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A study exploring whooping cough protection in infants following vaccination

Submission date
27/01/2020

Recruitment status
No longer recruiting

Registration date
09/03/2020

Overall study status
Completed

Last Edited
20/09/2024

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
Whooping cough is caused by infection with the bacterium Bordetella pertussis. It can cause chest infections and difficulty in breathing, with some affected babies needing admission to hospital. There are two different types of whooping cough vaccine (one called a 'whole cell' vaccine and one called an 'acellular' vaccine) used in different countries across the world. Both these vaccines are safe and effective. Currently in the UK, the 'acellular' vaccine is used, but prior to 2004 the 'whole cell' vaccine was used. It is thought that whole cell pertussis vaccines give longer-lasting protection from disease than acellular vaccines. The current use of acellular vaccines might explain why there has been an increase in the number of whooping cough infections recently in the UK, despite good vaccination coverage.
The researchers want to understand what it is about the immune response to the whole cell vaccine that gives longer-lasting protection from infection than the acellular vaccine. This may enable a better understanding of why the number of cases has increased, and how better vaccines can be produced in the future.

Who can participate?
Infants aged 8-10 weeks who have not yet received their first vaccinations and whose mothers received the whooping cough vaccine during pregnancy

What does the study involve?
Participants will receive either wP or aP whooping cough (pertussis) vaccines at 2 and 4 months of age (57 per group), as well as their normal vaccines. They will be followed up until they are 13 months old. A total of 7 visits and 4 blood tests and nasal samples will be performed over a 12-month period. All vaccines will be given at home, and parents or carers will have 24-hour contact with a study doctor for the duration of the study.

What are the possible benefits and risks of participating?
The vaccines will be administered in a slightly different schedule, when compared with the routine UK schedule, but the total number of doses will be the same. Although the pertussis vaccine will be given at 2, 4 and 12 months (instead of 2, 3 and 4 months), the researchers do not anticipate that participating children will have an increased risk of infection between the 2- and 4-month doses and the change in schedule does not reduce the effectiveness of the vaccine.

This is because the researchers will only be recruiting children whose mothers have received the whooping cough (pertussis) vaccine during pregnancy, and will therefore be receiving additional protection from this.
Although whole cell vaccines may be associated with increased side effects, most of these are mild and they are not associated with long-term problems in healthy children. Parents and carers will have telephone access to a study doctor 24 hours a day for the duration of the study. This doctor will be able to clarify any questions about side effects, give instructions on how to proceed, including advising on non-prescription medications and advice in case they think that the child should be assessed by a doctor at a clinic. The child will receive their routine immunisations at home, an environment your child is familiar with, rather than at a GP surgery or clinic.
The child will receive two doses of the pneumococcal vaccine (PCV13) at 2 and 4 months, which is in line with the previous UK schedule, rather than a single dose at 3 months which is the UK schedule for babies born from January 2020 onwards. There is not thought to be a difference in the protection given by either schedule but for the study infants giving doses at 2 and 4 months means that there does not need to be an additional visit at 3 months of age.

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

When is the study starting and how long is it expected to run for?
August 2019 to June 2024

Who is funding the study?
The European Union (EU)

Who is the main contact?
Nelly Owino, nelly.owino@paediatrics.ox.ac.uk

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2019-001789-13

Integrated Research Application System (IRAS)
218431

Protocol serial number
CPMS 43441, IRAS 218431

Study information

Scientific Title
A randomised, open label study, exploring the differences in immunogenicity and reactogenicity of infants after immunisation with either an acellular (aP) or whole cell pertussis (wP) vaccine

Acronym
AWARE

Study objectives
Pertussis is an acute respiratory infection. The classical form, whooping cough, commonly affects newborns and nonvaccinated infants and can be life-threatening. There are two different types of pertussis vaccine available worldwide, whole-cell (wP) and acellular (aP). The wP has been available for over 60 years and its introduction was associated with a significant decrease in disease rates. In the last 2-3 decades aP has replaced wP in several countries including the UK. However, recent pertussis outbreaks in these countries have raised the question of whether aP provides the same level of protection against pertussis as wP.

This study aims to determine whether infants have different immune responses to wP and to aP. We will use novel laboratory techniques developed by the PERISCOPE consortium to understand how the infant's immune system responds after the administration of either wP or aP vaccine. We will investigate whether these responses are connected to differences in long-term vaccine effectiveness, and whether vaccination of mothers in pregnancy affects infant immune responses.

114 infants will be recruited and randomised to receive either wP or aP at 2 and 4 months of age (57 per group). They will be followed up until they are 13 months. A total of 7 visits and 4 blood tests and nasal samples will be performed.

The knowledge acquired through this study will ultimately provide clues as to how current pertussis vaccines and vaccination schedules can be modified to increase protection.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 29/08/2019, South Central - Hampshire B REC (Health Research Authority, Level 3, Block B, Whitefriars, Bristol, BS1 2NT; +44 (0)207 104 8054; nrescommittee.southcentral-hampshireb@nhs.net), ref: 19/SC/0368

Study design

Randomised; Interventional; Design type: Prevention, Vaccine

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Response to pertussis (whooping cough) vaccination in infants

Interventions
The study will recruit a total of 114 infants and randomise 1:1 to receive either wP or aP at 2 and 4 months of age (primary immunisations). The randomisation lists will be generated by the study statistician using block randomisation. All infants will be born from mothers who received aP vaccine during pregnancy. All procedures will be identical in both groups. The participants will be recruited at 2 months of age, in time for their primary immunisations and they will be followed up until they are 13 months of age.

There will be 7 study visits with 4 blood tests and 4 nasal samples performed on each participant in both groups.

1. Visit 1 (at age 2 months). Informed consent and enrolment; blood sample and nasal fluid sampling; immunisation either of DTaP-IPV-Hib-HepB vaccine (Infanrix-hexa) or DTwP-Hib-HepB /IPV vaccines (ComVac5 + Imvax Polio) together with routine vaccines, which are pneumococcal conjugate (PCV13) and rotavirus (Rotarix).
2. Visit 2 (7 days after Visit 1). Meningococcal B (MenB) immunisation.
3. Visit 3 (56 days after Visit 1 [+14 days]). Immunisation with second dose of DTaP-IPV-Hib-HepB (Infanrix-hexa) or DTwP-Hib-HepB/IPV (ComVac5 + Imvax Polio) together with routine vaccines, which are pneumococcal conjugate (PCV13) and rotavirus (Rotarix).
4. Visit 4 (7 days after Visit 3). Second Men B immunisation.
5. Visit 5 (at age 5 months): Blood samples and nasal fluid sampling.
6. Visit 6 (at age 12 months): Blood sample, nasal fluid sampling and immunisation with DTaP-IPV-Hib-HepB (Infanrix-hexa) and pneumococcal conjugate (PCV13).
7. Visit 7 (at age 13 months): Blood sample, nasal fluid sampling and immunisation with meningococcal C conjugate (MenC), measles, mumps and rubella (MMR) and MenB vaccines.

At the visits V1, V3 and V6 all participants will be issued a diary (either eDiary or paper diary) in order to record adverse events, axillary temperature records and medication administered during the study. Participants will also have a continuous temperature monitoring device that would be applied to the child for a period of 24 h after immunisation.

Intervention Type
Biological/Vaccine

Phase
Phase III

Drug/device/biological/vaccine name(s)
1. Infanrix-hexa 2. ComVac5

Primary outcome(s)
Pertussis toxin (PT)-specific antibody geometric mean concentration (GMC) measured using a flow cytometry method with antigen-coated fluorescent beads (Bioplex/Luminex) at 13 months of age

Key secondary outcome(s))
1. Pertussis toxin (PT)-specific antibody geometric mean concentration (GMC) measured using using a flow cytometry method with antigen-coated fluorescent beads (Bioplex/Luminex) at 2, 5 and 12 months of age
2. Filamentous hemagglutinin (FHA)-specific antibody GMC measured using using a flow cytometry method with antigen-coated fluorescent beads (Bioplex/Luminex) at 2, 5, 12 and 13 months of age
3. Pertactin (PRN)-specific antibody GMC measured using using a flow cytometry method with antigen-coated fluorescent beads (Bioplex/Luminex) at 2, 5, 12 and 13 months of age
4. Bordetella pertussis fimbriae (FIM)-specific antibody GMC measured using using a flow cytometry method with antigen-coated fluorescent beads (Bioplex/Luminex) at 2, 5, 12 and 13 months of age
5. Pertussis antigen-specific memory B-cell geometric mean frequencies measured by ELISpot at 5, 12, and 13 months of age
6. Pertussis antigen-specific T-cell responses measured following antigen-specific restimulation at 5 months of age. Whole blood will be stimulated with antigens according to a protocol developed as part of the PERISCOPE consortium. The stimulated cells and supernatants will then be frozen pending subsequent transfer to collaborators in the PERISCOPE consortium for analysis by flow cytometry and cytokine detection in supernatants.
7. Hib-specific antibody responses measured using using a flow cytometry method with antigen-coated fluorescent beads (Bioplex/Luminex) at 2, 5, 12 and 13 months
8. Diphtheria-specific antibody responses measured using using a flow cytometry method with antigen-coated fluorescent beads (Bioplex/Luminex) at 2, 5, 12 and 13 months
9. Tetanus-specific antibody responses measured using using a flow cytometry method with antigen-coated fluorescent beads (Bioplex/Luminex) at 2, 5, 12 and 13 months
10. Pneumococcal-specific antibody responses measured using using a flow cytometry method with antigen-coated fluorescent beads (Bioplex/Luminex) at 2, 5, 12 and 13 months
11. Functional assessment of pertussis-specific antibodies (which might include assays of adherence inhibition, bacterial agglutination, bactericidal activity, bacterial opsonization and phagocytosis) undertaken on serum or plasma samples taken at 2 (prior to immunisation), 5, 12 and 13 months of age
12. Mucosal response assessed by measurement of substances such as antibodies and cytokines in mucosal lining fluid analysed by Luminex multiplex immunoassay at 2, 5 and 12 months of age
13. Local and systemic symptoms (solicited and unsolicited) assessed using parents' report after vaccine doses at 2, 4 and 12 months of age

Completion date
06/06/2024

Eligibility

Key inclusion criteria
1. Infants due to receive their primary immunisations, aged up to 10 weeks at first vaccinations
2. Born at ≥37 weeks of gestational age
3. Written informed consent given by parent(s) or legal guardian(s) aged ≥18 years
4. Parent(s) or legal guardian(s) willing and able to comply with the requirements of the protocol

for the duration of the study
5. Mother received DTaP vaccine during pregnancy with participating infant

Healthy volunteers allowed
No

Age group
Child

Upper age limit
10 weeks

Sex
All

Total final enrolment
112

Key exclusion criteria
1. Parent/guardian has any condition which in the opinion of the investigator may interfere with the ability to fulfil study requirements. This may include plans to move house and language comprehension.
2. Mother was receiving immunosuppressive treatment during pregnancy or is known to be HIV-positive
3. In care (with safeguarding in place)
4. Child of parents who are on the delegation log for this study
5. Prior or planned receipt of any other investigational vaccine/drug or if currently participating in other research study, at investigator discretion
6. Major congenital defects or serious chronic illness
7. Bleeding disorder
8. Confirmed or suspected immunodeficiency
9. Family history of congenital or hereditary immunodeficiency
10. Receipt of more than 1 week of immune-suppressants or immune modifying drugs (e.g. oral prednisolone >0.5 ml/kg/day or intravenous glucocorticoid steroid). Nasal, topical or inhaled steroids are allowed.
11. Administration of immunoglobulin and/or any blood products since birth or planned administration during the study period
12. History of allergy to any component of the vaccines
13. History of pertussis disease/whooping cough confirmed by laboratory analysis (serology, culture or other available methods)

Temporary exclusion criteria
Visits where vaccines are administered should be delayed:
14. In the presence of an acute illness or the presence of fever ≥38°C, until 72 h after resolution
15. For at least 6 h since last dose of ibuprofen/paracetamol
16. For 48 h after finishing an antibiotic treatment
All the treatments should be documented in the CRF at the time of the visit (name, dose, duration of treatment).

Date of first enrolment
08/03/2021

Date of final enrolment
31/07/2021

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Oxford Vaccine Centre
Centre for Clinical Vaccinology and Tropical Medicine
Churchill Hospital
Old Road
Oxford
United Kingdom
OX3 7LE

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
European Commission

Alternative Name(s)
European Union, Comisión Europea, Europäische Kommission, EU-Kommissionen, Euroopa Komisjoni, EC, EU

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request directed to Dominic Kelly (dominic.kelly@paediatrics.ox.ac.uk), Chief Investigator or upon written approval of the sponsor.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Protocol file	version 4.1	08/12/2023	13/12/2023	No	No