STUDY TITLE: THE IMMUNOGENICITY AND EFFICACY OF PNEUMOCOCCAL VACCINES: PROTOCOL FOR A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS OF INDIVIDUAL PARTICIPANT DATA

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1 Contents

2 Background

2.1 Pneumococcal infections

Streptococcus pneumoniae (pneumococcus) is a leading cause of bacterial pneumonia, meningitis, sepsis, and otitis media in children.(1) There are over 90 different 'serotypes' (strains of disease) of pneumococcus. A small number of serotypes cause the majority of disease and the distribution of these serotypes varies between countries.(2)

Pneumococcal infections can be prevented by vaccination programmes. The UK has a well-established publically-funded infant vaccination programme with high coverage. Public Health England estimates that pneumococcal conjugate vaccines have prevented 40,000 cases of invasive pneumococcal disease in England and Wales since the introduction of the programme in 2006.(3)

Currently licensed pneumococcal conjugate vaccines (PCVs) are formulated to include either 10 or 13 serotypes of pneumococcus. The two vaccines are produced by different manufacturers: PCV10 ("Synflorix") is manufactured by GSK, and PCV13 ("Prevenar 13") is a Pfizer vaccine. A licensed 23-valent non-conjugated pneumococcal polysaccharide vaccine is also available that is in use for older adults but is non-immunogenic in infants (does not induce antibody production) and is not licensed for children under 2 years of age.

Little is known of the relative efficacy of PCV10 versus PCV13

The World Health Organisation (WHO) recommends vaccination of all children worldwide with at least 3 doses of a PCV in infancy and does not recommend one product over another. There is little evidence to show whether one vaccine is better than the other therefore both vaccines (PCV10 and PCV13) are widely used and both are considered efficacious. In cost-effectiveness models both vaccines have been assumed to have the same efficacy as the older PCV7 vaccine (the precursor to the current vaccines that have extended numbers of serotypes).[4, 5] This is unlikely to be correct, however more accurate estimates do not exist for use in cost-effectiveness modelling.

Serotypes included in the vaccines

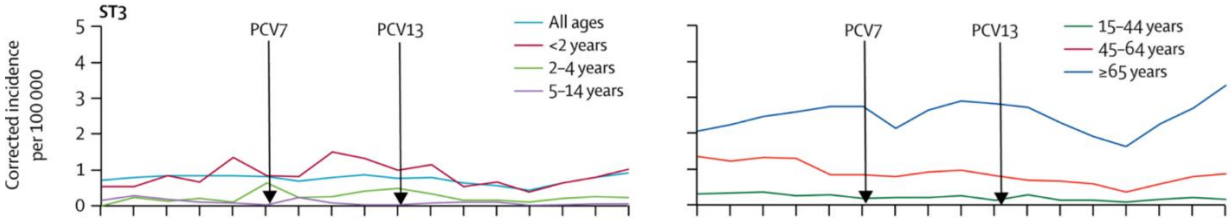
One factor that is an important consideration in the choice of vaccine are the serotypes included ('covered') in the vaccine and how these relate to the epidemiology of disease caused by these serotypes in the population of interest.

There are 10 serotypes in common between the two licensed vaccines but an extra three serotypes are covered by the PCV13 vaccine (serotypes 3, 6A, and 19A). For countries in

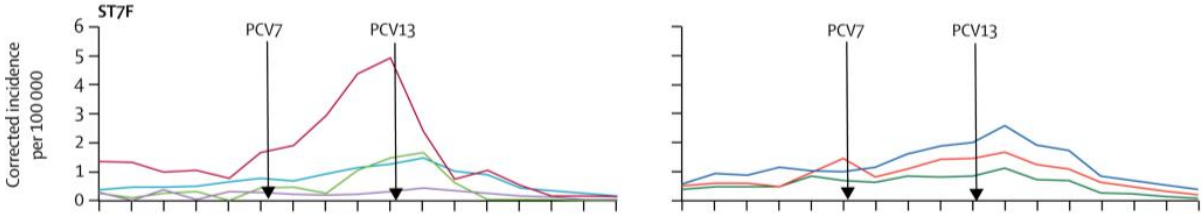
which these three additional serotypes do not cause very much disease, the PCV10 vaccine may be more suitable as it is less expensive. In the UK, PCV13 has been in use since 2010. However, efficacy of PCV13 against serotype 3 in the UK has not been demonstrated. Incidence of serotype 3 disease has fluctuated over time in England and Wales (Figure 1: top) with no substantial or sustained reduction in incidence seen since the introduction of the vaccine.(6) In contrast, other serotypes in PCV13 such as serotype 7F are now almost non-existant (Figure 1: bottom). Therefore it could be argued that PCV13 acts as a "PCV12" in the UK, and similar results have been observed in other countries.

Figure 1 Age group-specific trends in invasive pneumococcal disease incidence due to serotype 3 in England and Wales from 2000 to 2017

Serotype 3



Serotype 7F



Adapted from Ladhani et al. Lancet Infectious Diseases, 2018.(6)

PCV10 does not contain serotype 19A, however it does contain the related serotype 19F which has been shown to provide some degree of cross-protection against 19A. The PCV10 vaccine could therefore be viewed as "PCV11".

In terms of the coverage of these vaccines, therefore, there is possibly little difference between them.

2.2 Current evidence comparing the efficacy of PCV10 and PCV13 is lacking

Although the vaccines contain 10 of the same serotypes, they are manufactured using different components and as a result may have variable efficacy. Pneumococcal conjugate vaccines are manufactured by 'conjugating' (joining) the pneumococcal polysaccharide

(outer coating of the bacteria) to an unrelated protein. The two vaccines use different proteins for this conjugation process, and different amounts of polysaccharide, therefore the amount of antibody produced may differ and this may affect the protective efficacy of the vaccines.

The first PCV vaccine (PCV7) was licensed based on large randomised placebo-controlled trials of efficacy against invasive pneumococcal disease. However, subsequent products have been licensed based on head-to-head non-inferiority trials of the new vaccines compared with the previously licensed vaccine (PCV7). For ethical reasons placebo-controlled studies were no longer possible once a licensed vaccine was in use and so these studies compared immunogenicity (antibody levels) only, not efficacy. Whilst antibody levels are an important mechanism through which the vaccines confer protection, measuring antibody levels alone has limitations and is not in itself a measure of efficacy. To measure efficacy one needs to assess infection rates or disease cases.

Immunogenicity is not the same as efficacy

Although the immunogenicity of different vaccines has been estimated in some studies, the degree to which this translates into differences in clinical efficacy is difficult to establish. The proportion of children with antibody above a threshold of 0.35 mcg/mL has been established as an indicator of protection and used to compare vaccines yet many authors have called into question the appropriateness of this value [7-9].

There are no randomised efficacy trials using head-to-head comparisons of different licensed pneumococcal vaccines with cases of invasive pneumococcal disease as the outcome. In the absence of head-to-head clinical efficacy studies we have previously used estimates of ‘sero-efficacy’ to compare vaccine products,(10) and to derive antibody thresholds for protection.(9)

Sero-efficacy differs from clinical efficacy in that the evidence of an infection having occurred is not defined by the detection of illness in a child, but by detection of an immune response to infection seen in a child’s serum antibody levels. Sero-epidemiological studies therefore use antibody data to assess whether an event (such as an infection) has taken place. Such infections occur more often than cases of disease, as infections can be asymptomatic. Antibody levels after vaccination with bacterial conjugate vaccines typically peak at approximately 4-6 weeks post-vaccination and then decline rapidly in the absence of exposure to the antigens contained in the vaccine. In randomised clinical trials of pneumococcal vaccines, the antibody measured one-month after the primary series of vaccinations (typically at age 5 – 7 months) is high and then declines to a much lower level

by the time of the booster vaccination (typically at age 12-18 months). When antibody levels rise during this period instead of falling, it is a sign that a child has been exposed to pneumococcus in the intervening period. This exposure most often will result in an asymptomatic infection in the nasopharynx ('carriage') that clears within a few weeks. The acquisition of nasopharyngeal carriage may be detectable using nasopharyngeal swabs if the timing of the swab happens at the time of the infection, however since this is a very short period of time, cross-sectional swabbing studies can easily miss these events. In addition, some key serotypes are almost never detected using nasopharyngeal swabs so for some serotypes, cross-sectional swabbing studies provide no useful data.

When nasopharyngeal carriage is established there is a subsequent immune response to the particular serotype of pneumococcus that shows in the antibodies measured in the blood, revealing the history of recent infection in the child. Whilst this infection may not cause any clinical symptoms in the child, it is the mechanism through which the bacteria spread from person-to-person. Thus reducing nasopharyngeal carriage will reduce disease We have previously shown that the proportions of children with a rise in antibody levels ('seroincidence') correlates closely with the proportions of healthy children with nasopharyngeal carriage (measured by swabbing) of the same serotypes in the same community, thereby validating the use of seroincidence as a useful marker of nasopharyngeal carriage acquisition and therefore a good endpoint for comparisons of vaccines in clinical trials.(9)

The previous systematic review was not able to answer the question

The WHO Strategic Advisory Group of Experts (SAGE) recently reviewed the available data on pneumococcal vaccines to inform country-level decision making about vaccine product choice and schedule.(11) The systematic review included five head-to-head studies of PCV10 vs PCV13 that reported some immunogenicity outcomes, from two published papers and three conference abstracts. Two of the trials (one from Papua New Guinea and one from Vietnam) were summarised graphically, however no confidence intervals were presented to show whether differences were statistically significant and no meta-analyses were conducted, either for specific serotypes or by combining across all serotypes. In the absence of good evidence to the contrary, both vaccines were considered equally immunogenic (they induce antibody production) but as efficacy data are lacking and head-to-head studies are few, a clear understanding of the relative benefits of the two products remained elusive. The WHO SAGE committee found that "*There is at present no evidence of different net impact on overall disease burden between the 2 products*."(12)

In the time since the systematic review, at least three additional trials have been either published in peer-reviewed journals or made available on company websites or on www.clinicaltrials.gov. An up to date systematic review that includes a meta-analysis of these additional studies will provide a more precise picture on the different antibody levels induced by these vaccines and whether they are both equally immunogenic, or whether one vaccine is more immunogenic for some (or all) serotypes.

In addition, by obtaining the raw individual participant data from all studies, an estimate of the comparative sero-efficacy could be made and give a robust estimate of the relative difference in infection rates than occur between the two vaccines.

It may be that one vaccine is better than the other and if that is the case it is imperative for policy-makers to have access to such information. In contrast, it may be that both vaccines offer equivalent protection. Based on the current lack of data, this has become the default position and therefore country-level decision-making regarding vaccine product choice is based mostly on financial considerations, supply, logistics, and whether the serotypes covered by the vaccine are the ones causing disease in the local setting, rather than efficacy.

Network meta-analysis

Network meta-analysis is a method of evidence synthesis whereby pair-wise comparisons of different treatments are combined and both direct and indirect treatment effects can be computed.(13, 14) Such methods combine data from a larger number of studies than traditional meta-analysis thereby increasing statistical power. In addition, it is possible to estimate treatment effects for pair-wise comparisons for which no data (or only limited data) are available (indirect effects). Pair-wise comparisons for which only a limited number of studies exist, are enhanced by ‘borrowing’ statistical power from the other comparisons in the network.

For pneumococcal vaccines the main network is of the simplest format – a network with three pairwise comparisons of the three licensed vaccines: PCV7 vs PCV10, PCV7 vs PCV13, PCV10 vs PCV13, and PCV7 vs PCV10 vs PCV13. Additional studies comparing one of the three licensed vaccines to a difference pneumococcal vaccine (e.g. PCV11 or PCV9) may also contribute to the network. Although the WHO review showed that few studies are available for the main comparison of interest (PCV10 vs PCV13), there are many studies in which these vaccines were compared to the older PCV7 vaccine and the inclusion of all studies into the network adds substantial statistical power to the comparison of PCV10 vs PCV13.

3 Objectives

The objective of this review is to compare randomised controlled trials of pneumococcal conjugate vaccines in healthy infants and children, specifically:

Primary Objectives:

1. The immunogenicity of PCV10 vs PCV13 for each serotype contained in the vaccines.

Secondary Objectives:

2. The sero-efficacy of PCV10 vs PCV13 for each serotype contained in the vaccines.
3. For PCV10 and PCV13 separately, to estimate immunogenicity and sero-efficacy in comparison to the older PCV7 vaccine
4. To determine how the comparisons of immunogenicity and efficacy of PCV10 to PCV13 are affected by the co-administration of different routine vaccines such as high and low dose diphtheria and tetanus vaccines, or co-administration of a different conjugate vaccine with a similar carrier protein.
5. To update mathematical models of the long-term effects of replacing PCV13 with PCV10 on pneumococcal disease in the UK.
6. To determine the cost-effectiveness of PCV10 and PCV13 for infants in the UK

4 Methods

We will conduct a systematic review and network meta-analysis of individual participant data from head-to-head trials of currently licensed or previously licensed pneumococcal vaccines administered to infants. The systematic review will be reported in line with recommendations from the PRISMA statement for reporting systematic reviews and meta-analyses of studies

that evaluate healthcare interventions plus the extension statements for network and individual patient data systematic reviews.(15-17)

The protocol and any subsequent amendments will be registered with PROSPERO.

4.1 Criteria for inclusion of studies for this review

Trials will be eligible for inclusion if they;

1. Randomised infants to receive different licensed pneumococcal vaccines.

   There are three different vaccines of interest. Studies will be included which randomised participants to at least one of the three licensed vaccines (e.g. PCV7 vs PCV10, PCV7 vs PCV13, or PCV10 vs PCV13, PCV7 vs PCV 10 vs PCV13, or a one of the three main PCVs compared to another pneumococcal vaccine). The main comparison of interest is PCV10 vs PCV13 since PCV7 is no longer in use.

2. Measured antibodies to pneumococcal serotypes between 4 and 6 weeks after the primary series of vaccinations and/or one-month after a booster vaccination.

Comparison of immunogenicity of pneumococcal conjugate vaccines may not have been the purpose of the study. For example, a study which compares a new experimental vaccine to the two other PCVs will be eligible and only the PCV arms of the study will be included even though the only comparisons conducted by the trialists were the comparisons with the new experimental vaccine.

4.1.1 Types of studies

Only randomised controlled trials which compared pneumococcal vaccines in head-to-head comparisons will be included in the review.

All trials that included at least one of the three licensed pneumococcal vaccines will be included.

Randomised trials of a single vaccine (e.g. administered at different doses or using different schedules) will be excluded.

4.1.2 Participants

Healthy infants and children less than 2 years of age. Studies enrolling immuno-compromised children (e.g. HIV) will be excluded. There will be no restrictions on gender.

4.1.3 Interventions

There are three current or previously licensed pneumococcal conjugate vaccines that will be included in the review. Trials must include at least one of the following three currently licensed (PCV10 and 13) or previously licensed (PCV7) vaccines;

1. 7-valent pneumococcal conjugate vaccine (PCV7: Prevnar, Pfizer), containing serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, each conjugated to diphtheria cross-reacting material (CRM).
2. 13-valent pneumococcal conjugate vaccine (PCV13: Prevenar 13, Pfizer), containing serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, each conjugated to diphtheria cross-reacting material (CRM).
3. 10-valent pneumococcal conjugate vaccine (PCV10: Synflorix, GlaxoSmithKline), containing serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F, conjugated to non-typeable *Haemophilus influenzae* protein D, for 8 serotypes, or tetanus or diphtheria protein (serotypes 18C and 19F respectively).

4.1.4 Outcome measures

The outcome will be serotype-specific anti-capsular pneumococcal immunoglobulin G antibodies measured by ELISA. Antibodies measured one month after the primary series of doses in infancy, prior to a booster dose at between 9 – 15 months of age, and one month post-booster dose will be included.

1. Serotype-specific anti-pneumococcal IgG measured one-month after the primary series of doses.
2. Serotype-specific anti-pneumococcal IgG measured prior to administration of a booster dose.
3. Serotype-specific anti-pneumococcal IgG measured one-month after the booster dose.
4. Difference between $\log_{10}$-transformed serotype-specific anti-pneumococcal IgG measured one-month after the primary series of doses and prior to administration of the booster dose.

4.2 Search methods for identification of studies

The search strategy will be devised with advice from an information specialist and experts in pneumococcal vaccination programmes.

English languages searches of EMBASE, MEDLINE, Cochrane register of controlled trials clinical trials registries, and conference abstracts (including specifically International Symposium on Pneumococci and Pneumococcal Diseases, European Society of Paediatrics Infectious Diseases) will be conducted.

Pharmaceutical company websites (GSK and Pfizer) will also be searched for relevant studies.

Any relevant study, whether published or unpublished will be included if the trial meets the inclusion criteria.

A flowchart will summarise the selection process.

4.3 Data collection and analysis

4.3.1 Selection of studies

Two reviewers will review the title and abstract of each reference to identify potentially relevant references. Considering the full texts of these references, two reviewers will independently select trials to be included in the review using the predetermined inclusion criteria. Discrepancies will be resolved by referral to a third party.

4.3.2 Data collection, extraction and management

For all included trials the trial publication authors and/or the pharmaceutical company will be approached for trial and individual participant level data. Data will be accepted in paper or electronic form and a desired format and coding will be specified. The following data will be requested (if available):

Trial level data:

- trial registration number/study identifier
- country where study was conducted
- vaccines administered as part of the study (both study vaccines and vaccines administered concomitantly as part of the routine immunisation schedule)
- details of laboratory assays conducted, including where assays were run, units of measurement, and the lower limit of quantification.

Individual patient level data:

- age at enrolment (to the nearest week)
- gestational age at birth (or indication of preterm /full term)
- sex
- vaccines received (both study vaccines and co-administered routine vaccines)
- dates of vaccination (or time between doses)
- serotype-specific anti-pneumococcal IgG measured by ELISA at all time-points

Data will be stored in a secure environment meeting the requirements of the General Data Protection Regulation 2016 (GDPR) and in concordance with data-sharing agreements in

place with each data supplier. Data will be cross checked with any published versions of the trial data and any inconsistencies queried with the trial contact.

Data extraction of published results will completed from trial publications by two people independently and discrepancies resolved by a third party. The extraction process will be piloted on the first 5 studies to ensure consistency of approach. Data to be extracted will be the same as for trial level data above and aggregated data as listed for individual patient level data above.

4.3.2.1 Data on potential effect modifiers

We will extract from each included study, data on the following characteristics that may act as effect modifiers:

1. Low-middle income or high-income country
2. Name of the laboratory where assays were conducted
3. Vaccine schedule of administration
4. Co-administered study vaccines or vaccines co-administered as part of the routine immunisation schedule.
5. Co-administration of anti-pyretics as part of the study
6. Whether study conducted in PCV naïve population or not

4.3.3 Assessment of risk of bias in included studies

We will use the version 2 of the Cochrane risk of bias tool to assess the methodological quality of included trials (https://www.riskofbias.info/welcome/rob-2-0-tool). Forming part of the extraction process, risk of bias will be assessed by two researchers independently with discrepancies resolved by a third party.

4.3.4 Measures of vaccine effect

4.3.4.1 Network meta-analysis of immunogenicity

Each trial that has individual participant data available will be analysed separately to obtain the log of the ratio of geometric means (log-GMR) and their standard errors for each serotype and time point of interest separately for each trial and each vaccine comparison. These estimates will form the input data for the network meta-analysis model.

If individual participant data are unavailable for some trials, published estimates and standard errors will be included.

4.3.4.1.1 Network meta-analysis of sero-efficacy

We will conduct a second set of network meta-analyses in a similar way as the comparison of immunogenicity, but the outcome of interest will instead be sero-efficacy. For each

participant we will define their recent infection status from their antibody data. This will be a binary variable equivalent to 1 if antibody levels have increased between the one-month post-primary time point and the booster visit, or 0 otherwise. Binary data can then be analysed in the network meta-analysis model to estimate odds ratios with corresponding standard errors for each vaccine comparison.

Only studies supplying individual participant data will be able to be included in analyses of sero-efficacy.

4.3.5 Data synthesis

Participant level data will be used to compute study-level means and standard errors and a two-stage approach will be taken for the network meta-analysis.

For the analysis of immunogenicity, study level log-GMRs and their standard errors will be computed from participant level data, and combined with published log-GMRs and standard errors if participant level data are unavailable for some studies.

For the analysis of seroefficacy using only studies with available participant level data, study level log-odds ratios (log-OR) will be computed with standard errors and combined in two-stage models.

Some participant level data will be missing due to laboratory errors, insufficient blood sample volume or participant withdrawal. Data will not be imputed and missing data will be considered missing-completely-at-random. Participant level data will be analysed according to the vaccine received.

A network graph will be produced for each of the network meta-analyses.

4.3.6 Methods for direct treatment comparisons

Initially, we will perform standard pairwise meta-analyses using a random effects model for every treatment comparison with at least two trials.

4.3.7 Assessment of clinical and methodological heterogeneity within treatment comparisons

We will assess the presence of heterogeneity within each pairwise comparison by comparing the trial and study population characteristics across all eligible trials.

4.3.8 Assessment of transitivity across treatment comparisons

We will assess the assumption of transitivity by comparing the distribution of the potential effect modifiers across the different pairwise comparisons.

4.3.9 Assessment of statistical heterogeneity and incoherence

In standard pairwise meta-analyses we will estimate different heterogeneity variances for each pairwise comparison. In network meta-analysis we will assume a common estimate for the heterogeneity variance across the different comparisons.

4.3.9.1 Measures and tests for heterogeneity

We will assess statistically the presence of heterogeneity within each pairwise comparison using estimated values of the heterogeneity variance parameters (τ^2) and the I-squared statistic and its 95% confidence interval that measures the percentage of variability in point estimates that cannot be attributed to random error.

The assessment of statistical heterogeneity in the entire network will be based on the magnitude of the heterogeneity variance parameter (τ^2) estimated from the NMA models. For dichotomous outcomes the magnitude of the heterogeneity variance will be compared with the empirical distribution as derived by Turner. We will also estimate a total I-squared value for heterogeneity in the network.

4.3.9.2 Measures and tests for incoherence

If we identify two or more sources of evidence on the same vaccine comparison (e.g. direct evidence and indirect evidence, or alternative types of indirect evidence via different common comparators), we will examine incoherence in the network using node-splitting.(18)

4.3.9.3 Evaluating confidence in the results of the network meta-analysis

We will use the Confidence In Network Meta-Analysis (CINeMA) tool to evaluate our confidence in the results of the network meta-analysis (http://cinema.ispm.ch/).(19) This approach is based on GRADE and examines six domains: risk of bias in the included trials, risk of publication bias, imprecision, heterogeneity, incoherence and indirectness.

4.3.10 Sensitivity analyses

Sensitivity analyses will be performed, where possible, to ensure our effect estimates were not sensitive to the quality of included trials or choice of models:

1. Excluding trials rated as low quality according to the risk-of-bias assessment (Section 4.3.3).
2. Excluding trials conducted solely in preterm infants.
3. Fixed-effect analyses for network meta-analysis (option or vice versa to check whether would have changed results).

4.4 Publication bias

We will include all data whether fully published, published as a conference abstract, or unpublished. This will help to limit publication bias which can occur when it is more likely that a study is published if it contains significant findings and thus the published and unpublished data may show varying results. For many of the studies that will be included in this meta-analysis, the immunogenicity results were a secondary or tertiary outcome (the primary one being safety or reactogenicity) therefore immunogenicity comparisons are unlikely to affect publication status.

4.5 Cost-effectiveness modelling

PCVs have been shown to be cost-effective as is required before a vaccine is introduced into the UK infant immunisation programme.(20, 21) The comparative cost-effectiveness of PCV10 and PCV13 in the UK has also recently been modelled, and results suggest there would be benefit in a change in policy to the PCV10 vaccine for routine use in infants.(22) However, efficacy estimates in the models were based on the older vaccine (PCV7), and were assumed to be the same for both PCV10 and PCV13. There are no data to show whether this is true. Subsequently, the authors state that; “owing to the lack of head-to-head studies comparing the two vaccines, some efficacy estimates are from different studies and might not be directly comparable.”(22) Such assumptions amongst others, lead to the conclusion that a switch to PCV10 would be cost-saving in the UK. However, with more accurate estimates of the comparative efficacy of these two vaccines, such as those described in this proposal, cost-effectiveness models may have very different conclusions. The network meta- analysis planned in this proposal will have the added benefit of producing robust estimates of the comparative sero-efficacy of the current licensed vaccines to the older PCV7 vaccine. We will apply our sero-efficacy estimates (odds ratios) from these comparisons to the clinical efficacy estimates from the original trials of PCV7 vs placebo that are generally used in cost-effectiveness models. This will result in efficacy estimates for PCV10 and PCV13 separately that can be applied in cost-effectiveness models so that they can be tailored to the relative effectiveness of the two vaccines rather than assuming the two vaccines to be exactly equivalent.

We will update previous mathematical models of the impact of PCVs in the UK and determine the cost-effectiveness of both vaccines.

4.6 Funding

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