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The impact and cost-effectiveness of pneumococcal immunisation strategies for the elderly in England

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ABSTRACT

Pneumococcal disease, presenting as invasive pneumococcal disease (IPD) or community-acquired pneumonia (CAP) is an important cause of illness and hospitalisation in the elderly. To reduce pneumococcal burden, since 2003, 65-year-olds in England have been offered a 23-valent pneumococcal polysaccharide vaccine (PPV23). This study compares the impact and cost-effectiveness (CE) of vaccination with the existing PPV23 vaccine to the new 15-and 20-valent pneumococcal conjugate vaccines (PCV15 and PCV20), targeting adults aged 65 or 75 years old.

We developed a static Markov model for immunisation against pneumococcal disease, capturing different vaccine effectiveness and immunity waning assumptions, projecting the number of IPD/CAP cases averted over the thirty years following vaccination. Using an economic model and probabilistic sensitivity analysis we evaluated the CE of the different immunisation strategies at current vaccine list prices and the willingness-to-pay at a median threshold of £20,000/QALY and an uncertainty threshold of 90% of simulations below £30,000/QALY.

PCV20 averted more IPD and CAP cases than PCV15 or PPV23 over the thirty years following vaccination: 353(360), 145(159) and 150(174) IPD and 581(673), 259(485) and 212(235) CAP cases at a vaccination age of 65(75) under base vaccine effectiveness assumptions. At the listed prices of PCV20 and PPV23 vaccines as of May 2023, both vaccines were cost-effective when vaccinating 65- or 75-year-olds with an ICER threshold of £20,000 per QALY. To achieve the same cost-effectiveness as PPV23, the additional cost of PCV20 should be less than £44(£91) at an ICER threshold of £20,000/QALY (£30,000/QALY) if vaccination age is 65 (or £54(£103) if vaccination age is increased to 75).

We showed that both PPV23 and PCV20 were likely to be cost-effective. PCV20 was likely to avert more cases of pneumococcal disease in elderly adults in England than the current PPV23 vaccine, given input assumptions of a higher vaccine effectiveness and slower waning for PCV20.

1. Introduction

Streptococcus pneumoniae is an important cause of serious infection, presenting as either invasive pneumococcal disease (IPD) [1] or pneumococcal pneumonia which requires hospitalisation. The highest rates of pneumococcal disease are observed in infants, the elderly, patients with chronic respiratory disease and patients who are immunocompromised [2].

The burden from pneumococcal disease in England is significant; over the period of 2010–2019, there were 400–600 annual cases of vaccine-type IPD [3] and 1200–2200 cases of non-vaccine-type annual IPD [4] in people over 65 years old. Additionally, prior to COVID-19, between 0.5 to 1% of adults in the UK suffered from community-acquired pneumonia (CAP) each year [5] (between 332,178 and 664,356 annual cases in 2018 [6]). Hospitalised CAP has a mortality rate of 5%–15%, which increases to more than 30% for patients admitted to intensive care units [7]. Although not all CAP cases are due to pneumococcal disease, a study of UK adults found that 37% of persons hospitalised with CAP between 2013 and 2018 had

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pneumococcal pneumonia [8]. CAP henceforth refers to pneumococcal CAP.

Vaccination against pneumococcal disease can reduce the burden of both IPD and CAP. There are two types of pneumococcal vaccines currently available based on different technologies: the polysaccharide vaccine and the conjugate vaccines. The 23-valent polysaccharide vaccine (PPV23) which covers 23 of the more than 100 known pneumococcal serotypes, has been recommended for risk groups in England since 1992; this was expanded in 2003 to include all adults over 65 years of age [9]. PPV23 offers protection against vaccine-type IPD but has limited effectiveness against CAP [10,11]. The 7-valent pneumococcal conjugate vaccine (PCV7) was first licensed in the UK in 2006 for use in children and was replaced by PCV13 in 2010 [9]. Conjugate vaccines have been shown to protect against vaccine-type IPD and vaccine-type CAP [12]; the introduction of PCV13 led to a reduction of the incidence of IPD strains covered by the vaccines and by 2013/14, more than 70% of all IPD cases were due to serotypes not covered by PCV13 [13]. Since 2013/14 an increase in overall incidence of IPD has been observed, largely due to increases in non-PCV13 vaccine serotypes.

Recently, two new, higher-valent conjugate vaccines – PCV15 and PCV20 – were approved by the Medicines and Healthcare products Regulatory Agency for use among adults in the UK. PCV15 and PCV20 cover the 13 serotypes included in PCV13 (1, 3, 4, 5, 6 A, 6B, 7F, 9 V, 14, 18C, 19 A, 19F, and 23F). PCV15 also covers serotypes 22F and 33F. PCV20 covers the two extra PCV15 serotypes as well as serotypes 8, 10 A, 11 A, 12F and 15B.

In 2016, van Hoek and Miller evaluated the cost-effectiveness of vaccinating 65-year-olds with PCV13, concluding such an immunisation strategy would not be cost-effective [14]. Their work estimated that the incidence of serotypes targeted by PCV13 would decrease over the period following their study, but observational data covering this period shows that PCV13 incidence remained stable and that the incidence of non-PCV13 serotypes increased [13].

The burden of pneumococcal disease increases significantly with age across all vaccine groups, notably with a large increase in CAP incidence from the 65–74 to 75–84 age group. This motivated our decision to model a higher vaccination age of 75 years in addition to the current policy of vaccinating at 65 years old.

In light of the observed epidemiology and availability of higher-valency vaccines there is a need to re-evaluate the current pneumococcal immunisation programme in England. In this study we evaluated the impact and cost-effectiveness of different elderly immunisation strategies against pneumococcal disease in England. These included vaccinating adults aged 65 or 75 years old with the new PCV15 or PCV20 vaccines or with the existing PPV23 vaccine. Across various immunisation scenarios of different vaccine type and targeting different age cohorts, we outputted the impact (via the number of IPD and CAP cases averted) and the cost-effectiveness (via QALYs averted) to determine the optimal age for vaccination and the optimal vaccine type.

2. Material and methods

We developed a static Markov model to evaluate the impact and cost-effectiveness of different immunisation strategies for the elderly in England. Our model comprised of two parts; an epidemiological model used to estimate disease burden (i.e., the number of cases and deaths caused by IPD and CAP), and an economic model used to calculate the costs incurred from disease burden. Over the next few sections we describe the epidemiological and economic models, the different scenarios considered in our study and a summary of the model outcomes generated.

2.1. Epidemiological model

2.1.1. Framework

We used a static Markov model based on a previous economic evaluation of pneumococcal vaccination [14]. A schematic of the model and its states is shown in Fig. 2.

We modelled a cohort of 65- or 75-year-olds. The population sizes of these groups were obtained from national census data (575,744 and 466,239 at ages 65 and 75 respectively) [15]. We assumed that the entire cohort was initially susceptible to pneumococcal disease. Individuals could contract either CAP or IPD, then subsequently recovered or died. Individuals who did not contract CAP or IPD might die via some other means. The transition of individuals from a disease-state to either recovering or dying is assumed to take place within a year. If an individual recovered they did not return to their initial state (susceptible) and so they could not get reinfected. The parametrisation of the transition probabilities between states is detailed in Section 2.1.2.

The model can be defined by a transition matrix, with elements consisting of the probability that an individual moves from one state to another:

$$\mathbf{x_t} = P\mathbf{x_{t-1}}, \tag{1}$$

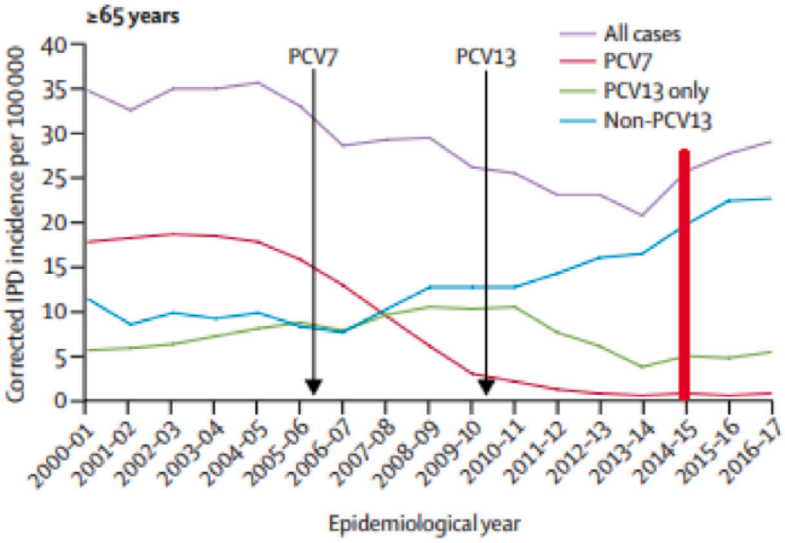
where $\mathbf{x_t}$ is the vector of the proportion of the cohort in each state at time t and P is the transition matrix. The model iterates yearly for a duration of 30 years, so that t represents the number of years elapsed since the start of the model run. Each model run only considers a single cohort that ages as time progresses. The model has five states: Susceptible, CAP (recovered), IPD (recovered), pneumococcoccal death and death other. These are respectively denoted: S, CAP, IPD, $death_{pn}$ and $death_{other}$. We define the vector of these states and the transition matrix as follows:

$$\mathbf{x_t} = \begin{bmatrix} p_S(t), & p_{IPD}(t), & p_{CAP}(t), & p_{death_{pn}}(t), & p_{death_{other}}(t) \end{bmatrix}, \tag{2}$$

$$P = \begin{bmatrix} P_{S-S}(t) & P_{S-CAP}(t) & P_{S-IPD}(t) & P_{S-death_{pn}}(t) & P_{S-death_{other}}(t) \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}. \tag{3}$$

p_X represents the proportion of the cohort within state X and P_{X-Y} denotes the transition probability from state X to state Y. Specifically, P_{S-S}, P_{S-CAP}, P_{S-IPD}, $P_{S-death_{pn}}$ and $P_{S-death_{other}}$ define the probabilities of a susceptible individual remaining susceptible, contracting CAP and recovering, contracting IPD and recovering, dying from pneumococcal disease or dying via other means respectively. All other probabilities are equal to 0 or 1 since individuals cannot transition to another state once recovered or deceased.

We modelled vaccinated and unvaccinated cohorts separately, with vaccination modelled via a reduction in the probability that an individual contracts CAP or IPD, with vaccine effectiveness (v_{eff}) defined as the proportion of cases of pneumococcal disease that the vaccine prevents. Hence, the probability that a vaccinated individual contracts CAP or IPD was scaled by $1-v_{eff}$. v_{eff} was dependent on the time since the vaccine was administered. Individuals in the vaccinated cohort received the vaccine once at time $t = 0$. In our model we assumed that vaccination did not reduce the Case Fatality Rate (CFR) of either IPD or CAP. However, we note that vaccination did indirectly affect pneumococcal deaths in the model through a lower incidence. Vaccine effectiveness and immunity waning values are detailed in the following section.



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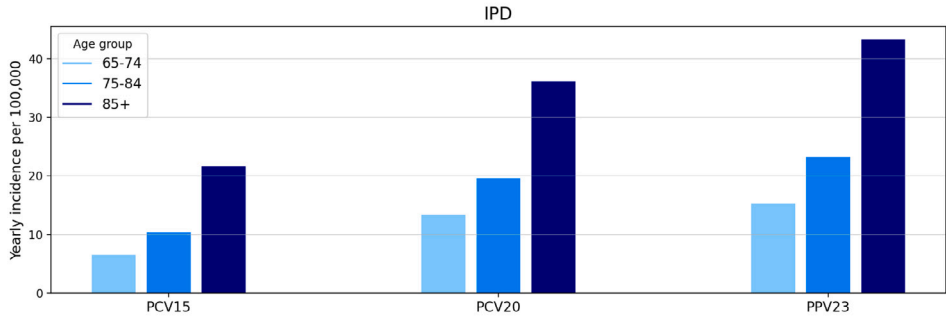

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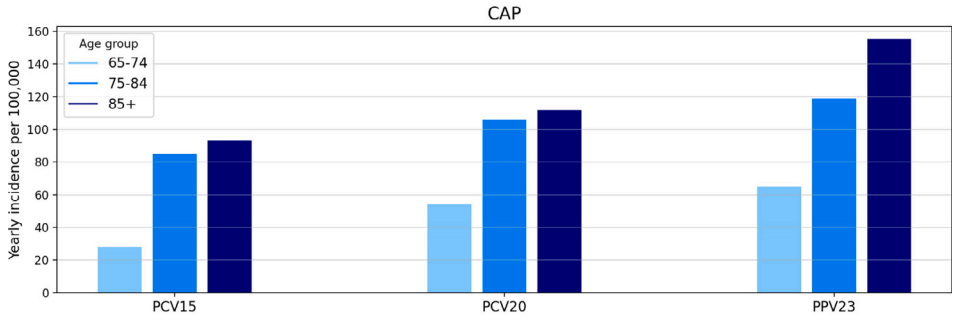


(c)

Fig. 1. England IPD incidence in over-65s per vaccine type between 2000 and 2017 adapted from [13] (a), 2018/19 England incidence values by age group and by vaccine for IPD (b) and CAP (c). 2018/19 incidence values are taken from UKHSA surveillance data for IPD (b) and from Nottingham hospital data for CAP (c). These represent the sum of the incidence values of serotypes covered by each vaccine. In (a) the red vertical bar indicates the end of the data analysed in [14]. Values with serotype 3 separated, as used in our analysis, are given in Supplementary Table 1.

2.1.2. Parametrisation

Incidence and case fatality rate (CFR) values. Incidence parameters for IPD and CAP, and the CFR parameter for IPD, were informed by empirical data from 2018/19 (Fig. 1). We selected this time period because data in subsequent years are confounded by effects arising from the COVID-19 pandemic [16–18]. The CFR for CAP was not available in our data and so we derived this parameter from the literature [14]. All incidence and CFR parameters were aggregated into three age groups: 65–74, 75–84 and 85+.

We used national surveillance data from the UK Health Security Agency (UKHSA) to define IPD incidence and CFR values. CAP incidence data were taken from a survey conducted in Nottingham [19], and the CAP CFR parameter was set to 0.1 for all age groups following [14]. The probability of dying of a cause other than pneumococcal disease was defined using mortality data taken from the Office for National Statistics (ONS) [15].

One important point to note is that because pneumococcal vaccines cover specific serotypes only, we required serotype-specific incidence

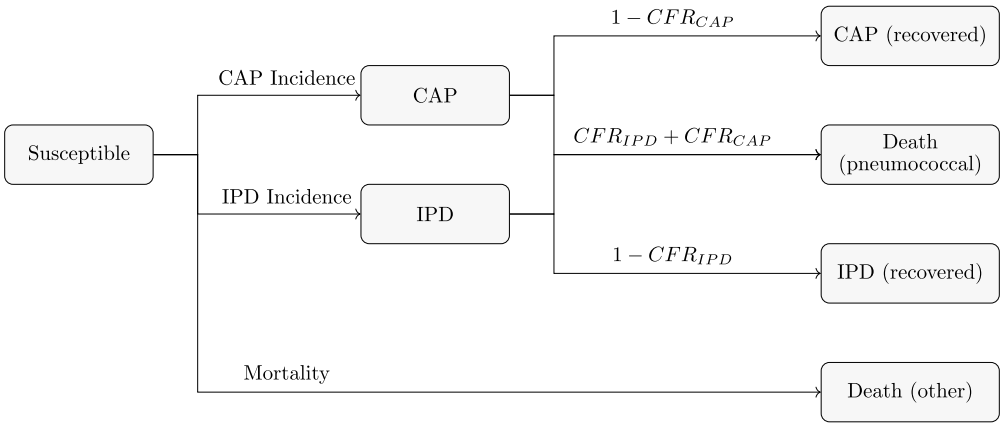


Fig. 2. Schematic of the Pneumococcal model detailing its compartments. The states are Susceptible, CAP (recovered), IPD (recovered), death due to pneumococcal disease (Death pneumococcal), or death via other means (Death (other)). Note that the CAP and IPD states are only transitory as the model moves an individual from Susceptible to CAP (recovered), IPD (recovered) or death due to pneumococcal disease instantaneously. Transition probabilities are determined by IPD/CAP incidence, IPD/CAP Case Fatality Rate (CFR) and mortality, the parametrisation of which is detailed in Section 2.1.2.

and CFR values (i.e. PCV15 incidence represented the incidence of the 15 serotypes covered only by PCV15). Thus, incidence and CFR parameters were inherently greater for vaccines that cover more serotypes, as shown graphically in Fig. 1. Additionally, since both conjugate and polysaccharide vaccines were shown to be less effective against serotype 3 [13,20], we modelled this serotype separately.

Vaccine effectiveness, waning and uptake. Vaccine effectiveness parameters are given in Table 1. Immunity waning was simulated by modelling a time-dependent decrease in vaccine effectiveness to zero. We modelled different waning assumptions for polysaccharide and conjugate vaccines based on previous research. The effectiveness of polysaccharide vaccines was assumed to decline linearly to zero from the point immediately after vaccination [21], whereas the waning assumptions of conjugate vaccines were based on results of the CAPITA study, which observed no decrease in conjugate vaccine effectiveness over the 4-year study duration [22]. We thus modelled a slight decline in conjugate vaccine effectiveness over the first 4 years, averaging to the values shown in Table 1, followed by a linear decline to zero in subsequent years. With these modelling assumptions, the conjugate vaccines modelled provided an additional four years of protection compared to the modelled polysaccharide vaccines.

To account for the large uncertainty associated with initial vaccine effectiveness and immunity waning parameters, we modelled three different scenarios for each of these. We note that we also used the same values for vaccination ages of 65 and 75.

We assumed vaccination uptake of 70% based on a 2021 report, which gave a coverage of 70.6% for individuals aged 65+ in England [23]. We also assumed 10% vaccine wastage.

Immunisation strategies. We modelled five immunisation strategies: three individual vaccine strategies with PPV23, PCV15 or PCV20 and targeting a naive population, and two combined immunisation strategies where PCV15 or PCV20 were administered to a population already vaccinated with PPV23. For each immunisation strategy we considered vaccination ages of 65 and 75.

The individual strategies were the main focus of the analysis and are presented in the main text. For the combined strategies, both the methods and the results are contained in the supplementary material.

To evaluate the individual vaccine strategies, we would ideally use incidence data from a naive population that has not benefitted from pneumococcal immunisation. However, due to the ongoing PPV23 campaign in England, no such data exists. Hence, to model this scenario, we generated new (back-calculated) incidence values using PPV23 vaccine effectiveness (v_{eff}) and coverage (c) parameters, and estimated pneumococcal incidence in a naive population (I_n) using the following equation:

$$I_n = \frac{I_v}{(1 - v_{eff} * c)}, \tag{4}$$

where I_v is the incidence observed in 2018/19 data.

We note that the vaccine effectiveness and coverage values used in Eq. (4) and defined below are distinct from those defined in the previous paragraph that were used throughout the main analysis.

Vaccine coverage c equals 60% for ages 65–74 and 83% for ages 75–84 and 85+[23]. The vaccine effectiveness parameter v_{eff} was defined based on the Canadian study [21]; it equalled 47% for ages 65–74 (as in the main analysis, Table 1), with a 10% compounded reduction in effectiveness every decade, which equated to vaccine effectiveness parameters of 42% and 38% for ages 75–84 and 85+ respectively. We note that the first parameter of 47% was derived from data, whereas the 10% reduction in effectiveness for the older age group of 75–84 was based on an assumption made in the Canadian study [21], which we extended to the age group of 85+. This is to account for the majority of individuals having received their vaccine while aged 65–74 [23], which means that the waning of vaccine effectiveness will be higher in the older age groups.

To account for uncertainty arising from this assumption, we performed sensitivity analyses using a lower assumed vaccine effectiveness of 27% for all age groups based on the average adjusted value from [13]. The results of this sensitivity analysis are shown in Figure 4 of the supplementary material.

Uncertainty scenarios on vaccine effectiveness and waning. To account for the wide range of initial vaccine effectiveness and waning parameters reported in the scientific literature, we considered three different vaccine effectiveness scenarios defined by the lower, central and upper limits of the range reported. A summary of these scenarios, and the vaccine effectiveness parameters used for each scenario, are contained in Table 1.

We also explored three immunity waning scenarios (fast, base and slow) and evaluated their effect on model projections. To replicate effects observed during the CAPITA trial [22], PCV effectiveness in the model declined slightly over the first 4 years, averaging to the vaccine effectiveness value in Table 1 over this period. PCV effectiveness then declined linearly to 0 over the next 5, 10 or 15 years depending on the immunity waning scenario (for a total waning duration of 9, 14 or 19 years). The vaccine effectiveness of PPV23 started to decline linearly to 0 immediately after administering the vaccine in 5, 10 or 15 years depending on the modelled immunity waning scenario.

Table 1
Vaccine Effectiveness (%) of PCV15, PCV20 and PPV23 against IPD and CAP. A separate, reduced value is given for vaccine effectiveness against serotype 3 (ST3). Due to large uncertainty surrounding these parameters, a low, base and high vaccine effectiveness are given, which were derived from the central estimate and uncertainty bounds of each reference. Sources of each value are given, with * indicating that the values were calculated under the assumption that the reduction in effectiveness for serotype 3 relative to the other serotypes is the same for IPD as it is for CAP.

Vaccine	Strain	Low vaccine effectiveness	Base vaccine effectiveness	High vaccine effectiveness
PCV15/20	IPD [22]	47	75	90
	ST3 IPD [24]	0	26	65
	CAP [22]	14	38	55
	ST3 CAP*	0	13	39.7
PPV23	IPD [21]	32	47	63
	ST3 IPD [13]	0	2	21
	CAP [11]	0	20	40
	ST3 CAP*	0	0.85	1.3

Table 2
Costs and QALYs associated with each disease outcome. These are taken from the literature [14], with hospitalisation costs inflated to 2022 values using the NHS cost inflation index (NHSCII) [27,28].

	Costs (per case, in £)		QALY loss (per case)
IPD hospitalisation	65–74	5412	0.123
	75–84	5365	0.086
	85+	5318	0.0397
CAP hospitalisation	795		0.006
Pneumococcal Death	Same as hospitalisation due to IPD or CAP		Life expectancy remaining at time of death

Model outcomes. Across the scenarios, the model outputted the annual number of CAP and IPD cases and pneumococcal deaths in both the vaccinated and unvaccinated cohorts, with their difference quantifying the number of cases and deaths averted by each immunisation strategy.

2.2. The economic model

2.2.1. Economic parameters

We estimated the costs and QALYs associated with each intervention relative to baseline and calculated the cost-effectiveness of the intervention. We calculated net costs, subtracting costs saved due to lower disease burden from the costs of the intervention. QALYs arise from CAP, IPD and pneumococcal death (Table 2).

A discount rate of 3.5% was applied to the costs and QALYs which replicated [14]. We take the perspective of the healthcare provider. The cost of vaccine administration was £10.06. Vaccine list prices were £16.80, £50.30 and £56.80 for PPV23 [25], PCV15 [26] and PCV20 [26] respectively.

2.2.2. Model outcomes: estimating cost-effectiveness

The costs and QALYs gained or lost by administering a vaccine were immediately derived from the pneumococcal case and death counts given by the epidemiological model. We use these values to calculate two measures of cost-effectiveness, the Incremental Cost Effectiveness Ratio (ICER) and Willingness-to-pay (WTP).

ICER. The ICER is expressed in QALYs gained per pound (£) spent. It is obtained by calculating the difference in costs and QALYs between the vaccinated and the unvaccinated cohorts and then taking the ratio of these two values.

Specifically, let us denote by HC the healthcare costs, by VC the costs incurred by vaccination and by AC the administration costs, with HC_V, VC_V, AC_V denoting these costs for the vaccinated cohort and HC_U, VC_U, AC_U those in the unvaccinated cohort. ΔHC indicates the cost-differential between the vaccinated and unvaccinated cohorts given by $HC_V - HC_U$. c is vaccine coverage and w is vaccine wastage. $\Delta QALY$ and $\Delta Costs$ represent the difference in total QALYs lost and costs respectively between the vaccinated and unvaccinated cohorts. As we are considering QALYs lost, $\Delta QALY$ represents a QALY gain, which we note $QALY_{gain}$.

The ICER is then given by:

$$ICER = \frac{\Delta Costs}{\Delta QALY} = \frac{(c+w)\Delta VC + c\Delta AC + c\Delta HC}{c * QALY_{gain}}.$$

A lower ICER indicates a more cost-effective vaccination strategy, with a negative ICER indicating that the gains in terms of healthcare costs exceed the costs of purchasing and administering vaccines.

Acceptability curves across immunisation scenarios. To fully investigate uncertainty in model parameters, we sampled different vaccine effectiveness and waning values using a triangular distribution. A triangular distribution is defined by a lower limit a, upper limit b and mode c such that $a < b$ and $a \leq c \leq b$. We used the values given in Table 1 to inform this distribution for initial vaccine effectiveness, with the lower and upper estimates representing the distribution endpoints and the central estimate giving the mode. Immunity waning was sampled from a distribution with limits of 5 and 15 and a mode of 10. This represented the total duration of vaccine effectiveness for PPV23, and for PCV20 gave the number of years in which the vaccine will wane after the initial 4 years at initial vaccine effectiveness. Note that this implies each sample will have different strengths of vaccine effectiveness for each immunisation strategy but similar immunity waning.

We used these samples to plot an acceptability curve for the immunisation strategies, showing for each ICER the percentage of strategies that are at or below this value.

Cost-effectiveness threshold. The National Institute for Health and Care Excellence (NICE) generally considers a treatment with an ICER below £20,000/QALY to be cost-effective, although this can vary based on a number of factors, one of which is the uncertainty surrounding the ICER estimate [29]. We therefore considered two cost-effectiveness thresholds, £20,000/QALY and £30,000/QALY.

In the probabilistic analysis, we consider an immunisation strategy to be cost-effective if 90% of samples have an ICER below £30,000/QALY and 50% have an ICER below £20,000/QALY. We calculate the ICER using 1000 samples.

Willingness-to-pay. In addition to exploring cost-effectiveness at the current list prices for vaccines, we investigated the threshold vaccine price in a willingness-to-pay (WTP) analysis, ie. the maximum vaccine cost per dose that would result in an ICER below the chosen threshold (£20,000 per QALY or £30,000 per QALY).

Table 3
Number of CAP and IPD cases averted through vaccination after 30 years, for vaccination ages of 65 and 75, for the three individual immunisation strategies. Values are given for the entire cohort, with values normalised per 100,000 given in brackets. These results are given under base vaccine effectiveness assumptions.

	Cases averted (for the cohort population, normalised per 100,000 in brackets)			
	Age 65		Age 75	
Immunisation strategy	IPD	CAP	IPD	CAP
PCV15	145 (25)	260 (45)	159 (34)	486 (104)
PCV20	354 (61)	581 (101)	360 (77)	673 (144)
PPV23	150 (26)	213 (37)	174 (37)	235 (50)

Using the same notation as previously, the ICER was given by:

$$ICER = \frac{\Delta Costs}{\Delta QALY} = \frac{(c+w)\Delta VC + c\Delta AC + c\Delta HC}{c * QALY_{gain}}.$$

This implies that:

$$\Delta VC = \frac{c}{(c+w)}\left(ICER * QALY_{gain} - \Delta HC - \Delta AC\right)$$

As vaccination costs in the unvaccinated cohort are 0, vaccination costs were given by ΔVC.

For the individual strategies we also calculated the difference between the WTP values for PCV15/20 and PPV23 — the incremental willingness-to-pay. This was an indicative value of how much more we are willing to pay at the given threshold for the new conjugate vaccines to replace the old PPV23 vaccine.

A higher willingness-to-pay indicates a more effective vaccine, as does a higher incremental willingness-to-pay.

3. Results

Results showing the impact of vaccination on IPD disease burden across modelling scenarios are shown in Fig. 3(a)–(c) while CAP outcomes are shown in Fig. 4(a)–(c). Plots (a)–(b) show the number of IPD and CAP cases averted by each immunisation strategy over time for vaccination ages 65 and 75. Three of the nine vaccine effectiveness and waning scenarios are shown: the baseline scenario with central effectiveness and waning parameter values; the scenario with the highest vaccine effectiveness parameter value and the slowest waning; and the scenario with the lowest vaccine effectiveness and the fastest waning. The bar charts in Figs. 3(c) and 4(c), and the results in Table 3 illustrate the comparison of the impact outcomes across different vaccine type and age of vaccination scenarios 30 years after vaccination (and derived from Figs. 3(a)–(b) and 4(a)–(b)).

Our results suggested that of the individual strategies, across both IPD and CAP cases averted, vaccination with PCV20 was the most effective strategy when vaccinating at either 65 or 75 years of age (bar charts in Fig. 3(c) for IPD and bar charts in Fig. 4(c) for CAP).

In the baseline scenario, PCV20 averted 353 IPD and 581 CAP cases when the vaccination age was 65 and substantially larger in comparison to using either PPV23 or PCV15 (with 150/212 and 145/259 IPD/CAP averted cases respectively; details in Table 3).

Accounting for population size, vaccinating at age 75, instead of at 65, was slightly more effective at reducing IPD disease burden (comparing the 2rd and 4th columns in Table 3), while the effect was much larger in the case of averted CAP cases (comparing the 3rd and 5th columns in Table 3). The largest reduction in CAP cases was when vaccinating with PCV20 (673 CAP cases averted when vaccinating at 75 compared to 581 when vaccinating at age 65). PCV15 also benefitted from an increased reduction in CAP burden when vaccinating at age 75, with 485 CAP cases averted when vaccinating at 75 compared to 259 when vaccinating at age 65. This was due to a significant increase in PCV15 CAP incidence in the 75–84 age group (Fig. 1) and to a substantial proportion of the incidence in the 65–74 age group being from serotype 3 (Supplementary Table 1), against which PCV15 has a lower vaccine effectiveness.

As expected, across all immunisation and age strategies, more IPD/CAP cases were averted in the higher vaccine effectiveness and/or the slower immunity waning scenarios (green compared to orange or blue curves across Figs. 3(a)–(b) and 4(a)–(b)).

Note that we present cases averted as an indication of the change in disease burden, however, due to the low amount of QALYs lost due to pneumococcal disease (Table 2), the majority of the health benefit realised in the cost-effectiveness analysis will be realised through a reduction in deaths.

Fig. 5 presents the ICER calculated using current vaccine list prices [25,26] for the three individual vaccine strategies and the nine vaccine effectiveness scenarios, at vaccination ages of 65 and 75.

When vaccinating 65-year-olds, under the base scenario of vaccine effectiveness and waning (centre of each heatmap on Figs. 5(c) and (e)), the ICER was lowest when vaccinating with PPV23 (£13,309/QALY), but was close to that when vaccinating with PCV20 (£14,865/QALY). The results were similar when vaccinating 75-year-olds (centre of each heatmap in Figs. 5(d) and (f)), with respective ICERs of £12,326/QALY and £13,223/QALY when vaccinating with PPV23 and PCV20 respectively. PCV15 was considerably less cost-effective than both PCV20 and PPV23, with an ICER of £30,632/QALY and £21,081/QALY when vaccinating at age 65 and 75 respectively (Figs. 5(a)–(b)).

There was significant variation in the ICER values when we modelled different vaccine effectiveness scenarios (Fig. 5). When vaccinating 65-year-olds, the ICER range in £/QALY was [5178, 62838] for PPV23, [7856, 43563] for PCV20, and [14200, 103145] for PCV15. Across scenarios, depending on the vaccine effectiveness and waning scenario, either PPV23 or with PCV20 was the most cost-effective vaccine with the lowest ICER value, although PCV20 tended to be superior in scenarios with lower overall vaccine effectiveness.

The heatmaps in Fig. 5 showed that the impact on the ICER of vaccine effectiveness was more substantial than that of vaccine waning. This is to be expected, as a vaccine with low vaccine effectiveness will provide limited protection immediately after vaccination, whereas one with fast waning but high initial effectiveness will still offer strong protection in the first few years following vaccination.

Overall, vaccinating at age 75 was more cost-effective than vaccinating at age 65 with a lower ICER across all scenarios (Figs. 6(a)–(b)). This was driven by the greater IPD and CAP incidence in the older age groups. The increase in cost-effectiveness was lower than the disease burden might suggest due to a reduced life expectancy with age, resulting in a lesser amount of QALYs lost per pneumococcal death. There was a substantial reduction in ICER when vaccinating 75 year olds with PCV15 compared to when vaccinating at age 65, as a result of the greater number of CAP cases averted for this vaccine, but this vaccine was not cost-effective at either age (blue curves in Fig. 6(a) and (b)).

Fig. 6 provided the acceptability curve for the ICER, giving for each ICER the number of samples that are below that value. We highlight two thresholds that are generally required by NICE for a treatment to be considered cost-effective, 50% of samples under £20,000/QALY and 90% of samples below £30,000/QALY. Fig. 6(a)–(b) showed that both PCV20 and PPV23 fulfil these requirements at their current list prices at vaccination ages of 65 and 75 and were thus both considered cost-effective (red and purple curves in Fig. 6(a)–(b)). PCV15 however was

Table 4
PCV15 and PCV20 incremental willingness-to-pay, given for the nine overall vaccine effectiveness scenarios and an uncertainty scenario. These represent the highest additional cost of each PCV vaccine relative to the price of PPV23 that would keep the PCV vaccine cost-effective. Values at a cost-effectiveness threshold of £20,000/QALY are given, with the value in brackets representing these at a threshold of £30,000/QALY. The uncertainty is generated using 1000 samples with varying initial vaccine effectiveness and immunity waning. For initial vaccine effectiveness, each sample is taken from a triangular distribution with limits and mode as in Table 1. For immunity waning, samples are taken from a triangular distribution with limits 5 and 15, and mode 10 representing the number of years of waning, with the same sample for PCV15/20 and PPV23 but with an initial 4 years at initial vaccine effectiveness for PCV15/20 and immediate waning for PPV23. In the uncertainty scenario, the £20,000/QALY value is the sample median and the £30,000/QALY value that of the 90th percentile.

	Incremental willingness-to-pay (in £) at a cost-effectiveness threshold of £20,000/QALY (£30,000/QALY)			
	Age 65		Age 75	
Scenario	PCV15	PCV20	PCV15	PCV20
Low initial vaccine effectiveness - fast waning	3.42 (5.12)	22.37 (32.9)	5.31 (7.88)	23.58 (34.48)
Low initial vaccine effectiveness - base waning	1.73 (2.7)	24.81 (36.48)	2.91 (4.46)	24.7 (36.14)
Low initial vaccine effectiveness - slow waning	0.06 (0.32)	27.21 (40.03)	0.37 (0.82)	24.59 (36.01)
Base initial vaccine effectiveness - fast waning	5.88 (8.68)	43.85 (64.5)	20.9 (30.87)	53.52 (78.44)
Base initial vaccine effectiveness - base waning	1.97 (2.97)	48.86 (71.83)	16.8 (24.97)	55.39 (81.15)
Base initial vaccine effectiveness - slow waning	−2.34 (−3.31)	51.81 (76.13)	11.37 (17.1)	54.71 (80.16)
High initial vaccine effectiveness - fast waning	9.55 (14.09)	60.13 (88.52)	39.68 (58.66)	80.94 (118.86)
High initial vaccine effectiveness - base waning	2.32 (3.51)	64.32 (94.64)	32.46 (48.18)	81.76 (120.02)
High initial vaccine effectiveness - slow waning	−3.68 (−5.26)	67.66 (99.5)	25.23 (37.7)	79.98 (117.43)
Uncertainty sampling	1.95 (20.23)	44.76 (91.04)	17.27 (46.59)	54.04 (103.82)

not cost-effective when vaccinating at age 65 but it was just under the cost-effectiveness threshold at age 75 (blue curves in Figs. 6(a)–(b)).

Table 4 gives the incremental WTP for the nine vaccine effectiveness scenarios and the uncertainty sample generated from the triangular distribution. For a vaccination age of 65 and a threshold of £20,000/QALY, the incremental WTP of PCV20 ranged from £22.37 to £67.66, increasing with initial vaccine effectiveness and waning. The incremental WTP for PCV15 varied significantly more, ranging from £9.55 for a high initial vaccine effectiveness and fast waning to £-3.68 for a high initial vaccine effectiveness and slow waning. This indicates that in some scenarios, the list price of PCV15 would have to be lower than that of PPV23 for the two vaccines to be comparable in terms of cost-effectiveness. Across all scenarios, the variation in incremental WTP and low values indicated that the vaccines should be comparably priced for their cost-effectiveness to be similar at a vaccination age of 65.

The sampled median value at a £20,000/QALY threshold equalled £44.76 for PCV20 and £1.95 for PCV15. These values were close to those of the base vaccine effectiveness scenario, which is consistent given that the mode of the sampling distribution is equal to the base scenario for both vaccine effectiveness and waning.

In the individual immunisation strategies the incremental WTP at £30,000/QALY was unsurprisingly higher, although it is interesting to note that the sampled value was also considerably higher at this threshold, indicating that 50% of samples at £20,000/QALY is a more stringent restriction than 90% of those at £30,000/QALY.

The incremental WTP of PCV20 when vaccinating at age 75 was slightly higher (£54.05 compared to £44.76 when vaccinating at age 65) due to the increased reduction in disease burden at this age. This increase was more significant for PCV15 (£17.27 compared to £1.95) due to the large relative increase in CAP incidence for ages 75–84 (Fig. 1(c) and Supplementary Table 1).

Discussion

In this paper we developed a static Markov model for pneumococcal transmission and immunisation, and combined it with an economic model to evaluate the impact and cost-effectiveness of different immunisation strategies targeting 65- or 75-year-olds across nine scenarios of vaccine effectiveness and immunity waning (Table 1). Our work has been commissioned by the Joint Committee on Vaccination and Immunisation (JCVI) and has been discussed both at the JCVI and its Pneumococcal-specific subcommittee meetings.

Our results suggested that, of the individual strategies, the biggest reduction in both IPD and CAP cases was when vaccinating with PCV20 and targeting 75-year-olds (Figs. 3(a)–(c) and 4(a)–(c)).

In terms of cost-effectiveness, both PCV20 and PPV23 could be cost-effective, with the more cost-effective vaccine depending on the effectiveness/waning scenario (Fig. 5(a)–(f)). At their current prices, as of May 2023, vaccination with either PCV20 or PPV23 could be cost-effective when vaccinating 65- or 75-year-olds. But vaccinating at age 75 was more cost-effective than vaccinating at age 65 with a lower ICER across all scenarios (Figs. 6(a)–(b)). PCV15 is not cost-effective under most scenarios, and is less cost-effective than PCV20 across all scenarios. When considering the combined scenarios, supplementing PPV23 with PCV15/20 is unsurprisingly less cost-effective than administering PCV15/20 to a naive population (Supplementary Figures 3(a)–(d)).

To achieve the same overall cost-effectiveness as PPV23, the additional cost of PCV20 needed to be less than £44 at an ICER threshold of £20,000/QALY for a vaccination age of 65 (or £54 at age 75; Table 4). The cost-differential of PCV20 compared to PPV23 at an ICER threshold of £30,000/QALY was higher: £91 for vaccination of 65-year-olds and £103 for that of 75-year-olds (Table 4).

Overall, our findings highlighted that both PCV20 and PPV23 can be cost-effective vaccines that would effectively reduce the pneumococcal burden in the elderly in England. Our findings complement the existing analysis from the government of Canada [21], the United States [30] and Japan [31], and industry-led evaluations [32,33] on the cost-effectiveness of PCV15 and/or PCV20.

The Canadian assessment [21] reviewed four US studies that focused on over-65s using American data. Although not all the studies considered our five immunisation strategies, all four studies modelled PCV20 only, with two of them finding it to be dominant in all scenarios and one finding it to range from dominant to cost-effective depending on scenario. One study found no conjugate vaccine to be cost-effective, with ICERs greater than $100,000/QALY for every vaccine scenario. The Canadian study hypothesised that this divergence could be due to the use of older incidence data. The study also used its own model on Canadian data, finding that PCV20 would be a cost-effective strategy, dominating PCV15 in most scenarios, in line with our findings.

Interestingly, the American assessment [30] found that both PCV20 alone and PCV15 in conjunction with PPV23 can be effective strategies in over-65s and in at-risk adults. Their updated vaccination policy is therefore to offer either a dose of PCV20 only or a dose of PCV15 followed by PPV23 to any individual over-65 or at-risk who has not yet been vaccinated with PCV20. This assessment also considered but rejected extending this policy to the general population over the age

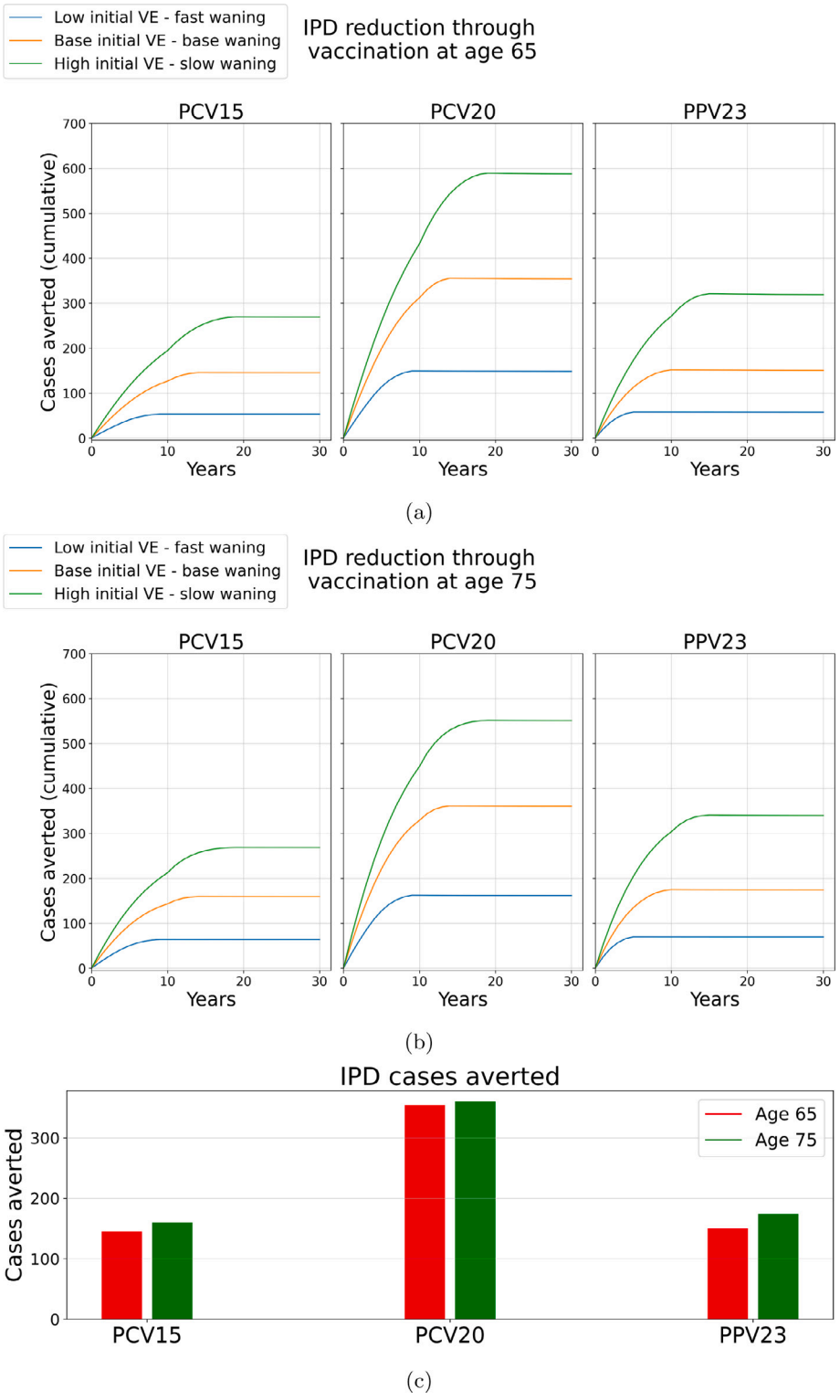
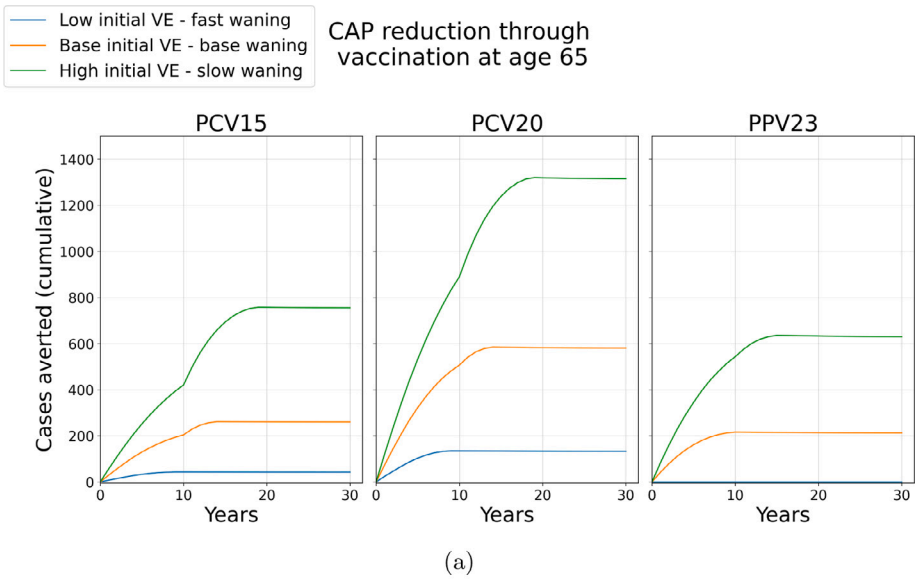


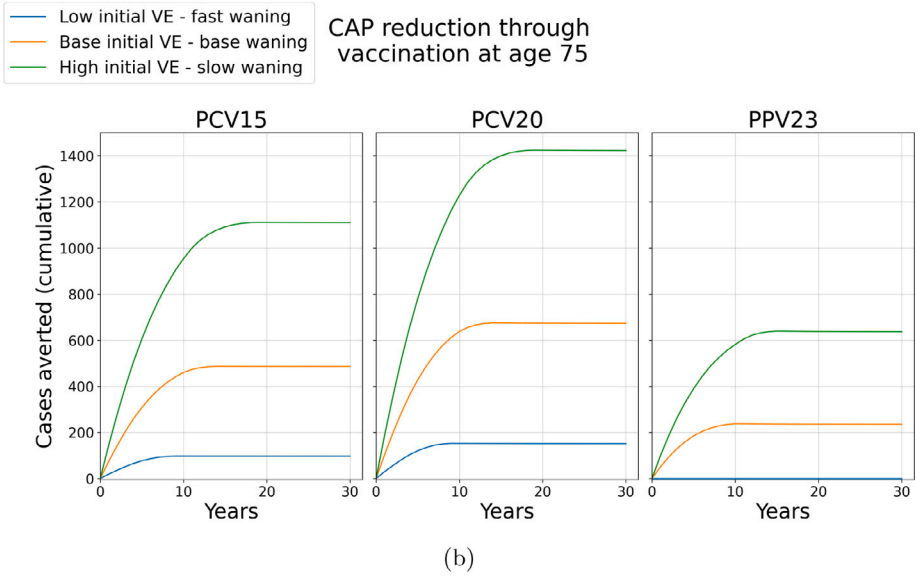
Fig. 3. Number of IPD cases averted through vaccination across the five immunisation strategies when vaccinating 65-year-olds (a), 75-year-olds (b) and comparing the total reduction over the 30 years of simulation under base vaccine effectiveness assumptions (c). The three individual vaccine strategies (PCV15, PCV20 and PPV23) indicate the number of cases averted relative to a strategy with no vaccination. Plots over time are given for the worst, base and best overall vaccine effectiveness (blue, orange and green respectively). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of 50. Unfortunately, the paper did not provide details of its cost-effectiveness models so it was difficult to gauge why this analysis differed from other studies in finding PCV15 in combination with PPV23 to be a cost-effective option.

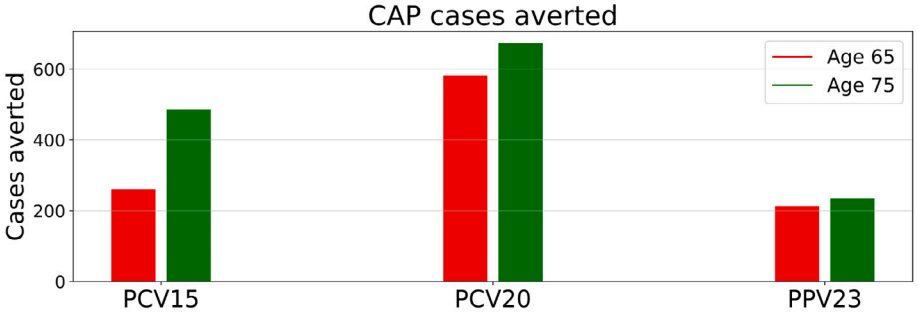
The Japanese study [31] found PCV20 to be more cost-effective compared to the current PPV23 vaccination strategy, with PCV15 of comparable cost-effectiveness to PPV23 (incremental ICER of $318/QALY relative to PPV23). These findings were in line with our results,



(a)



(b)



(c)

Fig. 4. Number of CAP cases averted through vaccination across the three individual immunisation strategies when vaccinating 65-year-olds (a), 75-year-olds (b) and comparing the total reduction over the 30 years of simulation under base vaccine effectiveness assumptions (c). The three individual vaccine strategies (PCV15, PCV20 and PPV23) indicate the number of cases averted relative to a strategy with no vaccination. Plots over time are given for the worst, base and best overall vaccine effectiveness (blue, orange and green respectively). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

concluding that PCV20 was the more cost-effective of the conjugate vaccines. Our work indicated an improved cost-effectiveness of PPV23 than the Japanese study, which was likely due to the PCV vaccine effectiveness of 66.7% against non-bacteremic pneumonia (NBP), which was higher than the base scenario PCV vaccine effectiveness of 45% against CAP in our work, while PPV23 effectiveness against CAP/NBP is identical at 20% between our studies. Indeed, this study found that 82% of PCV20 cost savings came from reductions in CAP, highlighting the importance of correctly evaluating CAP incidence and vaccine effectiveness against it.

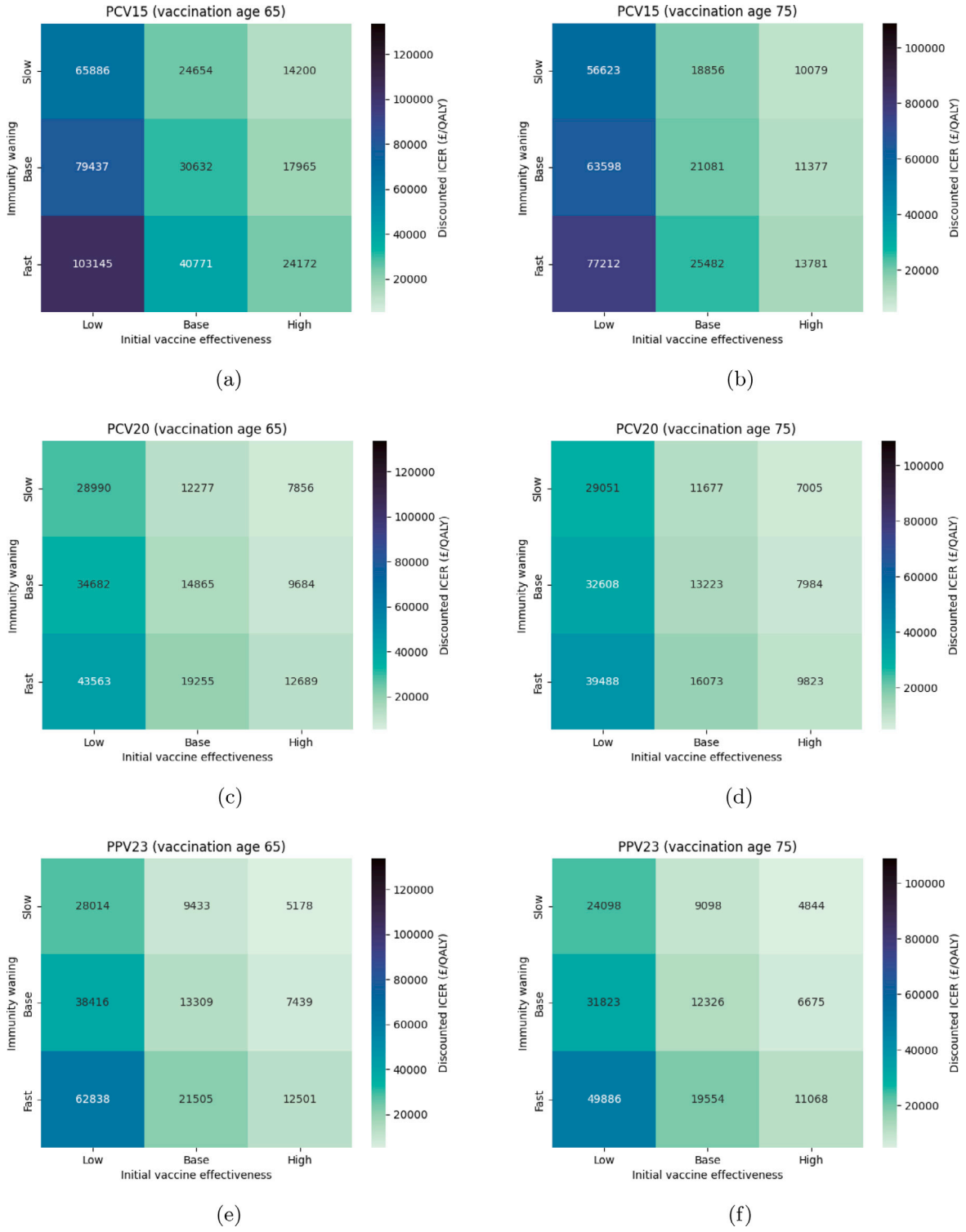


Fig. 5. ICERs for the individual vaccine strategies (PCV15, PCV20 and PPV23) across the nine overall vaccine effectiveness scenarios, at vaccination ages of 65 ((a), (c), (e)) and 75 ((b), (d), (f)). These are calculated using current (as of May 2023) vaccine list prices of £50.30, £56.80 and £16.80 for PCV15, PCV20 and PPV23 respectively. Overall vaccine effectiveness is split into three scenarios each for initial vaccine effectiveness (x-axis) and immunity waning (y-axis).

The industry-led evaluations compared the effectiveness of PCV20 and PPV23 against CAP and IPD in England [32] and in Denmark [33], finding PCV20 to be the more cost-effective vaccination strategy compared to PPV23, both across the main analysis and the sensitivity analyses. These findings differ from our results that suggest that PCV20 and PPV23 provide a comparable cost-effectiveness benefit to the English population, with the preferred vaccine depending on input parameters, particularly vaccine price and effectiveness. The divergence in our results to [32,33] are due to the modelling assumptions. While all three studies use the same Markov model and most of the assumptions across studies are similar, there is a notable difference in the modelling of PPV23 effectiveness in [32,33]. In particular, they consider PPV23 to have no effectiveness against CAP, citing inconclusive evidence. Setting PPV23 CAP effectiveness to 0 results in the vaccine being

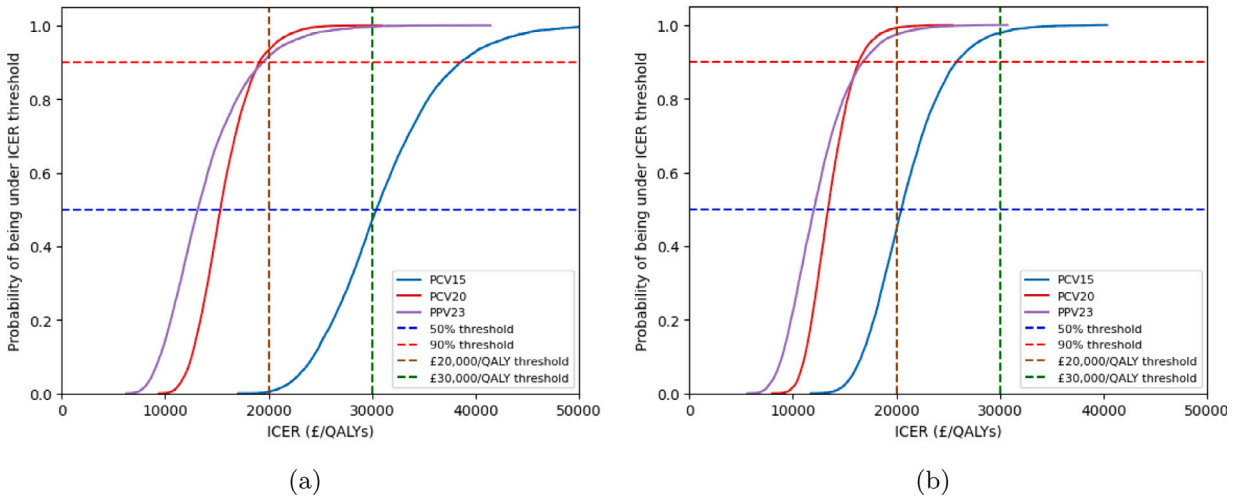


Fig. 6. ICER acceptability curves using current vaccine list prices for PCV15, PCV20 and PPV23, vaccination ages of 65 (a) and 75 (b), generated using 1000 samples with uncertainty on initial vaccine effectiveness and immunity waning. For initial vaccine effectiveness, each sample is taken from a triangular distribution with limits and mode as in Table 1. For immunity waning, samples are taken from a triangular distribution with limits 5 and 15, and mode 10 representing the number of years of waning, with the same sample for PCV15/20 and PPV23 but with an initial 4 years at initial vaccine effectiveness for PCV15/20 and immediate waning for PPV23. These curves represent the proportion (y-axis) of samples that have an ICER below the value on the *x*-axis. Two cost-effectiveness threshold values are highlighted with the dotted lines, 50% of samples at £20,000/QALY and 90% of samples at £30,000/QALY. For an immunisation strategy to be deemed cost-effective, its acceptability curve must intersect the vertical dotted line (indicating it passes below the cost-effectiveness threshold) before it intersects the corresponding horizontal line.

cost-effective at current list prices only under scenarios with high overall vaccine effectiveness (Supplementary Figure 6), and hence explains their findings. Another difference with Olsen et al.'s model [33] is that they model repeat infections, which we do not. This would lead to an underestimate of the disease burden in our model, which should favour the more effective conjugate vaccines, however it is difficult to estimate the impact of this change without altering our model to include re-infections. Another modelling assumption where we differ from [32,33] is our decision to treat serotype 3 separately, and assuming reduced vaccine effectiveness against it. This would explain the improved performance of PCV20 in Olsen et al. [33] and Mendes et al. [32] as PCV20 effectiveness against serotype 3 is around one-third of that against other serotypes in our analysis. Given that Olsen et al. [33] and Mendes et al. [32] assume no effectiveness of PPV23 against CAP, modelling reduced effectiveness against certain serotypes in their work would reduce PCV20's effectiveness more than that of PPV23. As serotype 3 represents 15%–20% of the total IPD incidence and 30%–50% of total CAP incidence in the 65–74 and 75–84 age groups (Supplementary Table 1), a reduced effectiveness against it is significant. Supplementary Figure 7 displays the ICERs for a vaccination age of 65 if serotype 3 were to have the same effectiveness as other serotypes. The ICERs are reduced for every immunisation strategy as expected.

Our work has several strengths. Firstly, we have used a simple static model which can be easily reproduced and updated with new parameters or data, allowing us to explore a wide range of scenarios for vaccine effectiveness and to extend existing studies [14]. We also incorporated uncertainty and sensitivity analysis, covering a number of scenarios and possible policy strategies. The creation of naive incidence data in our model representing a population without PPV23 vaccination is crucial for the evaluation of both the current PPV23 vaccination regime and of a replacement with PCV20. Finally, the separation of serotype 3 in our analysis, unlike in previous studies, was based on evidence of reduced vaccine effectiveness against it [13,20] and its high incidence. In future this approach could be extended to other frequent pneumococcal serotypes with diverging vaccine effectiveness properties.

Our work has some limitations. Firstly, as we only vaccinate the cohort once with no vaccine catch-up, we do not model the vaccination of individuals at an older age. We also use the same vaccine effectiveness for 65- and 75-year-olds, as a reasonable approximation given the high uncertainty surrounding this parameter. Additionally, when calculating the naive incidence in the individual vaccine scenarios, the vaccine effectiveness may be optimistic as it represents the initial vaccine effectiveness after administration of the vaccine, with only a slight adjustment for vaccine waning. This would become more prevalent among older age groups as it is more likely that more time has passed since vaccination with PPV23. We account for this by performing sensitivity analysis using a lower vaccine effectiveness value, which does not change the comparison between vaccines but does reduce overall cost-effectiveness, increasing ICER values by around 10% (Supplementary Figure 4). Moreover, our incidence estimates are informed by 2018/19 data to avoid potential confounding from the COVID-19 pandemic, which perturbed pneumococcal transmission. We assume that incidence will return to this pre-pandemic baseline, but this may or may not occur. Incidence data has a considerable impact on disease burden and therefore on cost-effectiveness, which could lead to our results being an overestimate if incidence data were to be lower post-pandemic than in 2018/19. Conversely, CAP data from the Nottingham study might be an underestimate of incidence due to the study not being strictly designed to determine the overall incidence of CAP [7], which would improve cost-effectiveness for all immunisation strategies. Additionally, our analysis includes serotypes which have been affected by the PCV13 infant vaccination campaign, but does not explicitly model any possible immunity acquired from this vaccine. However, this will partly be accounted for in the incidence data and vaccine effectiveness estimates. Finally, hospitalisation costs are taken per case, and hence do not include any modelling of length of stay. We are planning to explore this more in future work.

We note that our analysis only considered vaccination ages of 65 and 75. We would ideally have considered each age individually to estimate the optimal age of vaccination, however we felt that the 10-year age bands within our incidence data lent insufficient precision for such analysis. Vaccination at age 85 was not considered due to the reduced population size and life expectancy at this age.

Overall, our findings highlight that both PPV23 and PCV20 can be cost-effective vaccines for the elderly in England. Hence, our analyses recommends that both vaccines are considered within the national

elderly pneumococcal immunisation programme in England. But we note that while our work focused on comparing immunisation strategies on impact and cost-effectiveness basis, national immunisation policy, and specifically changing it, has a number of other considerations to take into account. Switching from the current PPV23 vaccine to a likely more effective and cost-effective one in PCV20 could create equity issues between individuals turning 65 in the coming years and those already aged 65 and vaccinated against pneumococcal disease without a choice of vaccine. Similarly, transitioning from the current vaccination age of 65 to one at age 75 alone, although likely to be more cost-effective based on our analysis, would result in individuals under 65 having to go a further decade without immunisation. Another consideration is that including the new conjugate vaccines in a national immunisation policy would yield further data on their effectiveness, helping to inform future decisions. This is all the more crucial given the current uncertainty around PCV immunity waning in particular. Our work has simply modelled the outcomes from an impact and cost-effectiveness modelling analyses, and our recommendations are based on this and caveated by the modelling assumptions made. Policy decision makers need to take into consideration the wider implications of amending or changing the national pneumococcal immunisation strategy for elderly in England.

Conclusions

In summary, our analyses of different immunisation strategies against pneumococcal disease in England has shown that both the existing polysaccharide PPV23 and the newly developed conjugate PCV20 are likely to be cost-effective. But the newly developed PCV20 is likely to avert more cases of pneumococcal disease in elderly adults in England than the current PPV23 vaccine, given input assumptions of a higher vaccine effectiveness and slower waning for PCV20.

CRediT authorship contribution statement

Gabriel Danelian: Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing – original draft. **Lucy Burton:** Formal analysis, Methodology, Writing – review & editing. **Thomas Bayley:** Validation, Writing – review & editing. **Alberto Sanchez-Marroquin:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Josie Park:** Conceptualization, Data curation, Formal analysis, Methodology. **Harrison Manley:** Validation, Writing – review & editing. **Yoon Choi:** Methodology, Validation, Writing – review & editing. **Nick Andrews:** Methodology, Writing – review & editing. **Shamez Ladhani:** Data curation, Writing – review & editing. **Andrew Earnshaw:** Conceptualization, Writing – review & editing. **Jenna F. Gritzfeld:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Caroline Trotter:** Conceptualization, Data curation, Investigation, Project administration, Writing – review & editing. **Jasmina Panovska-Griffiths:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.05.001.

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