Study Title: Sero-epidemiological survey of England in 2019/2020

Internal Reference Number / Short title: OVG 2019/01. What’s the STORY? (Serum Testing Of Representative Youngsters)

Ethics Ref: 19/LO/1040

IRAS Project ID: 263097

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Conflicts of Interest

Professor’s Snape and Faust act, on behalf of their employing institutions, as Chief and/or Principal Investigators on research studies funded and/or sponsored by vaccine manufacturers including Novavax, Glaxosmithkline, Sanofi-Pasteur, Medimmune and Janssen. These investigators receive no personal financial benefit for this work.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

Protocol signature page

The undersigned has read and understood the research study protocol detailed above and agrees to conduct the research study in compliance with the protocol.

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Signature</th>
<th>Site name or ID number</th>
<th>Date</th>
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1. KEY CONTACTS

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| Funder(s)         | National Institute for Health Research (NIHR) |
| Clinical Trials Unit | Oxford Primary Care Vaccine Collaborative Clinical Trials Unit |
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2. LAY SUMMARY

Public Health England has an ongoing sero-prevalence programme to assess how well the population is protected from vaccine preventable and emerging infectious diseases. The current way to check this is by testing left over blood samples from participating healthcare laboratories around the country. However, these samples may not be representative of the general population, particularly in younger age groups who are often most at risk from vaccine preventable diseases.

In the Netherlands, they use a different system to assess how well the population is protected from vaccine preventable diseases, actively collecting blood samples from a representative cross section of society. This type of approach would address the limitations of using residual serum samples and allows the collection of additional relevant history e.g. number of family members and previous vaccines received.

Having a large number of blood samples from a range of age groups is also useful when gathering information about an emerging disease such as the current novel coronavirus (COVID-19). These samples can help provide answers regarding the true number of infections in the population. This allows us to work out the severity of the infection on a population basis.

We are therefore proposing a pilot study to assess the feasibility of establishing a national sero-epidemiological survey in England in individuals aged 0 – 24 years. We will be focusing initially on
Diphtheria and Group C invasive meningococcal disease, both of which are vaccine preventable. This will involve collecting a blood sample from 2300 participants in the study from different geographical and socioeconomic backgrounds across our test sites.

3. SYNOPSIS

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Sero-epidemiological Study of Vaccine Preventable Diseases in England</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal ref. no. / short title</td>
<td>2019/01. What’s the STORY</td>
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<tr>
<td>Study registration</td>
<td>NCT04061382</td>
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<td>Sponsor</td>
<td>University of Oxford</td>
</tr>
<tr>
<td>Funder</td>
<td>National Institute for Health Research (NIHR)</td>
</tr>
<tr>
<td>Study Design</td>
<td>Prospective, cross-sectional sero-prevalence study</td>
</tr>
<tr>
<td>Study Participants</td>
<td>Individuals living in England aged 0–24 years</td>
</tr>
<tr>
<td>Sample Size</td>
<td>A total sample size of 2300 will be used across all study sites, comprising of 100 in each age band with 12 month age bands from 0–&lt;22 years and a 36 month age band from 22–&lt;25 years.</td>
</tr>
<tr>
<td>Planned Study Period</td>
<td>June 2019 – December 2020 (with potential to extend if required for the COVID-19 outbreak)</td>
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<tr>
<td>Planned Recruitment period</td>
<td>Beginning of July 2019 – December 2020 (with potential to extend if required for the COVID-19 outbreak)</td>
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</table>

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>1. To evaluate the feasibility and added public health benefit of a UK, population based sero-epidemiological programme in 0 to 24 year olds</td>
</tr>
<tr>
<td></td>
<td>• Representativeness of participants sampled, in terms of the local population’s ethnicity, community identity, migrant population and socioeconomic background</td>
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<tr>
<td></td>
<td>• Comparison with serological markers of immunity for vaccine preventable diseases as measured in an age matched cohort in current residual sera programme</td>
</tr>
<tr>
<td>Secondary</td>
<td>1. To evaluate the effectiveness of recruitment methods employed</td>
</tr>
<tr>
<td></td>
<td>• Recruitment rate per month, recruitment rates as percentage of potential participants contacted,</td>
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<tr>
<td></td>
<td>• cost per sample obtained of ‘disease specific correlates of protection/markers of immunity, e.g. Anti-Diphtheria Toxoid IgG concentrations and capsular Group C meningococcal Serum</td>
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<td>2. To assess, in relevant age groups, immunity against infections and vaccine preventable diseases including, but not limited to diphtheria and group C meningococcus and novel coronavirus (COVID-19)</td>
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</table>
3. To develop a store of sera from a representative section of 0 to 24 year olds available for future testing of immunity against other infectious diseases of relevance to UK immunisation schedule and public health.

4. ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CI</td>
<td>Chief Investigator</td>
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<tr>
<td>CCVTM</td>
<td>Centre for Clinical Vaccinology and Tropical Medicine (CCVTM)</td>
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<tr>
<td>CDM</td>
<td>Clinical Data Management</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CHIS</td>
<td>Child Health Immunisation Service</td>
</tr>
<tr>
<td>COVID-19</td>
<td>Coronavirus Disease 2019 (also known as 2019-nCoV)</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
</tr>
<tr>
<td>CTRG</td>
<td>Clinical Trials &amp; Research Governance, University of Oxford</td>
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<tr>
<td>EDC</td>
<td>Electronic Data Capture</td>
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<tr>
<td>ESEN</td>
<td>European Sero-epidemiology Network</td>
</tr>
<tr>
<td>ESPGHAN</td>
<td>European Society for Paediatric Gastroenterology Hepatology and Nutrition</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GDPR</td>
<td>General Data Protection Regulation</td>
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<tr>
<td>GMT</td>
<td>Geometric mean titre</td>
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<td>GP</td>
<td>General Practitioner</td>
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<td>HRA</td>
<td>Health Research Authority</td>
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<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
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<tr>
<td>IMD</td>
<td>Index of Multiple Deprivation</td>
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<td>IRAS</td>
<td>Integrated Research Application</td>
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bactericidal activity (SBA) titres’
- IgG to COVID-19 spike protein
- A collection of anonymised sera from participants with appropriate consent and known demographic details and immunisation history’
5. BACKGROUND AND RATIONALE

Public Health England has an ongoing sero-prevalence programme to assess population level immunity using residual serum samples from participating laboratories. However these samples may not be representative of the general population particularly in younger age groups. National sero-epidemiological surveys have successfully taken place in the Netherlands, which consist of a prospective collection of serum samples from a representative cross section of society to assess population level immunity. This type of approach would address the limitations of using residual serum samples, and would potentially allow assessment of a number of diseases.

We are therefore proposing a pilot study to assess the feasibility of establishing a national sero-epidemiological survey in England in individuals aged 0 – 24 years, focussing initially on COVID-19, diphtheria and Group C invasive meningococcal disease. Specifically, we wish to assess the population level immunity to diphtheria following the pre-school booster vaccine in children aged between 3 and 14 years, and the immunity to Men C in individuals aged 12 – 24 years who may have received either the adolescent Men C or Men ACWY vaccine, or did not receive either of these vaccines. Furthermore, in response to the potential outbreak of COVID-19 these samples will be used to look for any increase in sero-positivity to COVID-19 in UK children +/- young adults through 2020 (and beyond if necessary) as a marker of infection with this novel coronavirus.

Previous seroprevalence studies

Seroprevalence studies using residual sera

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PHE has been utilising residual serum samples from participating laboratories across the country as part of its ongoing seroprevalence programme for many years. These samples are used as a serum bank for investigating population immunity to a range of infections including vaccine preventable infections.

These samples have been previously used to assess the population immunity for diphtheria with the last study undertaken using samples collected in 2009 ([5], Box 1), whilst a number of seroprevalence studies have been undertaken at different times to study Men C population immunity. The most recent sampling was undertaken in 2014 (Box 2) when the teenage MCC vaccination programme was newly introduced.

Box 1. Wagner et al (2012) Immunity to tetanus and diphtheria in the UK in 2009

In this study, 150 residual sera were tested in each age group, in order to estimate the proportion of the population protected to within ± 8% with 95% confidence. It found that:

- 75% of the UK population had antitoxin levels ≥0.01IU/mL correlating to basic diphtheria protection
- 41% had antitoxin levels ≥0.1IU/mL correlating to full diphtheria protection
- Between ages 1 and 9 years, the proportion with antitoxin levels correlating to full protection remained stable (65%-71%)
- Thereafter, the proportion with antitoxin levels correlating to full protection declined to a low of 44% amongst those aged 10-11 years.
- The proportion with antitoxin levels ≥0.01IU/mL increased again for teenagers and young adults, before declining in older adults.
- The highest number of susceptibles with antitoxin levels < 0.01IU/mL were observed in the age groups <1 year (37%), 35-44 years (27%), 45-69 years (41%) and 70+ years (33%).

Figure 1: Diphtheria antitoxin distribution by age group in England, 2009. Error bars indicate 95% confidence intervals for full protection (Fig 5 from Wagner et al. (2012))
Box 2. Seroprotection against serogroup C meningococci measured by proportions with serum bactericidal antibody (SBA) titres of ≥8. Comparison of levels in 2014 with the previous surveys conducted prior to MCC vaccine introduction in 1996-1999 and following introduction in 2000-2004 and 2009. Source: Findlow, H et al. accepted for publication, Eurosurveillance

Disadvantages of residual seroprevalence studies

1. Samples may not be representative of the whole population. Previous review of the source of these samples have shown considerable variation by age e.g. paediatric samples from immunocompromised children and samples for adults sourced from those attending Genito-Urinary Medicine clinics.

2. Generally, the number of samples obtained from children is low and thus unlikely to be sufficient for stratification by individual age bands and region, which are particularly relevant to evaluate childhood vaccine programme for specific antigens.

3. Individual vaccination histories are not available but are derived from vaccination programmes and known coverage at a population level.

National seroprevalence study in the Netherlands

In 2006 / 2007, a large serum bank was established in the Netherlands by means of a cross-sectional population based study (6). A similar serum bank was collected in 1995 / 1996 (7).
Dutch inhabitants (aged 0 – 79 years), identified from the national population register, were invited to participate from 40 municipalities throughout the country. Oversampling took place in areas with low vaccine coverage and migrant populations.

Over 17 000 individuals were invited to participate. Individuals received a letter of invitation together with a brochure containing information on the study, a questionnaire, an informed consent form, and a prescheduled appointment form for blood donation at a local clinic. Participants were offered a gift voucher.

Overall, a 32% response rate was achieved (6386 serum samples). The highest response rate was in women aged 10–49 and aged 50–79 with a response rate of 38%. A response rate of 27% and 26% was seen in male and female children aged 0-9 respectively.

In the first study in 1995 / 1996 – an overall response rate of 50% was achieved. It was suggested that the response rate fell in the second study because the distance to travel to the clinic was much further compared to the first study.

Use of seroprevalence studies in pandemics

In a worldwide pandemic, such as the current novel coronavirus (COVID-19) outbreak, residual samples are used to help determine the true number of infections by detecting asymptomatic and mild infections. This will enable us to more accurately describe the severity of infection across the population. The timing of this study allows us to use the serological library alongside the residual sample method which is already being used in the COVID-19 response. This is important as the study will gather samples from healthy children who are not well represented in the residual sample model and this information will be used to evaluate the public health benefit of running a sero-epidemiological programme.

6. OBJECTIVES AND OUTCOME MEASURES

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<td>• Comparison with serological markers of immunity for vaccine preventable diseases as measured in an age matched cohort in current residual sera programme</td>
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| Secondary Objectives          | Recruitment rate per month, recruitment rates as percentage of potential participants contacted, |
|-------------------------------|• Cost per sample obtained of ‘disease specific correlates of protection/markers of immunity, e.g. Anti-Diphtheria Toxoid IgG |
| 1. To evaluate the effectiveness of recruitment methods employed | |
| 2. To assess, in relevant age groups, immunity against infections and vaccine preventable diseases including, | |
but not limited to diphtheria, group C meningococcus and novel coronavirus (COVID-19)

3. To develop a store of sera from a representative section of 0 to 24 year olds available for future testing of immunity against other infectious diseases of relevance to the UK immunisation schedule and public health.

concentrations and capsular Group C meningococcal Serum bactericidal activity (SBA) titres’
• IgG to COVID-19 spike protein

A collection of anonymised sera from participants with appropriate consent and known demographic details and immunisation history’

7. STUDY DESIGN

7.1. Study design
Cross-sectional sero-prevalence study

7.2. Inclusion criteria
Individuals living in England aged 0 – 24 years.

7.3. Study Sites
The study sites will be:

- University of Oxford
- Sheffield Children’s Hospital NHS trust
- Bradford Teaching Hospitals NHS Foundation Trust
- Leeds teaching Hospitals NHS trust
- University Hospitals Bristol NHS Foundation Trust
- University of Southampton NHS Foundation trust
- Royal Manchester Children’s Hospital – Manchester University NHS trust
- St George’s University Hospitals NHS Trust

7.4. Identification of individuals
Refer to section 9.1

7.5. Sample Size
A total of 2300 blood samples will be collected across all study sites, comprising of 100 in each age band with 12 month age bands from 0-<22 years and a 36 month age band from 22-<25 years.

7.6. Collection of samples
Serum samples will be collected in specially designated clinics. This approach may be adapted to suit different age groups depending on local needs. For example, home visits may increase the response rate for preschool children, whilst specially designated clinics run during school holiday periods or weekends may be appropriate for school aged children.

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7.7. **Questionnaire & Vaccination History**

Basic demographic characteristics will be collected by questionnaire and/or case report form (CRF) and will include: DOB, gender, GP details, ethnic group, association with communities of special interest (e.g. faith communities) household income, vaccination history and history of recent respiratory or coronavirus infections.

Vaccination history will be verified during serum sample collection using the Red Book or other vaccination records, or checking with the general practitioner or the Child Health Immunisation Service (CHIS) database. Where possible this will include batch information for diphtheria pre-school booster to determine which specific product was received.

Contemporaneous vaccination history can also be obtained from CHIS for children aged 0 –5 years, and historical vaccination history can be obtained via GP records in participants aged 2 – 24 years. It is however acknowledged that the quality and completeness of vaccination history in GP records varies from practice to practice, particularly in older age groups that may have been vaccinated at a different practice or at school.

7.8. **Compensation**

Participants will be offered a £20 voucher as reimbursement for travelling to the study clinic. If they are seen at home there will be no reimbursement. Based on the average EU income levels, the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) suggest that an incentive of up to the value of 30 Euros is considered acceptable for children and adolescents, and may be offered as cash, vouchers or gifts or toys (9). Other studies in adolescent age groups in the UK have had approval to use £10 book vouchers, and incentives such as these, or age appropriate gifts or toys would be preferable to cash for recruiting adolescents and younger children.

7.9. **Comparison with Residual Serum Samples**

Data collected in this study will be compared with that obtained in the anonymised residual serum samples collected in 2019 from individuals aged 0 – 24 years by the PHE seroepidemiology unit from participating laboratories across the UK. These will be used as the basis of comparisons between immune responses measured through residual sample testing and through the active sample collection outlined in this protocol. The age, sex and year of collection will be known via a unique identity number: immunisation status will not be known.

In 2017, 3290 samples were collected in individuals aged 0 – 24. It is envisaged that a similar sample size will be collected in 2019, and that testing of the residual sera can take place in 2020.

8. **PARTICIPANT IDENTIFICATION**

8.1. **Study Participants**

Individuals living in England aged 0– 24 years.

8.2. **Inclusion Criteria**

For recruitment to all study groups, participants MUST FULFILL each of the below criterion:
• Parents/legal guardians or adult participant* is willing and able to give informed consent for participation in the study.

• Male or Female, aged 0 - 24 years inclusive.

• Parents/legal guardians or adult participants are willing to allow their General Practitioner or relevant NHS databases to be contacted for a full immunisation history

* For the purposes of this study an adult will be defined as all those 16 years of age or over.

8.3. Exclusion Criteria
The participant may not enter the study if ANY of the following apply:

• If participants do not live in the postcode districts selected by PHE

• Participants who have a member of their household already enrolled in the study where their ages are less than 5 years apart.

• Any significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the research study, or may influence the result of the research study, or the participant’s ability to participate in the research study. Examples of disorders or diseases which would be excluded include
  o Medically diagnosed bleeding disorder
  o Medically diagnosed platelet disorder
  o Anticoagulant medication
  o Pregnancy

9. PROTOCOL PROCEDURES

9.1. Recruitment
The recruitment plan below aims to recruit a representative sample of the region. Potential participants will be contacted by mailing out invitation letters with study information booklets to the parents/legal guardians of age appropriate children via the NHS England Databases, the Child Health Information Service or through the Clinical Research Network. There may also be other promotion such as website based advertising, social media, contacting families registered with a study site research database and poster advertisements. Dissemination of the study information booklets, including at GP practices and with health visitors may also be employed. The participant information will be available on websites if available and recruitment material can direct potential participants to this. Participants interested in taking part will contact sites to arrange visits. In the first stage recruitment will be capped (e.g. at 10 per age group per region) to allow for corrections if the initial sample is not representative of the region.

We are aiming to ensure that the sample is broadly representative of the region according to IMD (Index of multiple deprivation scores). Other details collected in the questionnaire such as ethnicity, community identity and FASiii are for later analysis.

We are mailing out using NHS England Databases with the expectation that 5-10% of those contacted will respond. There will be a two or three stage approach to recruitment, we expect to recruit approximately 60% of participants in the first instance allowing for subsequent corrections.

Recruitment plan
1. PHE will be generating a list of all postcodes in recruiting regions and determining the quintiles of IMD (index of multiple deprivation scores) within that region.

2. All sites to email us postcodes in their catchment areas (i.e. areas from which they can recruit). They will also indicate whether they are rural or urban areas. There is a recognition that there is no formal definition of these terms, and many post codes will be mixed, but this is an area where local knowledge could be applied.

3. For each region (i.e. Bristol, Yorkshire and Humber, Southampton etc.) PHE will randomly select 5-7 postcode districts stratified to match the ratio of rural to urban postcode districts to the region’s urban/rural population distribution. A postcode district is the first two letters and number e.g.

<table>
<thead>
<tr>
<th>Area</th>
<th>District</th>
<th>Sector</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>OX</td>
<td>3</td>
<td>7</td>
<td>LE</td>
</tr>
</tbody>
</table>

4. OVG will coordinate a mail out through NHS England Databases to each age band to the selected postcode districts.

5. We will aim to recruit ~60% of participants in the first recruitment stage, and in each region recruitment will be reviewed when this figure is reached. This means approximately 10 participants in each age group.

6. This will allow us to review the postcode unit of the participants recruited to see if we are achieving a representative sample (i.e. does the quintile distribution match those of the region). Subsequent recruitment can then be amended to focus on under-recruiting IMD quintiles, e.g. by selectively recruiting from these postcode sectors for those that have already responded to the first mail out, or increased mailouts to selected post codes in a second (or third) mail out.

7. To help manage recruitment, the first mail out will randomly select a sub-population within each selected postcode district and age band using birth date (e.g. 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd}, 4\textsuperscript{th} of the month). As an example, if expecting a recruitment rate of 10%, approximately 100 potential participants will be mailed to within each age band across the selected post code districts.

8. Given the potential that some age cohorts might be over-prescribed, sites will make an effort to ensure they cover the whole of their selected region in a representative manner, not just those that are most convenient.

9. It will be made clear in the participant information that participants (and/or their families) may not hear from us immediately, as the aim is to achieve a representative sample for that region. Therefore, every participant that contacts us from the first mail out can go into a study database containing basic contact details and age. This can be searched to see if any of the participants are from quintiles that are under-represented in the sample.

Timings of mail outs will be adjusted for sites dependent on their own local recruitment rates.
Those parents/legal guardians that indicate that they do not want to take part in the study and/or receive further communication about the study will not be included in any subsequent contact lists.

For non-responders, postcode and therefore deprivation level (according to Index of Multiple Deprivation) could potentially be estimated. Alternatively, a non-responder questionnaire, with basic demographic details could be administered by mail as per the Dutch study, enabling an assessment of potential bias due to non-response.
9.2. Screening and Eligibility Assessment

Given the low risk nature of the study there is no formal requirement for screening prior to the first study visit. However sites may choose to arrange contact with potential participants to discuss the study and a
arrange clinic appointment or visit. This is where exclusion criteria can be checked prior to arranging a visit.

Responses received from postcode districts not selected by PHE will not be eligible. Each postcode district has been selected based on sampling all quintiles of the IMD and to ensure representative data of the region.

To ensure that there is a representative cohort from each age group from each IMD, multiple eligible participants from one household will only be eligible to take part if there are 5 years or greater between their ages.

During the study visit, the participant’s eligibility will be assessed by a member of the study team. A brief medical history will be taken where participants will be asked about current health issues and medications as well as taking a vaccine history and history of respiratory/coronavirus infections from February 2020 onwards. Parents/legal guardians must have given written informed consent prior to an eligibility check being performed if the participant cannot consent for themselves. In these instances where the child is older than 11 years old there will be an assent form to complete.

9.3. Informed Consent
The parent/legal guardian of the participant or the participant themselves if able to consent will personally sign and date the latest approved version of the Informed Consent form.

A written version and verbal explanation of the Study Information leaflet and Informed Consent will be presented to the participant/parent/legal guardian of the participant detailing:

- the exact nature of the study
- what it will involve for the participant
- the implications and constraints of the protocol
- the known side effects and any risks involved in taking part
- sample handling – participants will be informed that anonymised samples taken during the course of study may be shared with study collaborators.

- Individual results will not be shared with participants

It will be clearly stated that the participant is free to withdraw from the research study at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal. Data up until that point will be kept unless the participant states they wish this data to be withdrawn.

The parent/legal guardian of the participant or adult participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written informed consent will then be obtained by means of the adult participant or the parent/legal guardian of the participant dated signature, and dated signature of the person who presented and obtained the Informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator and listed on the delegation log. A copy of the signed informed consent will...
consent will be given to the participant or parent/legal guardian of the participant. The original signed form will be retained at the research study site.

For the purposes of this study it will be assumed that participants over the age of 16 years are able to self-consent, but as with all participants will only be enrolled if the staff member taking consent is confident that the potential participant understands the study and is therefore able to give informed consent.

For the primary and secondary objectives of this research study only the serum is required, which is obtained by centrifugation of whole blood, leaving a residual ‘blood clot’. As an optional item on the consent form we will ask participants if they would consent to donating the blood clot to the biobank at the Oxford Vaccine Group. This would allow for extraction of DNA to interrogate the influence of donor’s genotype on vaccine/infection induced immunity, and other aspects related to the interdependence between genetics and immunity against infectious diseases (see section 9.5).

9.4. Study visit
One study visit will be conducted by research study staff either at the participant’s home, or at convenient and suitable venues.

- Provide explanation of the study to participant or parents/legal guardians.
- Obtain written informed consent from the participant or parents/legal guardians of the participant.
- Appropriately trained staff will perform a thorough check of inclusion and exclusion criteria using recall of relevant medical history and record findings, including:
  - Medical history of relevance to the inclusion/exclusion criteria
  - Details and indications of any prescription medications and vaccines
- If all inclusion and exclusion criteria are met the participant will be considered enrolled into the study.
- Ask participant or parent/guardian (if participant below 16 years of age) to fill in questionnaire which will demographic data.
- Study staff to complete paper source or electronic CRF which will include the participants immunisation history.

Blood sampling will be carried out in line with local SOPs. A local anaesthetic cream or spray will be offered to child participants prior to venepuncture but will be made available to all age groups if required. When a visit has been booked and will take place in the participants home or at a suitable convenient venue, the anaesthetic cream will be sent by post with written instructions for application. If the cream is sent by post, parents will be asked to apply the cream an hour before the appointment. If participants are coming to a clinic then anaesthetic cream will be applied on their arrival after verbal consent. Formal consent processes, medical/vaccine history and the questionnaire can be filled in while the cream is taking effect. If anaesthetic spray is used, this is applied immediately before the procedure to numb the skin. If the initial attempt at venepuncture is not successful verbal consent will be sought for a further attempt at that visit. No more than two attempts will be made in one visit. An additional visit may be rescheduled for another day if no blood is obtained at all. Maximum blood volumes based on 0.8ml/kg in line with guidance given by the European Commission of public health are tabled below in table 1. The weights for each age group are based on the 0.4th centile on the female UK-WHO growth chart.

A participant is only considered enrolled when a blood sample has been taken.

Table 1

<p>| What’s the STORY?; OVG 2019/01; Protocol; REC Ref 19/LO/1040; IRAS 263097; Version 3.0; Dated 21-FEB-2020 |</p>
<table>
<thead>
<tr>
<th>Age</th>
<th>Maximum (target) volume of blood (mls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 months</td>
<td>2ml</td>
</tr>
<tr>
<td>2-6 months</td>
<td>3ml</td>
</tr>
<tr>
<td>6-12 months</td>
<td>5ml</td>
</tr>
<tr>
<td>1-2 years</td>
<td>6ml</td>
</tr>
<tr>
<td>3-7 years</td>
<td>10ml</td>
</tr>
<tr>
<td>8-11 years</td>
<td>15ml</td>
</tr>
<tr>
<td>12-14 years</td>
<td>20ml</td>
</tr>
<tr>
<td>15 -24 years</td>
<td>30ml</td>
</tr>
</tbody>
</table>

The blood samples which are obtained will be centrifuged, separated and frozen at local sites at -80 degrees Celsius. Ideally this will happen within 24 hours but there is a window of up to 72 hours. Up to two 2ml aliquots per participant will be shipped to PHE in batches of up to 500 on dry ice. Residual sera beyond this volume will be shipped to the Oxford Vaccine Group for storage. For participants where consent is obtained for DNA extraction and storage in the Oxford Vaccine Centre biobank residual blood clots will be shipped to the Oxford Vaccine Group for this purpose.

9.5. Laboratory methods

Diphtheria
A multiplexed fluorescent bead assay will be used to quantify IgG antibodies to diphtheria toxoid, based upon previously published methodology (11). For diphtheria, anti-toxin levels < 0.01 IU/mL denote susceptibility, antitoxin levels 0.01 – 0.099 IU/mL provide basic protection, and antitoxin levels ≥ 0.1 IU/mL are fully protective, as per the international standard (12).

Meningococcal C
Serum bactericidal antibody (SBA) assays will be performed against the serogroup C target strain, C11 (phenotype C:16:P1.7-1,1) as previously described (13). The complement source that will be used in the SBA is pooled serum from 3-4 week old rabbits (Pel Freez Biologicals, WI USA). Titres will be expressed as the reciprocal serum dilutions yielding ≥50% killing after 60 min. The lower limit of detection will be a titre of 4. Titres of <4 will be assigned a value of two for geometric mean titre (GMT) analysis. Titres of ≥8 will be considered protective against MenC disease (14).

Novel Coronavirus (COVID-19)
An assay currently under development by Respiratory Virus Unit, Public Health England to measure IgG concentrations specific to COVID-19 spike proteins.

DNA storage
The DNA samples obtained in the course of this study will be added to our existing ‘Biobank’ of stored biological samples to facilitate further research on immunisation, immunity and infectious diseases.

One area of particular interest is the role for host genetics in dictating immune responses, hence the benefit of storing genetic material from study participants. Elucidating the genetic determinants of vaccine or infection induced responses may expand our understanding of vaccine/microbe-host interactions and anticipate an era of ‘predictive vaccinology’.
Previous studies investigating genetic determinates of vaccine/microbe responses have explored a limited number of candidate genes and have not been able to account for the degree of heritability inferred by twin studies. Many genes are likely to play a small but significant part in determining responses to vaccination/infection. We intend to use contemporary genotyping techniques to help elucidate these complex vaccine/microbe-host interactions.

### 9.6. Discontinuation/Withdrawal of participants from research study

The participants have the right to withdraw from the research study at any time. In addition, the Investigator may discontinue a participant from the research study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (e.g. if this becomes apparent during the study visit)
- Significant protocol deviation
- Withdrawal of Consent

Data from participants will continue to be analysed for the study unless the parents/legal guardians or adult participant request this to be withdrawn. Systems are in place to recover stored samples if the participants wish to withdraw their sample.

The reason for withdrawal will be recorded in the CRF.

### 9.7. Definition of the end of research study

The end of study will be defined as the last study visit.

### 10. SAFETY REPORTING

#### 10.1. Reporting Procedures for All Adverse Events

A blood sample is all that is required of participants. No medicinal products will be administered. Given this fact, it is not intended to report non-serious adverse events.

#### 10.2. Reporting Procedures for Serious Adverse Events

A blood sample at a single visit and completion of questionnaire is all that is required of participants. No medicinal products will be administered. Given this fact and the scale of the study we will only report serious adverse events that are the result of the study procedure.

All SAEs must be reported on the Oxford Vaccine Group SAE reporting form to the Chief Investigator or delegate within 24 hours of the Site Study Team becoming aware of the event. The CI or delegate will perform an initial check of the report, request any additional information, and ensure it is forwarded to the Medical Monitor on a weekly basis. It will also be reviewed at the next Research Study Safety Group meeting. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and emailed to CTRG.

The principal Investigator’s opinion will be used to determine if the event was ‘related’ (resulted from administration of any of the research procedures) and/or ‘unexpected’ in relation to those procedures. Reports of related and unexpected SAEs will be submitted to the ethics committee within 15 working days of the Principal Investigator becoming aware of the event, using the NRES report of serious adverse event form (see IRAS/NRES website).
10.3. Criteria for the Termination of the Study
The study does not involve the administration of any medications to participants. It is therefore unlikely that any safety issues would lead to termination of the study.

The investigator has the right to discontinue this study at any time. Recruitment will stop immediately if the study is prematurely terminated.

11. STATISTICS AND ANALYSIS

11.1. Description of the Statistical Methods
A detailed statistical analysis plan will be produced prior to receipt of the data by the Statistician.

Data analysis will include:

Primary Objectives and Outcomes

- Representativeness assessment by comparison to census or other population data on sex, ethnicity, community membership, migrant population, socioeconomic background, vaccination uptake (from PHE Cover data). At a site level representativeness will be to local census data and/or according to characteristics of those who respond to those who do not. Overall representativeness will be compared to national data. This will be done descriptively, and differences assessed by Chi-squared or Fisher’s exact test and multivariable methods as appropriate to adjust for the age distribution.

- A comparison of the proportions protected against diphtheria and Men C using residual and prospectively collected samples. This will be done overall and within broad age groups (see sample size section) with adjustment in a logistic regression analysis for confounding factors such as finer age groups and, if necessary, sex and region.

Secondary Objectives and Outcomes

- Description of recruitment rates (participants recruited per month) and cost per sample obtained. This will be done overall, by site and by method of survey.

- Description of response rates (proportion invited that respond and the proportion that respond that are recruited and bled). This will be overall and by site and survey method as well as by age group. Proportions will be calculated with 95% confidence intervals. A more detailed analysis of response rates will be done by post-code and other demographics collected from the non-response survey.

- For prospectively collected samples where vaccination history is known in children aged between 3 and 14 years, the proportion of individuals within each age band that have antibodies to diphtheria antitoxin ≥0.01IU/mL and antibodies to diphtheria antitoxin ≥0.1IU/mL, and whether levels of diphtheria antitoxin are associated with the brand of diphtheria pre-school booster administered. Trends by age and differences by vaccination status will be assessed by Chi-squared or Fisher’s exact test as well as by using logistic regression. Comparisons by geometric mean titres will also be done by t-tests or Kruskal Wallis as appropriate and by plotting geometric means with 95% confidence intervals by age groups.
For prospectively collected samples where vaccination history is known, in individuals aged 12 - 24 years, the proportion of individuals within each age band that have serum bactericidal titres of ≥8 to group C meningococcal disease, and whether SBA titres are associated with adolescent Men ACWY or MCC vaccine or not having received vaccine. Trends by age and differences by vaccination status will be assessed by Chi-squared of Fisher's exact test as well as by using logistic regression. Comparisons by geometric mean titres will also be done by t-tests or Kruskal Wallis as appropriate and by plotting geometric means with 95% confidence intervals by age groups.

Across the whole age range (0-24 years) a comparison of proportions protected with previous seroprevalence studies carried out in 2009 and 1996 for diphtheria and 1996-99, 2002-4, 2009 and 2014 for Men C. This will be done by using all the samples and calculating prevalence within individual age bands with 95% confidence intervals and inferring differences based on non-overlapping 95% CIs which is conservative to allow for multiple testing when assessing many age bands.

For participants aged up to 24 years, the geometric mean titres (with 95% CI) of antibodies against COVID-19 spike protein, and proportion (with 95% CI) of participants with detectable anti COVID-19 antibodies prior to widespread circulation of COVID-19 and over the months following any circulation in the UK

For participants aged up to 24 years, changes from baseline and between consecutive months in the geometric mean titres (with 95%CI) of antibodies against COVID-19 spike protein, and changes in the proportion (with 95% CI) of participants with detectable anti COVID-19 antibodies during the duration of this study.

Exploratory analyses

Whether ethnicity, household income or other factors collected on the questionnaire are associated with immunity to Diphtheria and / or Men C. This will be done by multivariable logistic regression.

11.2. Sample Size Determination
The sample size is determined based on the primary objectives as well as the secondary objective to have a store of sera for future testing of immunity.

Historically serosurveys such as those done as part of the European Sero-epidemiology Network (ESEN) have had target sample sizes per age band of interest of 100-200. Age bands of interest have usually been one year bands until adult ages. For the purpose of this calculation this is taken as one year age bands to age 21 then a single band for 22-24 year olds. For the secondary objective 100 per age band will allow the precision of estimates of seroprevalence to be as given in table 2.

Table 2: Precision of seroprevalence estimates

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>95% CI Observed around the estimate with 100 per age band (2300 total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>4.9-17.6</td>
</tr>
<tr>
<td>20%</td>
<td>12.7-29.2</td>
</tr>
<tr>
<td>30%</td>
<td>21.2-40.0</td>
</tr>
<tr>
<td>40%</td>
<td>30.3-50.3</td>
</tr>
</tbody>
</table>

What’s the STORY?; OVG 2019/01; Protocol; REC Ref 19/LO/1040; IRAS 263097; Version 3.0; Dated 21-FEB-2020
Precision will be improved when combining age bands for specific questions or when assessing trends by age for other secondary objectives. For example for diphtheria age bands of interest could be divided into <4,4-8,9-13,14-24 and for Men C into 0-10,11-12,13-15,16-19,20-24.

Sample size for COVID-19 incidence based on change in prevalence

The table below shows the precision (95% CI (of estimates of change in prevalence (incidence) with 100 samples at each of two time points. For example with a prevalence of 10% at baseline and 30% at the next time point the incidence is 20% with 95% CI 9.3-30.7. The aim is to achieve 100 in each of 4 age groups at each time point.

<table>
<thead>
<tr>
<th>Prevalence At next time point</th>
<th>baseline prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>10%</td>
<td>10 (4.1, 15.9)</td>
</tr>
<tr>
<td>20%</td>
<td>20 (12.2, 27.8)</td>
</tr>
<tr>
<td>30%</td>
<td>30 (21.0, 39.0)</td>
</tr>
<tr>
<td>40%</td>
<td>40 (30.4, 49.6)</td>
</tr>
<tr>
<td>50%</td>
<td>50 (40.2, 59.8)</td>
</tr>
<tr>
<td>60%</td>
<td>60 (50.4, 69.6)</td>
</tr>
<tr>
<td>70%</td>
<td>70 (61.0, 79.0)</td>
</tr>
</tbody>
</table>

Focussing on the primary objectives

Representativeness of participants sampled

Within a study site representativeness is assessed by comparison to local population demographics. Each study site will target approximately 383 individuals. Overall all 2300 samples can be used. With these numbers the precision of estimates of characteristics in the population and differences that would be significant to population data are given in Table 3. So, for example, if a specific ethnic group was 20% of the survey sample then in a region this would have a 95% CI of 16.1-24.4% and would allow a proportion in the population of <14.3% or >26.6% to be detectable as different.

Table 3: Assessment of representativeness, precision and detectable differences

<table>
<thead>
<tr>
<th></th>
<th>Region (N=383)</th>
<th>Overall (N=2300)</th>
</tr>
</thead>
</table>

What’s the STORY?; OVG 2019/01; Protocol; REC Ref 19/LO/1040; IRAS 263097; Version 3.0; Dated 21-FEB-2020
Comparison with residual samples

For comparison with the residual samples this is considered within age strata and is based on the 2017 data on residual samples for the numbers of residual strata by age. Due to the smaller number of residual samples in younger age groups (one of the key reasons for undertaking a community based seroprevalence survey), detectable differences are relatively large in those <4 years. In older age groups, relatively, small differences can be detected in >4 year age bands. The example given below is for when the observed prevalence is 50% is the survey which is conservative as this gives the largest detectable differences.

Table 4: Comparison to residual samples by age strata with a total sample size of 2300

<table>
<thead>
<tr>
<th>Age</th>
<th>Detectable difference from 50% (80% power, 5% significance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>10.7</td>
</tr>
<tr>
<td>4 to 8</td>
<td>8.7</td>
</tr>
<tr>
<td>9 to 13</td>
<td>8.1</td>
</tr>
<tr>
<td>14 to 24</td>
<td>5.7</td>
</tr>
<tr>
<td>All Age</td>
<td>3.9</td>
</tr>
</tbody>
</table>

11.3. Analysis populations

The analysis population for recruitment rates will be all individuals invited, for representativeness will be all individuals providing a sample and for seroprevalence will all individuals providing a sample for which a laboratory result is obtained.

11.4. The Level of Statistical Significance

5% and 95% confidence intervals will be reported. For comparison across individual age bands for seroprevalence differences will be inferred based on non-overlapping 95% confidence intervals.

11.5. Procedure for Accounting for Missing, Unused, and Spurious Data.

The reason for missing data (consent withdrawn or unable to obtain any laboratory results) will be indicated. Missing data will not be imputed.
11.6. Procedures for Reporting any Deviation(s) from the Original Statistical Plan
If there are any changes after finalisation of the analysis plan that would be documented and justified in
the analysis plan.

12. DATA MANAGEMENT

12.1. Source Data
Source documents are original documents, data, and records from which participants’ CRF data are
obtained. These include, but are not limited to, hospital records (from which medical history and previous
and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and
pharmacy records, diaries, radiographs, and correspondence.

Information on study participants will either be recorded directly into a web based electronic CRF or onto
paper source document and later transferred into a web based electronic CRF (e.g. REDCap database
stored on a secure University of Oxford server). REDCap is clinical research study software for electronic
data capture (EDC) and clinical data management (CDM), which enables compliance with regulatory
guidelines such as 21 CFR Part 11.

12.2. Access to Data
Direct access will be granted to authorised representatives from the Sponsor and host institution for
monitoring and/or audit of the study to ensure compliance with regulations.

12.3. Data Recording and Record Keeping
CRF data will be recorded directly into an EDC system (e.g. REDCap) or onto a paper source document for
later entry into EDC if direct entry is not available. Any additional information that needs recording but is
not relevant for the CRF (such as sites for venepuncture, parental availability etc) will be recorded on a
separate paper source document. All documents will be stored safely in confidential conditions. The
database includes a complete suite of features which are compliant with EU and UK regulations and NHS
security policies, including a full audit trail, user-based privileges, and integration with the institutional
LDAP server. The MySQL database and the web server will both be housed on secure servers operated by
the University of Oxford IT Services. The servers are in a physically secure location in Oxford and are backed
up in Oxford, with the backups stored in accordance with the IT department schedule of daily, weekly, and
monthly tapes retained for 1 month, 3 months, and 6 months, respectively. Weekly backup tapes are
stored offsite. The IT servers provide a stable, secure, well-maintained, and high capacity data storage
environment, Drupal and MySQL are widely-used, powerful, reliable, well-supported systems. Access to
the study’s database and the diary will be restricted to the members of the study team by username and
password.

All entries made to the research notes should be printed legibly. If any entry error has been made, to
correct such an error, a single straight line should be drawn through the incorrect entry and the correct
data entered above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT
ERRORS. For clarification of illegible or uncertain entries, the clarification should be printed above the item,
and this should also be initialled and dated. Information entered into the research notes must be
subsequently transferred onto the database by the site collecting the data. The participants will be
identified by a unique study specific number in any database. The name and any other identifying detail will NOT be included in any study data file.

The investigator at each investigational site must make arrangements to store the essential study documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (International Conference on Harmonisation (ICH) E6, Guideline for Good Clinical Practice) including the Investigator Site File. Copies of all study documents with participant identifiable information will be retained after the completion or discontinuation of the study for 3 years after the youngest participant turns 18 years. In addition, the investigator is responsible for archiving of all relevant source documents so that the study data can be compared against source data after completion of the study (e.g. in case of inspection from authorities). Storage of anonymised research data will be reviewed every 5 years and files will be confidentially destroyed if storage is no longer required. The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation of this transfer of responsibility to their successor must be documented in writing.

The participants will be identified by a unique research study specific number and/or code in any database.

13. QUALITY ASSURANCE PROCEDURES
The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. The study may be inspected by the Clinical Trials and Research Governance Office (CTRG), University of Oxford.

Following a risk based monitoring plan, the monitors will verify that the clinical research study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

14. PROTOCOL DEVIATIONS
A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

15. SERIOUS BREACHES
A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the research study subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.
16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki
The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice
The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals
The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Reporting
The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

16.5. Participant Confidentiality
All documents will be stored securely and only accessible by research study staff and authorised personnel. The study will comply with the General Data Protection Regulations (GDPR) which requires data to be anonymised as soon as it is practical to do so. Any data or samples that relate to participants and that leave the study site will be identified by study number only. All documents will be stored securely and only accessible by study staff and authorised personnel.

16.6. Expenses and Benefits
Participants will not be reimbursed for taking part in the study if we travel to their home. Should participants attend a clinic then they will be reimbursed £20 in the form of a voucher for travel e.g. a book voucher.

The information gained from this study will help to inform any strengths or vulnerabilities in vaccine strategy and may help future vaccine design.

17. FINANCE AND INSURANCE

17.1. Funding
This study is being funded by the National Institute for Health Research Policy Research Programme

What’s the STORY?; OVG 2019/01; Protocol; REC Ref 19/LO/1040;
IRAS 263097; Version 3.0; Dated 21-FEB-2020
17.2. Insurance
The University of Oxford has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd’s of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17.3. Contractual arrangements
Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY
The investigators will co-ordinate dissemination of data from this study. All publications (e.g. manuscripts, abstracts, oral/slide presentations, book chapters) based on this study will be reviewed by all investigators prior to submission. Participants will have access to a summary of our study results either by post or an emailed link to our website with an abstract.

19. REFERENCES
12. The immunological basis for immunization series. Module 2: Diphtheria, Update 2009
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a multilaboratory comparison of Neisseria meningitidis group A and C serum bactericidal assays. Clin
## APPENDIX C: AMENDMENT HISTORY

<table>
<thead>
<tr>
<th>Amendment No.</th>
<th>Protocol Version No.</th>
<th>Date issued</th>
<th>Author(s) of changes</th>
<th>Details of Changes made</th>
</tr>
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</table>
| 1             | V1.1                 | 21-June-2019 | Helen Ratcliffe       | 1. Clarification information storage according to GDPR guidelines  
| 2             | V2.0                 | 09-Aug-2019  | Helen Ratcliffe       | 1. Change of PI for Bristol University NHS Trust to Dr Marion Roderick  
2. Change of PI for St Georges NHS trust to Dr Eva Galiza  
3. Clarification of reimbursement which is for travel and not time taken to participate in study.  
4. Addition of anaesthetic spray which can be used instead of anaesthetic cream.  
5. Change in exclusion criteria.  
6. Clarification of data storage durations in section 13.3 |
| 3             | V2.1                 | 03-Oct-2019  |                      | 1. Removal of duplicated section heading and addition of section numbering  
2. Removal of sentence from section definition of end of research study  
3. Change in table numbering |
| 4             | V3.0                 | 21-Feb-2020  |                      | 1. Addition of testing for COVID-19  
2. Questionnaire questions regarding respiratory infections introduced  
3. Clarification that if it has not been possible to obtain a blood sample from an individual then they would not be considered enrolled. |
List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).