OXFORD VACCINE GROUP

A Study Exploring Whooping Cough Protection in Infants

Study Information Booklet

You are invited to take part in a study to understand how well `whooping cough` (also known as Pertussis) vaccines work in babies.

Before you decide whether to take part, it is important for you to understand what the study is about and what participation would involve. Please take time to read the information carefully, and discuss with others if you wish. If anything is unclear or you would like further information, please contact the study team.

Thank you for taking the time to consider taking part in the study.

Summary

- Whooping cough (Pertussis) causes chest infections, difficulty in breathing and some babies need 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 we use the 'acellular' vaccine but prior to 2004 we used the 'whole cell' vaccine.
- 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.
- **What do we want to know?** – we 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 allow us to better understand, why the number of cases has increased, and how we can produce better vaccines in the future.
- **How are we going to do it?** – OVG will recruit children aged 8-10 weeks who have **NOT** yet received their first vaccinations. They will have one of two whooping cough (pertussis) vaccines, as well as their normal vaccines. They will have 7 visits and 4 blood and nasal samples over a 12-month period.
- All vaccines will be given at your home, and you will have 24-hour contact with a study doctor for the duration of the study.

Why has my child been invited to take part?

You have been approached because your child will shortly be due their routine immunisations and you live in an area where the study is being carried out. Taking part in this study is voluntary.

Who is doing this study?

This study, which is being run by the Oxford Vaccine Group (OVG), is one of many projects that are part of the PERISCOPE Consortium. The consortium is a group of scientists who have come together to research and improve our current understanding and knowledge of whooping cough (pertussis) disease and improve the future development of whooping cough (pertussis) vaccines.

The Oxford Vaccine Group (OVG) is part of the University of Oxford and is an independent research team of doctors, nurses, play assistants and scientists. We carry out research studies of new and improved vaccines for babies, young children, teenagers and adults and teach doctors and nurses about immunisations. In the past 5 years alone, over 7000 participants in the Thames Valley area have taken part in our research studies.

What is pertussis and whooping cough?

Pertussis, most commonly known as 'whooping cough', is caused by a bacteria called *Bordetella pertussis* and affects the airways and chest. Whooping cough normally presents with a cough which can continue for 2-3 months and when severe can cause vomiting and difficulty in breathing.

In infants, particularly in those that have not received the whooping cough (pertussis) vaccine, the disease can lead to severe complications such as pneumonia (chest infection), difficulty with breathing and seizures (or fits). Some infants require hospital admission and sometimes need a ventilator to help them breath. In some of these cases, whooping cough (pertussis) can result in death. Children are not the only ones affected by whooping cough. In high-income countries like the UK, the number of cases in older children and the elderly are increasing, and there is an increased risk of the disease spreading to the most vulnerable groups.

What are we interested in?

In this study, we would like to learn more about two vaccines that protect against whooping cough. **Vaccines** (or immunisations) stimulate our immune system to make antibodies, which move around the body in the blood and help to protect us from

infections. If a child or an adult is exposed to an infection, which they have been vaccinated (or "immunised") against, their body will be able to recognise and fight this infection. This is known as an **immune response.** Without vaccines, people are at increased risk of catching many serious infections.

There are two different types of whooping cough (pertussis) vaccine available worldwide. One is called an 'acellular' vaccine and the other a 'whole cell' vaccine (more information on these vaccines is available on page 11). The whole cell vaccine was the first whooping cough (pertussis) vaccine to be used across the world. All infants in the UK were given the whole cell vaccine until 2004, when the UK changed to using the acellular vaccine. The main reason for this change was that the acellular vaccine was known to cause less symptoms (such as fever and redness and swelling at the site of the injection) when compared with the whole cell vaccine. Other countries (including Australia, the US and others in Europe) also changed to using to the acellular vaccine.

However, in many of these countries (including the UK), cases of whooping cough (pertussis) have increased again despite most children receiving their vaccinations. In 2012, the number of whooping cough (pertussis) cases rose significantly, causing 14 deaths in England and Wales, all in children under 3 months of age. Although, the exact reason for this increase is unknown, researchers wonder whether giving the acellular vaccine instead of the whole cell vaccine has been a factor. Throughout the world, most countries continue to use whole cell pertussis vaccines. The World Health Organization recommends that these countries do not change to acellular vaccines because it is uncertain if the protection against infection is as good after having the acellular vaccine. We hope that the information we get from this study will help us to better understand the differences between these two vaccines.

As a result of the whooping cough (pertussis) outbreak in 2012, the UK started to give the whooping cough (pertussis) vaccine to pregnant women (using the acellular vaccine). The World Health Organization recommended this approach. The main reason for giving the vaccine to pregnant women is to protect their babies. Babies and young children are more at risk from whooping cough (pertussis) because they have not yet had their first immunisations.

What happens in the study?

The Oxford Vaccine Group are looking to recruit children born to mothers who **did receive** a whooping cough (pertussis) vaccine during their pregnancy.

We want to recruit children who:

- Are 8-10 weeks of age, healthy and were born after 37 weeks gestational age
- Have **not** yet received their first vaccinations

This study involves:

- Your child receiving either the acellular or whole cell whooping cough (pertussis) vaccine along with their other routine vaccines
- 7 visits over a 12-month period
- 4 blood samples taken at different time points and sampling of nasal secretions with a small paper swab
- Temperature recordings following vaccination for 7 days (following the 2, 4 and 12 month vaccinations)
- 24 hour continuous temperature recordings will also be taken at 2, 4 and 12 months of age
- Completion of an electronic diary for 7 days following vaccinations at 2, 4 and 12 months
- We will also ask the mother to provide evidence of their whooping cough (pertussis) immunisation history during pregnancy. Alternatively, mothers will be sent either a paper or an electronic consent form giving permission for the study team to access their medical records to confirm their pertussis immunisation status.

Vaccines

If your child were to take part, they would receive either the whole cell vaccine or the acellular vaccine alongside their other routine vaccinations. The group your child is allocated to is decided by chance, like tossing a coin. In this study, we will use a computer program to allocate the group and there will be a 50% chance that your

child will enter either group. Neither you, nor the study team will be able to influence which vaccine your child is given. Once the vaccines have been given to your child at the first visit, you and the study team will know which group they have been allocated to and which vaccine they received. Your child will be given either the whole cell or acellular vaccine at 2 and 4 months of age. All children (ie: both groups), will then receive the acellular vaccine at 12 months of age.

The table below describes the schedule. The short forms of the vaccine names used in the table are explained before the table. There are some differences from the routine UK schedule, and some further explanation immediately after the table.

Short forms of vaccine names used in table 1:
DTaP/Hib/HepB/IPV: diphtheria, tetanus, acellular pertussis (whooping cough), Haemophilus influenzae b, hepatitis B, inactivated polio vaccine
DTwP/Hib/HepB: diphtheria, tetanus, whole cell pertussis (whooping cough), Haemophilus influenzae b, hepatitis B
IPV: inactivated polio
PCV13: pneumococcal
Rotarix: rotavirus
MenB: meningococcal B
MenC: meningococcal C
Hib: Haemophilus influenzae b
MMR: measles, mumps, rubella
X: no vaccines given

Table 1: Vaccine schedules

Age	Current UK schedule	Acellular vaccine group	Whole cell vaccine group
2 months	DTaP/Hib/HepB/IPV Rotarix (oral) MenB	DTaP/Hib/HepB/IPV PCV13 Rotarix (oral)	DTwP/Hib/HepB + IPV PCV13 Rotarix (oral)
2 months + 1 week	X	MenB	MenB
3 months	DTaP/Hib/HepB/IPV PCV13 Rotarix (oral)	X	X
4 months	DTaP/Hib/HepB/IPV MenB	DTaP/Hib/HepB/IPV PCV13 Rotarix (oral)	DTwP/Hib/HepB + IPV PCV13 Rotarix (oral)
4 months + 1 week	X	MenB	MenB
12 months	Hib/MenC PCV13 MenB MMR	DTaP/Hib/HepB/IPV PCV13	DTaP/Hib/HepB/IPV PCV13
13 months	X	MenC MenB MMR	MenC MenB MMR

- Your child will receive 3 vaccines containing whooping cough (pertussis). The timing of these vaccines will be different from the current UK schedule (2, 4, and 12 months instead of 2, 3 and 4 months) but the number is still the same.
- The MenB vaccine (Bexsero®) is being given 1-2 weeks after the vaccines at 2 and 4 months of age, instead of at the same time. Studies show that about 2 out of every 3 babies get a fever over 38º C when they are given the MenB vaccine with other routine vaccines at 2 and 4 months of age. Giving the MenB vaccine separately at least

7 days after the 2 and 4-month vaccinations will allow us to better understand the side effects that are associated with the whooping cough (pertussis) vaccines without the interference of the MenB vaccine.

Blood/ nasal Samples

In order to understand the effect of the vaccines, your child will have 4 blood samples and 4 nasal swabs (taken with a small paper swab) during the study. (the visit outlines are shown in table 2).

Table 2: Study visits, vaccinations and sampling timelines

Visit	aP vaccine group	wP vaccine group
V1 (2 months)		
V2 (V1 + 7 days)		
V3 (4 months)		
V4 (V3 + 7 days)		
V5 (5 months)		
V6 (12 months)		
V7 (13 months)		

 Blood sample  Nose swab  Vaccinations (as per table 1)

The blood samples will allow us to see how your childs' immune system has responded to their vaccinations. The samples will also allow us to understand what genes are involved in this response (genes act as a set of instructions that are transferred from parents to their children and determine the childs' characteristics and immune responses).

We will take up to 4ml (less than a teaspoon) when your child is under 5 months and 6ml after they turn 1 year of age.
We will use local anaesthetic cream to help numb the skin prior to the blood samples. This will help to reduce any pain. The study team will explain how to use the cream before the visits. We also have play assistants who will help distract your child during the blood sampling. The study team will have a maximum of 2 attempts when taking blood. If the first attempt is unsuccessful, it is your decision whether we have another attempt or not.

Nasal (Mucosal) fluid sampling

We will also collect samples of nasal secretions at 4 of the study visits. This will be done using a paper nose swab, which looks like blotting paper. This will be inserted up the nostril and then the outside of the nose is pressed gently closed with a finger, so it touches the passage of the nostril. The procedure may tickle a bit but is painless. These swabs will give us information about how the immune system in the nose changes after vaccination.

Diary

After your childs vaccinations at 2, 4 and 12 months, we will ask you to fill in an electronic or paper diary for 7 days. This will record if your child has a temperature or any reactions following their vaccinations.

Temperature Monitoring

After the 2, 4 and 12 month visits, we will issue you with a special 24 hour temperature monitoring device. You will be shown how to fit and remove this device (ie: when your child has a bath, is going swimming or if needed for another reason). This will give us detailed information about what happens to your child's temperature in the 24hrs following their whooping cough (pertussis) vaccines. We will either collect the device at the following visit or provide you with a prepaid envelope to post the device back to us.

What are the possible side effects of the vaccines and of blood sampling?

Blood Sampling

The blood sampling may be uncomfortable but will be performed by trained staff and anaesthetic (numbing) cream will be provided to reduce any pain. There may be some short-lived bleeding and/or bruising following the blood sampling.

Vaccines

During this study, most of the vaccines that your child will receive are the same as those that your GP or nurse would give (see table 1). With those vaccines, the side effects are the same for all children. It is expected that children may experience some redness and mild swelling where the injection is given. Fever, irritability, sleepiness or reduced sleep, reduced feeding, diarrhoea or a rash are often seen. These reactions are usually mild and short-lived. Much less frequently, children may develop a high temperature (>40 degrees) which resolves after a day.

Very occasionally, infants may become pale, floppy and less responsive than normal (Hypotonic-hyporesponsive episode) following their vaccinations. This can occur immediately or up to 48 hours after vaccinations. If this does occur, it will resolve without long-term consequences and does not usually happen again with further doses. Very rarely, children can also have allergic reactions. An immediate, severe allergic reaction (anaphylaxis) can result in a rash, swelling of the body and breathing difficulties. The study team would observe your child for 15-30 minutes following their vaccinations as this is the time when most significant reactions are expected to

happen. The study team members carry medicine to treat these reactions (adrenaline) and are trained to administer it should such a reaction occur.

The study team will issue (only if parent's do not have any) and provide instructions on the use of paracetamol prophylaxis to those whose infant is randomised to receive wholecell vaccine.

Information on specific vaccines

With the **MenB** vaccine, there is a higher risk of your child developing a fever when compared with the other vaccines in the UK schedule. This is more common (~ 7 in 10 cases) when given at the same time as the other routine immunisations. In our study, this side effect may be reduced because MenB is given alone and not at the same time as the other vaccines.

The **rotarix vaccine** is a weakened form of rotavirus itself and so can cause mild symptoms of diarrhoea, nausea and irritability.

In this study, we are going to administer two different types of whooping cough (pertussis) vaccines, to two different groups, as previously described (table 1).

The **acellular whooping cough (pertussis) vaccine** is part of a combined vaccine called Infanrix hexa® (DTaP-IPV-Hib-HepB) that protects against diphtheria (D), tetanus (T), whooping cough (acellular component,aP), hepatitis B (Hep B), poliomyelitis (IPV) and *Haemophilus influenzae* type b (Hib). This vaccine is part of the routine UK schedule. The side effects described for this vaccine are similar to the other routine UK vaccines. Mild fever may also occur in around 1 in 2 children in the first day after administration and can be associated with irritability, increased crying and reduced feeding. Although very rare (less than 1 in 10,000 cases) it is also reported that some children might experience fits (seizures).

The **whole cell whooping cough (pertussis)** vaccine that we are going to use in the study is called ComVac5 (DTwP-Hib-HepB) and protects against diphtheria (D), tetanus (T), whooping cough (pertussis) (whole cell,wP), hepatitis B (Hep B), and *Haemophilus influenzae* type b (Hib). ComVac5 is manufactured in India and is not licensed for use in the UK. The Medicines and Healthcare Products Regulatory Agency

(MHRA) have however reviewed all the information about this vaccines safety and effect on immune reponse and have approved it for use in this study. For whole cell whooping cough (pertussis) vaccines in general, the most common side effects are similar to the ones described for the other vaccines. However, these side effects may happen more frequently: including crying, reduced feeding, irritability and local reactions (redness, and swelling where the vaccine was given). In a study undertaken in India with ComVac5, fever (either from parental observation or measurement) was the most common side effect, occurring in between 5 to 9 out of 10 infants depending on the dose of the vaccine. In the majority of children, the episodes were rated as mild. Where temperature was measured, 1 in 5 children with fever had temperatures of ≥ 38 degrees, and around 1 in 100 had a temperature ≥ 40 degrees. Again, this was dependent on the vaccine dose that was given.

The World Health Organisation (WHO) recognises that pale, floppy episodes (Hypotonic Hyporesponsive events) following vaccinations are rare events. They are more commonly seen after whole cell whooping cough (pertussis) vaccines than acellular vaccines.

All whole cell whooping cough (pertussis) vaccines also contain very small amounts of a mercury compound (thiomersal or thimerosal), which acts as a preservative. The amount in the vaccine is similar to the amount in a can of tuna fish. The World Health Organization has stated that there is no evidence of risk from this.

Do I have to take part?

No. Taking part in this research study is voluntary and if you decide to say no, it will not affect your child's routine care in any way. If you did take part you are also free to change your mind and withdraw your child at any time without giving an explanation. If you did withdraw your child from the study and a blood sample(s) has already been taken, we would use the sample(s) and data we have collected from you in our analysis up until the point you informed us that you wanted to withdraw. If consent was obtained for storing samples for future research beyond the end of the study period, we will ask if you wish to withdraw from this also. We would not collect any further samples, but we may ask you to allow us to make a follow up phone call to check for any side effects your child may have had during their time in the study or after withdrawal.

Whatever you choose, it is important that you are happy with your decision and it is not the role of the study team to help decide for you. We will help present the details of the study and answer all your questions so you can make an informed decision.

What are the possible risks as well as benefits of taking part?

The vaccines will be administered in a slightly different schedule, when compared with the routine UK schedule (see table 1), 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), we do not anticipate that, your child will have an increased risk of infection between the 2 and 4 month doses and it does not reduce the effectiveness of the vaccine. This is becasuse we 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 outcomes in healthy children. You 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 your child should be assessed by a doctor at a clinic.

You will benefit from having your child receive their routine immunisations at your home, an environment your child is familiar with.

Your child will receive 2 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. This means that your child will receive an extra dose of PCV13 starting 1-month earlier compared to the current schedule. This has been done to avoid an additional study visit at 3-months which would be needed for a single dose PCV13 schedule

Information from this study will help us learn more about the differences between these vaccines and could consequently help future vaccine design.

If you wish to take part

If you are interested in your child taking part, please register your interest using the contact details provided at the end of this booklet. A member of the study team will then contact you to discuss the study in more detail and potentially arrange an appointment for your first study visit, at your home and at your convenience. At or prior to the visit, we will need to confirm what immunisations (in particular the pertussis/ "whooping cough" vaccine) the mother received during pregnancy. We will ask the mother to get this information from their GP or ask for their consent to access this information from their GP/medical records. At the visit any further questions you have will be answered, your child's health will be checked and you will be asked to complete a consent form if you wish to proceed with the study.

The first appointment should last around 1.5 hours, and all following appointments between 30-45 minutes. We will let your GP, health visitor and child health department know that your child is taking part in the study.

In light of the current COVID-19 pandemic in the UK, the government has advised reducing social interaction between people to help reduce the transmission of the virus in the community. To enable us to follow these recommendations as much as possible during our visits, certain infection control procedures will be followed. These procedures will be outlined to you during your telephone screening.

What will happen to any samples from my child?

The samples we take for this study will be labelled with a study number and tested in certified laboratories. If you choose to take part in this study, you will be asked to consent to the PERISCOPE consortium storing components of your child's nasal secretions and blood, including DNA, in a collection of samples within the PERISCOPE Biobank (located at the Radboud University Medical Centre, Nijmegen, the Netherlands), for the duration of the study. Samples from the biobank will only be used for the study purposes and objectives of the PERISCOPE project. The material given to researchers will not have information that identifies your child. However, DNA is unique so it can never be completely anonymous.

The PERISCOPE biobank also includes the storage of left over samples following the end of the project. Samples that are left over will only be used to answer the research questions of the PERISCOPE project, but may be shared with hospitals, universities, non-profit institutions or commercial laboratories worldwide. The storage and use of **left over** samples is voluntary. If you do consent to this, we will need to store a copy of your consent form until the sample(s) is depleted or destroyed, or until the youngest participant has reached 21 years of age – whichever is longer. If you do not consent to the further use of your child's samples, they will be destroyed immediately following the completion of this study.

What happens when the study stops?

Once all infants within the study have completed their relevant visits, we will start the analysis and interpretation of the findings. Once complete, we will publish these results, and provide you with a link to the published paper on the Oxford Vaccine Group website. None of the reports will contain any information that might allow the readers to identify anyone who took part in the study.

When your child has completed all the relevant study visits, all-future vaccinations will be provided by your GP surgery.

What if relevant new information becomes available?

Sometimes we get new information about vaccines or vaccination schedules that might be relevant to this study. If that happens or if the study is stopped for any reason, we will write to you and your GP with information about you and your child's continuing care.

Will our participation in the study be kept confidential?

The Oxford Vaccine Group (OVG) alone will hold any study records with your child's name and address. Your child's participation in the study will remain confidential and when the results of the study are published, your child would not be identified. If you and your child decide to take part in the study, we would inform your GP practice that

your child is enrolled in the study and of the dates that we gave your child their study vaccine.

To ensure that all personal information is kept confidential your child would be allocated a study number. This would be used to identify your child on any paperwork or samples taken. Your child would not be identifiable to laboratory staff handling study samples.

Information kept by the OVG would include your child's demographic details (such as name, address and date of birth), medical history and results of blood sample analysis. To check that the study was being conducted correctly, your child's study records might be read (but not kept) by representatives of the following groups who are obliged to treat your information confidentially:

- UK Medicines and Healthcare products Regulatory Agency (MHRA)
- Responsible members of the University of Oxford may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations.

You and your child's study information, removed of any identifying information, may be sent outside of the European Union, including to commercial partners.

By signing the consent form for this study, you would be giving permission for this. Any information that identified your child would remain with the OVG.

Your Data

We will be using information collected from you, your child and your medical records in order to undertake this study. Research is a task that we perform in the public interest. The University of Oxford, as sponsor, is the data controller. This means that we, as University of Oxford researchers, are responsible for looking after your child's information and using it properly. We will use the minimum personally-identifiable information possible. We will store the anonymised research data and any research documents with personal information, such as consent forms, securely at the University of Oxford for a period of 10 years after the last participant has completed the study or until the youngest participant has reached 21 years of age after the end

of the study. This will be reviewed every 5 years and files will be confidentially destroyed if no longer needed. Electronic data will be stored securely for the same time in the University of Oxford electronic archives.

What else do I need to know?

We do not anticipate any harm resulting from obtaining blood samples.

All vaccines used in this study are licensed for use in the UK apart from the whole cell whooping cough (pertussis) vaccine (ComVac5). Whole cell whooping cough (pertussis) vaccines are routinely used in different countries around the world including the UK until 2004 and are recommended by the World Health Organization. ComVac5 is manufactured and used in India where it is approved by the Indian National Regulatory Authority and as it is unlicensed in the UK the data on the safety and immunity generated by ComVac5 has been reviewed by the UK Medicines and Healthcare Products Regulatory Agency (MHRA). Safety will be monitored according to standard practice in clinical trials and will include reporting to an independent Data Safety Monitoring Committee.

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study.

Who is organising and funding the research?

The study is funded by the Innovative Medicines Initiative (IMI), who are funded jointly by the European Union and the Bill and Melinda Gates Foundation (represented by the European Commission) as well as the European pharmaceutical industry (represented by EFPIA, the European Federation of Pharmaceutical Industries and Associations).

The study is being sponsored by the University of Oxford (UK).

Who reviewed the study?

An independent group of people called a Research Ethics Committee looks at all research in the NHS, to protect the safety, rights, well-being and dignity of

individuals. This study has been reviewed and given favourable opinion by theSouth Central - Hampshire B Research Ethics Committee (Ref: 19/SC/0368). Details of the study can also be found on the following website: http://www.isrctn.com/ISRCTN17271364

What if I wish to complain?

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact the Oxford Vaccine Group on 01865 611400 or email info@ovg.ox.ac.uk You can also contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480 or email ctrg@admin.ox.ac.uk

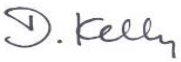
What do I do now?

You do not need to make a final decision straight away. Please contact us by:

- **E-mail: info@ovg.ox.ac.uk**
- **Telephone: 01865 611400**
- **Website: https://www.ovg.ox.ac.uk/recruiting-studies**

Members of the research team will be happy to discuss the study with you and answer any questions you may have.

Yours sincerely,



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