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RATIONALE-15: Carriage to assess the protection of new pneumococcal vaccines-PCV15

Submission date
12/11/2024

Recruitment status
No longer recruiting

Registration date
06/01/2025

Overall study status
Ongoing

Last Edited
10/02/2026

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Streptococcus pneumoniae (pneumococcus) causes around 3.7 million infections every year. You can find pneumococcus as part of the nose microflora of healthy adults and children. This harmless state is called “carriage”. Carriage is important because from the nose the bacteria can transmit to others that are susceptible causing life-threatening disease.
Pneumococcus is surrounded by a sugar capsule that is variable and classifies pneumococcus into distinct serotypes. Approved vaccines contain those sugar capsules and protect against the most common disease-causing serotypes. A vaccine called PCV13 has been effective globally because it controls carriage and protects against diseases. Vaccines giving protection against more disease-causing serotypes are becoming available worldwide. PCV15 is like PCV13 but contains two other serotypes, offering wider protection. The aim of this study is to determine if PCV15 protects against carriage.

Who can participate?
Healthy adults aged 18-50 years

What does the study involve?
Participants will have up to 9 visits over 2 months. The study involves “challenging” volunteers by putting a small amount of the pneumococcus into their noses. Before they are challenged, volunteers will either be vaccinated with PCV15 or a placebo. Researchers will then be able to compare the two groups to find out who was protected and who was not. A group of 5 volunteers will have a biopsy to collect samples from inside their nose before and after PCV15 vaccination.

What are the possible benefits and risks of participating?
The information gained will help us understand how PCV15 protects people against pneumococcus, meaning that we will be able to improve both this vaccine and future pneumococcal vaccines to protect many lives around the world.
Pneumococcus is responsible for infections including otitis media (OM), sinusitis, pneumonia, bacteraemia and meningitis. Due to inoculating participants with pneumococcus, there is a very

low risk of OM, sinusitis, pneumonia, bacteraemia and meningitis. While the risk to individuals of developing any infection is very low, the study is designed to ensure that any risk of invasive disease is minimal (strict inclusion/exclusion criteria, strict safety follow-up, pneumococcal strain that is sensitive to antibiotics and healthy young adult study cohort).
This study can be safely run based on the following experience and provisions. The research team has 14 years of experience in human challenge studies, following very similar protocols and facing similar risks as previous studies. The selected pneumococcal serotype (SPN3) is fully antibiotic sensitive and has been safety tested in 60 healthy participants without safety concerns. Participant selection and exclusion criteria reduce the excess risk of invasive pneumococcal disease associated with comorbid conditions. Participant education regarding the risks of study participation, provision of a safety information leaflet, and close interaction with the study staff. Rigorous and frequent monitoring of the development of symptoms and body temperature. Provision of standby antibiotics to reduce time to treatment, if it is required. 24-hour emergency telephone contact with researchers (including individual daily monitoring for the first 7 days following inoculation) will facilitate access to hospital and/or prompt treatment if required. Within the safety information sheet, participants will be warned to look out for specific symptoms relating to infections caused by Streptococcus pneumoniae.
The researchers now have experience of inoculating and following over 2000 participants using several serotypes, in different adult cohorts and at a range of doses with participants being experimentally colonised, naturally colonised and not colonised during our studies.
In the event that symptoms occur during the inoculation follow-up period, participants will contact the team on the day that the symptoms are noted. The clinical team will assess the participant and use a pre-defined to determine if antibiotics should be commenced, irrespective of the colonisation status at that point. Participants may be reviewed in the study clinic or asked to attend an NHS healthcare treatment facility directly at the investigator's discretion.
The most commonly reported solicited adverse reactions in adults 18 to 49 years of age described in the PCV15 Summary of Product Characteristics (SmPC) were: injection-site pain, fatigue, myalgia, headache, injection-site swelling, injection-site erythema, and arthralgia. The majority of solicited adverse reactions were mild (based on intensity or size) and of short duration (≤3 days); severe reactions (defined as an event that prevents normal daily activity or size of injection site reaction >10 cm) occurred in ≤1.5% of adults across the clinical program. There are no risks of developing pneumococcal pneumonia attributable to a serotype(s) in PCV15 (i.e. given the modification of the infective organism and according susceptibility of that organism to antibiotics).
The majority of sampling methods utilised are not invasive and have no associated risks. The following have the potential for mild, self-limiting risks. Venepuncture may cause slight pain, bruising, light-headedness or fainting. The amount of blood collected during the study will be within the NHS Blood and Transplant guidelines for blood donation. Collection of nasal cells taken during the trial may cause discomfort, eye watering or minor local bleeding. Collection of throat swabs may cause slight discomfort and may elicit a gag reflex. Collection of nasal Wash: participants may swallow saline which may taste salty. Collection of nasopharyngeal/nasal swab: this may cause some discomfort, eye watering or a minor local bleeding. Participants may have mild nasal discomfort or rhinorrhoea following the procedure, which typically settles within 48 hours. Rarely, subjects undergoing nasal biopsy may have an adverse reaction to the local anaesthetic used. The risk of local bleeding which may require further outpatient ENT intervention such as nasal packing or cautery is <1%. Rarely, subjects may need to be admitted for observation to an ENT acute ward for management of bleeding. Surgical intervention to manage epistaxis in the operating theatre following this procedure is extremely rare. All participants who undergo a nasal biopsy will receive a safety telephone review at 24 hours post-procedure and will have 24/7 access to a study doctor for up to 3 weeks post-procedure.

Where is the study run from?
University of Oxford (UK)

When is the study starting and how long is it expected to run for?
November 2024 to December 2026

Who is funding the study?
Merck Sharp and Dohme (UK)

Who is the main contact?
Dr Carla Solorzano Gonzalez, Carla.SolorzanoGonzalez@paediatrics.ox.ac.uk

Contact information

Type(s)
Public

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT06731374

Integrated Research Application System (IRAS)
1010658

Central Portfolio Management System (CPMS)
63987

Protocol serial number
OVG2024/02

Study information

Scientific Title
A Phase IV, Experimental Human Pneumococcal Challenge (EHPC) model to investigate Streptococcus pneumoniae Serotype 3 (SPN3) colonisation following PCV15, a Double Blind Randomised Controlled Trial (DBRCT) in healthy participants aged 18 – 50 years in the UK

Acronym
RATIONALE-15

Study objectives
Merck Sharp & Dohme has developed a pneumococcal vaccine (PCV15) that protects against pneumococcal disease. This study involves “challenging” volunteers by putting a small amount of the pneumococcus bacteria into their noses. Before participants are challenged, they will either be vaccinated with the real PCV15 vaccine or a dummy (“placebo”). We will then compare both groups to evaluate if PCV15 can protect against pneumococcal carriage by assessing if the participant acquired the bacteria in their nose or not.

In those volunteers that become pneumococcal carriers, we want to understand how many bacteria they have in their nose and for how long they carry the bacteria. We will also compare blood and nasal samples obtained from participants to better understand what kind of responses the body produces due to vaccination that will lead to protection against carriage.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 06/01/2025, South Central - Oxford C Research Ethics Committee (Health Research Authority, 2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 1048144, +44 (0)207 104 8089, +44 (0)2071048063; oxfordc.rec@hra.nhs.uk), ref: 24/SC/0388

Primary study design
Interventional

Study design
Interventional double-blind randomized placebo-controlled trial

Study type(s)
Efficacy

Health condition(s) or problem(s) studied
Pneumococcal nasopharyngeal colonisation

Interventions
VAXNEUVANCE (PCV15) is a 15-valent PCV containing capsular polysaccharides from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 22F, and 33F adjuvanted with aluminium phosphate. VAXNEUVANCE has marketing authorisation and is licensed for active immunisation for the prevention of invasive disease, pneumonia and acute otitis media caused by S. pneumoniae in infants, children and adolescents from 6 weeks to less than 18 years of age. It is also indicated for active immunisation for the prevention of invasive disease and pneumonia caused by S. pneumoniae in individuals 18 years of age and older.

The placebo control is commercially available sterile 0.9% sodium chloride (NaCl, saline) for injection.

The intervention is given at one timepoint only through the study (vaccination visit) and will be administered according to the marketing authorisation and therapeutic indication. Participants will receive 1 dose of 0.5 ml. The vaccine will be administered by intramuscular injection into the deltoid region of the upper arm (right or left).

Randomisation and vaccination will occur at vaccination visit and will be conducted by the un-blinded team. Participants will be randomised to two groups to receive: PCV15 vaccine or 0.9% saline in a ratio of 1:1. The study statistician will generate a randomisation list using stratified block randomisation stratified based on participant's sex (male/female) and study sites.

Participants will be followed up for 56 days after vaccination regardless of which treatment arm they are allocated to.

Participants will be challenge with pneumococcus at 28 days after vaccination. The study team will use a pipette to put small amounts of saline containing a defined number of pneumococcal bacteria into each nostril of participants. Participants will be inoculated with a dose of bacteria (80,000 colony forming units) in each nostril. Participants will be asked to complete a symptom diary for 7 days following inoculation. At the end of the challenge visit, participants will be given a safety pack including a course of antibiotics (to be taken if the participant is unwell), a thermometer, a safety information sheet, and a study contact card. There will be a doctor or nurse available by telephone 24 h a day, 7 days a week to answer questions. If participants are feeling unwell, they should contact the research team at the provided number.

Nasal wash samples are taken from participants to determine the presence of pneumococcus by microbiological culture. These samples are taken on vaccination visit and then a further 5 times throughout the study at days 23, 30, 35, 42 and 56 after vaccination. Blood and nasal samples will be obtained throughout the study for immunological and microbiological assessments.

A cohort of 5 participants will be enrolled in the nasal biopsy cohort. For this cohort, participants will consent to 2 nasal biopsy procedures at 21 days before and 28 days after PCV15 vaccination. Nasal biopsy procedures will be performed by an ENT doctor in an NHS acute hospital setting. These participants will not be randomised as they will only receive PCV15 and will not be challenged with pneumococcus.

Intervention Type
Biological/Vaccine

Phase
Phase IV

Drug/device/biological/vaccine name(s)
VAXNEUVANCE

Primary outcome(s)
The rate of experimental SPN3 colonisation determined by the presence of experimental SPN3 in NW by classical culture at any evaluated timepoint (Days 2, 7, 14 and 28) following experimental challenge with pneumococcus (EHPC)

Key secondary outcome(s)
1. The density of experimental SPN3 colonisation is measured using classical culture and molecular methods from NW at D2, 7, 14, 28 following EHPC at 1-month post PCV15 vaccination
2. The duration of experimental SPN3 colonisation is measured using classical culture and molecular methods from NW at each timepoint between the first and the last NW in which SPN3 is detected following EHPC at 1-month post PCV15 vaccination
3. Vaccine-induced immune responses, including mucosal and systemic antibody levels, antibody functionality, and cellular populations levels, are measured at baseline and after vaccination and EHPC

Completion date
31/12/2026

Eligibility

Key inclusion criteria

1. Adults between 18 to 50 years old (inclusive) at the time of screening.
2. Medically healthy, such that according to investigator judgement, hospitalisation within the study period is not anticipated, and the participant appears likely to be able to remain a study participant through to the end of protocol-specified follow-up. Planned elective procedures for pre-existing conditions may be allowable.
3. Fluent spoken English – to ensure a comprehensive understanding of the research project and their proposed involvement.
4. Able to attend the scheduled visits and to comply with all study procedures, including internet access for the recording of electronic diary after inoculation.
5. Willing and able to give informed consent for participation in the study.
6. Willing to allow confirmation of past medical history either through provision of, or access to, a medical record summary or other medical documentation or allowing investigators to obtain a copy of their medical history from their GP practice or accessed via electronic patient records.
7. Willing to allow their GP and/or consultant, if appropriate, to be notified of participation in the study.
8. Willing to provide their national insurance number or passport number to be registered on The Over-Volunteering Prevention System (TOPS).
9. For participants of childbearing potential only: willing to use effective contraception for the duration of the study AND to have a pregnancy test on the day of screening and challenge.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
50 Years

Sex
All

Total final enrolment
107

Key exclusion criteria
Current key exclusion criteria as of 30/07/2025:
1. Research Participants:
1.1. Participation in another research study, in which procedures performed could compromise the integrity of this study (such as significant volumes of blood taken), or are planning to do so within the trial period
1.2. Currently a participant in a previous EHPC trial within the last 2 years
2. Vaccination (self-reported or confirmed from GP questionnaire or medical records/summary if deemed necessary at clinician discretion):
2.1. Have had any previous pneumococcal vaccination in the past 5 years (including in a research

study)
2.2. Planned vaccination during the study
3. Allergy:
3.1. Have an allergy to penicillin or amoxicillin (for main study cohort only)
3.2. History of a bleeding disorder (e.g., Factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
3.3. Have previous anaphylaxis or severe adverse reaction to any component/excipient of the vaccine or to any vaccine
3.4. Allergy to Lidocaine local anaesthetic (for nasal biopsy cohort only)
4. Health History (self-reported or confirmed from GP questionnaire or medical records /summary if deemed necessary): moderate ill health including but not limited to:
4.1. Asplenia or dysfunction of the spleen
4.2. Chronic respiratory disease (e.g. asthma [on medication], COPD, emphysema, bronchiectasis)
4.3. Chronic heart disease (e.g. angina, ischaemic heart disease, chronic heart failure) [controlled stable hypertension +/- angina may be included]
4.4. Chronic kidney disease (e.g. nephrotic syndrome, kidney transplant, on dialysis)
4.5. Chronic liver disease (e.g. cirrhosis, biliary atresia, hepatitis)
4.6. Chronic neurological conditions
4.7. Connective tissue disease
4.8. Dementia
4.9. Diabetes mellitus (including diet controlled)
4.10. Immunosuppression or history of receiving immunosuppressive therapy – at the discretion of the investigator
4.11. Individuals with cochlear implants
4.12. Individuals with major cerebrospinal fluid leaks (e.g. following trauma, major skull surgery, or requiring CSF shunt)
4.13. Recurrent otitis media
4.14. History of significant unexplained bleeding after a surgical or dental procedure (for nasal biopsy participants only)
4.15. Have any uncontrolled medical/surgical/mental health conditions at the discretion of the study doctor
4.16. Major pneumococcal illness requiring hospitalisation within the last 10 years
4.17. Significant mental health problems (uncontrolled condition or previous admissions in a psychiatric unit, at the discretion of the clinician) that would impair the participant's ability to participate in the study
5. Taking Medications:
5.1. Any medication that may affect the immune system in the last 3 months (e.g. systemic steroids [IM/IV], Roaccutane, disease modifying anti-rheumatoid drugs)
5.2. Long-term use of antibiotics (see also section of Temporary Exclusion Criteria)
5.3. Use of nasal steroids from 1 month prior to screening date until visit 8 (day 56)
5.4. Use of any medication affecting blood clotting (any oral/injectable anticoagulants)
6. Female participants who are pregnant, lactating or intending on becoming pregnant during the study
7. Direct caring role or close contact with individuals at higher risk of infection (for main study cohort only):
7.1. Children under 5 years of age
7.2. Chronic ill health or immunosuppressed adults
7.3. Older adults
8. Smoker:
8.1. Current or ex-smoker (regular cigarettes/cigars/e-cigarette/vaping/smoking of recreational drugs) in the last 6 months
8.2. Previous significant smoking history (more than 20 cigarettes per day for 20 years or the

equivalent [>20 pack years])
9. Suspected or known current alcohol or drug abuse, as per investigator's discretion
10. Overseas travel during the follow-up period (from the time point of inoculation to antibiotic treatment or completion of the 23-day follow-up period post inoculation)
11. Any other issue which, in the opinion of the study staff, may:
11.1. Put the participant or their contacts at risk because of participation in the study
11.2. Adversely affect the interpretation of the study results, or
11.3. Impair the participant's ability to participate in the study
12. Study site staff or a partner or dependent child of study site staff

Previous key exclusion criteria:
1. Research Participants:
1.1. Participation in another research study, in which procedures performed could compromise the integrity of this study (such as significant volumes of blood taken), or are planning to do so within the trial period
1.2. Currently a participant in a previous EHPC trial within the last 2 years or at the discretion of the study team
2. Vaccination (self-reported or confirmed from GP questionnaire or medical records/summary if deemed necessary at clinician discretion):
2.1. Have had any previous pneumococcal vaccination in the past 5 years (including in a research study)
2.2. Planned vaccination during the study
3. Allergy:
3.1. Have an allergy to penicillin or amoxicillin (for main study cohort only)
3.2. History of a bleeding disorder (e.g., Factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
3.3. Have previous anaphylaxis or severe adverse reaction to any component/excipient of the vaccine or to any vaccine
3.4. Allergy to Lidocaine local anaesthetic (for nasal biopsy cohort only)
4. Health History (self-reported or confirmed from GP questionnaire or medical records /summary if deemed necessary): moderate ill health including but not limited to:
4.1. Asplenia or dysfunction of the spleen
4.2. Chronic respiratory disease (e.g. asthma [on medication], COPD, emphysema, bronchiectasis)
4.3. Chronic heart disease (e.g. angina, ischaemic heart disease, chronic heart failure) [controlled stable hypertension +/- angina may be included]
4.4. Chronic kidney disease (e.g. nephrotic syndrome, kidney transplant, on dialysis)
4.5. Chronic liver disease (e.g. cirrhosis, biliary atresia, hepatitis)
4.6. Chronic neurological conditions
4.7. Connective tissue disease
4.8. Dementia
4.9. Diabetes mellitus (including diet controlled)
4.10. Immunosuppression or history of receiving immunosuppressive therapy – at the discretion of the investigator
4.11. Individuals with cochlear implants
4.12. Individuals with major cerebrospinal fluid leaks (e.g. following trauma, major skull surgery, or requiring CSF shunt)
4.13. Recurrent otitis media
4.14. History of significant unexplained bleeding after a surgical or dental procedure (for nasal biopsy participants only)
4.15. Have any uncontrolled medical/surgical/mental health conditions at the discretion of the study doctor
4.16. Major pneumococcal illness requiring hospitalisation within the last 10 years

4.17. Significant mental health problems (uncontrolled condition or previous admissions in a psychiatric unit, at the discretion of the clinician) that would impair the participant's ability to participate in the study
5. Taking Medications:
5.1. Any medication that may affect the immune system in the last 3 months (e.g. systemic steroids [IM/IV], Roaccutane, disease modifying anti-rheumatoid drugs)
5.2. Long-term use of antibiotics (see also section of Temporary Exclusion Criteria)
5.3. Use of any medication or other product (prescription or over-the-counter) for symptoms of rhinitis or nasal congestion within the last 1 month
5.4. Use of any medication affecting blood clotting (any oral/injectable anticoagulants [except aspirin])
6. Female participants who are pregnant, lactating or intending on becoming pregnant during the study
7. Direct caring role or close contact with individuals at higher risk of infection (for main study cohort only):
7.1. Children under 5 years of age
7.2. Chronic ill health or immunosuppressed adults
7.3. Older adults
8. Smoker:
8.1. Current or ex-smoker (regular cigarettes/cigars/e-cigarette/vaping/smoking of recreational drugs) in the last 6 months
8.2. Previous significant smoking history (more than 20 cigarettes per day for 20 years or the equivalent [>20 pack years])
9. Suspected or known current alcohol or drug abuse, as per investigator's discretion
10. Overseas travel during the follow-up period (from the time point of inoculation to antibiotic treatment or completion of the 23-day follow-up period post inoculation)
11. Any other issue which, in the opinion of the study staff, may:
11.1. Put the participant or their contacts at risk because of participation in the study
11.2. Adversely affect the interpretation of the study results, or
11.3. Impair the participant's ability to participate in the study
12. Study site staff or a partner or dependent child of study site staff

Date of first enrolment
27/01/2025

Date of final enrolment
09/09/2025

Locations

Countries of recruitment
United Kingdom

England

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Centre for Clinical Vaccinology and Tropical Medicine (CCVTM)
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Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Industry

Funder Name
Merck Sharp and Dohme United Kingdom

Alternative Name(s)
MSD United Kingdom, Merck Sharp & Dohme, Merck Sharp & Dohme Corp., MSD

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

De-identified study data sets will be made available upon requests directed to the chief investigator. Proposals will be reviewed and approved by the sponsor, chief investigator, and collaborators on the basis of scientific merit. After approval of a proposal, data can be shared through a secure online platform after signing a data access agreement.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		24/11/2025	26/11/2025	Yes	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes