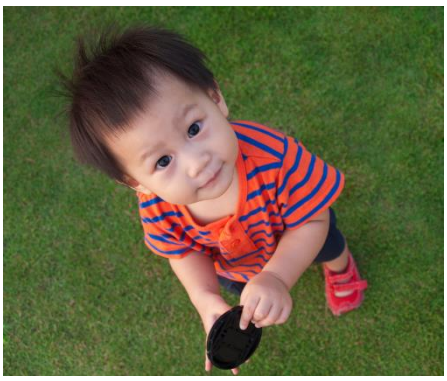
Bristol Vaccine Centre
Tel: 0117 342 0160 / 6in1-study@bristol.ac.uk

The 6-in-1 Part 2 Vaccine Study

Full Title: Heterologous Boosting for Hexavalent Paediatric Vaccines in the UK Schedule



Study Information Booklet

We are inviting 12-month-old children to take part in a study which will guide decisions on future changes to the routine UK immunisation schedule.

Before you decide that you would like your child to take part in this study, it is important for you to understand what the study is about and what participation would it involve. Please take time to read the information carefully and discuss it with others if you wish. If you have any questions, please contact the study team. Thank you for taking the time to consider volunteering for this study.

Contact the local study team at:

Bristol Vaccine Centre

Email : 6in1-study@bristol.ac.uk

Telephone: +44 (0)117 342 0160

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Summary

- This study will evaluate proposed changes to the UK childhood vaccination schedule.
- We aim to enrol up to 572 healthy 12-month-old children. Some of these children would be ex-pre-term (born at <32 weeks gestational age).
- Children will have three study visits, at ages 12, 18 and 19 months and a phone call at about 17 months.
- Children will receive immunisations Bristol Royal Hospital for Children at ages 12 and 18 months. Parents will be asked to fill in a symptom diary after the 18-month vaccination (on the day of vaccination and for the following 28 days).
- All immunisations are with licensed vaccines.
- Children will have two blood samples taken (each of a volume equivalent to about two teaspoons) at ages 18 and 19 months. We will use a local anaesthetic cream to numb the skin for blood tests.
- All children will be offered two optional doses of a licensed vaccine that helps protect against chickenpox.

Contents

Why has my child been invited to take part?

You have been approached as your child is in the age range for this study and lives in one of the study areas. If you have received this invitation through the post, it has been mailed to you by the Child Health Information Service, or another equivalent NHS database. Please note that Bristol Vaccine Centre has not been given your child's name or address.

What is this study about?

One of the vaccines currently given to 12-month-old children in the UK routine immunisation programme, Menitorix, will no longer be available after 2025. Menitorix protects against two bacterial infections, *Haemophilus influenzae* type b (Hib) and group C *meningococcus* (MenC). Both infections can cause serious illnesses in children. The immunisation programme will therefore need to be modified. The Joint Committee on Vaccination and Immunisation (JCVI), the independent expert group which advises on vaccination policy in the UK, has considered various possible options for adapting the current schedule. This study is to evaluate the proposed schedule which is most likely to be adopted.

The JCVI has suggested that a new vaccination timepoint could be included in the routine schedule, when children are 18 months old. Two vaccines would be given at this age:

- a second dose of measles, mumps, rubella (MMR) vaccine
- a booster dose of a "6-in-1" vaccine

At present, the booster dose of MMR vaccine is given before starting school, at the age of about 3 years and 4 months. By giving the MMR booster earlier in life, at 18 months of age, it is hoped that more children would be protected against the highly infectious diseases of measles, mumps and rubella.

An initial course of the 6-in-1 vaccine is already routinely given at 2, 3 and 4 months of age. The vaccine protects against diphtheria, tetanus, poliovirus, whooping cough (pertussis), hepatitis B and *Haemophilus influenzae* b (Hib). It is hoped that a booster dose given at 18 months of age, will increase the protection against these diseases.

There are two licensed 6-in-1 vaccines available, Infanrix hexa and Vaxelis. Both are used for infants in the UK routine immunisation schedule. The components of these two vaccines are not quite identical. At present, it is recommended, where possible, that the same vaccine (either Infanrix hexa or Vaxelis) is used for each of the three doses in the infant course.

If a booster dose is introduced at 18 months of age, it will be valuable to know whether the two vaccines can be "mixed and matched". In other words, if the booster vaccine is different from the vaccine given in the initial course, is the body's immune response as good as if the same vaccine is given for all doses? And is there any difference in unwanted effects? This study will investigate these questions. If either vaccine can be used for the booster, it makes the delivery of the vaccine

programme easier and more flexible; it also ensures that if one of the vaccines becomes unavailable, the other can be used instead.

Additionally, as there is limited information on vaccine responses in ex-premature infants born at less than 32 weeks gestational age, as compared to those born at greater than or equal to 32 weeks, this study will also examine how 6-in-1 vaccine affects ex-premature infants.

The JCVI has also suggested that MenC vaccination is no longer required in the infant schedule in the UK. A successful vaccination programme in teenagers, which has been in place since 2015 in the UK, has led to effective "herd immunity" against MenC (levels of immunity in the population are high enough to ensure that the disease is very unlikely to spread). Serious MenC disease is now exceedingly rare in children and so it is no longer necessary to give MenC vaccine to all infants.

The Hib/MenC vaccine (which is given at age 12 months in the current schedule) will not be given to children in the study. Instead, they will be given two extra vaccinations at 18 months of age, which are not currently routinely offered at this time point: 6-in-1 vaccine and MMR vaccine.

All children taking part will also be offered optional two doses of a vaccine that protects against varicella. Varicella is the virus which causes chickenpox. Previously, varicella vaccination was only offered to children in UK selectively based on clinical risk, and was routinely given in many other countries, including Australia and USA. However, in November 2023, JVCI recommended that two doses of chicken-pox vaccine should be offered to children at 12 and 18 months of age but this has not yet been introduced in the current UK routine childhood schedule.

If your child takes part, you will be asked to record possible expected side effects (symptoms) of the licenced vaccines in a diary for one week (and to record daily temperature measurements for three weeks). Participants will have two blood tests during the study to assess their immune response to the different components of the vaccines.

Can my child take part?

Children must be aged between 12 months and 12 months 42 days when they enrol in the study. They must have received all the recommended vaccines routinely given at 2, 3 and 4 months of age (completed before 6 months of age), including three doses of either Infanrix hexa or Vaxelis 6-in-1 vaccine. Children who have already received the vaccines scheduled for age 12 months cannot enrol in the study. Children who have received extra vaccinations, in addition to those routinely given, may not be eligible to take part.

Children with some medical conditions are not able to take part. These include impaired immunity and severe allergic reactions to certain chemicals (including latex and gelatine); other serious conditions may also preclude participation.

What happens in the study?

This study involves three study visits and a phone call over approximately 7 months. All study visits will be conducted Bristol Royal Hospital for Children at Upper Maudlin Street, BS2 8BJ.

The study includes:

- Immunisations at ages 12 and 18 months
- Completion of a symptom diary after the 18-month immunisations (on the day of vaccination and for the following 28 days)
- Two blood samples, taken at ages 18 and 19 months
- A phone call at around 17 months of age to confirm the visit at 18 months and check whether you child is still eligible to participate in the study

Please note that children taking part in the study will not receive the Hib/MenC vaccine, which currently is routinely given at age 12 months.

If you decide you might like to take part in the study, our study team are available to answer your questions and make an appointment to see you and your child.

During the first visit, the study team will discuss the study with you and answer your questions. If you decide to participate in the study, and your child is eligible to do so, we will ask you to complete a consent form.

What happens at each study visit is summarised in the following table, and then described in more detail.

Table to show what will happen in the study

	Visit 1	Visit 2*	Visit 3
Age	12 months	18 months	19 months
What happens at this visit?			
Vaccines given	PCV13 MenB MMR (Var)	Hex-I **or** Hex-V MMR (Var)	

 Blood test

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Vaccinations

PCV13: Pneumococcal vaccine (Prevenar 13)
MenB: Group B meningococcal vaccine (Bexsero)
MMR: Measles, mumps, rubella vaccine (M-M-RvaxPro or Priorix)
Var: Varicella (chickenpox) vaccine (Varivax or Varirix). This is OPTIONAL.
Hex-I: Infanrix hexa
Hex-V: Vaxelis

* Before Visit 2, you will receive a phone call from the study team to confirm your appointment date, confirm that you are still willing and able to continue in the study.

Visit 1

At the **first study visit**, we will ask you some questions about your child's medical history, including previous vaccinations and medication. We will record details such as date of birth. If necessary, a study doctor or nurse may examine your child. We will check your child's temperature and ensure that they are fit to receive their vaccinations. In some situations, it is necessary to delay vaccination, for example if your child has:

- a fever (under arm temperature of ≥38.0°C) in the previous 24 hours
- received any live vaccine (e.g. against yellow fever or chickenpox) in the previous 4 weeks or any other vaccine in the previous 2 weeks
- planned elective surgery, admission to hospital or any other procedure that may require a general anaesthetic (within 7 days of being vaccinated)
- had a Tuberculosis (TB) skin test which has not been read

If your child is well, we will give three vaccinations at the first visit: Pneumococcal vaccine (Prevenar 13), group B meningococcal vaccine (Bexsero), and MMR vaccine (M-M-RvaxPro or Priorix). These three vaccines are given routinely at this time point in the routine UK immunisation schedule. If you wish, we will also give a vaccine against chickenpox (Varivax or Varilrix).

Phone call and randomisation

Before your second visit, we will contact you to confirm the visit, and that you are still willing to proceed with the study, and to check again your child's eligibility. We will then determine which 6-in-1 vaccine (Infanrix hexa or Vaxelis) your child will receive for their booster dose at their second visit. This is decided by chance, by a process called randomization, which is like tossing a coin. There is an equal (50%) chance of being allocated to receive either vaccine. Neither you nor the study team will be able to influence this. Initially, we will not tell you which vaccine your child has been allocated to receive. This is to ensure that completion of the symptom diary is unbiased. You will be told at the third study visit which 6-in-1 vaccine your child was given. Each participant will be assigned to one of

four groups (see the table above), determined by whether they received Infanrix hexa or Vaxelis 6-in-1 vaccine for their infant course, and whether they are randomized to receive the same vaccine or the alternative for their booster dose.

Visit 2

At the **second visit**, we will enquire about any medical problems since the first visit. We will again check that your child is well enough to be vaccinated.

Your child will have a blood sample taken to assess their immune response. We use an anaesthetic cream to help numb the skin. Taking blood from children can sometimes be difficult and it is important to us that your child is not unduly upset by the process. If necessary, we may ask to make a second attempt. We might also ask you to take blood using finger or heel prick, or re-schedule the appointment to attempt to obtain a sample another day (in which case the Visit 2 vaccinations would be deferred until the new appointment); this would be your decision. We will take a maximum of 10 ml of blood (about 2 teaspoons) for each sample.

Your child will then be given two vaccinations: the 6-in-1 vaccine (either Infanrix hexa or Vaxelis, as allocated by the randomization) and MMR (measles, mumps, rubella) vaccine. If you wish, we will also give a vaccine against chickenpox.

We will provide you with access to an electronic diary to record any symptoms your child may have in the 7 days after their Visit 2 vaccinations, including the day of the vaccination. A paper version of the diary may be provided as a back-up. We will explain how to complete this diary. We will give you a thermometer to record your child's temperature and ask you to record this daily for 21 days after the Visit 2 vaccinations, including the day of the vaccination. We will ask you to record any medications given to your child.

Visit 3

At the **third visit**, at 19 months of age, we will enquire about any medical problems since the previous visit and take a blood test (maximum of 10 ml), as described above.

Study staff will observe your child for 15 minutes after each vaccination.

Whilst you child is in the study, you will have 24-hour telephone access to a study doctor or nurse, should you have any concerns.
You will be asked to contact the study team if your child is admitted to hospital at any point during the study.

Do I have to take part?

No, taking part in research is voluntary. If you decide you would like your child to take part in the study and later you change your mind, you can withdraw them from the study at any time. You don't have to give a reason. If you withdraw from the study, no further data will be collected and we will keep your child's samples, unless you request that they are destroyed. We may offer follow up checks to children who withdraw from the study, if there are any concerns about their health.
Your child's routine care would still be available if your child does not participate in the study, or if they withdraw from the study.

What are the benefits of taking part?

By taking part in this study, your child will receive some of their routine vaccinations at the Bristol Royal Hospital For Children at Upper Maudlin Street, BS2 8BJ. If a study visit is carried out at a location other than your home, you will be offered £25 reimbursement per attended visit for your travel expenses. No reimbursement will be offered for the phone call at about 17 months of age.

Your child will be offered two optional doses of a vaccine which helps to prevent chickenpox. This vaccine is not routinely offered in the UK. Chickenpox is a very common, highly infectious condition, most often occurring in children. The symptoms include fever and a very itchy rash. It usually lasts for about a week. Minor scarring is a common consequence. More rarely, it can cause complications such as pneumonia, arthritis, meningitis and encephalitis (inflammation of the brain). A single dose of a varicella vaccine provides around 80% protection against chickenpox (and almost 100% protection against severe disease requiring hospitalisation). You can agree to one or two doses of chickenpox vaccine, or decide for your child to receive none. The chickenpox vaccine is completely optional, and your choice would not affect your child's participation in the study.

Participants in the study will receive their booster dose of an MMR vaccine at age 18 months instead of at 40 months; this may result in increased protection against measles, mumps and rubella from an earlier age. Similarly, by receiving the 6-in-1 vaccine at age 18 months, participants may gain increased immunity against tetanus, diphtheria, pertussis, polio and hepatitis B.

What are the potential risks of taking part?

Vaccines (like any medicine) can sometimes cause side effects. The most common side effects reported from the vaccines given in this study are irritability, crying, fatigue, fever, reduced appetite, vomiting and redness/swelling and pain at the site of injection. The MMR vaccine can rarely cause a febrile convulsion (a fit precipitated by high temperature), typically 7 to 10 days after vaccination. The majority of children who have a febrile convulsion never have another fit. A severe allergic reaction (anaphylaxis) after vaccination is extremely rare (with a risk of less than one in a million). The study nurses and doctors are trained and equipped to treat anaphylaxis; they will observe your child for 15 minutes after vaccination.

The varicella vaccine contains a weakened, live virus. In rare circumstances, it is possible to catch chickenpox, including severe chickenpox, from a person who has been vaccinated with varicella vaccine. This may occur in people who have not previously been vaccinated or had chickenpox, as well as people who fall into one of the following categories:

- Individuals with a weakened immune system.
- Pregnant women who have never had chickenpox
- Newborn babies whose mothers have never had chickenpox

Whenever possible, individuals who have been vaccinated with varicella vaccine should attempt to avoid close contact, for up to 6 weeks following the vaccination, with anyone who falls into one of the categories above.

Omitting the Hib/MenC vaccine at age 12 months (which your child would receive as part of the UK vaccination schedule if they do not take part in this study) might potentially increase the risk of disease from Hib or MenC. Similarly, giving the Hib vaccine booster (as part of the 6-in-1 vaccine) at age 18 months, may not provide the same level of protection against Hib as the existing schedule. However, in the view of the Joint Committee on Vaccination and Immunisation (JCVI), the risk of either of these diseases is extremely low, because of very good herd immunity in the UK.

Blood sampling may cause temporary bruising or tenderness.

Who is organising this study?

The study is sponsored by the University of Oxford. The study is being coordinated by the Bristol Vaccine Centre, including scientists, doctors, nurses, who investigate infectious diseases and vaccines. The study will be also carried out at several other sites across the UK.

Funding has been received from MCM Vaccine, the manufacturer of Vaxelis. The funder will have no influence on study decisions or the results from the study.

What will happen to the samples obtained in the study?

Samples will be processed at Bristol Royal Hospital for Children and stored at Microbiology & Molecular Laboratories and sent to other laboratories in the UK and Europe for analysis. Samples will be labelled with a number, not your child's name. No genetic analysis will be undertaken for this study. However, we may also ask you whether part of the samples, remaining after the study tests have been done, may be stored in the Oxford Vaccine Group library of samples ("Biobank"). If you agree to this, we will provide you with the relevant information booklet and ask you to sign a separate consent form. If you decide to consent to Biobank, then storing samples for genetic analysis is an option. Otherwise your left-over samples will be destroyed after the end of the study. You can opt out of having samples stored in the Biobank and still take part in the study.

What will happen to the information collected in the study?

An online screening questionnaire is used to determine your child's eligibility. For those participants who proceed to take part in the study, the data from the screening questionnaire will be kept with their study records. For those who do not proceed to participate in the study, all answers from the screening questionnaire will be kept until the end of the study recruitment period and then will be deleted.

Your child will be given a study number, which will be used on study paperwork and all samples. Any paper notes will be held securely at the study site. With your permission, we may need to obtain information from your child's medical records to confirm medical history or vaccinations received. We will inform your child's GP practice that your child is taking part in the study and that we will be giving some of the routine vaccinations. We may ask you and/ or your GP for your health visitor contact details, so that we could contact them prior to the first study visit. The services responsible for recording all childhood vaccines given in the UK will be informed of the vaccines your child has received in this study.

General Data Protection Regulation (GDPR) requires that we state the legal basis for processing information about you. Medical research is regarded as "a task in the public interest". The University of Oxford is the 'data controller' and is responsible for looking after your information and using it properly. We will be using information from you and your child's medical records in order to undertake this study.

We will use as little personally identifiable information as possible. We will store the anonymised research data and any research documents with personal information, such as consent forms, securely for up to 25 years after the end of the study, or as per national regulatory requirements. Your email address is required for the electronic diaries, in order for them to function. Only site research staff and sponsor data managers will have access to view your email address and you will need to consent to this. It will not be possible to identify your child in any publication or report.

You may be required to provide you bank details at the first study visit for travel and parking reimbursement purposes, if you attend a visit at a location different from your home. Bank details are kept confidential and will be stored for the duration of the study in line with local site policy. Personal information such as your name and bank details may be shared with the University finance team to process or verify your reimbursement payments. Financial auditors may also audit the records where this information is held. All confidential data will be stored according to the GDPR.

The Bristol Vaccine Centre will use your and your child's name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your child's care, and to oversee the quality of the study. Individuals from the Bristol Vaccine Centre and regulatory organisation may look at your child's medical and research records to check the

accuracy of the research study. The only people in the Bristol Vaccine Centre or University of Oxford who will have access to information that identifies you and your child will be people who need to contact you about the study, or the care of your child, or to monitor/audit the data collection process. The people who analyse the information collected and the samples will not be able to identify your child and will not be able to find out your child's name or your contact details. If you withdraw from the study, we will keep the information about your child that we have already obtained, including blood samples and symptom diary data, but if you prefer you can request for the samples to be destroyed (they may already have been analysed). We may contact you about future studies if you have indicated this on the consent form.

We will keep your contact details confidentially to inform you about the results of the research. Once the research has been published, we will only keep your child's date of birth and name, to allow us to identify your child should you make an enquiry about the study. Files will be confidentially destroyed when storage is no longer required.

Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited so that the research is reliable and accurate. You can find out more about how we use your information by contacting the Bristol Vaccine Centre either by telephone +44 (0)117 342 0160 or by emailing 6in1-study@bristol.ac.uk.

Further information about your rights with respect to your personal data is available at https://compliance.web.ox.ac.uk/individual-rights. Contact details of the sponsor's data protection office: The Information Compliance Team, University of Oxford, Wellington Square Oxford OX1 2JD; data.protection@admin.ox.ac.uk.

What happens at the end of the study?

Final and interim results of this study will be shared with the Joint Committee on Vaccination and Immunisation (JCVI) to facilitate their review of the potential changes to the UK national immunisation schedule.

Also, we will inform your GP practice when you complete (or withdraw from) the study. We will provide the published data on our website; a summary of this will be sent to you with a link, to enable you to access the full information.

Who has reviewed this research study?

A Research Ethics Committee must approve all research studies of this sort. This project has been approved by Research Ethics Committee East of England - Cambridge South Research Ethics

Committee (REC reference: 23/EE/0121). The Oxford Vaccine Centre Patient and Public Involvement group has reviewed the main participant-facing documents associated with this study (study information booklet, consent form, lay summary, invitation letter and advertising materials).

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 this study, you should contact your local study team at at +44 (0)117 342 0160 or 6in1-study@bristol.ac.uk**.** You may also contact the University of Oxford RGEA (Research Governance and Ethics Assurance) at RGEA.Sponsor@admin.ox.ac.uk. The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that your child suffers any harm as a direct consequence of their participation in this trial. NHS indemnity operates in respect of the clinical treatment which is provided.

The Patient Advisory Liaison Service (PALS) is a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient. PALS is unable to provide information about this research study.
If you wish to contact the PALS team please contact PSCT@uhbw.nhs.uk or call 0117 342 1050.

In summary, what would happen if I would like my child to take part in the study?

- We would make an appointment to see you and your child at the Bristol Royal Hospital for Children at Upper Maudlin Street, Bristol BS2 8BJ.
- At this visit we would discuss the study with you and answer any questions.
- If you are happy to participate in the study, we would ask you to sign a consent form.

What should I do now if I am interested in taking part?

You do not need to make a final decision straight away. If you decide for your child to take part in this study or have any questions, you can:

- Contact the research team by the phone number or e-mail address given below.
- Contact the research team by the phone number or e-mail address given below.
- Complete the online screening questionnaire HERE.

If your response reaches us after the study has finished recruitment, we will let you know.
A postcard reminder may be posted to you by the Child Health Information Service, or another equivalent NHS database, as described above. If we do not hear from you after this, we will assume that you do not want to take part.

Thank you for taking the time to read this information sheet and for considering taking part in this study.

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