Potential impact of replacing the 13-valent pneumococcal conjugate vaccine with 15-valent or 20-valent pneumococcal conjugate vaccine in the 1 + 1 infant schedule in England: a modelling study

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Summary

Background Paediatric pneumococcal conjugate vaccine (PCV) programmes in England using seven-valent PCV (PCV7) in 2006 and 13-valent PCV (PCV13) in 2010 have reduced vaccine-type invasive pneumococcal disease, but the overall effect has been reduced by an increase in invasive pneumococcal disease due to non-vaccine serotypes and serotype 3. We developed pneumococcal transmission models to investigate the potential effect on invasive pneumococcal disease of higher valency PCVs covering an additional two (ie, 15-valent PCV [PCV15]) or seven serotypes (ie, 20-valent PCV [PCV20]) in England.

Methods We conducted a modelling study using realistic, age-structured, and compartmental deterministic models fitted to carriage data from before the introduction of PCVs and invasive pneumococcal disease data from before and after the introduction of PCV7 and PCV13 in England from the UK Heath Security Agency invasive pneumococcal disease surveillance system. We estimated key parameters, including PCV7 and PCV13 efficacy against vaccine-type carriage and invasiveness of PCV7 serotypes; the additional serotypes in PCV13, PCV15 and PCV20; and non-vaccine serotypes. We simulated the effect of transitioning from PCV13 to PCV15 or PCV20 in infants under the current 1+1 vaccination schedule and investigated the effect of reduced carriage protection against PCV13 serotypes due to attenuation of immunogenicity in higher valency vaccines.

Findings Our results suggest that PCV15 might increase overall invasive pneumococcal disease as the reduction in vaccine-type invasive pneumococcal disease would be counterbalanced by an increase in non-PCV15 invasive pneumococcal disease. By contrast, PCV20 is projected to have a substantial impact on overall invasive pneumococcal disease due to higher invasiveness of the additional serotypes covered by PCV20 than the replacing non-vaccine serotypes. Reduced carriage protection against PCV13 serotypes with higher valency vaccines would amplify these effects.

Interpretation Replacing PCV13 with PCV20 is likely to have a substantial public health benefit, but PCV15 could potentially increase the overall burden of disease.

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See Comment page e638

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Introduction

Streptococcus pneumoniae, also known as pneumococcus, is usually carried asymptomatically in the nasopharynx. The bacteria can lead to mucosal infections, such as acute middle ear infection and sinusitis, but also has the potential to spread to sterile sites, causing more severe invasive disease, such as pneumonia, bacteraemia, and meningitis. Invasive pneumococcal disease is a notable cause of morbidity and mortality worldwide,[1] with the highest incidence typically observed among young children and older people. Pneumococcal conjugate vaccines (PCVs) are highly effective in preventing invasive pneumococcal disease in children and can also provide protection against carriage.[2] Consequently, WHO recommends the inclusion of PCVs in national childhood immunisation programmes worldwide.[3]

The UK introduced the seven-valent PCV (PCV7) in 2006 for infants, with two primary doses at 2 months and 4 months of age, followed by a booster at 12–13 months (ie, a 2+1 schedule). In April, 2010, PCV7 was replaced with 13-valent PCV (PCV13), which covered an additional six serotypes. Except for serotype 3, these PCV programmes have been successful in reducing vaccine-type invasive pneumococcal disease cases and, by reducing carriage of vaccine serotypes, have indirectly protected older unvaccinated individuals through the induction of herd protection. The overall population effect has, however, been reduced by serotype replacement, particularly in people older than 65 years,

Research in context

Evidence before this study

We searched PubMed for articles published from database inception to Feb 13, 2024, using the search terms ("impact*" OR "predict*") AND "vaccin*" AND ("PCV20" OR "PCV15") AND ("infant*" OR "pedi*"), without any language restrictions. The search resulted in 30 papers, 20 of which were descriptive epidemiological studies reporting the coverage of 15-valent pneumococcal conjugate vaccine (PCV15) or 20-valent pneumococcal conjugate vaccine (PCV20) additional serotypes among people with invasive or non-invasive pneumococcal disease. The remaining ten papers were all modelling studies, with most including cost-effectiveness analyses; all ten were funded by vaccine manufacturers. Nine of ten papers used static cohort models or single serotype or serotype-grouping dynamic models without considering interactions with other serotypes or serotype groupings, and the remaining one model considered interactions with a constant competition between compartments looking at potential coverage of PCV15 and PCV20 among remaining invasive pneumococcal disease cases after seven-valent pneumococcal conjugate vaccine (PCV7) and 13-valent pneumococcal conjugate vaccine (PCV13) introduction in Germany. None of the models considered herd protection and the potential for replacement disease arising from the reduction in carriage of the serotypes covered by the higher valency vaccines.

Added value of this study

We developed a realistic, age-structured, compartmental, and deterministic model of pneumococcal transmission dynamics that simulated herd immunity and serotype replacement from the existing paediatric pneumococcal conjugate vaccine (PCV) programmes in England and allowed investigation of the potential direct and indirect effects of replacing PCV13 with PCV15 or PCV20, a novel aspect that has not previously been explored. Furthermore, we examined the potential effect of the progressive reduction in immunogenicity with increasing PCV valency on vaccine efficacy against carriage. Our results suggest that PCV15 has the potential to increase overall invasive pneumococcal disease incidence due to the greater invasiveness of the replacing non-PCV15 serotypes compared with the two additional PCV15 serotypes, whereas PCV20 is predicted to result in a net reduction in invasive pneumococcal disease. The model simulations also indicate some loss of carriage protection when valency increased from seven to 13, which might further attenuate the effect of PCV20 and result in some increase in invasive pneumococcal disease due to PCV13 serotypes in young children should similar reductions in carriage protection to the existing PCV13 serotypes occur.

Implications of all the available evidence

The decision to replace current PCVs with higher valency vaccines in paediatric vaccination programmes requires careful evaluation, considering the complexity of the dynamic changes in pneumococcal transmission and the relative invasiveness of emerging serotypes in carriage. Multivalent vaccine formulations that preserve immunogenicity with increasing valency or the development of PCVs that complement existing PCVs by including only the main highly invasive non-vaccine serotypes could offer additional public health benefit.

in whom the increase in non-vaccine invasive pneumococcal disease after the introduction of PCV13 has largely negated the reduction in vaccine-type invasive pneumococcal disease.[4]

With the substantially reduced incidence of vaccine-type pneumococcal disease in all age groups, the UK shifted from a 2+1 to a 1+1 schedule in January, 2020, with a primary dose at 12 weeks of age and a booster at 1 year of age. This decision was based on findings from an immunogenicity study that showed similar serotype-specific IgG responses after the booster in the 2+1 and 1+1 schedules[5] and a mathematical modelling study that predicted that the schedule change was likely to have little overall effect on invasive pneumococcal disease incidence, with any increase in vaccine-type invasive pneumococcal disease offset by a reduction in non-vaccine-type invasive pneumococcal disease.[6] Although evaluation of the effect of this schedule change has been complicated by the perturbations of pneumococcal transmission resulting from physical distancing measures to reduce SARS-CoV-2 infections during the COVID-19 pandemic,[7,8] most cases of invasive pneumococcal disease in England between April, 2022, and March, 2023, were caused by non-PCV13 serotypes and serotype 3.[9] The development of higher valency PCVs than PCV13 that cover some of the most common replacing serotypes could potentially reduce this residual burden of invasive pneumococcal disease. Two such vaccines have recently been licensed for paediatric use by the European Medicines Agency: 15-valent PCV (PCV15; ie, covering an additional two serotypes) in December, 2021, and 20-valent PCV (PCV20; ie, covering an additional seven serotypes) in March, 2024.

We developed realistic, age-structured, compartmental, deterministic models to simulate the effect of the PCV7 and PCV13 programmes in England on pneumococcal transmission and the effect on invasive pneumococcal disease of changing from PCV13 to PCV15 or PCV20 with the current UK 1+1 schedule.

Methods

Model design and parameters

A full description of the compartmental, deterministic model is given by Choi and colleagues.[6] As previously described, the models used in this study simulate

pneumococcal carriage infections and transmission, with invasive disease outcomes of a carriage infection derived from case-carrier ratios (CCRs), but have additional serotype groupings to accommodate the new serotypes covered by PCV15 or PCV20, with separate models for each vaccine. The structure, data sources, fitting, parameter derivation, and underlying equations for the models are described in detail in appendix 1 (pp 9–12, 32–50).

Serotypes in the models are grouped according to existing and new PCVs: vaccine type 1 (VT1) includes the PCV7 serotypes (ie, serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F), vaccine type 2 (VT2) includes the additional serotypes in PCV13 excluding serotypes 1 and 3 (ie, serotypes 5, 6A, 7F, and 19A), and vaccine type 3 (VT3) includes the additional serotypes in PCV15 (ie, serotypes 22F and 33F) or PCV20 (ie, serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F), with non-vaccine serotypes (ie, serotypes not included in VT1, VT2, and VT3) comprising a fourth serotype grouping. Serotype-1 invasive pneumococcal disease cases increased before the introduction of PCV7, decreased after PCV7 implementation, and have maintained a very low incidence since then, whereas serotype-3 invasive pneumococcal disease cases had an increase after PCV13 introduction in England (appendix 1 p 2).[9] Therefore, as in our previous models, serotype 1 was excluded from the models and serotype 3 was included in the non-vaccine serotype group.[6,7,10] The serotype-3 component is the same in PCV20 and PCV13 but differs in PCV15, inducing around a 1·3-fold higher response after the booster under the 2+1 schedule than PCV13 (geometric mean concentration ratio 1·31, 95% CI 1·20–1·43; 1·28, 1·17–1·39).[11,12] For the baseline scenario in the PCV15 model, serotype 3 is in the non-vaccine serotype group, and in a sensitivity analysis, serotype 3 is included in the VT3 group with an assumed efficacy of PCV15 against carriage of serotype 3 that is a quarter that of the other two VT3 serotypes, 22F and 33F. Since the number of cases caused by serotype 3 and the number caused by serotypes 22F and 33F are similar,[9] we assumed for the sensitivity analysis that the vaccine efficacy against carriage (VEc) of VT3 serotypes and serotype 3 was 0·625 of that assumed for VT3 serotypes in the base case scenario without serotype 3.

The sequencing method now used for serotyping invasive pneumococcal disease at the UK Health Security Agency[13] does not always distinguish between serotypes 15B and 15C, so serotypes in this serogroup might be reported as 15B/C. Whereas serotype 15B is included in PCV20, serotype 15C is not, although immunogenicity studies suggest cross-protection from serotype 15B against serotype 15C.[14] Between January, 2019, and December, 2022, there were ten invasive pneumococcal disease cases identified as 15C, 178 cases identified as 15B, and 153 cases reported as 15B/C. Given the few cases caused by serotype 15C and potential for cross-protection, we included serotypes 15B, 15C, and 15B/C in the VT3 serotype group for PCV20.

Model parameters were estimated as previously reported,[6] with some modifications to accommodate the extra serotype grouping representing the additional serotypes covered by PCV15 and PCV20. The rate at which susceptible individuals acquire a new carriage infection (ie, the force of infection) in the pre-PCV equilibrium state was obtained by fitting a static model to age-stratified carriage data from a longitudinal household carriage study conducted before the introduction of PCV7.[15] Forces of infection for the different serotype groupings together with invasive pneumococcal disease data from before the introduction of PCVs (appendix 1 p 7) were then used to estimate age-group stratified CCRs for VT1, VT2, VT3, and non-vaccine serotype groups. A dynamic model was fitted to invasive pneumococcal disease data for England after the introduction of PCV7 and PCV13 up to 2018–19 (appendix 1 p 7) to estimate the degree of competition in carriage between serotype groupings, which is reflected in the extent of serotype replacement after the introduction of PCV7 and PCV13. Since the competition between VT3 and non-vaccine serotypes (appendix 1 p 10) cannot be estimated as there is currently no population experience with PCV15 or PCV20, the value for this competition parameter was assumed to be 1 (ie, complete replacement in carriage [C8=1]), consistent with the results of carriage studies after introduction of PCV7 and PCV13 in England,[16] and 0·5 (ie, partial replacement [C8=0·5]) in sensitivity analyses.

See Online for appendix 1

The efficacy of PCV7 and PCV13 against carriage of VT1 and VT2 serotypes (denoted as VEcVT1 and VEcVT2) was also estimated by fitting to invasive pneumococcal disease data after PCV introduction. For VEc of VT1 serotypes, we estimated the value between September, 2006, and March, 2010, when PCV7 was in use, and separately from April, 2010, to June, 2019, when PCV13 was used, because immunological studies indicate some reduction in responses to PCV7 serotypes after booster when changing to PCV13 with a 2+1 schedule.[17–19] Immunogenicity studies comparing PCV15 and PCV20 with PCV13 show further reductions in post-booster geometric mean concentrations for the existing 13 serotypes.[11,12,19,20] VEc estimates against VT1 and VT2 serotypes from the post-PCV13 fitting were therefore adjusted when changing to PCV15 and PCV20 based on the reduction in the VEc against VT1 estimated when replacing PCV7 with PCV13. Because the efficacy against carriage of the additional serotypes covered by PCV15 and PCV20 (VEcVT3) is currently unknown, we assumed values based on the adjusted VEcVT1 and VEcVT2 estimates. We also ran the models with the VEcVT1 and VEcVT2 values obtained from the PCV13 period without adjustment for any loss of protection against carriage when incorporated within higher valency vaccines; for these model runs we assumed that VEcVT3 had an efficacy similar to that of the unadjusted VEcVT1 or VEcVT2 values.

In summary, there are six model scenarios for assessing the effects of PCV15 and PCV20 vaccines (appendix 1

	PCV15 model	PCV20 model
Values obtained from model fitting during PCV7 and PCV13 periods		
PCV7		
VEcVT1	46·2% (45·2–47·2)	45·8% (44·8–46·9)
PCV13		
VEcVT1	36·4% (36·2–36·9)	36·3% (35·8–36·8)
VEcVT2	18·6% (18·0–18·9)	18·6% (18·2–19·1)
Reduction in VEcVT1 in PCV13 period	78·9% (77·2–80·4)	79·2% (77·3–81·0)
Values assumed for the PCV15 or PCV20 models		
Adjusted*		
VEcVT1	28·7% (27·9–29·7)	28·7% (27·7–29·8)
VEcVT2	14·7% (13·9–15·2)	14·8% (14·1–15·4)
VEcVT3_1†	28·7% (27·9–29·7)	28·7% (27·7–29·8)
VEcVT3_2‡	14·7% (13·9–15·2)	14·8% (14·1–15·4)
Unadjusted§		
VEcVT1	36·4% (36·2–36·9)	36·3% (35·8–36·8)
VEcVT2	18·6% (18·0–18·9)	18·6% (18·2–19·1)
VEcVT3_3¶	36·4% (36·2–36·9)	36·3% (35·8–36·8)
VEcVT3_4‖	18·6% (18·0–18·9)	18·6% (18·2–19·1)

Data are vaccine efficacy against carriage. Medians of 100 parameter sets (uncertainty intervals) of the estimated VEcVT2 and VEcVT1 during the PCV7 and PCV13 periods for the base case model scenarios, and the values assumed for VEcVT1, VEcVT2, and VEcVT3 for both PCV15 and PCV20 models in the long-term simulations. Four different values of VEcVT3 are assumed based on whether adjusted or unadjusted values of VEcVT1 or VEcVT2 as measured for PCV13 are used in the model simulations. PCV15=15-valent pneumococcal conjugate vaccine. PCV20=20-valent pneumococcal conjugate vaccine. PCV7=seven-valent pneumococcal conjugate vaccine. PCV13=13-valent pneumococcal conjugate vaccine. VEcVT1=vaccine efficacy against carriage for the PCV7 serotypes. VEcVT2=vaccine efficacy against carriage for the additional serotypes in PCV13 excluding serotypes 1 and 3. VEcVT3=vaccine efficacy against carriage of the additional serotypes covered by PCV15 or PCV20. *Adjusted for assumed reduction in carriage protection with PCV15 or PCV20 vaccines by use of proportionate reduction in VEcVT1 in PCV13 compared with PCV7 vaccine (21%). †Adjusted VEcVT1 of PCV13. ‡Adjusted VEcVT2 of PCV13. §Unadjusted values obtained from fitting in the PCV13 period. ¶Unadjusted VEcVT1 of PCV13. ‖Unadjusted VEcVT2 of PCV13.

Table 1: **Estimated and assumed median values of vaccine efficacy against carriage of different serotype groupings for PCV15 and PCV20**

p 4), each of which was run with different values for the protection against carriage of VT1, VT2, and VT3 serotype groupings, and with the base case for both models assuming full replacement in carriage and serotype 3 in the non-vaccine serotype group.

Fitting procedure and statistical methods

The fitting procedure for the dynamic model was initiated with the parameters from the static model and a randomly selected set of parameters for the dynamic model. The fitting procedure was conducted to estimate the model parameters by maximising the likelihood of the model outputs given the invasive pneumococcal disease data. As described in appendix 1 (pp 15–16), we obtained the uncertainty of the fitted model parameters using the Poisson maximum likelihood and the Nelder–Mead Downhill Simplex method. We used R (version 4.3.3), Matlab (version 2023b),[21] and C++[22] for the data and result analysis and performed modelling fitting and simulation procedures in Windows computers and a high-performance computing cluster in the UK Health Security Agency.

The fitting procedure was conducted for each of the six model scenarios until 100 parameter sets were found for which likelihood values were within the 5% χ^2 critical value of the maximum likelihood for each model scenario. Uncertainty intervals (UIs) represent the range of the model outputs (minimum to maximum) for the 100 selected parameter sets for each model scenario.

We used the invasive pneumococcal disease cases in 2018–19 (appendix 1 p 7) as the baseline (vaccine year 0) with transition from PCV13 to PCV15 or PCV20 occurring in vaccine year 1, assuming that at the time of transition, pneumococcal transmission dynamics perturbed by the COVID-19 lockdowns would have returned to pre-pandemic levels. The vaccine simulation was run for 25 years from vaccine year 1 to reach the steady state after changing to the higher valency PCV, as required for cost-effectiveness analyses, with cumulative differences in invasive pneumococcal disease cases shown over the first 5 years as a more realistic time horizon than 25 years, during which further vaccine changes are likely.

Data sources

Carriage data from before the introduction of PCVs and invasive pneumococcal disease data from before and after the introduction of PCVs from England were used for parameter estimation and model fitting. As previously described,[4,9] the UK Health Security Agency invasive pneumococcal disease surveillance system is a national enhanced dataset of electronic reports of invasive pneumococcal disease cases from diagnostic laboratories in England, linked to serotype information from isolates referred to the UK Health Security Agency Respiratory and Vaccine Preventable Bacteria Reference Unit for serotyping. Invasive pneumococcal disease cases organised by epidemiological years (from July to June) spanning 2000–01 to 2018–19 were used in the fitting.[4,9]

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The force of infection estimates in the PCV15 and PCV20 models for the base case were similar, with VT1 (ie, the PCV7 serotypes) and VT2 (ie, the additional PCV13 serotypes, excluding serotypes 1 and 3) showing the highest values in children younger than 2 years and VT3 (ie, the additional PCV15 or PCV20 serotypes) showing a peak in children aged 3–4 years, whereas non-vaccine

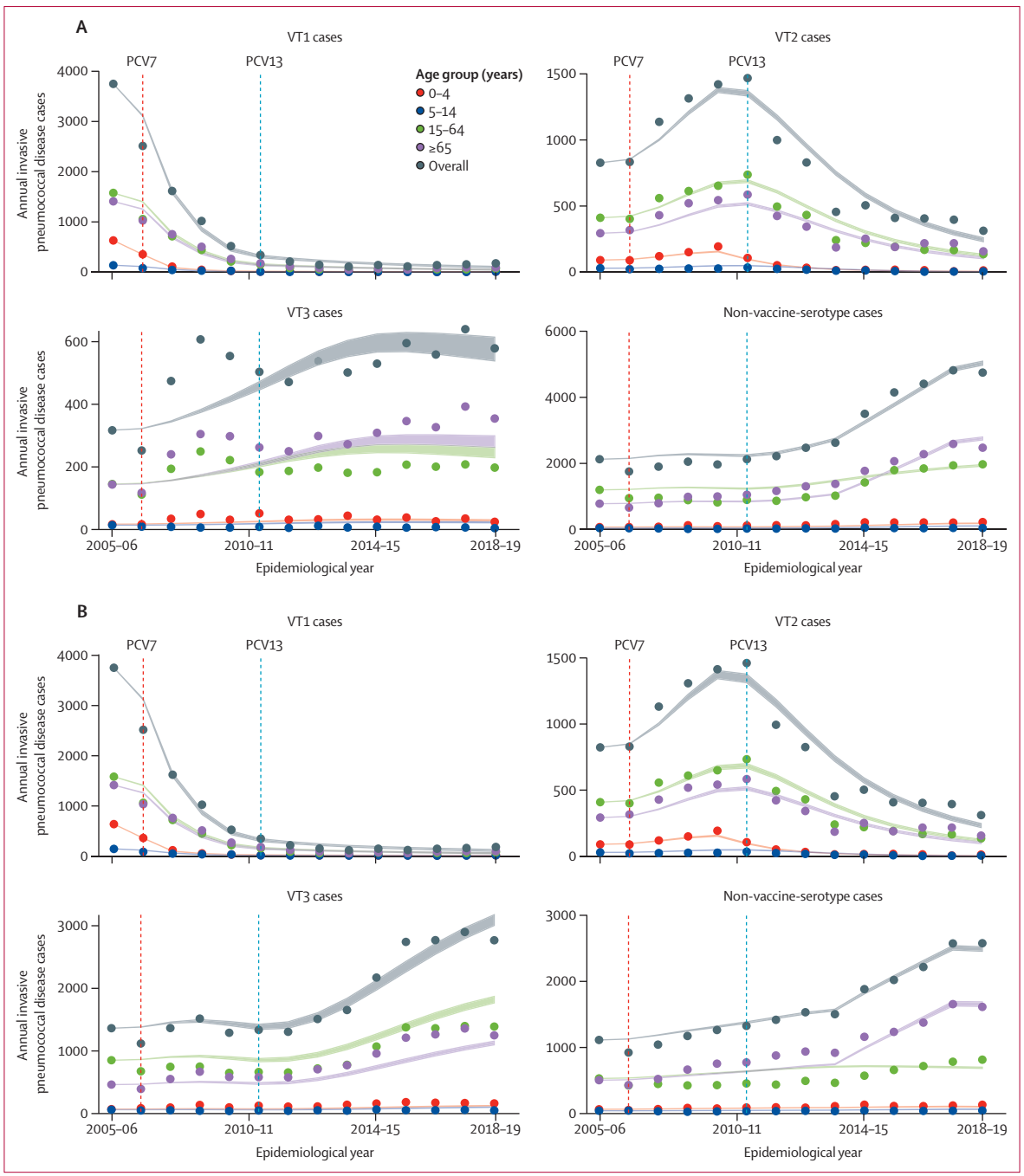

Figure 1: **Annual invasive pneumococcal disease cases and fitted model outputs by serotype groupings and age group for the base case scenario**
Note that scales on y axes differ between plots. Comparison of annual invasive pneumococcal disease cases (shaded area indicates uncertainty intervals) and the fitted model outputs from 100 parameter sets by four serotype groupings and by age group for the base case scenario for the PCV15 model (A) and the PCV20 model (B) between 2005–06 and 2018–19 in England. VT1 includes the PCV7 serotypes; VT2 includes the additional serotypes in PCV13 excluding serotypes 1 and 3; VT3 includes the additional serotypes covered by PCV15 or PCV20; and NVT includes serotypes now included in VT1, VT2, and VT3. NVT=non-vaccine serotype. PCV7=seven-valent pneumococcal conjugate vaccine. PCV13=13-valent pneumococcal conjugate vaccine. PCV15=15-valent pneumococcal conjugate vaccine. PCV20=20-valent pneumococcal conjugate vaccine. VT1=vaccine type 1. VT2=vaccine type 2. VT3=vaccine type 3.

serotype forces of infection peaked in those aged 10–19 years (appendix 1 p 13). By contrast, CCRs show marked differences between models, with the non-vaccine-serotype CCR higher than the VT3 CCR in adults aged 25 years and older in the PCV15 model but lower than the VT3 CCR in the same age group in the PCV20 model (appendix 1 p 14). For the PCV15 model, the force of infection and CCR results in the sensitivity analyses in

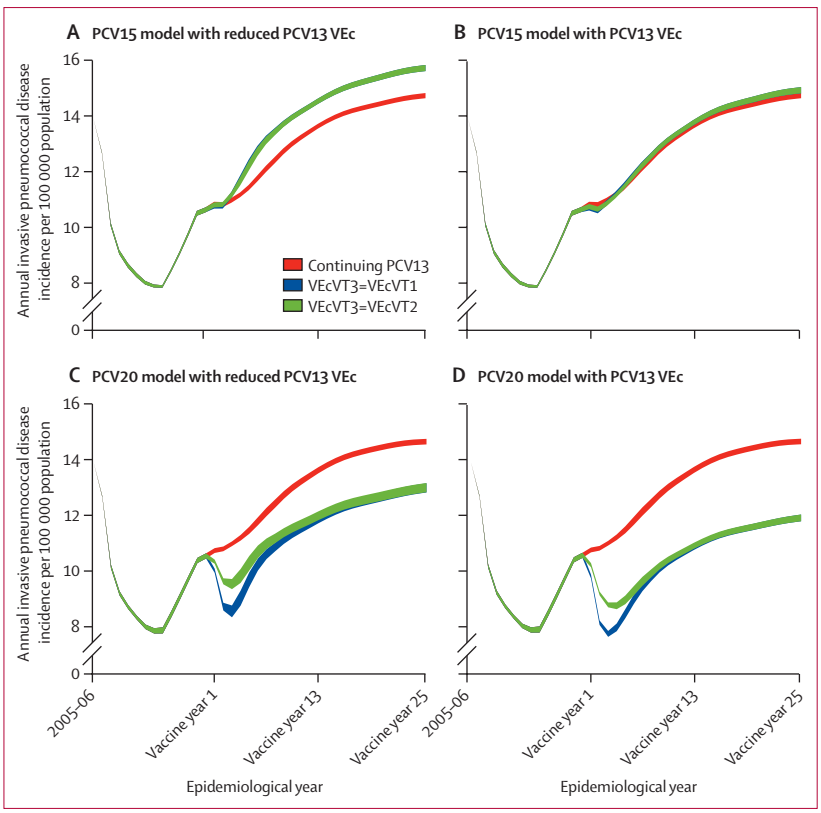

Figure 2: **Long-term simulation results for invasive pneumococcal disease incidence**
Incidence per 100 000 population under base case scenarios of replacing PCV13 with PCV15 (A, B) or PCV20 (C, D) from vaccine year 1 assuming adjusted or unadjusted values for VEcVT1, VEcVT2, and VEcVT3, as shown in table 1, and complete replacement (C8=1) in carriage of the additional serotypes covered by PCV15 or PCV20 with non-vaccine serotypes in England. Shaded bands indicate the uncertainty intervals. Vaccine year indicates the epidemiological year since the change of PCV13 to the new PCV. PCV13=13-valent pneumococcal conjugate vaccine. PCV15=15-valent pneumococcal conjugate vaccine. PCV20=20-valent pneumococcal conjugate vaccine. VEc=vaccine efficacy against carriage. VEcVT1=vaccine efficacy against carriage for the PCV7 serotypes. VEcVT2=vaccine efficacy against carriage for the additional serotypes in PCV13 excluding serotypes 1 and 3. VEcVT3=vaccine efficacy against carriage of the additional serotypes covered by PCV15 or PCV20.

which serotype 3 was included in VT3 were similar to those in the base case scenario (appendix 1 pp 13–14).

The VEcVT1 estimates during the period when PCV7 was used were higher than in the subsequent period when PCV13 was used, and both estimates were higher than the VEcVT2 estimate (table 1). The reduction in VEcVT1 when PCV7 was replaced by PCV13 was 21%. This reduction was, therefore, applied to the VEcVT1 and VEcVT2 values assumed for PCV15 and PCV20, with VEcVT3 assumed to have the adjusted VEcVT1 or VECVT2 values. The PCV15 and PCV20 models were also run with the unadjusted efficacy estimates for VT1 and VT2 obtained during the PCV13 period and with VEcVT3 assumed to be similar to VEcVT1 or the lower value of VEcVT2.

The fitting comparison between invasive pneumococcal disease data and model outputs by serotype groupings up to 2018–19 is shown in figure 1 for the PCV15 and PCV20 models under the base case scenario. Fitting results for the other four scenarios are available in the appendix 1 (p 16).

There was an increase in invasive pneumococcal disease cases caused by VT3 serotypes (both 22F and 33F) after PCV7 introduction in 2006–07 in England, followed by a decline before the replacement of PCV7 with PCV13 in 2010–11 (figure 1A). The model was not designed to simulate these short-term secular trends and therefore underestimated VT3 serotype cases in this period. The underestimation by the PCV20 model of VT3 cases reflects the increase and subsequent decline in serotype 12F cases that occurred between 2014–15 and 2017–18 (appendix 1 p 2).

Model outputs are shown as incidence per 100 000 population rather than absolute numbers (appendix 1 pp 21–23), as absolute numbers will be affected by demographic changes; for example, the increasing proportion of people aged 65 years and older in future years will result in an overall increase in invasive pneumococcal disease cases without any change in vaccination. Even when expressed as an incidence, rates will increase over time in the absence of any change in vaccine (appendix 1 p 30). This increased incidence is due to the increasing mean age of the cohort aged 65 years and older who make a disproportionate contribution to the overall incidence.

The predicted effect out to vaccination year 25 of a change from PCV13 to PCV15 or PCV20 assuming complete serotype replacement in carriage (C8=1) is shown in figure 2. PCV15 is predicted to result in an increase in overall invasive pneumococcal disease incidence when adjusted values are used for vaccine efficacy against carriage, with little difference when the unadjusted values for VEcVT1 or VEcVT2 are assumed for VEcVT3 (table 1). Using unadjusted VEc values, the long-term predictions of the PCV15 model indicated an overall increase in invasive pneumococcal disease cases but with a small decrease among children aged 0–4 years (appendix 1 pp 24–25). For PCV20, under all four VEcVT3 assumptions, there is predicted to be an overall reduction in invasive pneumococcal disease incidence; the initial effect is bigger if the higher VEcVT1 value is assumed for VEcVT3 than the lower VEcVT2 value, although the longer-term effect is similar irrespective of the value assumed for VEcVT3 (figure 2C, 2D).

The cases averted by replacing PCV13 with PCV15 or PCV20 are shown by age group in figure 3, assuming the highest (36·4%) and the lowest (14·7%) VEcVT3 values as shown in table 1. For both vaccines, there is predicted to be a small, long-term increase in invasive pneumococcal disease cases among children aged 0–4 years, which is greater for PCV20. The PCV15 model also shows a longer-term increase in invasive pneumococcal disease cases in people aged 65 years and older, as does the PCV20 model unless assuming the highest VEc values. Cases averted by age group for all model scenarios and VEc assumptions are shown in the appendix 1 (pp 24–26).

The annual cases averted by serotype grouping with all model scenarios considered are shown in the appendix 1

(pp 27–30). For both PCV15 and PCV20, the models that assume some reduction in carriage protection against VT1 and VT2 serotypes when changing to the higher valency vaccine predict an increase in VT1 and VT2 cases (appendix 1 pp 27, 29). Some of that increase will be in children aged 0–4 years, which depending on the VEcVT3 assumption, could be up to 609 additional cases (UI 542–663) for PCV15 (ie, an additional 9%) and 457 (382–534) for PCV20 (ie, an additional 7%) over the first 25 years after introduction of the higher valency vaccine with a full replacement assumption (appendix 1 p 31).

Table 2 shows the predicted cumulative number of averted invasive pneumococcal disease cases for the first 5 years after changing from PCV13 to PCV15 or PCV20 in vaccine year 1 in England with cumulative numbers over 25 years shown in appendix 1 (p 31). With PCV15, there is predicted to be no benefit if efficacy against carriage of existing PCV13 serotypes is reduced (adjusted VEcVT1 and VEcVT2 values) in PCV15 and only a small benefit if efficacy is preserved in PCV15 (unadjusted VEcVT1 and VEcVT2 values). With PCV20 it is predicted that there will be a sustained overall benefit under all scenarios. For PCV15, there is little difference in effect if the efficacy against carriage of the additional serotypes in PCV15 is similar to that estimated for VEcVT1 or the lower VEcVT2 value, although for PCV20 the predicted benefit is greater when the higher VECVT1 value is assumed for efficacy against carriage for the additional serotypes in PCV20.

Appendix 1 (pp 21–23) shows the predicted effect on overall invasive pneumococcal disease incidence under the scenario of partial replacement in carriage of VT3 serotypes with non-vaccine serotypes (C8=0·5). For PCV15, the increase in overall invasive pneumococcal disease incidence with partial replacement is predicted to be smaller and, for PCV20, the reduction is predicted to be larger compared with the same model scenario in which there is full carriage replacement of VT3 by non-vaccine serotype. In the sensitivity analyses in which serotype 3 is included in VT3 for the PCV15 model, there was a predicted overall reduction in invasive pneumococcal disease incidence irrespective of the VEcVT3 value assumed and whether full or partial carriage replacement is assumed (appendix 1 pp 21–23).

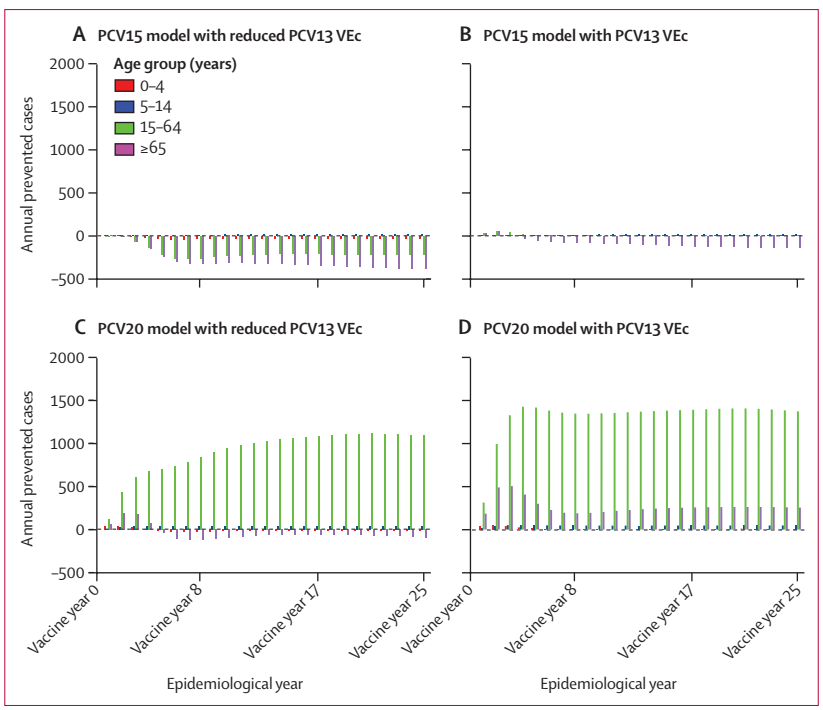

Figure 3: **Median annual averted number of invasive pneumococcal disease cases**
Median annual averted number of cases for the first 5 years after replacing PCV13 with PCV15 or PCV20 in England by age group from the long-term simulation model with 100 uncertainty parameter sets for each model scenario when changing PCV13 to PCV15 assuming unadjusted values (A) and adjusted values (B) for VEcVT1 and VEcVT2 and when changing from PCV13 to PCV20 assuming unadjusted values (C) and adjusted values (D) for VEcVT1 and VEcVT2 in VacYear 1, assuming full replacement of the additional serotypes covered by PCV15 or PCV20 by non-vaccine serotypes in carriage (C8=1). VEcVT3 is assumed to have the same value as the unadjusted VEcVT1 value when in PCV13 (36·4%) or the adjusted VEcVT2 value (14·7%), as shown in table 1. Vaccine year indicates the epidemiological year since the change of PCV13 to the new PCV. PCV13=13-valent pneumococcal conjugate vaccine. PCV15=15-valent pneumococcal conjugate vaccine. PCV20=20-valent pneumococcal conjugate vaccine. VEc=vaccine efficacy against carriage. VEcVT1=vaccine efficacy against carriage for the PCV7 serotypes. VEcVT2=vaccine efficacy against carriage for the additional serotypes in PCV13 excluding serotypes 1 and 3. VEcVT3=vaccine efficacy against carriage of the additional serotypes covered by PCV15 or PCV20.

Discussion

We used pneumococcal transmission models to investigate the likely effect of replacing PCV13 with higher valency PCVs covering an additional two or seven serotypes. In addition to direct protection against vaccine-type pneumococcal disease, vaccination also results in a reduction in carriage of vaccine serotypes which, by assuming some degree of competition in carriage, leads to replacement with non-vaccine serotypes. There is currently no population experience with PCV15 or PCV20, so key model parameters, such as the efficacy of the higher valency vaccines against carriage of the additional serotypes and the extent of serotype replacement had to be assumed based on previous experience with PCV7 and PCV13. Our results indicate a potential overall increase in invasive pneumococcal disease if changing to PCV15, whether serotype replacement is full or partial, whereas a sustained reduction in overall invasive pneumococcal disease is predicted for PCV20.

Although the transmission dynamics in the models are based on carriage, the outcome of interest for policy decisions is the overall effect on invasive pneumococcal disease, which is determined by the relative invasiveness of the replacing non-vaccine serotypes compared with the former vaccine serotypes. The estimated CCRs in our study show striking differences between PCV15 and PCV20 for the additional serotypes covered by each of these vaccines (VT3 serotypes) and the remaining non-vaccine serotypes. For the PCV15 model, VT3 comprises just two serotypes (22F and 33F), with other highly invasive serotypes, such as serotypes 8, 12F, and 15B,

	PCV15 model		PCV20 model	
	0–4 years	Overall	0–4 years	Overall
VEcVT3 with adjusted VEcVT1	–53 (–61 to –38)	–899 (–1019 to –699)	60 (41 to 79)	5407 (5041 to 5745)
VEcVT3 with adjusted VEcVT2	–41 (–51 to –27)	–886 (–1002 to –687)	97 (78 to 114)	3275 (2975 to 3586)
VEcVT3 with unadjusted VEcVT1	35 (32 to 39)	206 (175 to 242)	170 (160 to 179)	7741 (7530 to 7920)
VEcVT3 with unadjusted VEcVT2	45 (42 to 50)	229 (203 to 259)	204 (195 to 210)	5514 (5369 to 5628)

Data are median number of cumulative cases prevented (uncertainty interval) over the first 5 years among children aged 0–4 years and overall from 100 parameter sets with the base case PCV15 and PCV20 model scenarios in England, assuming full replacement in carriage of additional PCV15 and PCV20 serotypes by non-vaccine serotypes and with different values of vaccine efficacy against carriage, as assumed in table 1. Adjusted values assume reduced efficacy against carriage due to attenuation of immunogenicity in higher valency PCVs while unadjusted values are those estimated for PCV13. Positive numbers represent a reduction in invasive pneumococcal disease cases, whereas negative numbers represent increased invasive pneumococcal disease cases after the pneumococcal conjugate vaccine change. PCV15=15-valent pneumococcal conjugate vaccine. PCV20=20-valent pneumococcal conjugate vaccine. VEcVT1=vaccine efficacy against carriage for the PCV7 serotypes. VEcVT2=vaccine efficacy against carriage for the additional serotypes in PCV13 excluding serotypes 1 and 3. VEcVT3=vaccine efficacy against carriage of the additional serotypes covered by PCV15 or PCV20.

Table 2: **Cumulative cases prevented over the first 5 years among children aged 0–4 years and overall in the base case PCV15 and PCV20 models assuming different values of VEcVT3**

included in the non-vaccine serotype group; as a result, the CCR for VT3 serotypes for PCV15 was lower than that for the non-vaccine serotype group in adults aged 25 years and older (appendix 1 p 14). For PCV20, which covers 22F and 33F as well as the other highly invasive serotypes, the CCR for the VT3 serotype group was higher than for the non-vaccine serotype group and, as a result, replacement disease resulting from an increase in non-vaccine serotype carriage prevalence did not offset the reduction in invasive pneumococcal disease caused by the reduction in carriage of the additional serotypes covered by PCV20.

Serotype 3 has shown a steady increase in England since 2014–15, after an initial decline following the introduction of PCV13 in 2010 (appendix 1 p 2), a pattern that has been observed elsewhere but is not understood.[23] In England, serotype 3 accounted for 760 (18%) of 4326 invasive pneumococcal disease cases between April, 2022, and March, 2023,[9] so a vaccine that was effective against carriage of this serotype could have an important public health impact even if, as shown by our PCV15 modelling, the efficacy was only a quarter that of the other VT3 vaccine serotypes. The difference between the model outputs with and without serotype 3 in VT3 is amplified by mitigation of further increases in serotype 3 when it is included in the VT3 serotype group rather than non-vaccine serotype group. There is no established correlate of protection against carriage, but evidence suggests that substantially higher antibody concentrations are required than those associated with disease prevention.[24] The 1·3-fold higher post-booster geometric mean anti-capsular IgG antibody concentrations for serotype 3 in PCV15 compared with PCV13 is, therefore, likely to have little effect on protection against serotype-3 carriage, especially as the post-booster IgG concentrations against serotype 3 induced by PCV15 are still below 1 µg/mL, which is substantially lower than the estimated threshold for protection for serotype 3 against invasive pneumococcal disease.[25] Moreover, functional antibody concentrations of serotype 3 after booster, as measured by the opsonophagocytosis assay, were not higher for PCV15 than PCV13.[11,12]

Without any information on the efficacy of PCV15 or PCV20 against carriage of the additional serotypes covered by these vaccines (VEcVT3), we used values estimated from the model for the existing PCV7 and PCV13 vaccines. In our model fitting, we allowed for a difference in vaccine efficacy against carriage of VT1 serotypes when PCV7 changed to PCV13. Although effectiveness studies using invasive pneumococcal disease cases as the outcome show similar protection against invasive pneumococcal disease caused by the serotypes common to PCV7 and PCV13,[26] an assumption that we make in our model, any reduction in efficacy against carriage would have an effect on herd immunity and serotype replacement. Our estimates of vaccine efficacy against carriage of the seven VT1 serotypes reduced by 21% when changing from PCV7 to PCV13. Although judged to be equivalent in the comparative immunogenicity studies that supported licensure of PCV13, equivalence was based on the lower 95% CI of the geometric mean ratios between PCV13 and PCV7 for each of the seven common serotypes being above 0·5. However, the mean of the post-booster responses for the seven common serotypes was 18% lower in PCV13 than PCV7 in the 2+1 schedule,[17,18] similar to the reduction in our model estimates for the difference in estimated efficacy against carriage of VT1 serotypes between the two vaccines. This finding of lower immunogenicity and lower efficacy against carriage for VT1 serotypes when changing from PCV7 to PCV13 was the basis of our assumption that the reductions in the post-booster responses to common serotypes in PCV13 in higher valency vaccines[11,12,20] would translate into a reduced efficacy against carriage of VT1 and VT2 serotypes. Under this assumption, some increase in invasive pneumococcal disease cases covered by PCV13 would occur, both in young children and older adults. Scenarios

in which we assumed no diminution in the efficacy against carriage with higher valency vaccines predicted a greater reduction in overall invasive pneumococcal disease with PCV20 but with some increase in invasive pneumococcal disease cases with PCV15.

Although the model outputs fitted reasonably well with observed trends in invasive pneumococcal disease caused by the different serotype groupings, there were discrepancies associated with poorly understood secular changes that appear to be unrelated to vaccination, such as the decline in serotypes 22F and 33F after an initial increase after PCV7 introduction and the later increase and subsequent decline in 12F (figure 1A; appendix 1 p 2). Additionally, the COVID-19 physical distancing measures in England in 2020 and early 2021 have perturbed pneumococcal transmission, with different effects on some serotypes. For example, although the number of 19A and 19F invasive pneumococcal disease cases in England from April, 2022, to March, 2023, was similar to that in 2018–19, these cases constituted a higher proportion of all invasive pneumococcal disease cases than in 2018–19 because other serotypes, such as 8, 9N, and 12F, remained low compared with pre-pandemic levels.[9] Whether such perturbations are short term or represent a longer-term resetting of the secular changes that were previously observed for these serotypes in England and Wales is unclear.[27] In our models, we were unable to take account of secular changes unrelated to vaccination and had to assume that the higher valency vaccines would be introduced at a time when pneumococcal epidemiology reflected the pre-pandemic situation in 2018–19.

Our models have additional limitations. The static model used to estimate forces of infection and CCRs for the different serotype groupings relied on a longitudinal household transmission study conducted in the pre-PCV7 era and, for some age groups, no carriage episodes were observed for the additional VT3 serotypes in the PCV15 or PCV20 models. We, therefore, assumed a minimum value of 0·5 carriage episodes to allow estimation of force of infection and CCRs, which might distort the estimates. Our higher CCRs for non-vaccine serotypes than for VT3 serotypes in adults in the PCV15 model and lower CCRs for VT3 than for non-vaccine serotypes in the PCV20 model are, however, consistent with the estimates of Løchen and colleagues,[28] who conducted a meta-analysis of carriage and invasive pneumococcal disease datasets spanning the pre-PCV and post-PCV periods. Another limitation of our study is that the individual serotypes grouped together in the models have different properties from each other in terms of invasiveness, carriage duration, and acquisition rates, which cannot be adequately represented by the current model structure. An analysis of individual serotypes with sufficient carriage episodes in the pre-PCV longitudinal study showed differences in carriage duration, transmissibility, and competition with other serotypes between four of the PCV7 serotypes (ie, 6B, 14, 19F, and 23F) and differences with a PCV13 serotype (ie, 6A).[29] However, a much larger longitudinal study would be needed to estimate these parameters for other vaccine and non-vaccine serotypes. With the currently available carriage data, it is not, therefore, possible to parameterise a more complex individual serotype model.

Although transmission models are needed to explore the complexity of serotype interactions with higher valency PCVs, they are imperfect predictive tools. Our earlier PCV13 model predicted that PCV13 serotypes would approach elimination within 10 years of starting immunisation,[10] but vaccine serotypes such as 19A and 19F have persisted despite the near elimination in carriage of other PCV13 serotypes.[30] Furthermore, assumptions about how new vaccines will perform based on immunogenicity data might not be valid. In our PCV13 model,[10] we assumed protection against serotype 3, whereas invasive pneumococcal disease cases due to serotype 3 have increased since the introduction of PCV13, and in our PCV15 and PCV20 models, we assume that a 1+1 schedule for PCV15 and PCV20 will be effective, although only a 2+1 for PCV15 and 3+1 schedule for PCV20 have been licensed for paediatric use. Evaluation of model predictions against real-world evidence of population effect after deployment is therefore essential.

Our study suggests that replacing PCV13 with PCV15 in the paediatric immunisation programme might potentially increase overall invasive pneumococcal disease incidence in England, whereas substantial reductions are predicted by the introduction of PCV20. Our model outputs will inform the cost-effectiveness analyses needed for policy decisions about transition to higher valency vaccines in the UK. In addition to the effect on invasive pneumococcal disease cases, these analyses will need to take account of the clinical presentation and severity of invasive pneumococcal disease in different age groups caused by the non-vaccine serotypes relative to the vaccine serotypes they replace and the contribution they make to community acquired pneumonia, which constitutes the major burden of pneumococcal-attributable disease in older adults.[31]

Contributors

YHC and EM designed the study and led the overall data interpretation. MB, DJL, and SNL provided data for model parameter estimation and critically reviewed the manuscript before submission. YHC built the model structure and programmed the fitting and simulation codes. YHC and EM drafted the manuscript, interpreted the results, and critically revised the manuscript for scientific content. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. EM and YHC accessed and verified that carriage data, and MB and DJL accessed and verified the invasive pneumococcal disease data.

Declaration of interests

The Immunisation and Vaccine Preventable Diseases Division of the UK Health Security Agency provides vaccine manufacturers with post-marketing surveillance reports on pneumococcal and meningococcal infections, which the companies are required to submit to the Medicines

and Healthcare Products Regulatory Agency in compliance with the companies' risk management strategy. A cost recovery charge is made for these reports. SNL performs contract research on behalf of St George's University of London and the UK Health Security Agency for pharmaceutical companies but receives no personal remuneration. The Respiratory and Vaccine Preventable Bacteria Reference Unit of the UK Health Security Agency has received grant funding from vaccine manufacturers for investigator-led research projects on pneumococcal surveillance. EM receives support from the National Institute for Health Research (NIHR) Health Protection Research Unit in Immunisation at the London School of Hygiene and Tropical Medicine in partnership with Public Health England (Grant Reference NIHR200929). All other authors declare no competing interests.

Data sharing

The pre-PCV pneumococcal carriage and historical invasive pneumococcal disease data by age groups and serotype groupings, monthly PCV coverage data by doses, population data by age in England, and Contact Matrix between age groups are shown in appendix 2. All other queries and requests should be directed to the corresponding author.

See Online for appendix 2

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