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Original article

Health and economic impact of PHiD-CV in Canada and the UK: a Markov modelling exercise

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Abstract

Objective:
The spectrum of diseases caused by *Streptococcus pneumoniae* and non-typeable *Haemophilus influenzae* (NTHi) represents a large burden on healthcare systems around the world. Meningitis, bacteraemia, community-acquired pneumonia (CAP), and acute otitis media (AOM) are vaccine-preventable infectious diseases that can have severe consequences. The health economic model presented here is intended to estimate the clinical and economic impact of vaccinating birth cohorts in Canada and the UK with the 10-valent, pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) compared with the newly licensed 13-valent pneumococcal conjugate vaccine (PCV-13).

Methods:
The model described herein is a Markov cohort model built to simulate the epidemiological burden of pneumococcal- and NTHi-related diseases within birth cohorts in the UK and Canada. Base-case assumptions include estimates of vaccine efficacy and NTHi infection rates that are based on published literature.

Results:
The model predicts that the two vaccines will provide a broadly similar impact on all-cause invasive disease and CAP under base-case assumptions. However, PHiD-CV is expected to provide a substantially greater reduction in AOM compared with PCV-13, offering additional savings of Canadian $9.0 million and £4.9 million in discounted direct medical costs in Canada and the UK, respectively.

Limitations:
The main limitations of the study are the difficulties in modelling indirect vaccine effects (herd effect and serotype replacement), the absence of PHiD-CV- and PCV-13-specific efficacy data and a lack of comprehensive NTHi surveillance data. Additional limitations relate to the fact that the transmission dynamics of pneumococcal serotypes have not been modelled, nor has antibiotic resistance been accounted for in this paper.

Conclusion:
This cost-effectiveness analysis suggests that, in Canada and the UK, PHiD-CV's potential to protect against NTHi infections could provide a greater impact on overall disease burden than the additional serotypes contained in PCV-13.

Introduction

Streptococcus pneumoniae is an important cause of respiratory disease worldwide, accounting for a range of illnesses in young, elderly, and immunocompromised individuals. These conditions include disseminated invasive diseases (ID) (e.g., bacteraemia and meningitis), non-invasive lower respiratory tract

infections (e.g., pneumonia), and non-invasive upper respiratory tract infections (e.g., sinusitis and acute otitis media [AOM])[1].

Haemophilus influenzae is another major cause of infection, particularly in young children[2]. It is often transmitted via contact with respiratory droplets emitted from asymptomatic nasopharyngeal carriers[2]; and carriage rates of *H. influenzae* can be increased in places of prolonged close contact, such as daycare centres and care homes[3,4]. Non-typeable *H. influenzae* (NTHi) strains (those without a polysaccharide capsule) are significant pathogens that can affect both adults[5] and children[6]. NTHi is most commonly linked with mucosal diseases, such as otitis media (OM) (that tends to predominate in children) and sinusitis (that occurs across all age groups)[7]. However, NTHi can also cause ID. Previously, ID caused by NTHi was believed to only occur in children with immunological or anatomical defects that pre-disposed them to bacterial infection[8]. However, it has now become clear that NTHi may cause bacteraemia and meningitis in otherwise healthy children[8]; although it is more likely to affect young children, children with underlying disease, and adults aged >65 years[9,10]. The relative importance of invasive NTHi infections has increased in parallel with the decline in invasive *H. influenzae* serotype b disease achieved through the routine immunization of infants[11]. In some populations, NTHi is now responsible for over 50% of ID cases caused by *H. influenzae*[9,12,13].

Pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV; GlaxoSmithKline Biologicals, Rixensart, Belgium) is a 10-valent pneumococcal conjugate vaccine that includes serotypes 1, 5, and 7F in addition to 4, 6B, 9V, 14, 18C, 19F, and 23F in the heptavalent pneumococcal conjugate vaccine (PCV-7; Pfizer/Wyeth, USA). Serotypes 1 and 5 are associated with complicated pneumonia or empyema, as well as other syndromes, in children aged 2–10 years[14–17]. The serotypes included in PHiD-CV should cover ~85% of all ID in children (up to 90%) in Europe[18]. PHiD-CV employs a novel carrier protein (protein D) derived from NTHi for eight of the 10 pneumococcal serotypes included in the vaccine. By virtue of this carrier protein, PHiD-CV is designed to offer the potential for protection against disease caused by NTHi. Prymula *et al.*[19] found that a predecessor of PHiD-CV that contained pneumococcal polysaccharides from serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F conjugated individually to NTHi-protein D reduced the overall incidence of OM by 33.6%, and the incidence of OM caused by *H. influenzae* (including NTHi) by 35.6%.

Here we describe a health economic analysis that compares the estimated economic impact of PHiD-CV with the recently licensed 13-valent pneumococcal conjugate vaccine (PCV-13; Pfizer Inc., New York) in the UK and Canada, under base-case conditions that include minimal estimations of NTHi infection rates in ID. PCV-13 contains serotypes 3, 6A, and 19A in addition to the 10 serotypes in PHiD-CV[20]. An assessment of health economic models for PCVs has identified two important parameters that should ideally be incorporated in all future pharmacoeconomic analyses, namely indirect (herd) protection of non-vaccinated people and the ecological replacement of vaccine-type pathogens by other serotypes (serotype replacement)[21]. Other important factors to consider include the potential for cross-reactivity between related *S. pneumoniae* serotypes and the impact of protection against NTHi[22]. The study presented here aims to meet these requirements for pharmacoeconomic models of pneumococcal conjugate vaccination while estimating the cost-effectiveness of PHiD-CV vs PCV-13 in Canada and the UK. Results from these two countries are presented together due to the relative similarity of their healthcare systems (citizens of both countries are eligible for free [tax-funded] visits to doctors and specialists, and free hospital treatment, but must pay towards prescription drugs).

Materials and methods

The model described here is a Markov cohort model, built to simulate the epidemiological burden of pneumococcal- and NTHi-related diseases (ID, community acquired pneumonia [CAP] and AOM) within hypothetical birth cohorts of 348,000 and 772,500 newborns in Canada[23] and the UK[24], respectively, in 2007 (Table 1). Cohort-based analyses represent one of the most common forms of health economic modelling and are particularly useful for determining the direct impact of medical interventions (as described previously by Sonnenberg and Beck[25] and Beck *et al.*[26]).

In a Markov model, the individuals of the birth cohort move between Markov states according to estimated transition probabilities[25,26]. In this model, a birth cohort is followed over a lifetime from birth to death with a cycle length of 1 month (1128 month-long cycles, corresponding to 94 years). Our model has a number of mutually exclusive disease-related outcomes including meningitis, bacteraemia, CAP, AOM, no pneumococcal infection, and death. During each cycle, the probability of entering a specific health state is calculated using incidence rates of disease caused by *S. pneumoniae* and NTHi. These incidence rates are then used to estimate the probability of disease-management options for each of the diseases considered (Figure 1).

The model utilizes serotype-specific distributions per disease type and per age group (Table 1 and Appendix Table A1) for both countries[27–30]. Furthermore, since factors such as disease frequency, contact matrix, and hospital uptake differ across geographical regions, parameters concerning epidemiology and disease management are also

Table 1. Country-specific model parameters.

Parameter	Canada value	UK value
Size of population in 2007	32,976,200[23]	60,975,400[24]
Size of birth cohort in 2007 (cohort model)	348,000[23]	772,500[24]
Serotype distribution	Age-specific data*[27,28]	Age-specific data*[29,30]
Discount rate (costs and effects)	3%[37]	3.5%[36]
Incidence of meningitis (cases per 100,000 people)	Age-specific data*[28,38]	Age-specific data*[39]
CFR for meningitis	Age-specific data*[38]	Age-specific data*[40]
% of cases of ID with long-term neurological sequelae	No data available (rate of sequelae assumed to be equal to that reported in the UK)	Age $<$ 18 years: 7%[38] Age $\geq$ 18 years: 19%[38]
% of cases of ID with long-term hearing-related sequelae	No data available (rate of sequelae assumed to be equal to that reported in the UK)	Age $<$ 18 years: 13%[38] Age $\geq$ 18 years: 26%[38]
Incidence of bacteraemia (cases per 100,000 people)	Age-specific data*[28,38] (for both hospitalized and outpatient bacteraemia)	Age-specific data*[42] (hospitalized bacteraemia only)
CFR for bacteraemia	Age-specific data*[41]	Age-specific data*[42]
Hospitalization rate for pneumonia (cases per 100,000 people)	Age-specific data*[28,38]	Age-specific data*[42]
CFR for pneumonia	Age-specific data*[41]	Age-specific data*[42]
GP/PCP consultation rate for pneumonia	Age-specific data*[28,38]	Age-specific data*[42]
Annual number of myringotomy procedures (per 100,000 people)	Age-specific data*[28,43]	Age-specific data*[44,45]
GP/PCP consultation rate for AOM (per 100,000 people)	Age-specific data*[28,43]	Age-specific data*[46]

*For the actual values used for each age group, please see the Appendix tables.
AOM, acute otitis media; CFR, case fatality ratio; GP, general practitioner; ID, invasive disease; PCP, primary care physician.

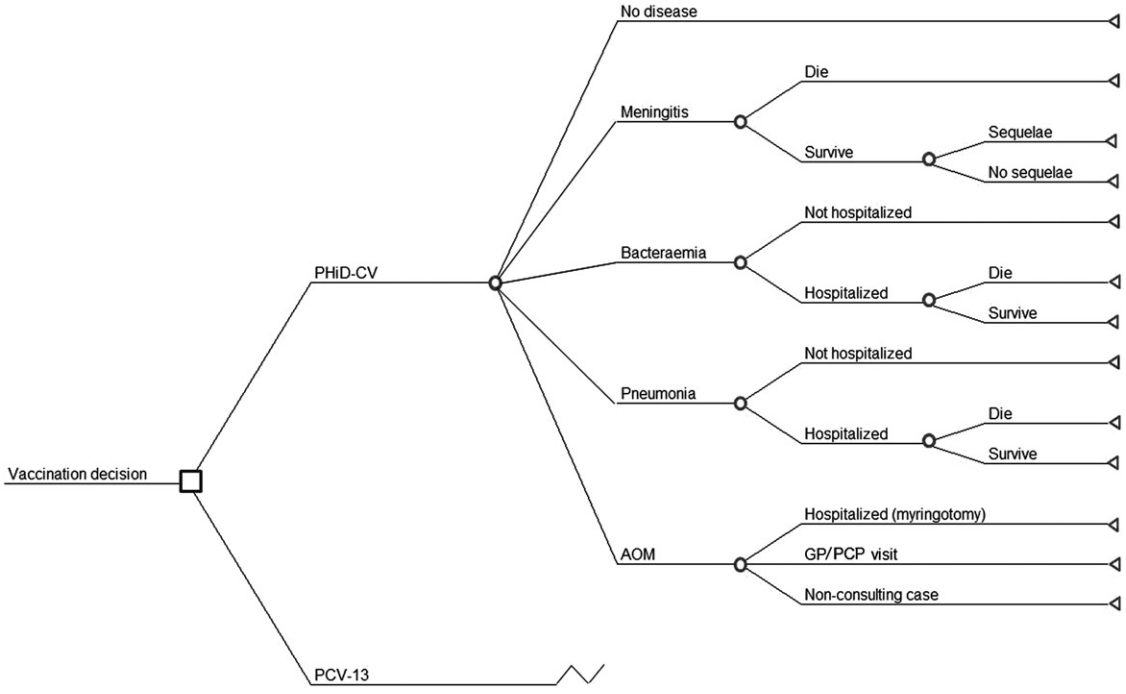

Figure 1. Markov cohort model design. The cohort model is Markov-based with three exclusive health states: no disease, sequelae, and death. The transition from 'no disease' to 'sequelae' or 'death' is calculated based on this decision tree. In the model, only meningitis can lead to long-term sequelae; meningitis and bacteraemia include NTHi meningitis and NTHi bacteraemia, respectively; and non-consulting AOM are accounted for in the quality-of-life impact calculation. AOM, acute otitis media; GP, general practitioner; PCP, primary care physician; NTHi, non-typeable *Haemophilus influenzae*.

specified in a country-specific manner. Age-specific overall monthly mortality rates (Appendix Table A2) were extracted from country-specific national databases[24,31]. Finally, specific unit costs and quality adjusted life years (QALYs) were estimated for each age–time unit so that an accumulated cost and QALY estimate for the birth cohort was reported by summing all of the unit estimates over the cohort's lifetime.

Serotype and pathogen replacement are both defined as the substitution of vaccine serotypes/pathogens by non-vaccine serotypes/pathogens in a vacant niche. Replacement has an individual component, which is the increased risk of nasopharyngeal colonization by a non-vaccine serotype/pathogen when exposed, and a collective component resulting from the increased circulation of non-vaccine serotypes/pathogens in a partially vaccinated population (the opposite of herd protection). Replacement may be observed in clinical trials (the individual component) and in post-marketing observational studies (a combination of individual and collective components). In the model presented here, the individual component of replacement is applied by reducing direct vaccine effectiveness estimates, while the collective component is combined with herd protection to estimate an indirect vaccine effectiveness rate, reported as net indirect effect, and applied directly to the number of predicted health outcomes (see 'Net indirect effect' section).

The analysis described here estimated the expected improvements in health outcomes provided by PHiD-CV and PCV-13 using background epidemiology data from Canada and the UK prior to the introduction of PCV-7. Currently, the UK employs PCV-13 for routine childhood immunization[32], whereas in Canada either PHiD-CV or PCV-13 is used, depending on province or territory[33]. While using pre-PCV-7 epidemiology as a basis to estimate the impact of PHiD-CV or PCV-13 may not accurately reflect the current status of routine vaccination in Canada and the UK, the pre-PCV-7 vaccine era epidemiology can be considered to be relevant for decision-making. This assumption simplified the calculation of vaccine impact, first by removing issues surrounding the heterogeneous deployment of vaccines in Canada; second, by removing the need to model the epidemiological ramifications of multiple transitions from one PCV to another; and finally, by removing the possibility of under-estimating the value of any of the vaccine formulations if that country had already been using PCV-7 for some time. The assumption of a vaccine-naïve setting was not expected to significantly influence the overall conclusions of the model, in terms of deciding which vaccine is expected to provide the greatest impact on disease and costs.

The model was used to compare two independent 3 + 1 regimens (doses at 2, 4, 6, and 13 months in Canada and at 2, 3, 4, and 13 months in the UK) of PHiD-CV and PCV-13. Although a 2 + 1 schedule for PCV-13 is currently used in the UK (given at 2, 4, and 13 months)[32] and in Quebec (the rest of Canada uses a 3 + 1 schedule), we simulated the impact of a 3 + 1 schedule for both vaccines in both countries, as vaccine efficacy is highest using a 3 + 1 schedule, and this is what was used in the vaccine efficacy trial from Prymula *et al.*[19]. For each vaccination scenario modelled in the analysis, the model estimates the expected effect of vaccination on invasive pneumococcal disease (acute episodes of meningitis and bacteraemia, and sequelae of meningitis), all-cause CAP (hospitalized and non-hospitalized cases) and all-cause AOM (hospitalized [myringotomies] and non-hospitalized cases). The residual burden of disease calculated by the model includes the number of pneumococcal/NTHi-related outcomes, the number of deaths and the number of survivors with sequelae. These estimates are then used to compute the total life-years and QALYs gained for all individuals in the cohort (lifetime gains). The model is also capable of calculating direct healthcare costs for the health system, families, and third-party payers, and the societal productivity gained as a result of preventing acute disease, early mortality, and disabilities. This is done using the human capital approach[34].

Since cohort models follow a group of individuals over time, it is generally accepted that outcomes should be discounted to allow a proper assessment of the benefit from the start of the intervention[35]. Country-specific discount rates on cost and effect are applied as the cohort is evaluated over a lifetime. For the UK, these discount rates were taken as 3.5% for both cost and effect[36], whereas in Canada a discount a rate of 3% was used[37] (Table 1).

A summary of all the data used to configure the model, including references to the original sources, is given in Tables 1–3 and in Appendix Tables A3–A6. Wherever possible, robust country- and vaccine-specific data were used to configure the model. However, when this was not possible, reliable published estimates from other countries, or from studies with the PCV-7 vaccine, were used instead.

Epidemiological data

Demographic input data for the birth cohorts and age-specific overall mortality rates were extracted from the published literature and from country-specific national sources, such as population censuses, life tables, and surveys wherever possible. Age-specific annual incidence data and case fatality ratios (CFRs) for each type of pneumococcal/NTHi disease were obtained from published literature or national databases from the pre-PCV-7 period (Table 1 and Appendix Tables A3–A6)[28,38–46]. For acute infectious disease events such as meningitis, bacteraemia, pneumonia, and AOM, prevalence rates over 1 year were

Table 2. Vaccine-specific model parameters.

Parameter	PHiD-CV value	PCV-13 value
Vaccine efficacy against ID	Serotype-specific efficacies were taken from a previous study of PCV-7 efficacy[48]. For serotypes not covered by PCV-7, the mean efficacy of the PCV-7 serotypes was used (94.7%). The reported rates of cross-protection for serotypes 6A (76%) and 19A (26%) were also included	Serotype-specific efficacies were taken from a previous study of PCV-7 efficacy[48] and additional data on serotype 3[49]. For serotypes not covered by PCV-7, the mean efficacy of the PCV-7 serotypes was used (94.7%)
Vaccine efficacy against NTHi ID	35.6% (based on a study on a predecessor vaccine to PHiD-CV; assumed to be the same as against AOM)[19]	0
Vaccine efficacy: reduction in GP/PCP visits (pneumonia)	4.3% (assumed to be the same as that found for PCV-7)[52]	4.3% (assumed to be the same as that found for PCV-7)[52]
Vaccine efficacy: reduction in hospitalized all-cause pneumonia	22.9%[53]	24.7%[53]
% of cases of *Sp* AOM due to vaccine serotypes	71.6%[58] (assuming PHiD-CV provides cross-protection against serotype 6A but not 19A)	82.2%[58]
Vaccine efficacy against AOM caused by *Sp* vaccine serotypes	57.6% (95% CI: 41.4, 69.3) (based on a study on a predecessor vaccine to PHiD-CV)[19]	57.6% (assumed to be equivalent to PHiD-CV)
Vaccine efficacy against AOM caused by *Sp* non-vaccine serotypes	−33%[59] (assumed to be the same as for PCV-7)	−33%[59] (assumed to be the same as for PCV-7)
Efficacy vs AOM caused by *H. influenzae* including NTHi	35.6% (95% CI: 3.8, 57.0) (based on a study on a predecessor vaccine to PHiD-CV)[19]	0

AOM, acute otitis media; ID, invasive disease; GP, general practitioner; NTHi, non-typeable *Haemophilus influenzae*; PCP, primary care physician; PCV-7, 7-valent pneumococcal conjugate vaccine; PCV-13, 13-valent pneumococcal conjugate vaccine; PHiD-CV, pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine; *Sp*, *Streptococcus pneumoniae*.

estimated from corresponding annual incidence rates. These data were used because they are readily available in the literature. The prevalence of long-term sequelae was estimated as a percentage of the acute events with or without the vaccine programme. Sequelae were only considered when accurate surveillance data could be obtained. As such, sequelae were only estimated for meningitis (and not for bacteraemia, CAP, or AOM) using UK incidence rates for both countries[38] (Table 1). Due to a lack of data, the general mortality of individuals with long-term sequelae was assumed to be the same as that of the general population.

Vaccine efficacy parameters

In both countries, vaccination coverage was assumed to be 100%. To simulate how vaccination protection alters over time, the model considers three distinct periods of protection: pre-vaccination, vaccination, and post-vaccination. Individuals of pre-vaccination age (0–2 months) and post-vaccination age (≥10 years) are considered to be not directly protected by the vaccine. Those within the vaccination age range (2 months to 10 years) are further sub-divided into three additional time periods: an initial ramp-up phase that occurs over the course of vaccine administration (2–13 months), a full efficacy phase (13 months to 3 years) and a waning efficacy phase (3–10 years) (Figure 2)[47]. This estimation of waning efficacy was based on the opinion of a board of experts and previous observations of efficacy with PCV-7[47]. To simulate waning over these time periods, the model linearly adjusts vaccine efficacy each month. Vaccine efficacy is also adjusted to account for the different serotypes covered by each vaccine and the serotype distribution for the various clinical manifestations of pneumococcal and NTHi disease in each country.

Invasive disease

The model estimates the number of cases of pneumococcal meningitis and bacteraemia separately (Table 1 and Appendix Tables A3 and A4). Vaccine effectiveness for PHiD-CV and PCV-13 against ID caused by *S. pneumoniae* serotypes included in PCV-7 was estimated from serotype-specific efficacies taken from a large case-control study using data from the US Centers for Disease Control and Prevention (CDC) Active Bacterial Core Surveillance on the effectiveness of PCV-7 in preventing ID (Table 2)[48]. Vaccine efficacy rates for ID caused by serotypes not included in PCV-7 were estimated using the mean

Table 3. Model parameters common to both countries.

Parameter	Value
Cases of ID (pneumococcal meningitis and bacteraemia) due to NTHi	5%[50]
Cases of AOM due to	
Sp	35.9%[57]
NTHi	32.3%[57]
Net indirect effect of vaccination on ID (% reduction in disease)	Age < 5 years: 15.4%[60] Age ≥ 5 years: 29.0%[61] (based on studies of PCV-7)
QALYs lost per episode of inpatient meningitis	0.0232 (value for meningitis with recovery)[66]
QALYs lost per episode of inpatient bacteraemia	0.0079 (value for hospitalization)[66]
QALYs lost per episode of inpatient pneumonia	0.0079 (assumed equal to bacteraemia)
QALYs lost per episode of outpatient pneumonia	0.0059 (value for local infection)[66]
QALYs lost per episode of outpatient AOM	0.005[67] as cited in Melegaro and Edmunds[42] (assumed to be the same as for AOM)
QALYs lost per episode of hospitalized myringotomy	0.005 (assumed to be the same as for outpatient AOM)
Disutility per case of neurological sequelae (meningitis)	0.400[38]
Disutility per case of hearing loss (meningitis)	0.200[38]

AOM, acute otitis media; CAP, community-acquired pneumonia; ID, invasive disease; NTHi, non-typeable *Haemophilus influenzae*; QALY, quality adjusted life year; *Sp*, *Streptococcus pneumoniae*.

serotype efficacy observed in the case-control trial (94.7%)[48]. Serotype 3 has been associated with an atypically abundant expression of capsular polysaccharide, which could make it less susceptible to anti-polysaccharide antibody defence mechanisms[49]. However, when estimating the efficacy of PCV-13, the decision was taken to include the full efficacy for serotype 3.

The model assumes the same efficacy for meningitis and for hospitalized and non-hospitalized bacteraemia. Mortality from ID was estimated using age-specific CFRs for hospitalized cases of pneumococcal meningitis and bacteraemia (Table 1 and Appendix Tables A3 and A4). All cases of meningitis were assumed to be hospitalized in both countries. However, for bacteraemia, all cases in the UK were assumed to be hospitalized, as was done by De Wals *et al.*[47]; while in Canada 62% of cases were assumed to be hospitalized, as reported by Petit *et al*[43]. For meningitis, neurological sequelae and severe hearing loss were estimated separately based on reported methods[38]. The model allows for sequelae specific to bacteraemia; however, due to a lack of data, bacteraemia sequelae were set to zero in the base-case analysis.

The model calculates the number of ID cases in children caused by NTHi, which was estimated to be 5% of the incidence of meningitis and bacteraemia caused by *S. pneumoniae* (Table 3)[50]. This figure was based on data from the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) in 2007, which reported the percentage of NTHi meningitis (median 6%; range 4–7%) and NTHi bacteraemia cases (median 7%; range 4–10%) related to the incidence of both pneumococcal meningitis and bacteraemia in children aged <10 years[50]. These estimates were based on isolates collected during 2002–2006. Mortality rates for NTHi ID in children aged <10 years were extrapolated from the 2006 European Union Invasive

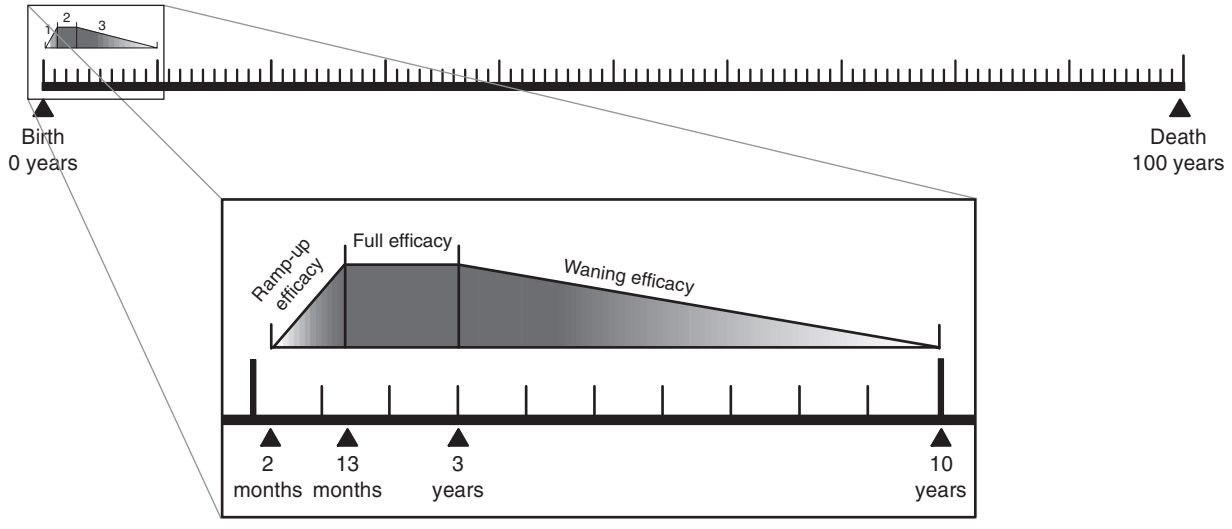

Figure 2. Modelled age compartments and vaccine efficacy periods. Reproduced from De Wals *et al.*[47].

Bacterial Infections Surveillance Network (EU-IBIS) report and assumed to be 10%[12]. No vaccine efficacy has been reported for invasive NTHi diseases, so the same efficacy shown for AOM was used (Table 2)[19]. This was a conservative assumption, as vaccine efficacy against ID is often higher than in mucosal diseases[51,52].

Community-acquired pneumonia

Identifying the influence of PCVs on pneumonia is challenging: serum sampling is unreliable and, while lung aspirates offer greater diagnostic sensitivity, this is an invasive procedure with a risk of pneumothorax[6]. As such, vaccine effectiveness estimates against pneumonia were not available by serotype. The Northern California Kaiser Permanente study with PCV-7 identified overall effectiveness rates of 4.3% for ambulatory pneumonia (Table 2) and 20.5% for hospitalized pneumonia[52]. The model assumes that the vaccine effectiveness of PHiD-CV and PCV-13 is the same as PCV-7 for ambulatory pneumonia. However, for hospitalized pneumonia caused by *S. pneumoniae*, estimates of effectiveness were taken from a previous health economic analysis of 7-, 10-, and 13-valent pneumococcal conjugate vaccines in The Netherlands[53]. Hence, the model uses vaccine efficacies of 22.9% and 24.7% for PHiD-CV and PCV-13, respectively, to calculate the percentage reduction in all-cause pneumonia hospitalization attributable to vaccine efficacy against *S. pneumoniae*[53] (Table 2). Vaccine efficacy for PHiD-CV against CAP caused by NTHi was not considered.

The model assumes that no deaths are related to ambulatory pneumonia cases. Country-specific hospitalization rates, general practitioner/primary care physician (GP/PCP) consultation rates, and CFRs were obtained from published sources[28,38,41,42] (Table 1 and Appendix Table A5).

Acute otitis media

The model estimates the annual number of GP/PCP visits due to AOM[28,43,46] and inpatient myringotomy procedures[28,43–45] (Table 1 and Appendix Table A6). These estimates were then used to calculate the resource use and costs under each of the vaccine scenarios. In the UK, there has been a large decrease in the rate of GP consultations for AOM[54,55], hence an adjustment for non-consultation was used to calculate the additional impact on QALYs incurred by infants with AOM who are not seen by GPs. This adjustment was derived from the ratio of total AOM cases as estimated in a previous cost-effectiveness analysis of pneumococcal vaccination in England and Wales[42] and the estimated total number of GP consultations for AOM, derived from a case-linked cohort study in the UK[46]. The adjustment for non-consultation does not consider the economic impact of missed cases of AOM, but instead aims to capture the full impact of AOM on quality-of-life, which is known to be considerable[56].

The model assumes that 35.9% of AOM cases are attributable to *S. pneumoniae* and that 32.3% of AOM cases are attributable to NTHi (Table 3), both of which were calculated as weighted averages based upon published estimates[57]. Published surveillance data were then used to estimate the percentage of overall AOM cases covered by vaccine serotypes, which was assumed to be 64.3% for PHiD-CV without 6A cross-reactivity, 71.6% with 6A cross-reactivity (see 'Cross-reactivity' section), and 82.2% for PCV-13 (Table 2)[58].

Vaccine efficacy is modelled for vaccine type pneumococcal serotypes, non-vaccine type serotypes, and *H. influenzae* (including NTHi). The efficacy of PHiD-CV against AOM caused by vaccine-type *S. pneumoniae* serotypes and *H. influenzae* including NTHi was based upon the POET trial[19] of the 11-valent predecessor vaccine and assumed to be 57.6% and 35.6%, respectively (Table 2). Due to a lack of data, the vaccine efficacy of PCV-13 against AOM caused by vaccine-type *S. pneumoniae* serotypes was assumed to be equivalent to that of PHiD-CV. Although the POET trial reported an efficacy of 8.6% against pneumococcal non-vaccine serotypes[19], a conservative assumption of serotype replacement was made, and PHiD-CV was assumed to result in the same level of serotype replacement in non-vaccine serotypes as that reported for PCV-7 (i.e., −33% efficacy or a 33% increase in non-vaccine serotypes; Table 2)[59]. This assumption was based on a previous modelling analysis of pneumococcal vaccination in the UK[47]. Lastly, the efficacy of PCV-13 against AOM caused by *H. influenzae* including NTHi was assumed to be zero (Table 2).

Using the aforementioned estimates of vaccine efficacy, total (maximal) efficacy against AOM was calculated as the summed products of the vaccine's efficacy against the pathogen, and the pathogens' distribution, as described in the following equation:

$$\begin{aligned} VE_{max} = {} & VE_{VT} \times \%\text{ of AOM cases due to vaccine} \\ & \text{serotypes} + VE_{NVT} \times \%\text{ of AOM cases due to} \\ & \text{non-vaccine serotypes} + VE_{NTHi} \\ & \times \%\text{ of AOM cases due to } \textit{H. influenzae} \\ & \text{including NTHi} \end{aligned}$$

where VE_{max} = maximal efficacy, VE_{VT} = vaccine efficacy against vaccine serotypes, VE_{NVT} = vaccine efficacy against non-vaccine serotypes, and VE_{NTHi} = vaccine efficacy against disease caused by *H. influenzae* including NTHi.

The number of myringotomies prevented by each vaccine was estimated from the predicted number of AOM

cases using a ratio of observations made by Black *et al.*[52], who reported that PCV-7 had 20.1% efficacy in preventing myringotomies and 7.0% efficacy in preventing AOM cases overall.

Net indirect effect

It is currently very difficult to predict the degree of herd protection that will be afforded by each vaccine in the adult population because of the lack of information about the dynamic processes of serotype replacement and interactions within a well-defined population structure. In practical terms, herd protection and serotype replacement may be hard to disentangle from each other when examining epidemiological data, since they apply contrasting influences on vaccine efficacy. Therefore, fixed values of net indirect effect, independent of vaccine type, were used to reduce the estimated ID frequency amongst the target age group (<5 years) and the rest of the population as a means of dispensing with the need to separate the two effects.

For the target population, a fixed net indirect effect of 15.4% was applied[60] (Table 3). This was based on the reduction in cases of ID among children aged <5 years in the US following the introduction of PCV-7, as estimated by the CDC National Immunization Survey[60]. The net indirect effect on ID amongst those aged ≥5 years (29%) was also based on CDC data from 2005[61] (Table 3). A net indirect effect was not applied when estimating the disease burden of AOM; however, serotype replacement was included in the calculations of vaccine efficacy for this disease (as described in the 'Acute otitis media' section) based on observations reported in the FinOM trial of PHiD-CV in Finland[59].

Cross-reactivity

Cross-protection (i.e., vaccine efficacy against non-vaccine serotypes in the same serogroup as those covered by the vaccine) was included for serotypes 6A and 19A and was estimated from a trial of PCV-7 reported by Whitney *et al.*[48]. Based on data from immunogenicity studies and the opinion of a board of experts, the same level of cross-protection was assumed for PHiD-CV as that observed for PCV-7[62–65]. The model therefore assumes the efficacy of PHiD-CV against ID to be 76% for serotype 6A and 26% for serotype 19A (Table 2)[48]. This assumption was fairly conservative since PHiD-CV has demonstrated improved opsonophagocytic activity relative to that reported for PCV-7 against serotype 19A[65]. The model also assumes that PHiD-CV will have an efficacy of 76% against AOM caused by serotype 6A (based on data from Prymula *et al.*[19] and Eskola *et al.*[59]), but no efficacy against that caused by serotype 19A (due to low case numbers and wide confidence intervals).

Health outcomes

The model estimates the overall impact of disease on quality-of-life by combining QALY losses due to acute episodes and disutility attributable to long-term sequelae. QALYs lost as a result of acute episodes of disease are presented in Table 3 and were derived from published studies[38,66,67]. These figures take into account the disutility value associated with the disease and the duration of time in the disease health state (in years). These were applied only once for each acute episode. QALYs lost because of long-term sequelae were estimated by applying a proportion of the disutility (equal to 1/12th) due to long-term sequelae (Table 3) each month during the person's remaining lifespan.

Disutilities for meningitis, bacteraemia, and pneumonia were taken from a study by Bennett *et al.*[66], which used computer-based utility assessment interviews to calculate utilities under several pneumococcal disease states. In this study, utilities were estimated from parents' responses to a series of sequential or chained 'standard gamble' options, designed to produce meaningful estimates of utility by comparing increasingly severe outcomes of pneumococcal infection. Since this parental assessment of utility compared acute yet recovering cases of hospitalized meningitis or local pneumococcal infection (e.g., pneumonia) against more severe disease outcomes (e.g., severe brain damage), the disutility of acute pneumococcal disease without permanent sequelae was comparatively small. Given the serious long-term consequences that can occur from pneumococcal infection, this parental assessment of disutility may provide a more realistic estimation of disutility than one based on the responses of children, who may be more likely to focus on short-term disutility. Moreover, this approach follows previous analyses that have assumed that the quality-of-life of two people (the patient and one caregiver) would be equally affected by the disease during its acute phase[37]. Disutilities for AOM were taken from a cost-utility analysis of second-line antibiotics, which estimated disutility from a survey of paediatricians performed by Oh *et al.*[67], and used in the analysis by Melegaro and Edmunds[42]. The disutilities of long-term neurological or hearing-related sequelae arising from meningitis were the same as those used in a study of pneumococcal disease burden in Canada[38].

It is important to note that disutility values greater than those used in this analysis have been estimated in a time trade-off analysis of parents and adults in the community[68]. However, concerns have been raised by other authors that the values presented in this study may overestimate the true impact of acute episodes of disease[42,69]. Accordingly, we use more conservative figures consistent with other work in this area[42,66,69].

Resource use and costs

Details of estimated unit costs and the references from which they were taken are available in Appendix Table A7. The model was used to estimate only direct costs of pneumococcal and NTHi disease; and direct medical costs were generally estimated as the product of the number of resource units and their unit costs. This included vaccine and administration costs, disease-related treatment costs, and costs associated with long-term sequelae incurred over survivors' lifetimes.

Unit costs for acute episodes in Canada are weighted averages inflated to 2007 prices based on data from Morrow *et al.*[38]. For the UK, unit costs were estimated using a micro-costing approach that specified detailed resource use categories and unit prices for each disease. Healthcare resource utilization for acute cases of meningitis, bacteraemia, CAP, and AOM were derived from the literature[42] or based on assumptions validated by expert opinion. Unit costs were taken from available public sources[70,71] and updated to 2007 UK pounds. Where multiple Health Research Group (HRG) codes exist for a disease, a weighted average was constructed using the proportion of hospital admissions for each HRG code as the weights.

Costs related to long-term sequelae were derived from the literature[37,72–75]. The lifetime costs of the long-term sequelae of meningitis were weighted by their respective age-specific probabilities of occurrence: 0.07 for children and 0.19 for adults for neurologic sequelae, and 0.133 for children and 0.254 for adults for hearing loss, as reported by Morrow *et al.*[38].

Although indirect costs and productivity loss were not included, these could be considerable. Indirect costs and productivity loss could result from lost earnings due to premature mortality from pneumococcal/NTHi-related diseases as well as a loss of earnings associated with time missed from work for employed adults with the disease or for parents caring for affected children.

The price for PCV-13 was assumed to be equivalent to the PHiD-CV list price per dose in Canada (Canadian $70) and the UK (£27.60). The costs of vaccine administration were based on the assumption that vaccination occurs as part of country-specific primary vaccination schedules. All financial costs prior to 2007 were adjusted to 2007 costs using price indices from the respective countries.

Sensitivity analysis

To evaluate the effects of uncertainty in the key parameters of the model, two forms of sensitivity analysis were undertaken. A one-way sensitivity analysis was performed using realistic ranges for each of the base-case parameters derived from published sources, as far as was possible. The ranges for each parameter in the model are summarized in Appendix Table A8. Mainly, one of three approaches were used: data were varied up and down for all age groups at the same time by ±20% (or ±50%) of the base case value; data were varied to the reported 95% confidence intervals; or a weighted average of studies was calculated to derive suitable values.

In addition, a probabilistic sensitivity analysis (PSA) was performed by recording the results of 1000 Monte Carlo simulations, each of which simultaneously sampled each of the model's input parameters from an appropriate probability distribution. These distributions were determined using the same source information as the one-way sensitivity analysis and are provided in Appendix Table A8.

Results

Estimated impact of vaccination on disease burden and costs

Canada had ~33.0 million inhabitants in 2007, with a birth cohort of 348,000 (Table 1)[23]. The corresponding figures for the UK were 61.0 million and 772,500[24] (Table 1). The estimated impact of vaccination on disease burden in Canada and the UK is presented in Table 4. For both countries, the estimated impact of PHiD-CV and PCV-13 were broadly similar for all-cause meningitis, bacteraemia, and pneumonia under the base-case conditions. Indeed, since the model assumes that PHiD-CV and PCV-13 have equal efficacy against preventing outpatient pneumonia, the impact of both vaccines was predicted to be identical when considering health outcomes related to this condition (PCP/GP visits, Table 4). While both vaccines were predicted to have an approximately comparable influence on ID and CAP under the base-case conditions, PHiD-CV was projected to have a much greater impact than PCV-13 on all AOM-related outcomes, including hospitalized myringotomy procedures GP/PCP visits.

Table 5 reports the estimated direct costs by disease type and vaccination regimen for Canada and the UK. In both countries, the greatest burden of cost was derived from pneumonia and AOM outcomes. While PCV-13 was expected to provide a greater quantity of savings associated with pneumonia and ID than PHiD-CV, the magnitude of these savings was dwarfed by the expected impact of PHiD-CV on AOM-related costs. Moreover, under the assumption of price parity for PHiD-CV and PCV-13, the model predicted considerable cost savings associated with the use of PHiD-CV in both countries.

Under base-case conditions, the model's projections indicate that PHiD-CV is the dominant intervention in both Canada and the UK, due to the greater number of QALYs gained and the substantially greater amount of

Table 4. Estimated impact of PHiD-CV and PCV-13 on lifetime disease burden in Canada and the UK.

Disease type/outcome	Canada			UK		
	Events PHiD-CV 3 + 1 regimen	Events PCV-13 3 + 1 regimen	Difference PHiD-CV vs PCV-13	Events PHiD-CV 3 + 1 regimen	Events PCV-13 3 + 1 regimen	Difference PHiD-CV vs PCV-13
Meningitis						
Cases of meningitis (*Sp* and NTHi)	117	116	1	158	155	3
Cases of sequelae	34	34	0	50	49	1
Bacteraemia						
Cases of bacteraemia (*Sp* and NTHi)	2463	2454	9	5026	5003	23
Pneumonia						
Pneumonia-related hospitalizations	87,046	86,842	204	72,857	72,758	99
GP/PCP visits	135,265	135,265	0	181,050	181,050	0
AOM						
Hospitalized myringotomy procedures	17,559	25,709	−8150	38,329	45,787	−7548
GP/PCP visits	1,345,317	1,441,654	−96,337	634,958	657,517	−22,559
Summary						
Deaths (pneumonia, bacteraemia, or meningitis)	21,214	21,213	1	25,099	25,098	1
Total LYs gained (undiscounted)	27,487,141	27,487,103	37	60,732,714	60,732,699	15
Total LYs gained (discounted)	9,312,026	9,312,014	12	20,662,384	20,662,379	5
Total QALYs gained (undiscounted)	24,317,878	24,317,331	547	51,882,671	51,882,260	412
Total QALYs gained (discounted)	8,560,707	8,560,219	488	18,414,599	18,414,225	374

AOM, acute otitis media; GP, general practitioner; LY, life-years; NTHi, non-typeable *Haemophilus influenzae*; PCV-13, 13-valent pneumococcal conjugate vaccine; PHiD-CV, pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine; PCP, primary care physician; *Sp*, *Streptococcus pneumoniae*; QALY, quality adjusted life year.

Table 5. Direct costs in Canada and the UK by disease and vaccine.

Cost category	Canada (Canadian $)			UK (£)		
	PHiD-CV 3 + 1 regimen	PCV-13 3 + 1 regimen	Difference PHiD-CV vs PCV-13	PHiD-CV 3 + 1 regimen	PCV-13 3 + 1 regimen	Difference PHiD-CV vs PCV-13
Vaccine	112,186,735	112,186,735	0	97,556,557	97,556,557	0
Meningitis	2,207,096	2,172,907	34,189	1,022,079	1,000,028	22,051
Long-term meningitis sequelae	3,372,108	3,331,742	40,366	1,418,787	1,372,445	46,342
Bacteraemia	24,481,003	24,443,707	37,296	20,682,142	20,560,630	121,512
Pneumonia	622,251,101	621,174,369	1,076,733	247,387,278	246,945,499	441,779
AOM	97,717,381	108,747,185	−11,029,804	50,467,371	56,728,842	−6,261,472
Total direct costs (undiscounted)	862,215,423	872,056,644	−9,841,221	418,534,213	424,164,000	−5,629,788
Total direct costs (discounted)	320,273,189	329,276,094	−9,002,905	180,376,006	185,275,445	−4,899,439

AOM, acute otitis media.

costs saved. Since this analysis identified a dominant comparator, the calculation of incremental cost-effectiveness ratios (ICERs) was not possible.

Sensitivity analysis

A one-way sensitivity analysis was performed using realistic ranges for each of the base-case parameters derived from published sources where possible (please see Appendix Table A8). In this analysis, each of the variables in the health economic model was independently varied and the corresponding cost and effectiveness results documented. The presentation of a univariate analysis for a dominant base case (i.e., where the comparator is the most effective and least costly intervention) can be difficult to interpret (e.g., using a traditional tornado diagram) due to the inability to calculate an ICER. Therefore, Figures 3a and b present the impact of the nine most influential variables on a cost-effectiveness plane generated by comparing PHiD-CV to PCV-13 in Canada and the UK, respectively.

While the majority of the model's variables were found to exert very little influence over the conclusion of dominance in either Canada or the UK (i.e., that PHiD-CV was both less costly and more effective than PCV-13), parameters relating to AOM-related outcomes were found to be particularly influential in the analysis of both countries. This observation was not surprising, since the potential of PHiD-CV to provide protection against AOM caused by NTHi is a major difference between the two vaccines.

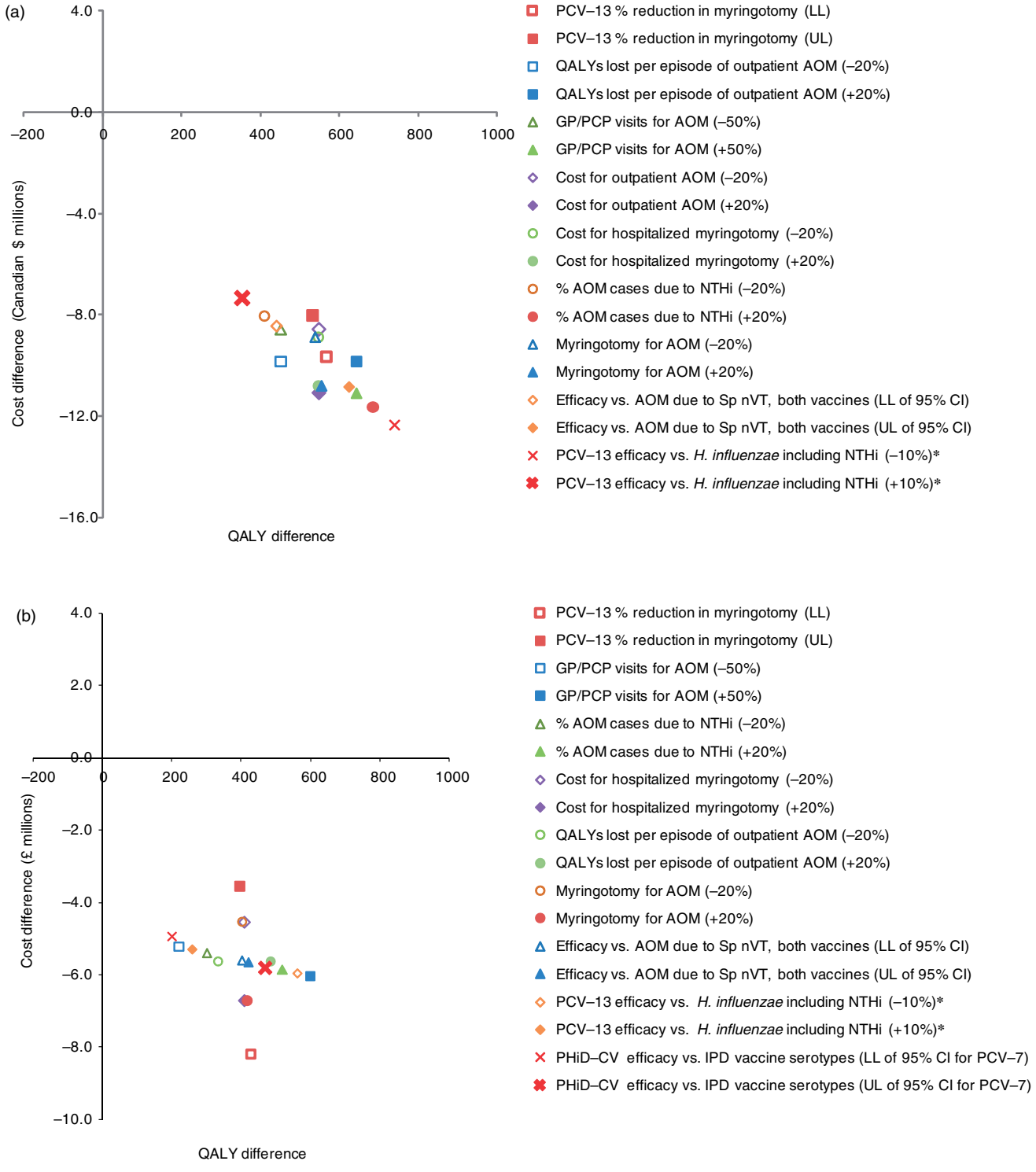

Figure 3. Univariate sensitivity analysis for (a) Canada and (b) the UK, comparing PHiD-CV to PCV-13 (discounted). * Most variables are ±20% of the base-case value, but PCV-13 efficacy against AOM caused by *H. influenzae* including NTHi was assumed to be 0%, so this value was varied to +10% and −10%, based on the −11% efficacy against *H. influenzae* reported by Eskola *et al.*[59]. AOM, acute otitis media; CI, confidence interval; GP, general practitioner; LL, lower limit; NTHi, non-typeable *Haemophilus influenzae*; nVT, non-vaccine type; PCP, primary care physician; PCV-7, 7-valent pneumococcal conjugate vaccine; PCV-13, 13-valent pneumococcal conjugate vaccine; PHiD-CV, pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine; QALY, quality adjusted life year; Sp, *Streptococcus pneumoniae*; UL, upper limit.

In the PSA, PHiD-CV was found to dominate PCV-13 both in terms of cost and impact on quality-of-life in 95% and 90% of the 1000 simulations in Canada and the UK, respectively. Simulations that ran into quadrants with less QALYs gained were predominantly attributed to samples in which only a small proportion of AOM was attributed to NTHi.

As a further sensitivity analysis, we used new, as yet unpublished, serotype distribution data for England and Wales that indicated a higher proportion of 19A serotype in children <2 years compared to the one used in this analysis. This resulted in decreases in discounted QALYs gained (from 374 to 297) and discounted cost savings (£4.9 to £4.3 million) for PHiD-CV vs PCV-13.

Discussion

The cohort model presented here demonstrates the potential impact of two different vaccines (PHiD-CV and PCV-13) in Canada and the UK over the lifetime of a birth cohort. Interestingly, the model predicted that both vaccines would have a broadly similar impact on the burden of morbidity and mortality from ID and pneumonia in both countries. This can be explained by the vaccine formulations: while PHiD-CV includes three fewer pneumococcal serotypes than PCV-13, it has demonstrated cross-reactivity against the invasive serotypes 6A and 19A, and has the potential to target NTHi. This attribute was predicted to balance the prevention of overall ID when the combined disease burden from the two pathogens was considered.

In contrast to ID and pneumonia, the model predicted a substantial difference in the number of AOM outcomes prevented under the two vaccination regimens in both countries. The efficacy of PHiD-CV against AOM was based on a study by Prymula *et al.*[19], which compared a predecessor vaccine to PHiD-CV with a control vaccine. In this study, pneumococcal vaccine efficacy was 33.6% against all clinical episodes of AOM ($p < 0.001$), 51.5% against culture-confirmed pneumococcal episodes ($p < 0.001$), and 35.6% against episodes caused by *H. influenzae* including NTHi ($p = 0.032$)[19]. However, there was no clear correlation between efficacy and enzyme-linked immunosorbent assay (ELISA) carrier protein D antibody concentrations. Therefore, it is possible that the vaccine effect on *H. influenzae* AOM could be an indirect effect, i.e., reducing the number of episodes of pneumococcal AOM could have reduced the number of infants subsequently vulnerable to *H. influenzae* infection[19]. However, this seems unlikely, as PCV-7 has been found to result in an increase in *H. influenzae* AOM episodes, rather than a decrease[59].

In the UK, PCV-13 was predicted to result in ~20% more myringotomies and 4% more AOM-related visits to GPs than an equivalent PHiD-CV regimen. In Canada, these proportional differences were twice as substantial, with ~46% more myringotomies and 7% more PCP visits occurring under a PCV-13 regimen compared with PHiD-CV. Considering the marginal improvements in ID and CAP estimated under the PCV-13 regimen, it was this substantial difference in AOM disease burden that contributed to the greater number of QALYs predicted to be saved with PHiD-CV. Furthermore, since this analysis only considered sequelae for meningitis, and not for AOM, the reported QALYs did not include the considerable disutility accrued during long-term AOM-related sequelae.

In Canada and the UK, the estimated direct cost of AOM-related disease was much less than that for pneumonia. However, the model predicts that the impact of PHiD-CV on the costs of AOM will far outweigh that of PCV-13 on pneumonia-related costs. Considering the model parameters, this proportionally greater saving in AOM costs (compared with pneumonia costs) can be attributed to the large volume of AOM cases prevented by vaccination, rather than high individual treatment costs. By the age of 3 years, ~75% of children are expected to have had at least one episode of AOM[76], and it is therefore not surprising that any intervention that targets this highly prevalent disease is likely to produce a considerable reduction in economic burden and improvement in quality-of-life. Moreover, sub-optimal management of AOM may result in high levels of antibiotic consumption that could lead to increases in resistance which may lead, in turn, to higher disease management costs and decreased quality-of-life.

The predictions of the model are supported by both univariate and multivariate sensitivity analyses that demonstrate its robustness. While permutations to the majority of the model's parameters had very little impact on its calculation of cost-effectiveness, those related to AOM (e.g., the percentage reduction in myringotomy expected with PCV-13 and the number of GP/PCP visits for AOM) were found to be particularly influential in determining the model's final outcomes. However, since the difference in predicted cost-effectiveness between PCV-13 and PHiD-CV is predominantly derived from the differential impact of the two vaccines on AOM, it is difficult to determine whether the prominent influence of these parameters is attributed to the structure of the model or to the crucial importance of this disease area to the comparison being undertaken.

One of the challenges of modelling diseases caused by NTHi is identifying reliable surveillance data. In many countries, the lack of routine national surveillance for *H. influenzae* has limited previous attempts to quantify its pathogenic potential and to document shifts in its prevalence or resistance profile. The need for surveillance of this organism has been recognized by organizations such as EU-IBIS, which previously collected data on *H. influenzae*

infection from 24 European countries, Australia and Israel[12]; a responsibility that has since passed to the European Centre for Disease Prevention and Control. One limitation of these surveillance data is that they are not stratified by immune status, and those who are immunocompromised may not respond well to vaccination. An additional concern is that epidemiological reports may under-estimate the prevalence of NTHi as a cause of disease[77], as *H. influenzae* may not be routinely distinguished from *Haemophilus haemolyticus* using standard methods[78]. This highlights the need for improved surveillance of *H. influenzae*, which would be valuable for future health economic models of NTHi disease.

Although NTHi is a recognized cause of pneumonia, the extent of its role remains unclear, as the typing of *H. influenzae* strains is not routine. It has previously been suggested that NTHi pneumonia may be under-detected as a cause of bacterial pneumonia[79]. However, there is considerable variation among estimates of NTHi pneumonia incidence reported in the literature. For example, results of lung tap studies in children from around the world have identified *H. influenzae* in ~2–42% of aspirates[6]. Although PHiD-CV may have the potential to provide protection against disease caused by NTHi, pneumonia caused by this pathogen was not included in the present analysis due to the uncertainty surrounding its prevalence. However, in a separate analysis, we considered a scenario where the incidence of pneumonia hospitalizations due to NTHi was assumed to be at the lower end of the range of estimates reported in the literature[6,80–82]. Accordingly, the incidence of NTHi pneumonia was estimated as approximately 3% of all-cause pneumonia incidence (which excludes NTHi) in children <10 years old. The potential efficacy of PHiD-CV against NTHi pneumonia was also considered, based on the efficacy of the PHiD-CV precursor vaccine against AOM caused by *H. influenzae* (including NTHi) as reported in the POET trial (35.6%)[19]. Including the effects of NTHi pneumonia and the corresponding potential efficacy of PHiD-CV (in a 3 + 1 regimen) resulted in additional savings of three and four discounted QALYs and £240,000 and Canadian $590,000 in discounted costs in the UK and Canada, respectively, compared to estimates where NTHi pneumonia was not considered.

The limitations of cohort models, such as that presented here, are most apparent in their estimation of how indirect vaccine effects develop over time. More specifically, cohort analyses require the long-term prediction of changes in disease epidemiology that extend over the cohort's lifetime. In real life, estimations of herd effect are obtained as static observations, thus making the abstraction of their temporal development a difficult process. Many studies have examined the magnitude of indirect effects (i.e., herd protection and serotype replacement), but the extent of these effects has varied considerably amongst published estimates. For instance, in Spain, the net indirect effect on those aged >65 years of PCV administration to infants has been estimated as an ~23% increase in ID[83], while in the US the impact of net indirect vaccine effect has been estimated as a 38% reduction in disease amongst the same age group[84]. It is clear that there is a substantial decrease in vaccine serotypes in all cases, but changes in non-vaccine serotypes, whether due to replacement or secular trends, appear to vary (geographically and temporally), contributing to the observed differences in net impact. Many different factors influence the end result, for example vaccine and non-vaccine serotype coverage, duration of national immunization, epidemiology, vaccine schedule, immunization coverage, force of infection, time of measuring the effect, rate and level of serotype replacement, vaccine dosing, contact matrices, and demography. Moreover, the replacement of existing vaccines with new alternatives will make estimates of the net indirect effect per vaccine serotype even more difficult to disentangle; hence, estimating precise and independent contributions may be nearly impossible[85].

Another limitation of this study is the input data for the model. There is limited clinical trial data for PHiD-CV and PCV-13 (and no head-to-head study) as most of the trials aimed to demonstrate immunogenicity, safety, and tolerability of these vaccines, and clinical effectiveness is inferred from these immunological data, based on earlier vaccine formulations. Therefore, vaccine efficacy data are largely based on studies of PCV-7[48,52,59] and a study on a predecessor vaccine to PHiD-CV[19]. It is interesting to note that the efficacy against AOM of PCV-7 in FinOM[59] was much lower than that of the precursor to PHiD-CV in POET[19] (7% vs 34%). While these trials are not directly comparable, PHiD-CV would be expected to have a greater effect on AOM due to its activity against NTHi. In the POET trial, no non-vaccine type serotype replacement was observed with the PHiD-CV precursor; whereas this was observed for PCV-7 in FinOM[86]. There were also different proportions of bacterial pathogens in the two studies. Palmu *et al.*[86], former investigators of FinOM, have assessed the impact of variations in case definition, design, and local epidemiology between the two trials, and concluded that these factors only had a slight impact on the estimated efficacy of the vaccines.

The GP/PCP consultation rates for AOM used in the study are ~10-fold higher for Canada[28,43] than the UK[46]. This may be due to a variety of factors, e.g., different ICD-9 codes, different age ranges included, and a lower rate of GP consultation for AOM in the UK. However, the key comparisons here are those between the two vaccines within either Canada or the UK, and not a between-country comparison. Therefore, these differences should not affect the results within each country.

A further limitation is the uncertainty surrounding the disutility value used for AOM. We used the same AOM

disutility value as Melegaro and Edumunds[42], namely 0.005. This came from a study by Oh *et al.*[67], who derived it from physician responses to scenarios of AOM with combinations of adverse events. This value has been used in most economic evaluations of pneumococcal vaccines[87–91]. However, some other analyses have used a higher AOM disutility value of 0.011[92,93], based on a study by Prosser *et al.*[94]. Performing a sensitivity analysis using the estimate of 0.011 QALY decrement resulted in an increase in the difference of QALYs gained for PHiD-CV vs PCV-13 to 1063 for Canada and 828 for the UK.

Conclusion

Direct comparison of the antigenic content of PCV-13 and PHiD-CV cannot be used to differentiate the potential benefits of the two vaccines: while PCV-13 contains antigens for an additional three *S. pneumoniae* serotypes, PHiD-CV has the potential to provide protection against disease caused by NTHi. Computational models are therefore the only option available for those wishing to compare the predicted impact of the two vaccines. The heavy burden of pneumonia (in terms of mortality and costly medical interventions) and AOM (in terms of high prevalence of disease) suggest that decision-makers should also take the impact of vaccination on these diseases into account when choosing a pneumococcal conjugate vaccine for routine infant immunization. While the two vaccines are predicted to provide broadly comparable impacts on overall ID and CAP under base-case conditions, PHiD-CV is expected to provide a substantially greater reduction in clinical AOM compared with PCV-13. As such, the cost-effectiveness analysis reported here suggests that in Canada and the UK, PHiD-CV's potential to protect against NTHi may provide a greater impact on overall disease burden than the additional serotypes contained in PCV-13.

Transparency

Declaration of funding

GlaxoSmithKline Biologicals was the funding source and was involved in all stages of the study and analysis. GlaxoSmithKline Biologicals also took responsibility for all costs associated with the development and publishing of the present manuscript. Gerhart Knerer was involved with the design of the model and validation of assumptions. David W Pearce and Afisi Ismaila were responsible for adapting the model to the UK and Canada.

Declaration of financial/other relationships

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