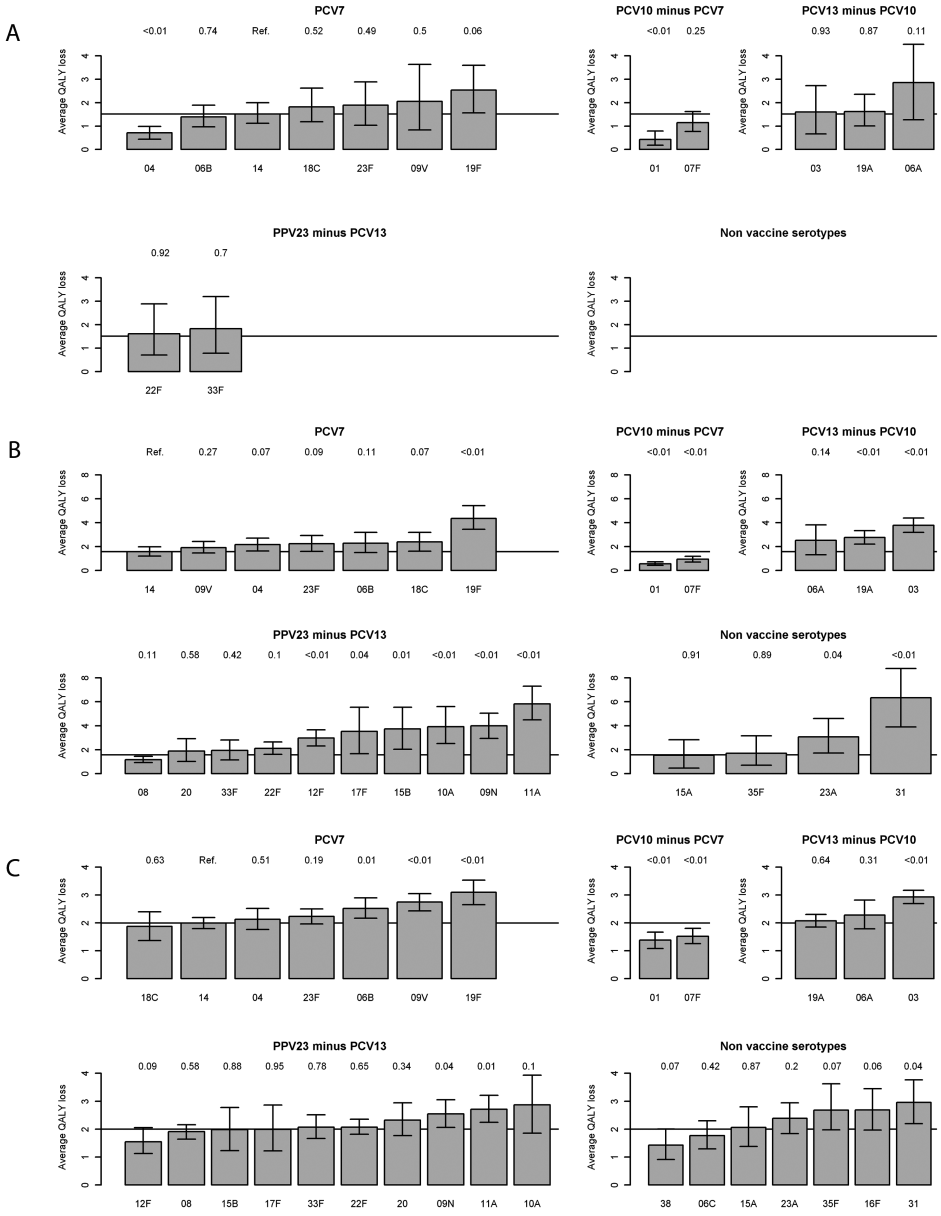

Figure 3. Serotype specific differences in QALY loss (discounted – see text) between serotypes and age groups. The line shows the absolute QALY loss for serotype 14, which was used as reference. The p-values of the bootstrap comparison are shown above each bar. The whiskers show the 95% CI based on 1000 bootstrap samples of the mean. When there are no serotypes with >50 cases an empty plot is shown. a) Under 5 years, b) 5-64, c) 65 and over

Table 1. Cumulative proportion of meningitis, mortality and QALY loss (discounted) in 2009/2010 in England attributable to invasive pneumococcal disease covered by different valency vaccines.

Cumulative contribution		PCV7*	PCV10**	PCV13***	PPV23	Remaining % Non-Vaccine types
<5 year olds	IPD	5%	41%	75%	90%	10%
	Meningitis	8%	39%	65%	88%	12%
	Mortality	6%	19%	67%	85%	15%
	QALY	7%	28%	66%	86%	14%
	QALY (disc)	7%	28%	66%	86%	14%
5-64 year olds						
	IPD	10%	43%	61%	90%	10%
	Meningitis	14%	24%	49%	78%	22%
	Mortality	12%	23%	52%	86%	14%
	QALY	12%	25%	52%	86%	14%
	QALY (disc)	12%	24%	52%	86%	14%
≥ 65 year olds						
	IPD	12%	23%	51%	81%	19%
	Meningitis	11%	19%	38%	65%	35%
	Mortality	13%	21%	53%	81%	19%
	QALY	13%	21%	53%	81%	19%
	QALY (disc)	13%	21%	53%	81%	19%

* Contains serotypes 4,6B,9V,14,18C,19F,23F. ** Contains additional serotypes 1,5,7F.
*** Contains additional serotypes 3, 6A,19A,

in that year and the disease focus and outcome for each serotype averaged over the nine year study period, there was an estimated total of 591 meningitis cases and 1,010 deaths in 2009/2010 year attributable to IPD, with an associated QALY loss of 18,454 (11,638 discounted) in England. The contribution of different age groups to these cumulative totals varied considerably (Table 2). The main burden of meningitis was among the young and the middle age group, but the majority of deaths were among the ≥ 65year olds (71%). For QALY loss (undiscounted), most of the burden was in the age group 5-64, though after discounting their QALY loss was similar to that in the ≥ 65 year age group.

DISCUSSION

Our study documents the clinical presentation, mortality and impact on the quality of life of the prevalent pneumococcal serotypes causing IPD in England in recent

Table 2. Number of cases of IPD, meningitis, deaths and the total QALYs lost by age group in England 2009/2010

	Number of cases		Number of meningitis cases		Number of deaths		QALYs lost (undiscounted)		QALYs lost (discounted)	
Age	Total	%	total	%	total	%	total	%	Total	%
0-4	572	10%	161	27%	17	2%	2414	13%	831	7%
5-64	2735	48%	310	53%	277	27%	9646	52%	5589	48%
65+	2413	42%	119	20%	716	71%	6394	35%	5218	45%
Total	5719	100%	591	100%	1010	100%	18454	100%	11638	100%

years. The serotype-specific clinical presentations were broadly stable over time, consistent with reflecting an inherent property of each serotype. To our knowledge, this is the first attempt to compare disease outcome between serotypes based on QALY loss and incorporating acute disease burden, long term sequelae, mortality and life years lost. Our results add to the understanding of the role of the capsular type of S. pneumoniae in determining pathogenicity and can guide decision making on the potential health gain of introducing vaccines with improved serotype coverage

Assigning QALY weights to different disease states is a well-established approach for comparing the potential health gain of different therapeutic or prophylactic interventions as it combines both duration and quality of life in a single measure. While for non-fatal diseases QALY estimation can be problematic because of reliance on subjective measures, for IPD the QALY differences between serotypes are mainly driven by the life years lost – a more objective measure. We believe QALY loss estimates provide a better platform to distinguish between serotypes causing a low and high disease burden than simply reporting mortality or meningitis rates. Expressed in QALYs the main IPD burden was found amongst 5-64 year olds, where the higher number of life years lost outweighed the higher case fatality rate among the ≥ 65 year olds with their lower life expectancy.

Serotypes with a high and low case fatality rate in our study were the same serotypes found to be linked to a high and low case fatality rate in a study in Denmark [6] and in a review on mortality by capsular type that included data from 9 different studies from the United States, Europe, Africa and the Middle East spanning the period 1952 to 2010 [22]. This supports the view that high or low mortality is a stable feature for those serotypes, though there was less consistency between the studies for the serotypes which were not on the extremes. Our results show that the differences between serotypes are most marked in the age group 5-64 years. This may reflect the greater vulnerability of the very young and elderly populations to IPD which may in part mask the inherent differences between serotypes.

It is not clear how the capsular differences between serotypes affect clinical presentation and outcome [22]. Differences in capsular size or molecular structure could possibly lead to a different interaction of the bacteria with its environment (including other bacteria in the nasopharynx) and/or immune system in the blood, brain or other tissues. Although the capsule is the major virulence factor [23], there are other factors such as surface proteins and enzymes, and the major toxin pneumolysin, which determine virulence. If these non-capsular virulence factors are also associated specifically with certain serotypes then some of the characteristics attributed to differences in serotype per se may be spurious. Whole genome sequencing has also identified a number of highly variable pathogenicity islands within the pneumococcal genome, with considerable variation between strains. Some serotypes are highly clonal while others exhibit considerable genetic diversity [24]. The extent to which genetically diverse strains within the same serotype exhibit different behaviour in terms of clinical presentation and outcome cannot be assessed by our study and would require parallel genetic information. Another caveat in attributing the observed characteristics to specific serotypes is that differentiation into serotypes within a serogroup is still evolving as shown for 6A for which the original serotyping methods failed to distinguish to 6A from 6C [25], each with a different clinical outcome.

Host factors can also affect clinical presentation, as shown by the lower propensity to develop meningitis in individuals aged over 5 years with co-morbidities. In addition, factors such as ethnicity, socio-economic or other environmental factors could influence disease focus as suggested by the strong association between serotype 1 and meningitis in west-Africa. In our study, as in a hospital-based study in Spain [26], serotype 1 was predominantly associated with empyema. Therefore caution should be exercised in translating our results to all epidemiological settings.

Our study has the potential limitation that we were not able to link all cases in the national IPD dataset with a HES admission. Failure to match could be due to an incomplete initial extract from the HES database omitting relevant diagnoses that could denote IPD, or be due to non-hospitalised invasive disease or incomplete information in the fields used in matching. Thus there is the possibility of a selection bias, excluding certain clinical presentations or more mild disease. However the similarity between the linked and the unlinked dataset in age and serotype distribution suggests that the linked subset is representative of the complete dataset.

From our analysis PCV13 is predicted to protect against a substantially greater burden of invasive disease than PCV10, especially mortality, based on its additional coverage of serotypes 3, 6A and 19A, and the serotype distribution in 2009 in England. However when deciding between the two vaccines, additional factors need to be taken into account. These include the serotype distribution and burden of non-invasive disease, the potential to prevent disease due to non-typeable Haemophilus influenza with PCV10 (which is conjugated to Haemophilus influenzae

protein-D [27]) and indirect effects due to differences in carriage prevalence of the serotypes covered by each vaccine; for example the extra three serotypes in PCV10 compared with PCV7 (1, 5 and 7F) have a very low carriage prevalence, due to this low carriage there is potential less space for replacement disease by non-vaccine types compared to the extra serotypes in PCV13, which are more prevalent in carriage [3]. The overall impact on the burden of IPD of each vaccine may therefore be affected by the potential for serotype replacement and the invasiveness of the replacing strains [3]. For the emerging non PCV serotypes 11A, 31, 10A and 9N could be prioritised for inclusion in future conjugated vaccines, as they have a relatively high QALY loss.

In conclusion, from our large linked dataset with information on serotype and clinical outcome, we were able to confirm marked and stable differences in morbidity and mortality between pneumococcal serotypes, provide estimates for the proportion of cases by age group and serotype with meningitis, empyema and mortality, and derive the estimated annual QALY loss from IPD four years after the introduction of PCV7 in England. While many of the clinical outcomes seem to be robustly linked to the capsular type, extrapolation of our findings to populations with vastly different epidemiological and socio-economic backgrounds should be done carefully. Our findings have relevance for future work on capsular differences and interaction with the host immune system, and can inform decision modelling of the relative merits of vaccines with different serotype-composition.

SUPPLEMENTARY MATERIAL

The supplementary material can be found at: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0039150

ETHICS APPROVAL

The Health Protection Agency has approval under PIAG Section 60 of the Health and Social Care Act 2001(now subsumed into the National Information Governance Board for Health and Social Care with Section 60, now Section 251 of the NHS Act 2006) to process confidential patient information for the purposes of monitoring the efficacy and safety of vaccination programmes.

ACKNOWLEDGMENTS

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chapter THIRTEEN

THE COST-EFFECTIVENESS OF A 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINATION FOR INFANTS IN ENGLAND

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ABSTRACT

Background

In the immunisation schedule in England and Wales, the 7-valent pneumococcal conjugate vaccine (PCV-7) was replaced by the 13-valent vaccine (PCV-13) in April 2010 after having been used since September 2006. The introduction of PCV-7 was informed by a cost effectiveness analysis using an infectious disease model which projected herd immunity and serotype replacement effects based on the post-vaccine experience in the United States at that time.

Aim

To investigate the cost effectiveness of the introduction of PCV-13.

Method

Invasive disease incidence following vaccination was projected from a dynamic infectious disease model, and combined with serotype specific disease outcomes obtained from a large hospital dataset linked to laboratory confirmation of invasive pneumococcal disease. The economic impact of replacing PCV-7 with PCV-13 was compared to stopping the use of pneumococcal conjugate vaccination altogether.

Results

Discontinuing PCV-7 would lead to a projected increase in invasive pneumococcal disease, costs and loss of quality of life compared to the introduction of PCV-13. However under base case assumptions (assuming no impact on non-invasive disease, maximal competition between vaccine and non-vaccine types, time horizon of 30 years, vaccine price of £49.60 a dose + £7.50 administration costs and discounting of costs and benefits at 3.5%) the introduction of PCV-13 is only borderline cost effective compared to a scenario of discontinuing of PCV-7. The intervention becomes more cost-effective when projected impact of non-invasive disease is included or the discount factor for benefits is reduced to 1.5%.

Conclusion

To our knowledge this is the first evaluation of a transition from PCV-7 to PCV-13 based on a dynamic model. The cost-effectiveness of such a policy change depends on a number of crucial assumptions for which evidence is limited, particularly the impact of PCV-13 on non-invasive disease.

INTRODUCTION

Streptococcus pneumoniae is responsible for significant morbidity and mortality in England and Wales, particularly in young children, the elderly and the immunocompromised [1]. It can infect mucosal tissue in the respiratory tract to

cause conditions such as upper respiratory tract infections, conjunctivitis and acute otitis media. Invasive disease occurs when it spreads to normally sterile sites such as the bloodstream and meninges, causing more severe symptoms such as pleural empyema, septicaemia and meningitis [2]. Pneumonia due to S. pneumoniae is also commonly (though not exclusively) invasive.

Two types of pneumococcal vaccines are used in the United Kingdom. The 23-valent pneumococcal polysaccharide vaccine (PPV-23; Merck & Co) has been available since the 1980s, but displays low efficacy, has a short duration of protection and is poorly immunogenic in children under two years old [3]. It is currently used routinely in clinical risk groups and adults aged 65 years and over [4]. Pneumococcal conjugate vaccines elicit longer lasting immune memory, are immunogenic in infants, and have the additional benefit of preventing nasopharyngeal carriage, thus reducing the likelihood that vaccinated individuals will transmit infection to other individuals. This can generate indirect (herd) protection, and so has the potential for population-level benefits beyond the groups targeted by vaccination [5].

The 7-valent pneumococcal conjugate vaccine (PCV-7; Wyeth, now Pfizer) was introduced into the UK infant immunisation schedule in 2006 with a 2+1 schedule [6] following favourable cost-effectiveness analyses. This was based on projecting indirect protection in non-vaccinated groups and serotype replacement from the post-vaccination experience in the United States [7]. Vaccine introduction was followed by a sharp reduction in invasive pneumococcal disease caused by vaccine serotypes in immunised children but also in adults who were mostly unvaccinated. However, this was largely offset by a larger than expected increase in disease caused by non-vaccine pneumococcal serotypes [8;9].

In April 2010 Pfizer discontinued marketing PCV-7 in the UK and replaced it with a 13-valent pneumococcal conjugate vaccine (PCV-13). In this paper we focus on the cost-effectiveness of introducing PCV-13 compared to discontinuing PCV vaccination altogether.

METHODS

Invasive pneumococcal disease following pneumococcal vaccination

A dynamic transmission model, described in detail by Choi et al. [10] was used to estimate the annual number of invasive pneumococcal disease (IPD) cases that are likely to occur following the introduction of PCV-13 in April 2010. The model was fitted to the total annual number of IPD cases confirmed by culture for PCV-7 types, the five new serotypes included in PCV-13 (excluding serotype 1, see below), and all non-vaccine serotypes (NVT), between epidemiological years 2005/06 and 2008/09. The model assumed an initial vaccine efficacy of 52% against carriage of vaccine serotypes (26% for partially vaccinated infants) and 100% efficacy against IPD; however vaccine protection is assumed to wane with an average duration of 5 years. Herd immunity was

estimated using a dynamic transmission model; serotype replacement was estimated using a competition parameter of 0, which means that an individual carrying a vaccine serotype (VT) is fully protected against acquisition of S. pneumoniae due to NVT so that there is complete replacement in carriage of VTs with NVTs.

The dynamic model did not explore the impact of vaccination on serotype 1 because its pre-vaccination epidemiology shows a cyclical pattern (as in other countries [11]). Therefore we inflated the number of IPD cases by the average annual incidence of IPD cases caused by serotype 1 between 2000 – 2006 [12]. Also, as the transmission model was only fitted to data on culture-confirmed IPD (i.e. excluding PCR confirmed cases), we increased the number of IPD cases based on the observed percentage of the overall cases which were confirmed using PCR in the national surveillance system (5.4% for the under 1s, 14.4% for 1 to 14 and 0.66% for the those aged 15 and over).

Invasive disease outcomes

Samples from patients with bacterial infections are often sent to the Health Protection Agency (HPA) for microbiological testing. If S. pneumoniae is discovered during this testing, they are usually serotyped. Cases with serotype information recorded between April 2002 and March 2011 were matched to the Hospital Episode Statistics database, which contains all admissions to National Health Service hospitals in England. This created a dataset of ~25,000 IPD cases with known serotype, diagnostic codes, duration of admission and mortality. Disease outcomes in the dataset were classified into meningitis, empyema, sepsis, pneumonia and other. The vaccine-specific (PCV7 serotypes, six additional PCV13 serotypes and non-vaccine serotypes) risk of developing each of these foci of disease, as well as the subsequent probability of death and the duration of hospitalisation resulting from the disease episode were estimated from the dataset. The methodology of matching and serotype-specific disease outcomes as observed in this dataset has been previously published [13].

To represent the uncertainty in outcomes of IPD estimated from this dataset, we took 10,000 bootstrap samples (with replacement) from the original database and obtained for each sample the probability of developing disease with one of the five disease foci, the subsequent probability of death and the duration of hospitalisation for the six age categories (under 2 years, 2-14 years, 15-64 years, 64-74 years and 75+ years) and three serotype categories. The frequency distributions of the observed probabilities and hospitalisation days are shown in the online-material. From these 10,000 samples, we subsequently selected 1,000 by Latin hypercube sampling for probabilistic sensitivity analyses.

Non-invasive disease outcomes

The effect of pneumococcal vaccination on primary care consultations and hospitalisations for non-invasive disease was estimated by fitting a linear model of

the change in these outcomes over the period 2005/6 to 2008/9 to changes in invasive pneumococcal disease due to PCV-7 and non-PCV-7 serotypes. Separate models were fitted for otitis media consultations, pneumonia consultations and pneumonia hospitalisations, and stratified by the age groups <1 year, 1 year, 2-4 years, 5-9 years and 10-14 years. A description of the model fitting is included in appendix I. The incidence of consultations for otitis media and community-acquired pneumonia (regardless of aetiology) was estimated using data from The Health Improvement Network (THIN), a database of three million active patients representative of the UK population [14]. For pneumonia hospitalisations, cases in the Hospital Episode Statistics database with a diagnostic code for unspecified pneumonia (ICD-10 code J18) were used. Both these data sets show a slight decline in the number of cases between 2005/6 to 2007/8 in 0-15 year olds, followed by a possible increase in 2008/9. The assumptions on pneumococcal attributable disease are influential on the outcome of the model fit. Therefore two scenarios were included: a base case scenario where a fixed number of pneumonia cases every year was considered to be caused by non-pneumococcal pathogens, and an alternative scenario where a fixed proportion of annual cases of pneumonia was assumed to be non-pneumococcal attributable.

Costs

Costs for hospitalised cases of bacteraemia, meningitis and pneumonia were obtained from standard NHS reference costs (codes WA03Y, AA22Z and DZ11A respectively) [15]. The cost per bed day for each of these presentations was multiplied by the number of bed days obtained from the analysis of the hospital data. For non-invasive pneumonia reference costs for pneumonia without complications (DZ11C) were used. No information was available on the duration of stay for the recorded hospitalisations; therefore the reference costs for an admission were used, which are based on an average duration of ~ 4 days [15].

The cost of a primary care consultation was obtained from standard sources, based on a surgery consultation inclusive of direct care staff and qualification costs [16]. Prescription costs for pneumonia were estimated based on a 6-capsule pack of azithromycin [17]. For bacteraemia and meningitis, prescription costs were based on a single dose of cefotaxime before transfer to hospital [17]. Antibiotics are not generally recommended for treatment of otitis media [18].

Hospital outpatient visits for meningitis and otitis media respectively were costed using NHS reference costs for miscellaneous disorders of the nervous system (code AA25Z) and minor ear procedures in children without complications (code CZ08T) [15]. A previous study estimated that only about 1% of otitis media consultations required an outpatient follow-up visit [7]. Meningitis patients without sequelae were assumed to have a single outpatient appointment following discharge. The cost of treatment and care for meningitis survivors with sequelae was obtained from case notes described in a previous cost-effectiveness analysis [7].

The cost of a single dose of PCV-13 was assumed to be £49.60, the prices at which the vaccines are available on the National Health Service [17]. Since a competitive tender is likely to result in lower prices, the threshold price for cost-effectiveness was also explored. Vaccine administration costs of £7.51 were assumed based on the item of service payment to general practitioners for vaccination.

Utilities

The QALY loss for acute meningitis was based on estimates by the parents of children hospitalised for meningitis (with full recovery) [19]. QALY loss for other invasive outcomes requiring hospitalisation was based on the estimated utility loss for hospitalisation due to occult bacteraemia presented in the same study. The survey results were not adjusted for the duration of hospitalisation since no duration information was included in the outcome descriptions presented to parents. The QALY loss for an episode of pneumonia not requiring hospitalisation were based on a United States-based cost-effectiveness evaluation [20]. Since only a point estimate was reported, the value was assumed to range between no utility loss and the loss associated with an inpatient hospitalisation for pneumonia. The QALY loss for an episode of otitis media was based on the EQ-5D utilities elicited from parents of children with otitis media in the placebo arm of a trial of topical steroids [21]. QALYs lost were estimated by subtracting the area under the utility curve, linearly interpolating between utility scores at baseline and 3 months, and assuming that children were back to normal health at 9 months.

Quality of life weights for sequelae of bacterial meningitis were obtained from a Dutch survey among paediatricians using the EQ-5D instrument [22]. The risk of different types of sequelae was obtained from a recent meta-analysis [23]. To match sequelae categories in the meta-analysis with those in the Dutch study, hearing loss was matched to the quality of life for "mild hearing loss" unless it exceeded 70 dB in both ears, in which case it was matched to "deafness", seizures were matched to "epilepsy", spasticity, paresis and palsy were matched to "leg paresis" while hydrocephalus was matched to "mild mental retardation". We assumed that patients could develop any combination of the individual sequela proportional to the individual risk of each of them. We rescaled the risk of these combinations such that the risk of at least one kind of sequela per patient did not exceed 31.7%, as reported in the meta-analysis [23]. Patients with more than one type of sequela were assumed to have the QALY loss associated with the most severe type. Using this method, the overall average QALY loss of a patient developing sequelae was estimated to be 0.255 a year.

Cost-effectiveness analysis

The cost-effectiveness analysis was performed from a health care payer's perspective. In the base case, a discount rate of 3.5% per annum was used for costs and benefits, in conjunction with a 30 year time horizon. The analysis was performed in R 2.15.0 (www.r-project.org)

Sensitivity analyses

When both the sample mean and its standard error were available, beta distributions were used to represent probabilities and utilities, and lognormal distributions to represent costs. When only the sample mean was available, a triangular distribution was used, with minimum and maximum based on the plausible minimum and maximum values the parameter could take. For costs obtained from NHS reference costs [15] lognormal distributions were fitted to the reported means, upper and lower quartiles. The parameters used and their distributions are shown in Table 1.

Scenarios

The effect of pneumococcal vaccination on non-invasive disease outcomes such as non-invasive pneumonia and otitis media is unclear, and is likely to be influenced by replacement by both non-vaccine pneumococcal serotypes and other organisms [24;25]. Consequently, we also considered a scenario where no change in non-invasive disease outcomes was assumed.

Model results using a discount rate of 3.5% for costs and 1.5% for QALYs are also presented, as well as a scenario using an infinite time horizon.

RESULTS

Changes to the burden of disease

Figure 1 shows the estimated health care costs and QALYs that may be saved by the introduction of PCV-13 vaccination in 2010. Most costs are saved by preventing non-invasive disease, while for QALYs saved, the majority of the contribution comes from invasive disease. Table 2 compares the annual number of cases, health care costs and QALYs lost due to pneumococcal disease during the final year of PCV-7 vaccination, and after at least 30 years of either discontinuing pneumococcal vaccination or changing to PCV-13.

Cost-effectiveness

The cost effectiveness of introducing PCV-13 instead of discontinuing pneumococcal conjugate vaccination is shown in Figure 2. Using a threshold of £30,000 per QALY gained, introducing PCV-13 is cost-effective in 100% of parameter combinations sampled if non-invasive disease outcomes are included, but only 53% if they are not. The total costs of the vaccination program, accumulated and discounted over 30 years will exceed the billion pounds (£1,004,639,395).

Threshold vaccine cost

The threshold price per dose of PCV-13 vaccine for vaccination to be cost-effective under thresholds of £20,000 and £30,000 per QALY gained in the base case scenario is £50.54 and £71.85 respectively (Figure 3). When non-invasive endpoints are excluded, this drops to £32.76 and £49.71.

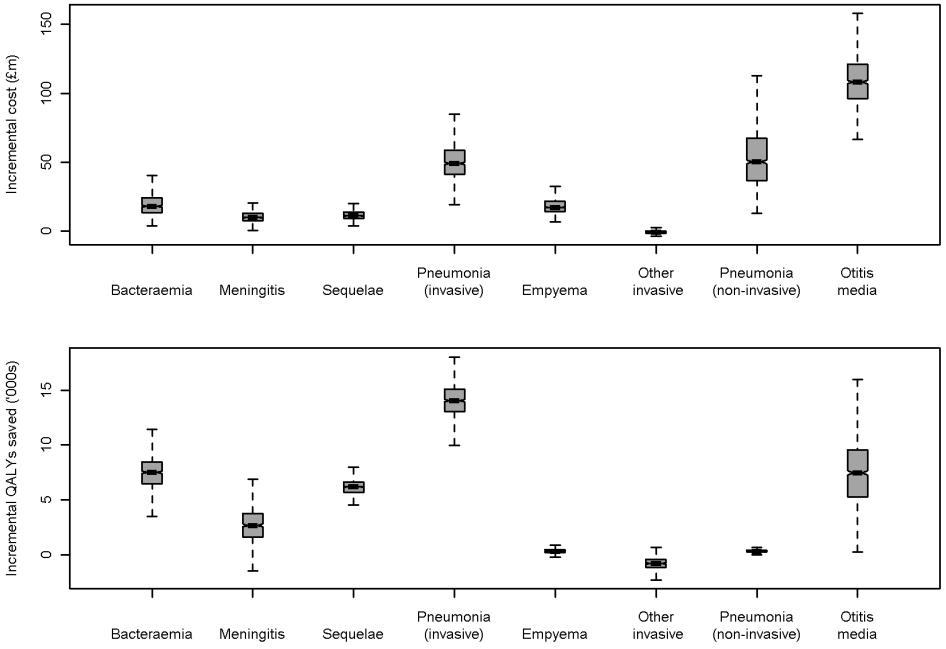

Figure 1. Incremental health care cost saved (above) and QALYs (below) saved by PCV-13 vaccination (start in 2010) compared to stopping infant pneumococcal vaccination. Boxes show the median and interquartile range of 1,000 samples, while whiskers show the full range excluding outliers.

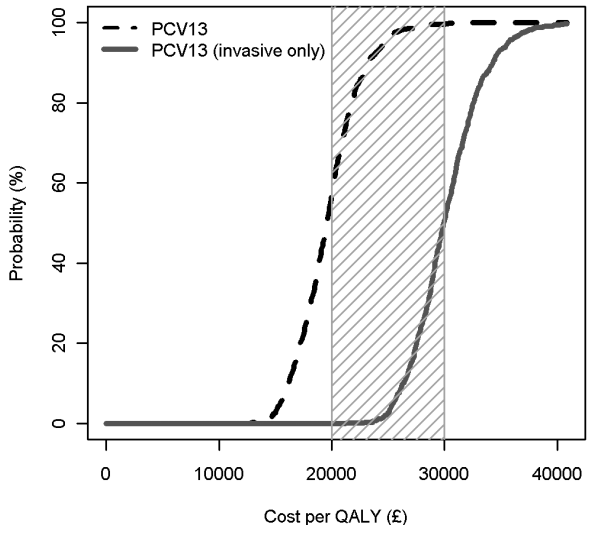

Figure 2. Cost-effectiveness acceptability curves showing the probability that PCV-13 vaccination beginning in 2010 will be cost-effective (compared to stopping infant pneumococcal vaccination). (cost per dose: £49.60 + £7.51 administration costs, discounting: 3.5%)

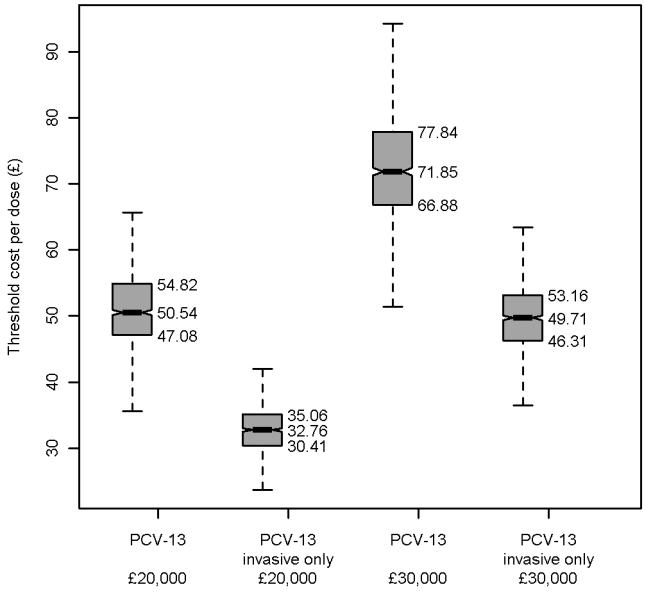

Figure 3. Threshold price per dose of PCV-13 for vaccination to be cost-effective (compared to stopping infant pneumococcal vaccination) using a threshold of either £20,000 or £30,000 per QALY gained. Boxes show the median and interquartile range of 1,000 samples, while whiskers show the full range excluding outliers. Base case assumptions are used, i.e. 3.5% discount rate for costs and benefits, 30 years time horizon, point estimate for the case ascertainment adjustment and full protection against non-PCV-13 serotypes.

Alternative scenarios

Using an infinite time horizon, discounting of benefits at 1.5% per annum instead of 3.5% makes PCV-13 more cost-effective; under this scenario PCV-13 is cost-effective even without considering non-invasive endpoints. However, excluding serotype 1 from the analysis makes PCV-13 unlikely to be cost-effective without non-invasive endpoints, and only marginally so with non-invasive endpoints. Assuming a different scenario in the estimation of non-IPD disease (see above and appendix) only has a mild effect on the cost effectiveness (see Figure 4).

DISCUSSION

Our economic evaluation of PCV-13 vaccination is based on a transmission dynamic model which estimates direct and indirect effects of vaccination targeting serotypes included in PCV-7, in PCV-13 but not PCV-7, and not in PCV-13. The evaluation shows that PCV-13 is borderline cost-effective (with 53% of the simulations below the £30,000 threshold) at current UK over-the-counter prices compared to stopping pneumococcal conjugate vaccination altogether, unless benefits due to prevention of non-invasive disease are taken into account or future benefits are discounted at a lower rate.

Table 1. Summary of parameters used in the economic evaluation.

Parameter	Mean	Distribution	Reference
Hospital bed day			
... for bacteraemia	£308	Lognormal (mean 5.73 sd 0.40)	[15]
... for meningitis	£261	Lognormal (mean 5.56 sd 0.29)	[15]
... for pneumonia	£299	Lognormal (mean 5.70 sd 0.31)	[15]
Lifetime costs following meningitis			
... in the first year	£6080	Lognormal (mean 8.71, sd 0.36)	[7]
... in subsequent years	£185	Lognormal (mean 5.22, sd 0.40)	[7]
GP consultation	£35	Fixed	[16]
GP prescriptions			
... for otitis media or pneumonia	£10.74	Fixed	[17]
... for bacteraemia or meningitis	£2.14	Fixed	[17]
Outpatient follow-up			
... for meningitis	£346	Lognormal (mean 5.85, sd 0.44)	[15]
... for otitis media	£116	Lognormal (mean 4.75, sd 0.37)	[15]
Vaccination costs			
... for PCV-13 (dose)	£49.60	Fixed	[17]
... for administration (dose)	£7.51	Fixed	Department of Health
QALY loss			
... for a hospitalisation for pneumococcal bacteraemia or pneumonia	0.079	Beta (mean 0.0079 se 0.031)	[19]
... for meningitis	0.023	Beta (mean 0.023 se 0.083)	[19]
... for a pneumonia outpatient visit	0.0037	Triangular (min 0, max 0.0074, mode 0.0038)	[20]
... for otitis media	0.0035	Beta (mean 0.0035 se 0.56)	[21]
Quality of life weights			
... for deafness	0.81	Beta (mean 0.81, se 0.028)	[22]
... for mild hearing loss	0.91	Beta (mean 0.91, se 0.015)	[22]
... for epilepsy	0.83	Beta (mean 0.83, se 0.015)	[22]
... for mild mental retardation	0.62	Beta (mean 0.62, se 0.023)	[22]
... for paresis	0.67	Beta (mean 0.67, se 0.047)	[22]
Sequalae prevalence			
... for deafness	0.08	Beta (mean 0.08, se 0.03)	[23]
... for mild hearing loss	0.21	Beta (mean 0.21, se 0.02)	[23]
... for seizures	0.07	Beta (mean 0.07, se 0.02)	[23]
... for hydrocephalus	0.07	Beta (mean 0.07, se 0.02)	[23]

Table 1. continued.

Parameter	Mean	Distribution	Reference
... for spasticity or paresis	0.09	Beta (mean 0.09, se 0.01)	[23]
... for cranial nerve palsy	0.12	Beta (mean 0.12, se 0.04)	[23]
... for visual impairment	0.02	Beta (mean 0.02, se 0.02)	[23]
Proportion non-IPD caused by S. pneumoniae			
Otitis media	0.285	Beta(mean 0.285, se 0.085)	see appendix
Pneumonia	0.245	Beta(mean 0.245, se 0.085)	see appendix

The impact of vaccination on non-invasive disease endpoints was not evaluated in the transmission model. It is difficult to infer directly, because pneumococcal serotypes causing invasive and non-invasive disease differ, and hence may be affected differently by vaccine protection, herd immunity and replacement by other serotypes or organisms. We estimated the potential vaccine impact on non-invasive endpoints by attributing the change in invasive pneumococcal disease since the introduction of PCV-7 to changes in health care attendances for otitis media and pneumonia. This method, while necessary due to data limitations (i.e. the lack of microbiological confirmation and serotyping for non-invasive disease), raises a number of issues. Firstly, although there was a reduction in GP consultations for otitis media in the THIN database following PCV-7 introduction, no such decline is observable in data from the Royal College of General Practitioners sentinel surveillance of general practitioners in England and Wales [26]. Indeed, a Finnish PCV-7 trial found that a decrease in pneumococcal-related otitis media in the vaccinated cohort due to vaccine serotypes was almost completely compensated for by an increase in otitis media due to non-vaccine serotypes [27]. Secondly, models were only fitted to GP and hospital visits and therefore did not include mortality. Although the mortality due to non-invasive disease is very low among those ages under 15, inclusion of this outcome might have made the non-invasive disease scenario even more cost-effective. Therefore scenarios that include the impact of non-invasive disease are subject to greater uncertainty than scenarios without. When the effect of vaccination on non-invasive disease is removed, PCV-13 vaccination remains cost-effective, albeit very marginally. The uncertainty around vaccine impact on non-invasive endpoints is difficult to reduce due to lack of data on non-invasive endpoints. This highlights the necessity of sentinel microbiological surveillance for non-invasive bacterial respiratory disease, as is already taking place for viral organisms [24].

A key debate surrounding pneumococcal conjugate vaccination that is highly influential in determining its cost-effectiveness is the degree of serotype replacement

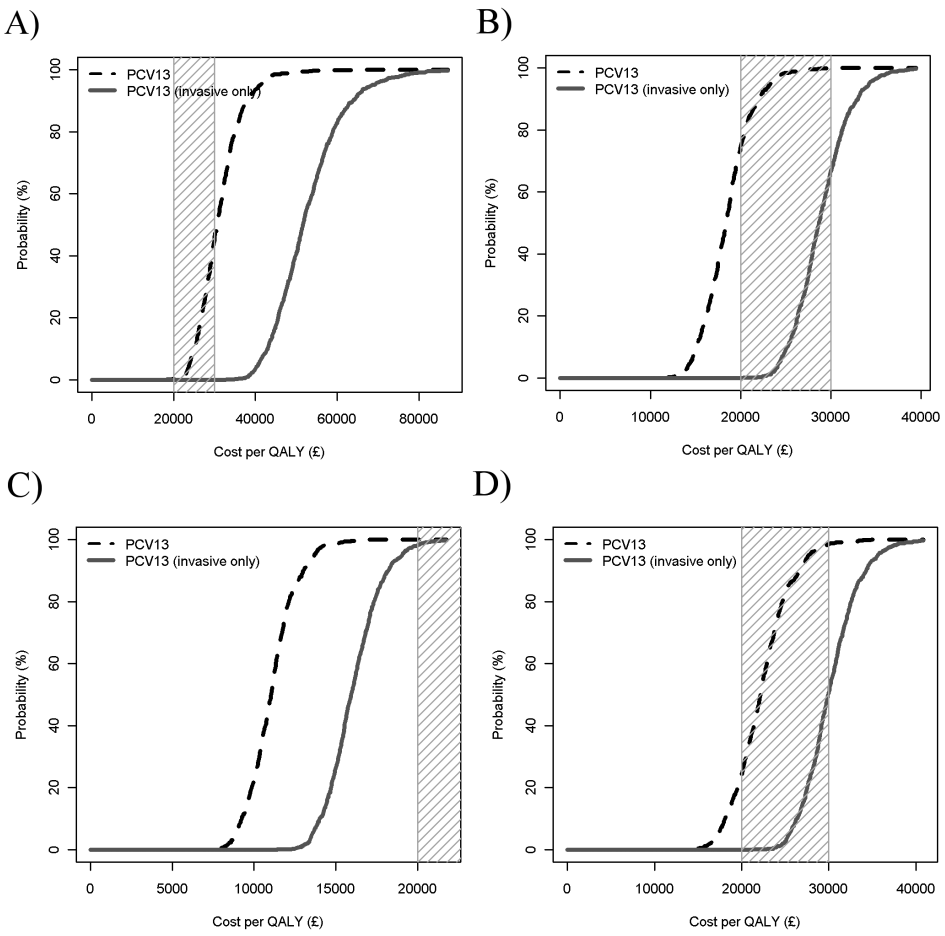

Figure 4. Threshold price per dose of PCV-13 for vaccination to be cost-effective (compared to stopping infant pneumococcal vaccination) using a threshold of either £20,000 or £30,000 per QALY gained. Boxes show the median and interquartile range of 1,000 samples, while whiskers show the full range excluding outliers. Scenarios shown are: (a) no inclusion of serotype 1 (upper left), (b) infinitive time horizon (upper right) (c) discount rate of 1.5% for benefits (lower left) (d) changing the assumption in the disease burden of non-invasive disease that is pneumococcal-related from a constant number to a percentage of all non-invasive disease (lower right).

to be expected after vaccine introduction. The base case scenario we used assumes that there is complete replacement in carriage with non-vaccine serotypes once carriage of serotypes in PCV-13 starts to decrease. This is based on the observation that there was almost complete replacement in carriage of the seven PCV-7 serotypes by non-PCV-7 serotypes following the introduction of PCV-7 vaccination in the United Kingdom. Hence the degree to which PCV-13 vaccination will be beneficial depends on the propensity of the vaccine serotypes to cause invasive disease when carried,

Table 2. Annual number of cases, health care costs and QALYs lost due to pneumococcal disease during the final year of PCV-7 vaccination, and after at least 30 years of either discontinuing pneumococcal vaccination or of changing to PCV-13.

	Final year of PCV-7	Discontinue PCV (at equilibrium)	PCV-13 (at equilibrium)
Cases:			
Invasive			
Meningits	662	886	678
Bacteremia	1,039	1,154	907
Pneumonia	3,345	3,609	2,575
Other focus	172	210	196
Overall	5,528	6,130	4,451
Non-invasive disease			
Otitis Media	176,376	285,729	89,190
Pneumonia (GP+Hospital)	4,746	10,657	2,363
Deaths:			
Meningits	90	101	96
Bacteremia	224	248	195
Pneumonia	423	462	349
Other focus	16	17	21
Overall	760	835	666
Costs:			
Invasive disease			
Hospital	£22,729,874	£25,141,469	£19,193,916
GP	£393,811	£470,968	£348,690
Sequelea	£2,071,974	£2,850,566	£2,107,250
Non-invasive disease			
Hospital	£3,580,642	£4,727,592	£1,801,225
GP	£6,466,996	£10,639,157	£3,269,921
Total costs	£31,662,654	£43,829,752	£26,721,002
QALYs lost:			
Invasive disease			
Meningits	1,228	1,466	1,297
Bacteremia	2,059	2,266	1,805
Pneumonia	3,325	3,535	2,686

Table 2. continued

	Final year of PCV-7	Discontinue PCV (at equilibrium)	PCV-13 (at equilibrium)
Other focus	202	219	269
Sequelae	915	1,324	919
Non-invasive disease			
Otitis Media	413	697	207
Pneumonia	6	25	3
Total QALYs lost	8,148	9,532	7,186

compared to non-PCV-13 serotypes. If the replacing (non-vaccine) serotypes are less invasive or virulent, then vaccination is likely to be beneficial despite not altering the overall prevalence of pneumococcal carriage. Post-PCV7 experience gives hope for replacement with less invasive serotypes [28], but this cannot be guaranteed. Hence an essential feature of our analysis is the use of a unique dataset linking pneumococcal serotypes detected in invasive cases with their clinical presentations.

Another point of discussion is the application of the same vaccine efficacy (80% over the first year) against all serotypes. Recent findings suggest that the vaccine efficacy against serotype 3 might be lower compared to the other vaccine types [29]. If this is true, then PCV-13 introduction will be less cost-effective than estimated.

Beside PCV-13, a 10-valent conjugate vaccine is also available (PCV-10 or Synflorix(R)). This vaccine was not considered for introduction in England and Wales [30] and was therefore omitted from this study. Given that the serotype formulation and impact on invasive and non-invasive disease of PCV-10 differs from PCV-13, a scenario with introduction of PCV-10 instead of a discontinuation of PCV-7 could be investigated in a situation where introduction of this vaccine is considered.

Several recent studies have been published of the cost-effectiveness of introducing PCV-13 in Europe [31-35], North America [36], Latin America [37], Asia [38;39] and Australia [40]. The studies only presented outcomes which included non-invasive disease, making a comparison to our main results difficult. However, all but two of these studies [34;38] found PCV-13 introduction to be clearly cost-effective. There are a number of differences between studies and ours in terms of setting, population, incidence of pneumococcal disease and health care costs that contribute to the difference in conclusions. There are also two important methodological differences. Firstly, all but one of the published studies used a static model, which makes realistic representation of herd immunity and serotype replacement following PCV-13 vaccination problematic, particularly since no country in the world has had sufficient post-PCV13 experience yet. Only one analysis used a dynamic model [39]; however, this model did not include competition between vaccine and non-vaccine

serotypes and hence could not explore the effect of serotype replacement. Secondly, although several studies compared PCV-7 and PCV-13 vaccination programmes [34-36;38;40] none compared introducing PCV-13 to discontinuing PCV-7. Replacing PCV-7 with PCV-13 is less cost-effective than introducing PCV-13 in a situation with no pneumococcal vaccination, since the effect on existing vaccinees is likely to persist for a number of years. To our knowledge this is the first economic study based on a dynamical model to examine a change of vaccine from PCV-7 to PCV-13, which is a highly relevant question to the many countries already using PCV-7 prior to its replacement on the market by its manufacturers.

APPENDICES AND ONLINE MATERIAL

The appendices and online material can be found at: http://www.sciencedirect.com/science/article/pii/S0264410X12014636

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CONFLICT OF INTEREST

All authors: no conflict of interest.

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chapter FOURTEEN

CONCLUSION

The aim of the research was to support sound vaccine-related decision making. The decisions which were supported were the introduction of Herpes Zoster vaccine in England and Wales (chapter 2), withholding childhood Varicella vaccination (chapter 4 & 5), recommendation of pandemic influenza vaccination of risk-groups (chapter 6 & 7), the introduction of a successor of PCV-7 in the Netherland (chapter 8), and the decision whether or not to vaccinate risk-groups with PCV-13 (the official decision was still pending on the day of writing the conclusion; chapter 9, 10 & 11). The cost-effectiveness model of PCV-13 (chapter 13) was originally performed to be used in a procurement process, however due to a lack of contenders in the procurement it was never used in practice.

Given that most of the presented research was actually used to underpin decision making it can be suggested that the main aim was accomplished. However the main aim was to support sound decision making, thus the presented work should have improved the final decision. A claim which cannot be made from the fact that the work was used. Therefore in the conclusion of this thesis the short comings of the presented work will be explored.

To highlight the various short comings and blind spots of the presented research it will help to disentangle the way information is used in a decision which is based on a cost-effectiveness analysis. To do so we can structure the information and analysis used into several hierarchical layers, see figure 1. The basis of the pyramid is the raw data; this includes the number of cases (surveillance data), the number of cases in the vaccine arm compared to the placebo arm (clinical trial data), the number of people in the vaccinated cohort (population data), the people who receive a vaccine (coverage data), the cost of a treatment or vaccine (cost data), the impact of disease on the different dimensions of health-related quality of life (EQ-5D data), the number of people who were infected (seroprevalence data), the carriage of the pathogens (prevalence data), the social structure and contacts of the population (contact data), etcetera. Analysis of the raw data can extract information and extend our knowledge. This data analysis can be seen as the second tier in the pyramid. Data analysis included in this layer are for example the estimation of vaccine efficacy parameters, the calculation of a QALY loss, the estimation of the percentage of susceptibles (by age) by the use of infectious disease models (combining incidence data, contact data, seroprevelance data and population data). The estimation of absolute incidence among risk groups etcetera. The outcomes and conclusions from the separate analysis from the second tier are brought together to estimate an overall reduction in the costs and burden of disease and are placed in relation to the overall programme costs, therefore the third tier in the hierarchical pyramid is the cost-effectiveness framework. The outcome of this third tier is presented graphically in a cost-effectiveness plain, and numerically in the cost-effectiveness ratio. Within decision making there is one more tier, the top of the pyramid, this is the decision rule, the rule which declares something cost-effective and worth considering its introduction.

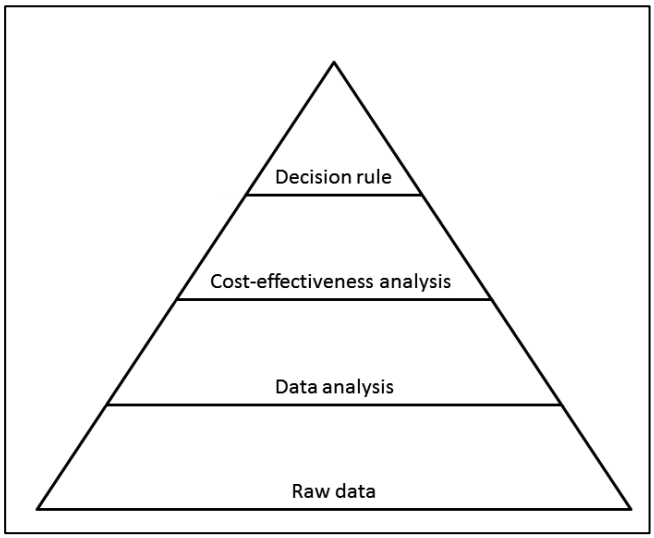

Figure 1. The hierarchical structure of the use of information in decision making in a cost-effectiveness framework.

In England the decision rule for public health interventions is based on the decision rule defined by the National Institute of Clinical Excellence (NICE). This decision rule is not strictly formulated, as in that an intervention should be introduced when the cost per QALY is below a certain threshold. However, when the cost per QALY is below £20.000 the recommendation can be based on the cost-effective outcome alone. When the cost per QAY is between £20,000 an £30,000 there is need for more caution towards introduction, and subsequent arguments has to be made; for example the innovative nature of the intervention. When the cost per QALY is above £30,000 a very strong case has to be made to prove that the intervention is an effective use of tax payers' money [1].

In the Netherlands the decision rule is much less clear compared to England. In the Netherlands the consideration of an intervention being value for money depends on the severity of the disease and the innovative nature of the intervention. When the disease is not severe the threshold is low, the lowest being €10,000 per QALY, when the disease is severe and the patients would die immediately or will suffer a very low quality of life when the intervention is withhold, the cost/QALY threshold can be up to €80.000 per QALY [2]. For vaccinations, where a plethora of disease severities are prevented the threshold is therefore unclear, thresholds of €20,000 [3] ; €40,000 [2] and €50,000 [4] are quoted to be adequate, leaving a lot of space for individual interpretation.

Although the two decision rules are by definition not using an explicit threshold per QALY, this can be the case in practice. In England vaccines are introduced on recommendation of the Joint Committee of Vaccination and Immunsation (JCVI);

this recommendation should include an assessment which demonstrate cost-effectiveness [5]. In practice the JCVI recommends the introduction of a vaccine before the price is known, as the procurement follows the positive recommendation. Therefore the JCVI state that the vaccine should be introduced when a price can be negotiated under which the programme is cost-effective [6]. Within the procurement process a benchmark price is defined, this benchmark price reflects the maximum price per dose to remain cost effective. When the price per dose in the procurement (corrected for certain award criteria) is above this benchmark price the offer will be rejected [7]. This suggests that there is an explicit threshold, however since these vaccine prices are kept in confidence the exact threshold is unknown.

In this decision pyramid there are lots of uncertainties and unknowns. From bottom to top: Data can be missing, or data collection can be biased, therefore starting the analysis with a flawed base. Analysis can be performed poorly, with inappropriate comparisons, or there can be uncertainties generated by model choice or approach, resulting in a distorted cost-effectiveness model. The cost-effectiveness model can be too simplistic, for example leaving out essential parts or investigates unrealistic scenarios or is heavily reliant on assumptions for which there is not much evidence. All those shortcomings accumulate in the robustness of the final decision.

However there are several reasons why the decision rule itself might be wrong (besides the uncertainties within the data-decision pyramid), so that a suboptimal decision is made even given a perfect cost-effectiveness analysis. The shortcomings of the decision rules will sound theoretical, but there are practical shortcomings which should be borne in mind when drawing conclusion from the analyses presented in this thesis.

First of all the following short comings are the most applicable for England, as in England public health decisions use the NICE guidance which has a more explicit threshold to define cost-effectiveness (£20.000-£30.000/QALY). NICE has the decision rule in place to optimize the budget allocation [8] of the National Health Serivce (NHS). In theory all possible health care interventions should be lined-up and money should be invested in the interventions with the lowest cost per QALY, until the complete budget is spent. In doing so the last intervention you are still able to fund will mark a cost per QALY. In practice it is impossible to line-up all possible health care interventions, therefore the decision rule is in place, where you can assess for each individual intervention if it is worth the money. This makes each analysis a piecemeal analysis [9]. Where not all options of spending the budget are compared together in one go, but where options are analysed on an individual basis and where decisions are made using the cost per QALY threshold. All CEAs in this thesis are piecemeal analyses. The decision rule should select the most effective programmes given the budget constraints.

The second problem is that NICE is optimizing the allocation of the NHS budget and vaccines are not funded out of this budget, but funded separately. Therefore it can be questionable whether the same cost per QALY should be applied. Thirdly, the NICE guidance mentions that in cases of a large budget impact (almost always the case for vaccines) the threshold is advised to be lower (due to the high budget impact you will compete with interventions who have a lower cost/QALY compared to the threshold, therefore in theory your new intervention should be more efficient as the intervention you will push out). It is therefore possible that the threshold does not reflect the available budget.

Fourthly, a cost-effectiveness analysis is a partial analysis, it focuses only on the disease burden and costs related to the particular disease intervention and exclude wider implications. Although there is a slight difference between countries; in the UK CEA includes only direct benefits, compared to the Netherlands where CEA does include indirect costs as work loss. Nevertheless for both countries the analysis remains partial as it is still focusses only on costs and burdens directly linked to only one particular disease, and does not include the wider implications. For example pandemic influenza [10]; when a pandemic hits health care workers may become ill, leading to constrains in the availability of health care workers affecting patients who are in the hospital for other reasons. Vaccination against pandemic influenza will reduce the disease burden among health care workers and therefore have a wider impact on the treatment of other patients, benefits which are not included in our analysis in chapter 7. This partiality is an important shortcoming. Although the impact of partiality can be reduced by incorporating more effects into the analysis, it is impossible to include all effects, or to foresee all implications, therefore any analysis will always be partial, focussed on only a part of the possible outcomes.

Fifthly, the time preferences are uncertain. The time preference in cost-effectiveness analysis are reflected in the time-horizon and the discounting. This time preference can become very important in the case of vaccination, where health benefits can happen far into the future, see for example chapter 5 with the cost-effectiveness of childhood vaccination against Varicella zoster. Unfortunately the time preferences within the population are very hard to estimate, and might be partially irrational or poorly consider the impact on future generations [11]. Therefore the actual used time horizon and discount rate is perhaps more based on assumption than on a population preference or on a strong rational. These preferences are very important in the interpretation of any outcome of the cost effectiveness models and can therefore result in suboptimal decisions.

Given the shortcomings listed above various improvements can be suggested for the work presented in this thesis. The suggestion can be divided into improvements within the data-decision pyramid and those outside this pyramid.

The improvements within the pyramid will affect the multiple tiers, from the collection of raw data, the analysis to the decision. For the research on varicella there are several improvements for the CEA models, firstly more data should be collected on the long term QALY loss by age for HZ as our approach was based on the experience of pain which assumed a constant relation between pain and QALY loss over the years after onset. In the infectious disease model the HZ disease incidence by age was only explained by the waning of immunity and boosting by varicella. However the incidence of zoster by age can be due to various other factors which were not included in the model, possibly over estimating the relation between the two diseases, and hence over estimating the impact of the childhood vaccine on the HZ burden. Closely monitoring HZ disease in countries where the vaccine has been introduced is therefore important. As childhood vaccination was not considered cost-effective other applications of the vaccine should be investigated, such as the vaccination of susceptible adolescents. The difficulty of an adolescent programme is however the identification of those who are still susceptible. Possible future research could therefore include the elucidation of the sensitivity and specificity of asking the adolescent/parent about their chickenpox history.

In the research on the cost-effectiveness of pandemic influenza A/H1N1 2009 the estimation of hospitalisation rates was weak, as it was based on the observations in the containment phase, when there was an active surveillance possibly leading to a higher likelihood to be hospitalised. A disease with very similar symptoms compared to other diseases, has to be monitored over several layers of care (antiviral consumption, GP visits, hospitalisations and morality) which is complicated to do. Systems to estimate the hospitalisation or death rate in a statistical sound way can be set-up and developed and tested each year on seasonal influenza. One of the parameters particularly difficult to monitor was the prevalence of symptoms in the population over the course of a pandemic. To improve the monitoring of symptoms online surveillance systems were set up, in the Netherlands (www.degrotegriepmeting.nl) before and in England (www.flusurvey.org) during the 2009 pandemic. Such online systems rely on a great number of registered volunteers who notify their flu-like symptoms on a weekly basis. Maybe these online system cover the need for future outbreaks, however the preparation can be improved by experimenting with weekly telephone surveys, selecting a perhaps more representative sample from the general population. Another system which can be set-up is the measurement of background immunity. In the 2009 pandemic this measurement was performed by testing residual laboratory samples. This system can be improved in two ways, firstly there can be an improved blood sample database reflecting the general population and secondly more knowledge can be gathered about the relation of antibodies and immunity, in particular against influenza strains previously circulated in the population. The existence of background immunity is important to access the possible problems by age group. Also protocols can be written and an infrastructure can be set-up to guarantee a quick intervention in case of mass vaccination.

In the analysis on the cost-effectiveness of PCV-13 it is assumed that the invasiveness of serotypes will remain constant, leading to a sustained reduction of disease if less-invasive serotypes increase in carriage. However given the genetic plasticity of the pneumococcus this does not have to be the case. Monitoring this invasiveness in parallel with carriage, will be important to understand and predict the post-vaccine disease burden. Given the benefits of a linked dataset of the confirmed cases containing serotype information with the medical records and the possibility to automate data analysis, linkage should be done on a routine basis, and outcomes should be routinely published, as this will improve the understanding of the disease. The relation of the role of co-infections in the disease burden caused by pneumococcus should be studied in more depth, as prevention of other diseases might reduce the burden of pneumococcal disease or vice versa. One of the main remaining challenges is the evaluation of the overall effect of PCV-vaccines on the burden of non-invasive disease, such as pneumonia. This group includes a much larger number of cases compared to invasive disease, leading to significant costs and QALY losses. The observed post-vaccination all cause pneumonia disease trends are hard to interpret, especially if they are split by risk and non-risk group patients (chapter 11).

The threshold cost per QALY is also an implicit award, because when you prevent the loss of one QALY this has a maximum value of £20-30,000 pounds in England and minimal €10,000 euro in the Netherlands. On the long term industry will therefore maximize their profit and set their price accordingly. As with any reward system it will therefore be important to update and maintain the methodology of the measurement of the quality of life, to guarantee a sound working system. In this the use of generic instruments to measure the quality of life are practical but may not be complete. For example the EQ-5D (used in chapter 6) constrains the quality of life to 5 dimensions, with each a score of only 3 levels. Therefore aspects which affect the quality of life beyond the 5 dimensions or in between the 3 levels is missed and are therefore not valuated in the decision making. In response to the latter shortcoming recently EuroQol presented a version with 5 levels for each dimension [12]. Another issue in context of the EQ-5D which merits constant update, or at least every 5 or 10 years, is the validation of the tarrif by use of time trade-off or standard gamble methods, because the perception of disease severity do change over time. Policy makers should be fully aware of these shortcomings, and policy should be in place to constantly improve and maintain the QALY measurement.

The weight the cost-effectiveness verdict receives in the final decision deserves constant evaluation. As mentioned above, in England the cost-effectiveness model forms the basis for the procurement process to comply with the recommendation from the JCVI. This direct application of the cost-effectiveness model outcome might be too explicit given the uncertainties within the analysis and the imperfections with the application of the decision rule. Also the cost-effectiveness model is

prepared by a small number of analysts who are not on the committee. Given the numerous decisions, assumptions and uncertainties within the CEA model the influence of these analysts can actually be large on the final introduction. Although these analysts are (perhaps) excellent they are not on the committee. Therefore the decision JCVI should make is whether or not the vaccine should be introduced given a certain (true) vaccine price. However this decision process will require a full understanding of the assumptions within the model by all participants. To obtain this involvement there should be more interaction between the analysts and the decision maker in the process of the analysis, as well as a strict confidentially agreement as knowledge of the vaccine price is commercially sensitive.

These short comings do not mean that the cost-effectiveness analysis is not valuable. It is a useful tool to understand the issues of a vaccination programme in detail. It forces consideration of the disease burden and/or costs. It is a structured approach, strongly propagating rational decision making, of which the outcome can be communicated to the public. All these aspects are useful additions to the decision making process.

A common theme in this thesis is the application of vaccines to control transmission or to prevent disease. For each of the three vaccines discussed there are issues with universal vaccination. Regarding varicella zoster there is a potential indirect effect on the burden of HZ, in case of the pandemic A/H1N1 2009 influenza vaccine universal childhood vaccination was not recommended due to the relative late arrival of the vaccine in respect to the peak and the concentration of severe disease among risk groups. For pneumococcal vaccination the verdict was the opposite of the influenza vaccination, introduction of vaccination among the risk groups was not thought to be cost-effective due to the indirect effects of the childhood vaccine, making vaccination with PCV of other groups in the population less valuable.

Among all three diseases the reason why certain vaccination programmes were less optimal were due to different reasons. This makes it hard to draw generic conclusions for this thesis, apart from that it is very important to consider disease specific characteristics in measuring and predicting the direct and indirect impact of the vaccination programme.

Let me finish this thesis with a quote from the Groningen (the Netherlands) born mathematician Daniel Bernoulli, who perhaps can be seen as the founding father of the field of vaccine decision making due to his work on smallpox inoculation. Although stated in 1760 (published in 1766) it is still timely [13].

"I simply wish that, in a matter which so closely concerns the well-being of mankind, no decision shall be made without all the knowledge which a little analysis and calculation can provide."

Daniel Bernoulli (1700-1782)

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ADDENDUM

SUMMARY

To build up immunity by means of a vaccine is a very successful strategy to prevent infectious diseases. When vaccines are applied on a population level they are also a good way to prevent or control the spread of infectious disease.

In the application of vaccines there are many choices to be made: for example the number of doses, the concentration, the timing of these doses (by age), which risk groups should be vaccinated, and which price is value for money. To determine what a good decision is with respect to these choices, we look at the possible consequences of these decisions and express these consequences in costs and benefits. The costs are those of the vaccination program, and the benefits are the prevented costs of disease (drugs, doctor visits, hospital visits and lost work time) and the gained health (quality of life).

The discipline of health economics is focused on the measurement of these costs and benefits in health. Within health economics various methods are developed; for example measuring the quality of life, discounting of future costs and benefits and decision-making guidelines to distinguish between good and poor interventions in respect to benefits and costs. However in the application of these techniques a detailed knowledge is essential about the effect of the vaccine, and the transmission of infectious diseases within the population. These latter factors are studied within the fields of vaccinology and epidemiology. In epidemiology we use computer models to simulate the spread of am infectious disease and predict the effects of vaccination. In this thesis health economics, vaccinology and epidemiology come together in analyses to underpin decision making regarding the vaccination programme against three different pathogens: Varicella zoster, Influenza and Steprococcus pneumoniae.

Varicella zoster

The first part of this thesis deals with the use of a vaccine to reduce disease burden caused by Varicella zoster. Varicella zoster is a virus that causes chickenpox and shingles, so there is one virus and two diseases. If a person gets infected for the first time it will get chickenpox, but once he/she is well again the virus remains in his/her body and it can reactivate later in life as shingles. There is a vaccine developed against this virus which is available in two different concentrations: a low concentration to vaccinate children and a high concentration to immunize elderly. Therefore you can ask if one or both of these vaccines should be introduced. In chapter 2 & 3 we investigate whether vaccinating the elderly (60 +) in England (Chapter 2) or the Netherlands (Chapter 3) is a good idea, and in chapter 4 and 5 we investigate whether vaccinating children (in addition to the elderly) is worth the costs (in England).

For shingles it is that the older you are the more likely it is you will get the disease, but also the more likely that the disease will be severe. Unfortunately, it is also less likely that the vaccine is effective at an older age. Through these three effects it is

best to vaccinate late, around 70 years of age, otherwise there is not enough disease to prevent, but also not too late, because at an older age the vaccine does not work sufficiently any more. Whether the vaccine is considered value for money differs between England and the Netherlands. In England, using the English incidence and the rules for conducting cost-effectiveness studies, set by the National Institute for Health and Clinical Excellence (NICE), the vaccine can be considered cost-effective, as the costs are less than 30,000 pounds per Qality Adjusted Life Year (a unit for quality of life). In Netherlands, using Dutch incidence and Dutch guidelines and assuming the price paid by the Centre for Disease Control (CDC) in the United States the vaccine is just a little too expensive given the predicted benefits.

The question of whether to vaccinate children is more difficult. This because there are (strong) reasons to believe that there is a relationship between chickenpox and shingles: the body develops a specific immune response each time it encounters the virus (signs of illness need not be exhibited). Without contact with the virus this specific immunity will disappear and increase the risk of reactivation of the dormant virus as shingles. This effect is important because it means that as the probability of encountering the virus declines, such as case when transmission is reduced by a childhood vaccination program, reactivation of the virus as shingles becomes more likely. Since almost everyone has had chickenpox as a child, almost everyone has an increased risk of shingles in case of such childhood program.

The impact of this effect on a population level is examined in Chapters 4 and 5. In these chapters we use mathematical models to study the transmission of chickenpox and its relationship with shingles. Our research shows that if you look over the 50 years after the introduction of a childhood chickenpox vaccine there is an increase of shingles, even if you vaccinate all older vaccinates against shingles. However when you look at the long term, that is more than 80 years into the future, then you reduce the total disease burden among children and elderly because vaccinated children are less likely to develop shingles. The question whether a childhood vaccination program is cost effective depends therefore on how policy makers validate future costs and benefits. If you aim for the long term benefits, and you are convinced that these long terms benefits can be achieved, the introduction of the vaccine can be cost-effective. However, on the shorter term (for example 30 years) an introduction is not cost-effective due to the expected increased incidence of shingles.

Influenza

The second pathogen discussed in this thesis is influenza, the virus that causes flu. Flu is a disease which affect many people each year, and takes many lives. However, despite the fact that many people get ill the severity of the disease is poorly described in the context of quality of life. Measuring the quality of life is part of health economics and the unit of measurement is called QALY (Quality Adjusted Life Year), where a value of 1 QALY is equivalent to one year enjoyed in perfect health. There are several methods

to measure the quality of life. One of these methods is called the EQ-5D, which stands for the 5-dimensional scale developed by EuroQol. The scale divides the quality of life in 5 dimensions: mobility, self-care, activities, pain and anxiety/depression. For each scale, there are three possibilities: not affected, slightly affected, severely affected. This generates a total of 125 combinations. The total QALY loss can be calculated based on scores given by healthy people to health states corresponding to the 5 dimensions and the time the patient suffers from the disease.

In the first few weeks after the pandemic H1N1v flu emerged in England in 2009 all new cases were recorded and monitored. This made it possible to send an EQ-5D questionnaire to patients and compare those who tested positive for influenza and those who tested negative. In total 655 questionnaires were sent and resulted in a total of 269 responders who met the inclusion criteria: fever plus another symptom of flu (186 H1N1v & 83 controls). Between the pandemic flu patients and controls there was not much difference in disease severity and the implications for quality of life: with a score of 2.74 QALD (Quality Adjusted Life Day) for H1N1v patients and 2.92 QALD for controls. However, the pandemic flu patients stayed longer at home, most likely due to specific advice from their GP.

An important part of the contingency plan for a pandemic flu is the decision whether or not to produce and purchase a pandemic vaccine. Early in the pandemic of 2009 the British government decided to purchase a vaccine against the pandemic H1N1v virus. However it takes time to develop and produce a vaccine, so much time that the first doses of the vaccine were not available until mid-October 2009. The arrival of the vaccine raised the question: to whom should they be given? And are the costs related to the distribution of the vaccine worth it? To answer these questions it was necessary to estimate how many people can still become ill after October 2009. As the population during a pandemic is almost constant and assuming that when people have had the flu they cannot get it again it is possible to estimate how many people are still eligible to get the disease. At least, when it is known how many people have had it and how many people cannot get it. People who cannot get it are people who were already immune before the pandemic flu arrived, for example because they were previously exposed to a H1N1 flu virus. In England there were two epidemic waves, one before the school summer holidays and one after. As the vaccine became available in October, it was possible to use the data from before and after the holiday to inform the mathematical model. This model combines the knowledge of immunity against H1N1 (which indicated that many elderly people were protected against infection), the estimated number of cases until that day and the growth rate of the epidemic curve after the summer break. It was possible to estimate the total number of people who were already infected and hence how many people were still eligible for infection and subsequent what the impact could be form a vaccine. Various different vaccination strategies were

simulated: vaccinating only children, vaccinating risk groups, vaccinating elderly and vaccinating everyone. Since children play a dominant role in the transmission of flu, vaccination of children has the biggest effect on the number of flu cases, much more compared to vaccinating the elderly. When children do not get flu, a lot of older people won't get flu either. However, vaccination against pandemic influenza is a race against the clock; every day you vaccinate later you reduce the chance that you have a significant impact on the overall outbreak size. On the day that the vaccine was available, 21 October 2009, it was clear that the clinical effects of H1N1 were very mild, with low mortality and low hospitalization, and people who went to the hospital were mainly patients in a risk group. The mild symptoms in combination with the fact that by the end of October many children already had encountered the virus the outcome of our analysis is that there should be a focus on risk groups in the distribution of the vaccine.

Streptococcus pneumoniae

The third part of the thesis deals with the transmission and disease caused by Streptococcus pneumoniae, a bacterium which inhabits the nasopharynx. To understand this section it is important to know that there are different types of this bacterium, called serotypes. There are over 90 different serotypes known. For reasons that are not entirely clear there is a difference in the transmission and disease severity between serotypes. There is also serotype-specific immunity. Pneumococci cause ear infections, pneumonia and meningitis. The highest disease incidence is among children and elderly. It is also important to know that there are different vaccines available, there is a polysaccharide vaccine against 23 serotypes and there are conjugate vaccines against 7, 10 and 13 serotypes. The 7 valent vaccine was available first and the 10 valent and 13-valent arrived later (PCV7 and PCV13 are from the same manufacturer). Since April and September 2006, the 7-valent pneumococcal vaccine (PCV-7) was introduced respectively in the Netherlands and England, and was replaced by PCV-10 in April 2011 in the Netherlands and by PCV-13 in England on April 2010. Although the vaccine is expensive it was still considered cost-effective because the vaccine protects not only against disease but also against transmission. As with influenza, children play a driving role in the transmission, when the children are vaccinated the transmission declines and the elderly are indirectly protected. However, there was a possibility that other serotypes would increase in transmission when the transmission of vaccine serotypes stopped due to the vaccine. The vaccine serotypes are therefore being replaced by non-vaccine serotypes. The experience in America, where the vaccine was introduced in 1999, was used as an indicator for introduction in the Netherlands and England. In America hardly any replacement was observed and therefore the vaccine was introduced. However soon after introduction in England and the Netherlands there were indications that the replacement might be higher.

In chapter 8 and 9, we examine what the implications are of this higher replacement on the cost effectiveness of PCV-7 and whether it actually did occur. We do the latter by looking for the presence of Strep. pneumoniae in the nasopharynx of children and their parents. The conclusion of these two chapters was that when there is a high degree of replacement the cost-effectiveness worsens and that there is indeed a great degree of replacement, so much that there is no decline in the total percentage of people who carry pneumococcus.

Because the PCV-13 conjugated vaccine seems to protect more effectively against the 13 serotypes compared to the 23-valent polysaccharide vaccine we can ask whether risk-groups should be vaccinated with 13-valent vaccine instead of the polysaccharide vaccine. In chapter 10 and 11, we examine this question. First by determining the additional risk of invasive disease in various risks groups (Chapter 10) and subsequently we investigated whether vaccination is cost-effective. However when the children are vaccinated others are indirectly protected, including patients in risk-groups, therefore the added benefit of vaccinating risk-groups with the 13-valent vaccine is marginal, and if there is a benefit this is only for a short duration after introduction of PCV-13 as herd immunity takes effect in the period after.

Due to the high degree of replacement the difference between serotypes become more important. When serotypes cause less severe disease there may be a decline in the expected overall disease-burden after introduction of the vaccine. To investigate this, we linked hospital data to serotype information, by doing so it was possible to investigate whether there is a difference in the degree of meningitis and mortality between the different serotypes. Subsequently we expressed this difference in the overall loss in quality of life for the different serotypes. This knowledge of the differences between serotypes was summarized by vaccine-types and used in an evaluation of the cost effectiveness of a switch of PCV-7 to PCV-13 in England and Wales (chapter 13). Showing that introduction of PCV-13 was more cost-effective compared to discontinuing PCV-7.

NEDERLANDSE SAMENVATTING

Het opbouwen van immuniteit door middel van een vaccin is een erg succesvolle strategie om ziektelast veroorzaakt bij infectie ziekten te voorkomen. Wanneer een vaccin op populatie niveau wordt gebruikt is het ook een goede manier om de verspreiding van de infectieziekte in de populatie te controleren of te elimineren.

In de toepassing van vaccins zijn er vele keuzes die gemaakt moeten worden: het aantal doses, de concentratie van die doses, het moment van die doses (leeftijd), welke risicogroepen moeten worden gevaccineerd, en de prijs die men bereid is te betalen. Voor elk van deze keuzes, zijn er goede, minder goede en slechte keuzes. Om te bepalen wat een goede en een minder goede keuze is kijkt men naar de mogelijke gevolgen van die keuzes en drukt deze gevolgen uit in kosten en baten. De kosten zijn de kosten voor het vaccinatie programma, en de kwantitatieve baten zijn het voorkomen van ziekte gevallen met de daarbij behorende kosten, zoals medicijnen, arts bezoek, ziekenhuis bezoek, verloren werktijd en de kwalitatieve baten in gezondheid gemeten in de kwaliteit van leven.

De gezondheids-economie houdt zich bezig met het meten van kosten en baten van gezondheid. Binnen de tak van de gezondheids-economie zijn er verschillende methoden ontwikkeld om dit te doen. Dit zijn bijvoorbeeld methoden voor het meten van de kwaliteit van leven, verdiscontering van toekomstige kosten en baten en een besluitvormingsregel om onderscheid te maken tussen interventies waarvoor de kosten opwegen tegen de opbrengst. In de toepassing van deze technieken is echter ook gedetaileerde kennis nodig over de werking van een vaccin en de transmissie van de infectieziekten waartegen het vaccine werkt. Deze factoren worden bestudeerd binnen de vakgebieden van vaccinologie en epidemiologie. Binnen de epidemiologie wordt er gebruik gemaakt van computermodellen om de verspreiding van ziekten te simuleren en om de gevolgen van een vaccin te voorspellen. In dit proefschrift komen de gezondheids economie, vaccinologie en epidemiologie samen en worden toegepast in vaccinatie beslissingen voor drie verschillende ziekteverwekkers: Varicella zoster, Influenza en Steprococcus pneumoniae.

Varicella zoster

Het eerste gedeelte van dit proefschrift gaat over het gebruik van een vaccin om de ziektelast door Varicella zoster te verminderen. Varicella zoster is een virus dat waterpokken en gordelroos veroorzaakt, er is dus één virus en twee ziekten. Als je voor de eerste keer in aanraking komt met het virus krijg je waterpokken, echter nadat je weer beter bent blijft het virus in je lichaam waardoor het virus later weer actief kan worden als gordelroos. Tegen het Varicella zoster virus is er een vaccin en dit vaccin is in twee verschillende concentraties beschikbaar: een lage concentratie om kinderen te vaccineren en een hoge concentratie voor ouderen. Hierdoor rijst de vraag of we één of beide vaccins moeten gebruiken. In hoofdstuk 2 & 3 onderzoeken we de vraag of we de ouderen (60+) in England (hoofdstuk 2) of Nederland (hoofdstuk 3) moeten

vaccineren tegen gordelroos, en in hoofdstuk 4 & 5 onderzoeken we of het vaccineren van kinderen (naast de ouderen) de moeite waard is (in Engeland).

Voor gordelroos geldt dat hoe ouder je bent hoe meer kans je hebt om de ziekte te krijgen, maar ook hoe erger de ziekte is wanneer je het krijgt en, helaas, hoe minder de kans dat het vaccin goed werkt. Door deze drie zaken kun je het beste vrij laat vaccineren (rond 70 jaar), omdat anders er niet voldoende ziekte wordt bestreden, maar ook weer niet te laat, want dan werkt het vaccin niet voldoende. Of de prijs van het vaccin het waard is verschilt tussen Engeland en Nederland. In Engeland, gebruik makend van de Englse incidentie en regels voor het uitvoeren van kosten effectiviteits studies is het vaccin het waard, dat wil zeggen dat het minder kost dan 30.000 Britse pond per Qality Adjusted Life Year (een eenheid voor kwaliteit van leven). In Nederland, gebruik makend van Nederlandse incidentie en Nederlandse regels, en uigaande van de prijs die het 'Centre for Disease Control' (CDC) in de Verenigde Staten betaalt is het vaccin net iets te duur in verhouding tot de opbrensten.

De vraag of we de kinderen moeten vaccineren is moeilijker te beantwoorden. Er zijn namelijk (sterke) redenen om aan te nemen dat er een relatie is tussen waterpokken en gordelroos. De relatie is dat het lichaam een speciefieke immuunresponse aanmaakt elke keer wanneer het in aanraking komt met het virus (je hoeft niet perse ziek te worden). Wanneer je niet in aanraking komt met het virus verdwijnt de specificiteit van de immuunrespons wat de kans op een reactivatie van het virus verhoogt. Dit effect is belangrijk, want dit betekent dat wanneer je niet meer met het virus in aanraking komt, zoals het geval is wanneer de transmissie van het virus veel minder wordt door het vaccineren van alle kinderen, je meer kans hebt op een reactivatie van het virus als gordelroos. Aangezien bijna iedereen waterpokken heeft gehad als een kind geldt dit voor een groot gedeelte van de populatie.

Hoe erg dit is hebben we onderzocht in hoofdstuk 4 en 5. In deze hoofdstukken maken we gebruik van wiskundige modellen om de verspreiding van waterpokken te bestuderen en de relatie met gordelroos. Uit ons onderzoek blijkt dat wanneer je de kinderen vaccineert en je kijkt over de komende 50 jaar er een toename is van gordelroos, zelfs als je alle ouderen vaccineert tegen gordelroos. Echter kijk je op de lange termijn, meer dan 80 jaar in de toekomst, dan is vaccinatie tegen waterpokken positiever, want dan verminder je de ziekte omdat gevaccineeerd kinderen minder kans hebben op gordelroos. De vraag of het waard is, want het kost veel geld, hangt of hoe je de opbrengsten in de toekomst waardeert. Als je de lange termijn voordelen erg belangrijk vindt en je bent ervan overuigd dat de lange termijn voordelen behaald kunnen worden dan is de introductie van het vaccin het waard. Echter als het vaccin zich moet terug betalen op de kortere termijn (bijvoorbeeld 30 jaar) dan is het vaccin het niet waard om te introduceren.

Influenza

De tweede ziekteverwekker besproken in dit proefschrift is Influenza, het virus dat griep veroorzaakt. Griep is een ziekte die elk jaar vele mensen treft en vele levens eist. Echter, ondanks dat er veel mensen ziek worden is de ernst van de ziekte slecht beschreven in de context van kwaliteit van leven. Het meten van de kwaliteit van leven is een tak van de gezondheidseconomie. Deze tak probeert een numerieke waarde te geven aan de staat van het leven. Het hanteert een eenheid met de naam QALY wat staat voor Quality Adjusted Life Year, waar een waarde van 1 QALY gelijk staat aan 1 jaar genoten in perfecte gezondheid. Er zijn verschillende methoden om deze waarde te meten. Een van de ontwikkelde methoden heet de EQ-5D, wat staat voor de 5 dimensionale schaal ontwikkeld door EuroQol. De schaal deelt de kwaliteit van leven in 5 dimensies: mobiliteit, zelfredzaamheid, normale activiteiten, pijn en depressie. Voor elke schaal zijn er drie mogelijkheden; niet, een beetje, erg. Dus in totaal zijn er 125 verschilende mogelijkheden om de schaal in te vullen. De score wordt vertaald naar QALYs door middel van een vergelijking met scores die gezonde mensen hebben gegeven aan een gezondheidsstatus die overeenkomt met de aangegeven score op de 5 dimensies.

Toen de pandemische griep H1N1v in 2009 opkwam werden in England gedurende de eerste paar weken alle nieuwe gevallen geregistreerd en gevolgd. Dit maakte het mogelijk om patiënten die positief waren getest voor influenza een EQ-5D vragenlijst voor te leggen, net als mensen die negatief waren getest. De laatst genoemde groep kon figureren als controle groep. In totaal verstuurden we 655 questionnaires naar patiënten waarvan er in totaal 269 reageerden die voldeden aan de inclusie criteria: koorts plus een ander symptoom van griep (186 H1N1v & 83 controles). Tussen de pandemische grieppatiënten en de controles zat niet veel verschil qua ernst van de ziekte en de implicaties voor de kwaliteit van leven, 2.74 QALD voor H1N1v patienten en 2.92 QALD voor controles. Echter de pandemische grieppatiënten bleven langer weg van hun werk, meest waarschijnlijk door specifiek doktersadvies.

Een belangrijk onderdeel van het opgestelde rampenplan voor een pandemische griep is de productie en aanschaf van een pandemisch vaccin. Al vroeg in de pandemie van 2009 was besloten door de Engelse overheid om een vaccin tegen het pandemische H1N1v virus aan te schaffen. Echter, het kost tijd om een vaccin te produceren, zoveel tijd dat de eerste doses van het vaccin niet beschikbaar waren voor half oktober 2009. Het arriveren van nieuwe doses brengt de vraag: aan wie moet het gegeven worden? En zijn de gemaakte kosten voor het verspreiden van het vaccin het waard? Om deze vraag te beantwoorden moet je een schatting maken van hoeveel mensen nog ziek kunnen worden na oktober 2009. Aangezien de bevolking tijdens een pandemie in een land nagenoeg constant is en onder de aanname dat wanneer je de griep hebt gehad je het niet weer krijgt kun je een schatting maken van hoeveel mensen de ziekte nog kunnen krijgen. Tenminste, als je weet hoeveel mensen de ziekte hebben gehad en hoeveel mensen de ziekte soieso niet konden krijgen omdat ze al immuun waren

voordat de pandemische griep arriveerde, bijvoorbeeld doordat ze al eens eerder een H1N1 griep hadden gehad. Voor Engeland waren er twee epidemische golven, één voor de zomervakantie en eentje erna. Aangezien het vaccin in oktober beschikbaar kwam was het mogelijk om de data van voor en na de vakantie te gebruiken voor het bijstellen van het computersimulatiemodel. Dit model combineert de kennis van immuniteit tegen H1N1v, dat aangaf dat veel ouderen beschermd waren tegen een infectie en de geschatte gevallen van de griep. Op basis van de groeisnelheid van de epidemische curve na de vakantie was het mogelijk om een schatting te maken van het aantal mensen (incl. kinderen) dat het virus al had gehad, en dus hoeveel het nog konden krijgen en vervolgens wat de mogelijke impact zou zijn van vaccinatie. We testten verschillende vaccinatie strategieën, zoals enkel het vaccineren van kinderen, het vaccineren van risicogroepen, het vaccineren van ouderen en het vaccineren van iedereen. Omdat kinderen een erg dominatne rol spelen in de transmissie van griep heeft het vaccineren van kinderen het grootste effect op het aantal griep gevallen, veel groter dan het effect van het vaccineren van ouderen, dit omdat wanneer kinderen het niet krijgen veel ouderen het ook niet krijgen. Echter, vaccinatie tegen pandemische griep is een race tegen de klok, elke dag dat je later vaccineert verklein je de kansen dat je een significante impact hebt op de totale grootte van de uitbraak. Op de dag dat het vaccin beschikbaar was, 21 oktober 2009, was het duidelijk dat de klinische gevolgen van H1N1v erg mild waren: een lage mortaliteit, een lage hospitalisatie en de mensen die naar het ziekenhuis gingen waren voor het grootste gedeelte in risicogroepen. De milde symptomen in combinatie met het feit dat tegen het eind van oktober erg veel kinderen het virus al hadden gehad maakte dat de uitkomst van onze analyse was dat een grote campagne tegen pandemische griep niet de moeite waard bleek. De eerste doses zouden beschikbaar moeten zijn voor risicogroepen. Dit is onder de aaname dat je de kosten voor het vaccin al hebt afgeschreven en dat alleen de toedieningskosten van het vaccin er toe doen.

Streptococcus pneumoniae

Het laatste gedeelte van het proefschrift gaat over de transmissie en ziekte veroorzaakt door Streptococcus pneumoniae, een bacterie die groeit in de neusholte. Voor het begrijpen van het onderzoek is het erg belangrijk om te weten dat er verschillende typen zijn van deze bacterie, zogenoemde serotypen. Er zijn wel 90 verschillende serotypen bekend. Om redenen die niet geheel duidelijk zijn is er een verschil in transmissie en ernst van de ziekte tussen de verschillende serotypen, ook is de immuniteit serotype-specifiek. Pneumokokken veroorzaken onder andere oorontsteking, long ontsteking en meningitis, waarbij de hoogste incidentie van ziekte voorkomt bij kinderen en bij ouderen. Het is belangrijk om te weten dat er verschillende vaccins zijn; een polysacharide vaccin tegen 23 serotypen en geconjugeerde vaccins tegen 7, 10 en 13 serotypen, waarbij het 7-valent vaccin het eerst beschikbaar was en het 10-valent en 13-valent pas later op de markt kwamen (PCV7 en PCV13 is van dezelfde

fabrikant). Sinds april en september 2006 is het 7-valent pneumokokkenvaccin (PCV-7) ingevoerd in respectievelijk Nederland en England. Echter, PCV-7 werd vervangen door PCV-10 in april 2011 in Nederland en in april 2010 vervingen de Engelsen PCV-7 voor PCV-13. Het vaccin is erg kostbaar, maar was het toch waard om in te voeren omdat het vaccin, naast de ziekte ook de transmissie voorkomt. Net als bij influenza spelen de kinderen de belangrijkste rol in transmissie. Wanneer er door vaccinatie geen transmissie meer is tussen kinderen worden de ouderen indirect beschermd. Je vaccineert alleen kinderen maar je voorkomt ziekte bij kinderen én ouderen. Echter, er was een mogelijkheid dat andere serotypen op zouden komen wanneer de transmissie van serotypen waar tegen is gevaccineerd wordt gestopt. De vaccin-serotypen worden vervangen door niet-vaccin-serotypen (replacement). De ervaringen in Amerika, waar het vaccin PCV-7 al in 1999 was geïntroduceerd, werden gebruikt als een leidraad voor introductie in Nederland en Engeland. In Amerika was nauwelijks iets van een vervanging waargenomen. Al snel na introductie waren er indicaties dat deze vervanging groter zou kunnen zijn in Nederland en Engeland. In hoofdstuk 8 en 9 onderzoeken we wat de gevolgen kunnen zijn van deze vervanging op de kosteneffectiviteit van PCV-7 en of deze vervanging daadwerkelijk heef plaats gevonden. Dit laatse doen we aan de hand van de aanwezigheid van Streptococcus in de neusholte van kinderen en hun ouders. De conlcusie van de twee hoofstukken is: wanneer er een grote mate van vervanging is verslechterd de kosteneffectiviteit. Tevens blijkt dat er inderdaad een grote mate van vervanging is, zoveel dat er geen enkele daling is in het totale percentage mensen dat streptokokken bij zich draagt.

Omdat het PCV-13 vaccin beter lijkt te werken tegen de 13 serotypen dan het 23-valent vaccin, kunnen we de vraag stellen of we risicogroepen moeten vaccineren met het 13-valent vaccin. In hoofstuk 10 en 11 onderzoeken we deze vraag, eerst door de extra kans op ziekte vast te stellen voor de verschillende risicogroepen (hoofdstuk 10) en vervolgens door te onderzoeken of vaccinatie kosten effectief is. De uitkomst is dat wanneer de kinderen worden gevaccineerd en dus andere mensen indirect worden beschermd, de extra voordeel van het vaccineren van risicogroepen met het 13-valent vaccin maar van korte duur is.

Door de hoge mate van vervanging wordt het belangrijk wat de eigenschappen zijn van de serotypen die de plaats overnemen. Wanneer deze serotypen minder erge ziekte veroorzaken kan er een verschuiving zijn in de verwachte ziektelast door de introductie van het vaccin. Om dit te onderzoeken hebben we ziekenhuisgegevens gekoppeld aan serotype informatie. Hierdoor was het mogelijk om te onderzoeken of er een verschil is in de mate van meningitis en sterfte tussen de verschillende serotypen. We gaven het verschil aan in het verlies van QALYs. Deze kennis tussen het verschil tussen serotypen hebben we opgesomd in vaccin-typen en gebruikt in een evaluatie van de kosteneffectiviteit van de switch van PCV-7 naar PCV-13 in England. De conclusie van deze analyse is dat het introduceren van PCV-13 een betere keuze is dan het stoppen met pneumokokken vaccinatie.

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CURRICULUM VITAE

Albert Jan van Hoek was born on 27th August 1980 in Hardenberg, the Netherlands. After graduating from the Greijdanus College Zwolle (VWO) in 1999, he attended the University of Groningen to study Economics. After obtaining his propedeutical exam and one additional year he started a degree in Biology. He studied Biology from September 2001 to January 2007.

Within the field of Biology he specialised in Medical Biology with a focus on the application of biology in business and policy. His two main internships were related to infectious diseases. At the end of his degree he worked for some months at the pharmacoeconomics department of Prof. M.J. Postma at the University of Groningen.

Having gained experience in the field of health economics, and with a background in infectious diseases he started in February 2007 as a health economist/infectious disease modeller at the Health Protection Agency (HPA) in London, England, where he works until today.

Initially he was based in the Modelling and Economics unit under the supervision of Prof. W.J. Edmunds, but later moved into the Immunisation department under guidance of Prof. E. Miller. In his role he gained experience in epidemiological and health economical research applied to various pathogens and vaccination scenarios.

During his time at the HPA he has been seconded twice: two months to the Medical Research Council in the Gambia, where he analysed data on pneumococcal disease, and three month to the Wellcome Trust in Kenya where he worked on Rotavirus.