Study Title: Incidence of SARS-CoV-2 infection and prevalence of immunity to SARS-CoV-2 in the UK general population as assessed through repeated cross-sectional household surveys with additional serial sampling and longitudinal follow-up - an Office of National Statistics Survey

Internal Reference Number / Short title: COVID-19 Infection Survey

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Note: for brevity only key representatives of the participating institutions are named, but a large number of individuals have contributed to this protocol

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Funder:	Department of Health and Social Care
Chief Investigator Signature:	

The investigators have no potential conflicts of interest.

Confidentiality Statement

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

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2. LAY SUMMARY

The Covid-19 pandemic is having a profound impact across the UK. This study aims to find out how many people have the infection and how many are likely to have had the infection, even if they haven't realised it at the time.

One way to find out whether a person has an infection is to directly look for the microbe in their nose and throat. Covid-19 is caused by a virus, and the main test we are using to diagnose it at the moment is a test to find this virus. Once an individual has recovered from the infection, the virus is no longer present. But, one way the body fights infections like Covid-19 is by producing small particles in the blood called "antibodies". It takes 2-3 weeks for the body to make enough of these antibodies to fight the infection. But once a person recovers, they still stay in the blood at low levels – this is what helps them not get the same infection again. So scientists try to measure levels of both the virus and these antibodies to work out who has Covid-19 now (with or without symptoms) and who has had it in the past.

In this study we want to work out how many people of different ages across the UK have Covid-19 now and how many have had Covid-19 in the past. We do this by testing for the virus in the nose and throat of people and by measuring levels of antibody in the blood. We also want to find out how many people have Covid-19 over time – either with symptoms or without knowing they have the infection because they don't have any symptoms. We want to do this in a group of people that reflect the population of the UK – so a range of ages and places where people live. We will begin by inviting 20000 households to participate with an assumed 50-60% opt-in rate, and a target enrolment of 11,000 households. We will be asking everyone aged 2 years or older in each household to have a nose and throat swab, and for those aged 12 years and older to answer a few short questions at a home visit undertaken by a trained individual (parents/carers will answer for younger children). Those aged 12 years and older can take their own swabs using self-swabbing kits, and parents/carers will use the same kits to take swabs from their children aged 2-11 years. This is to reduce the risk to the study health workers. We will ask adults from around 1000 of these enrolled households aged 16 years or older to also give a sample of blood which will be taken by a trained nurse, phlebotomist or healthcare assistant. We will take swabs from all households, whether anyone is reporting symptoms or not. We will not take blood from anyone in a household where someone has symptoms compatible with Covid-19 infection, or is currently self-isolating or shielding, to make sure that study staff stay at least 2m away from them at all times. The trained study health workers will use all the recommended precautions to protect themselves and everyone in the household from getting the virus.

We will ask people who have this first home visit whether they would be happy to have the same kind of visit and nose and throat swabs repeatedly, every week for the first month (swab and questionnaire only, no blood draw), and then every month from their first visit for a year (including monthly blood draws for those with blood taken originally). This is to find out how rates of infection and immunity change over time in individual people, and whether they can get the virus again with or without having symptoms.

We will do an enrolment home visit with invitations being sent to a new group of 20,000 households approximately every month, targeting recruitment of around 11,000 households. This is to find out how the number of people infected at any one time, the levels of immunity to Covid-19, and the rates of infection with and without symptoms, are changing across the country.

This information will help scientists and the government work out how to manage the pandemic better moving forwards and protect the NHS from being overwhelmed.

3. SYNOPSIS

Study Title	Incidence of SARS-CoV-2 infection and prevalence of immunity to SARS-CoV-2 in the UK general population as assessed through repeated cross-sectional household surveys with additional serial sampling and longitudinal follow-up
Internal ref. no. / short title	COVID-19 Infection Survey
Study registration	Non-interventional study (information will be available on the HRA website)
Sponsor	University of Oxford Joint Research Office 1st floor, Boundary Brook House Churchill Drive, Headington, Oxford OX3 7GB
Funder	Department of Health and Social Care (funding) Office for National Statistics (in-kind contribution) University of Oxford (in-kind contribution through the Biomedical Research Centre and the Health Protection Research Unit)
Study Design	Repeated cross-sectional surveys of representative households across the UK, with nested serial sampling of a subset of participants providing additional optional consent for this
Study Participants	Adults, adolescents and children aged 2 years or older, in households who have participated in Office for National Statistics (ONS) surveys and provided consent to be contacted about future research.
Sample Size	20,000 new households per cross-sectional survey will be contacted with an opt-in rate of 50-60%, and a target enrolment of around 11,000 households. All consenting/assenting adults, adolescents and children aged 2 years and older within each enrolled household will be recruited, anticipating approximately 27,500 individuals per survey Phase I will start with one cross-sectional survey: in Phase II surveys will be repeated in new households approximately every month for one year.
Planned Study Period	Depending on the consent/assent provided by each individual participant, their involvement may be • for one home visit only (cross-sectional survey) • for four home visits (optional: repeated every week for one month) • for 16 home visits (optional: repeated every week for one month and then monthly for a total of 12 months from the first visit). All participants would have follow-up through routine electronic health records to assess use of healthcare within the NHS and mortality for one year from their final study visit. The total study duration is therefore 3 years (one year recruitment, one year serial sampling from the last recruited participant, and one year follow-up through existing electronic records from the final serial sampling timepoint of the last recruited participant).
Planned Recruitment period	24 April 2020 to 23 April 2021
Objectives and Endpoints	See Section 6 below.

Intervention(s) and Comparator	Not applicable, non-interventional study

4. ABBREVIATIONS

A&E	Accident and Emergency
CI	Chief Investigator
CT	Cycle threshold
CTRG	Clinical Trials & Research Governance, University of Oxford
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
HCP	Healthcare professional
HRA	Health Research Authority
NHS	National Health Service
ONS	Office for National Statistics
PPE	Personal protective equipment
REC	Research Ethics Committee
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
SOP	Standard Operating Procedure
WHO	World Health Organisation

5. BACKGROUND AND RATIONALE[1]

The first cases of infection with a novel coronavirus, subsequently designated SARS-CoV-2, emerged in Wuhan, China on 31st December 2019.[1] Despite intensive containment efforts, there was rapid international spread and by 17 April 2020, SARS-CoV-2 had caused over 2 million confirmed infections and 140,000 reported deaths globally.[2] A global pandemic was declared by the World Health Organisation (WHO) on 12th March 2020.[3]

Containment efforts have relied heavily on population quarantine ('lock-down') measures to restrict population movement and reduce individual contacts.[4,5] In order to develop public health strategies for exit from lock-down, there is an urgent need for scale-up of diagnostic testing, in parallel with collection of robust data that describe recent and past SARS-CoV-2 exposure at an individual and population level.

In most settings, laboratory diagnosis of infection has been based on real-time reverse transcriptase polymerase chain reaction (RT-PCR). Diagnostic RT-PCR typically targets the viral ribonucleic acid (RNA)-dependent RNA polymerase (RdRp) or nucleocapsid (N) genes using swabs collected from the upper respiratory tract (nose and throat).[6,7] However, the requirement for specialist equipment, skilled laboratory staff, and PCR reagents has created bottlenecks. Clinical care and public health containment efforts are thus impeded by diagnostic delays even for clinically unwell patients, and further limited by a lack of wider testing including both mass screening, and specific high-risk groups (contacts of confirmed cases, and health care workers and their families). Further the numbers who are asymptomatically infected are currently completely unknown. Poor population-level data adds uncertainty to dynamic models that inform planning of lockdown restrictions (as exemplified by experiences in other countries[8]). Furthermore, even when available, RT-PCR from upper respiratory tract swabs may be falsely negative, due to quality or timing of collection; viral titres in upper respiratory tract secretions peak in the first week of symptoms,[9] but may have declined below the limit of detection in patients who present with symptoms beyond this time frame.[10] In individuals who have been infected and recovered, RT-PCR provides no information about prior exposure or immunity.

For these reasons, attention has turned to the potential for antibody testing to provide data to support individual or population-level release from lock-down and inform mathematical models to predict the future trajectory of the epidemic, as well as supporting diagnosis of individuals with a clinical COVID syndrome. In contrast to RT-PCR, assays that reliably detect antibody responses specific to SARS-CoV-2 could contribute both to diagnosis of both acute infection (via rises in IgM and IgG levels) and identify those who have been exposed and recovered with or without symptoms (via persisting IgG).[11] Receptor-mediated viral entry to the host cell occurs as a result of the interaction between the unique and highly conserved trimeric SARS-CoV-2 spike (S) glycoprotein and the ACE2 cell receptor.[12] This S protein is the primary target of specific neutralising antibodies, and serology assays for SARS-CoV-2 therefore typically seek to identify these antibodies (see Figure 1 in [13]). Within this study we plan to use two different antibody assays; one for the IgG and IgM immunoglobins and one for the neutralising antibodies directly.

In this study, we aim to address crucial unknowns regarding the extent of transmission and infection in the UK. We will use a repeated cross-sectional survey design, inviting 20000 households to participate with an assumed 50-60% opt-in rate, and a target enrolment of 11,000 households, providing a cohort of approximately 11,000 population-representative households in the first month in Phase I, and then new cohorts of approximately 11,000 newly enrolled households approximately each month over the

[1] With grateful thanks to Dr Philippa Matthews and Dr David Eyre for most of the introductory text.

following year to estimate the proportion of the population that are currently infected with SARS-CoV-2, symptomatically and asymptomatically, based on diagnostic RT-PCR performed on a nose and throat swab collected by the participant (self-swabbing) or by a parent/carer from participants aged 2-11 years, and self-reported symptoms. In approximately 1000 of enrolled households in each cross-sectional survey, a trained healthcare professional (HCP) will also collect blood to estimate seroprevalence using these two antibody assays, to quantify the percentage of the adult population in the UK that has previously been infected with SARS-CoV-2. This would substantially improve/decrease uncertainty of models that have been used to predict the effect of school closures, social distancing, and other interventions aimed at reducing the spread of the virus.

However, additional critically important questions remain about onward transmission and waning immunity in individuals who are positive, whether such individuals can be re-infected symptomatically or asymptomatically, and about incidence of new infection in individuals without prior exposure. Incorporating nested serial sampling of consenting individuals can efficiently provide estimates of these outcomes in different subgroups. We will therefore also serial sample individuals from these cross-sectional surveys who provide additional consent 1, 2, 3 and 4 weeks (1 month) after their first visit; if further consent is provided, we will continue this sampling at 2 months and every month for 12 months from their first home visit to assess this over the longer term.

In addition, for planning the continuing response to the pandemic, it is essential to understand the relationship between symptomatic/asymptomatic infection, immune status and use of health resource within the NHS, and with mortality. In this study, we will therefore seek consent to link study results with NHS data for one year after the last study visit for each participant to estimate the impact on the NHS and future requirements, and to ONS data to estimate the impact on mortality.

The goal is to obtain results which can be generalised across the UK and help manage the pandemic moving forwards.

Risks to participants will be minimised by the use of trained study nurses and other healthcare professionals (HCPs) to take blood samples; visits where blood is not being drawn may be conducted by other trained individuals to ensure HCP are not diverted from the NHS. Visits will also be split into two types, contact visits, and non-contact visits to households where anyone is currently symptomatic/self-isolating/shielding (detailed definitions below). Study health workers will follow NHS guidance regarding protective equipment.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure
Primary Objective To estimate prevalence of symptomatic and asymptomatic SARS-CoV-2 infection in the general population and how this varies over time	Presence or absence of SARS-CoV-2 virus assayed from a nose and throat swab	Individual cross-sectional surveys; repeated at each follow-up timepoint in those consenting to serial sampling
Secondary Objectives To estimate the incidence of new symptomatic and asymptomatic SARS-CoV-2 infection in the general population, and how this varies over time	Presence of SARS-CoV-2 virus in a nose and throat swab, separately in previously negative and previously positive individuals (after clearing the virus)	The end of serial sampling in those consenting to serial sampling
To estimate immunity to SARS-CoV-2 in the general adult population and how this varies over time, as reflected by immunoglobins	Optical density readings for IgG and IgM from an ELISA assay for SARS-CoV-2 antibodies assayed from blood, categorised according to predefined thresholds[13] as positive or negative	For all other secondary objectives, timepoints are the individual cross-sectional surveys; and repeated values at each follow-up timepoint in those consenting to serial sampling
To estimate immunity to SARS-CoV-2 in the general adult population and how this varies over time, as reflected by neutralising antibodies	Concentration of neutralising antibodies to SARS-CoV-2 assayed from blood, categorised according to predefined thresholds[14] as positive or negative	
To estimate the association between prevalence of symptomatic and asymptomatic infection in individual members of households	Presence or absence of SARS-CoV-2 virus assayed from nose and throat swabs taken from different members of the same household*	
To estimate the association between immunity to SARS-CoV-2 assayed by different methods across individual members of households	Concentrations and thresholds of IgG, IgM and neutralising antibodies to SARS-CoV-2 assayed from blood of different members of the same households*	

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure
Exploratory Objectives To assess how prevalence and incidence of symptomatic infection, and immunity to SARS-CoV-2 assayed by different methods varies by participant characteristics, particularly age, geographical location and time	Presence or absence of SARS-CoV-2 virus assayed from a nose and throat swab Presence of SARS-CoV-2 virus in a nose and throat swab, separately in previously negative and previously positive individuals (after clearing the virus) Optical density readings for IgG and IgM from an ELISA assay for SARS-CoV-2 antibodies assayed from blood Concentration of neutralising antibodies to SARS-CoV-2 assayed from blood	In individual cross-sectional surveys; repeated at each follow-up timepoint in those consenting to serial sampling
To assess how immunity to SARS-CoV-2 assayed by different methods affects future use of NHS resources and mortality	Inpatient admissions, outpatient attendances, A&E attendances, consultations with a general practitioner as collected from routine electronic NHS health records; overall mortality and cause of death as collected from ONS	Over the year following each visit; at the final follow-up one year after the last visit

* estimated from statistical random effects models, see Section 12.

7. STUDY DESIGN

The overall study design is repeated cross-sectional surveys of representative households across the UK, identified by one adult from the household having participated in existing ONS surveys and providing consent for future contact regarding research. All adults and adolescents aged 16 years and above in the household who are willing and able to consent will be included in the study, as will all adolescents and children aged 2 years and older for whom a parent/carer is willing and able to consent to their participation. Assent will be sought from adolescents and children aged 10 years or older. Children are included in this study is because it is essential to understand prevalence and incidence of symptomatic and asymptomatic infection in children, particularly to inform continued school closures.

These cross-sectional surveys will be repeated over time, recruiting new additional households each month, following standard sampling methods (for example as employed in the Labour Force Survey) to ensure that the study represents the UK population and can estimate reliably prevalence over time of symptomatic and asymptomatic infection and immunity (as assessed by various antibody profiles) (Figure *1*). In each cross-sectional survey, study participants who provide additional optional consent/assent will undergo repeated serial sampling at 1, 2, 3 and 4 weeks (approximately 1 month) to assess incidence of new infection, viral clearance and changes over time in immunity. If further additional consent is given, this will then be further repeated at month 2 and every month for 1 year from their first study visit to assess these outcomes over the longer term.

Data collection will be done via home visits. This method is used to minimise risk to the participant from having to attend a central facility. Home visits will be either contact visits where the study health workers enter the household or non-contact visits where study health workers do not enter the household and stay 2m away from the household at all times, passing any necessary sterile equipment for self-swabbing using standard precautions. Non-contact home visits will be conducted if anyone in the household is symptomatic, self-isolating or shielding on the home visit date.

At every visit (contact or non-contact), all participants will have a self-swab of their nose and throat and complete a short questionnaire. The self-swab can be done by those aged 12 years and older and is currently being successfully used in drive through testing centres; those 2-11 years will be swabbed by their parent/carer. The swab is the same size as that used routinely in paediatric practice and there is no modification to the technique needed. Self-swabbing minimises the risk to study health workers of contracting SARS-CoV-2 from an asymptomatically infected individual. At the enrolment visit to households where a contact visit is planned (that is, no one is symptomatic, self-isolating or shielding), optional consent will also be sought for adults aged 16 years or older to have a blood draw. In the first cross-sectional survey (Phase I, see below), the invitation to undergo additional blood sampling will be sent to those sampled from the ONS Opinions COVID-19 Survey for practical reasons and to enable future data linkage to more detailed data on reported self-isolation behaviours. The first 1000 households in each cross-sectional survey where one or more participant agrees to a blood draw will be included in this part of the study. If participants have also consented to serial sampling, blood will also be drawn monthly for the duration of their consented serial sampling. The choices available to participants are illustrated in **Figure 2**.

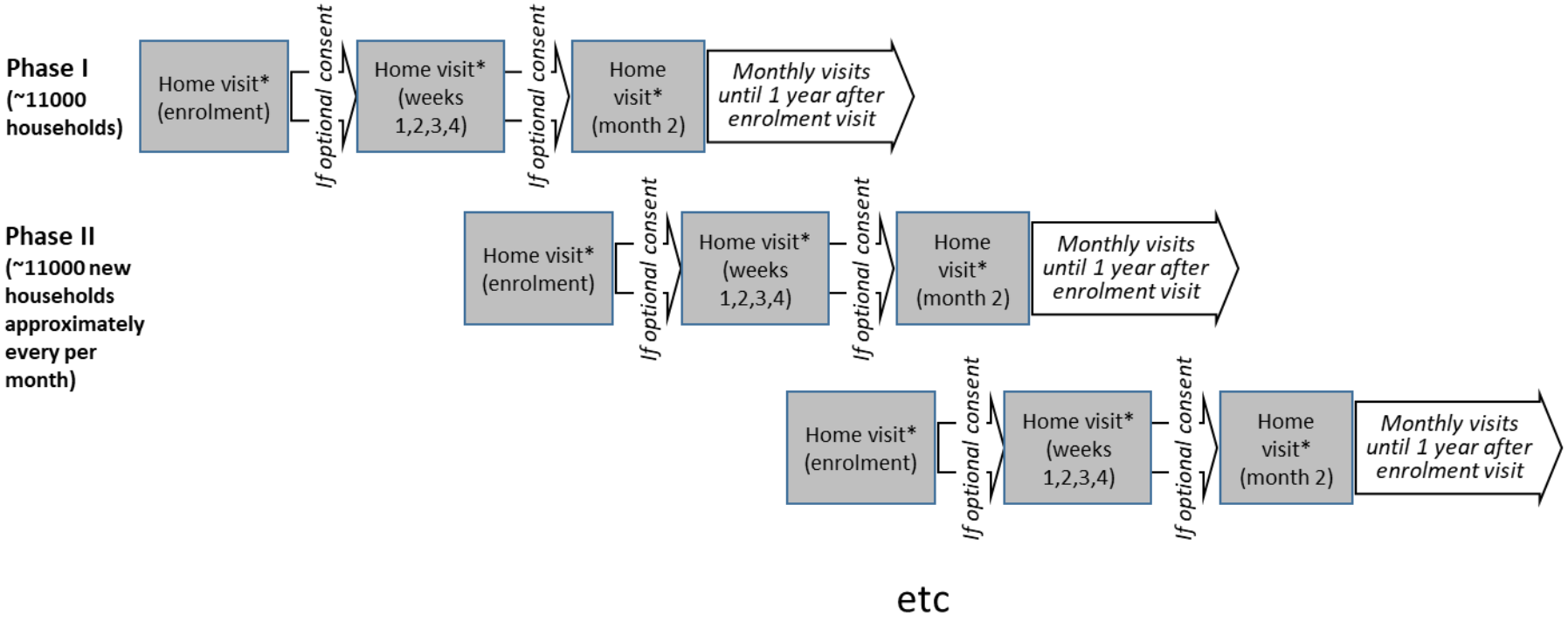
Participants who consent to one cross-sectional survey would have just one visit. Participants who consent to serial sampling would have either have five study visits over one month (enrolment, weeks 1, 2, 3, 4) or 16 study visits over one year (enrolment; weeks 1, 2, 3, 4; then every month from 2 to 12

months from the enrolment visit). All participants would have follow-up through routine electronic health records for health utilisation and mortality for one year from their final study visit.

The study will start with one cross-sectional survey in Phase I, aiming to enrol 11,000 households from England, based on respondents to waves 1-4 of the ongoing ONS Opinions COVID-19 Survey and other ONS surveys. Households in England where an adult participant has agreed to future contact regarding research will be targeted (n~20,000), assuming a 50-60% response rate. All eligible participants in these households who consent to serial sampling will be included in the serial sampling component (no data available to inform this estimated proportion), and the first 1000 households from the ONS Opinions COVID-19 survey where one or more individuals consent to the blood draw will be included in that component.

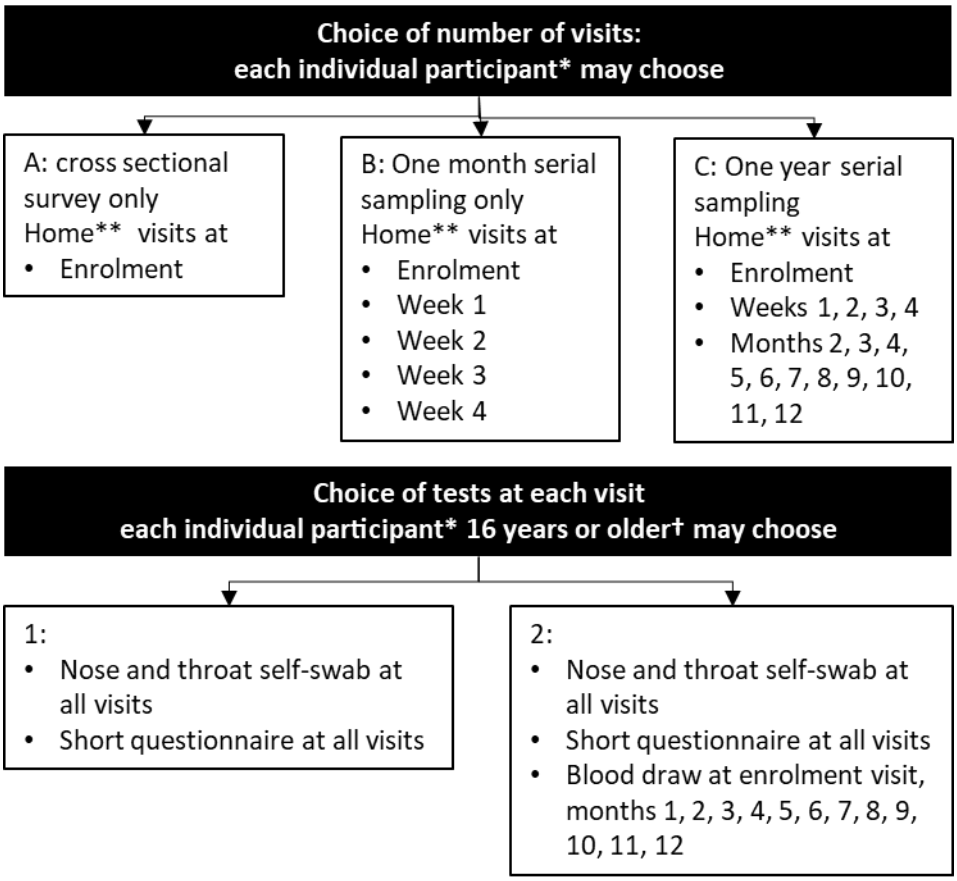
In Phase II, sampling from ongoing and further ONS surveys will likely be stratified by geographical location and age in order to provide more precise regional estimates of incidence and seroprevalence by age. Any specific stratification will be determined based on response rates to Phase I, and reflected in a protocol amendment that will be approved before Phase II starts. Similarly the proportion of participants who are approached for longitudinal sampling will be determined based on the consent rate for this component in Phase I, and reflected in this protocol amendment. The visit schedule will also be considered for Phase II, both in terms of number and timing of visits and number of blood draws, taking into account rates of consent for serial sampling, and attrition over time.

Figure 1 Repeated cross sectional survey design



* Home visits are defined as contact (participant self-swab of nose and throat, questionnaire, blood draw if participant has consented for this) or non-contact (participant self-swab of nose and throat, questionnaire; HCP stays 2m away from household at all times)

Figure 2 Choice of serial sampling frequency and tests



* Different participants within the same household may make different choices as to number of visits

** Home visits are defined as contact (participant self-swab of nose and throat, questionnaire, blood draw if participant has consented for this) or non-contact (participant self-swab of nose and throat, questionnaire; HCP stays 2m away from household at all times). Non-contact visits are based on the status of the household at the planned visit date: if anyone in the household is symptomatic, self-isolating or shielding, then the visit will be non-contact.

† Those aged 2-11 years will only have a nose and throat swab taken by their parent/carer who will answer the questionnaire for them; those 12-15 years will self-swab and be administered the short questionnaire, but are not eligible for the blood draw

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Healthy volunteers aged 2 years or older (no upper age limit), who are currently resident in a household where an adult member has participated in an ONS Survey and has consented to be approached for future research.

In Phase I, the target is to recruit all adults, adolescents and children aged 2 years or older from a sample of 20,000 households, inviting 20,000 households to participate with an assumed 50-60% opt-in rate, and a target enrolment of 11,000 households, (expect ~27500 individuals if this is achieved) to the cross-sectional survey.

In Phase II, the target is to recruit all adults, adolescents and children aged 2 years or older from a new set of approximately 11,000 enrolled households approximately every month for 12 months to each repeated cross-sectional survey (Figure *1*).

8.2. Inclusion Criteria

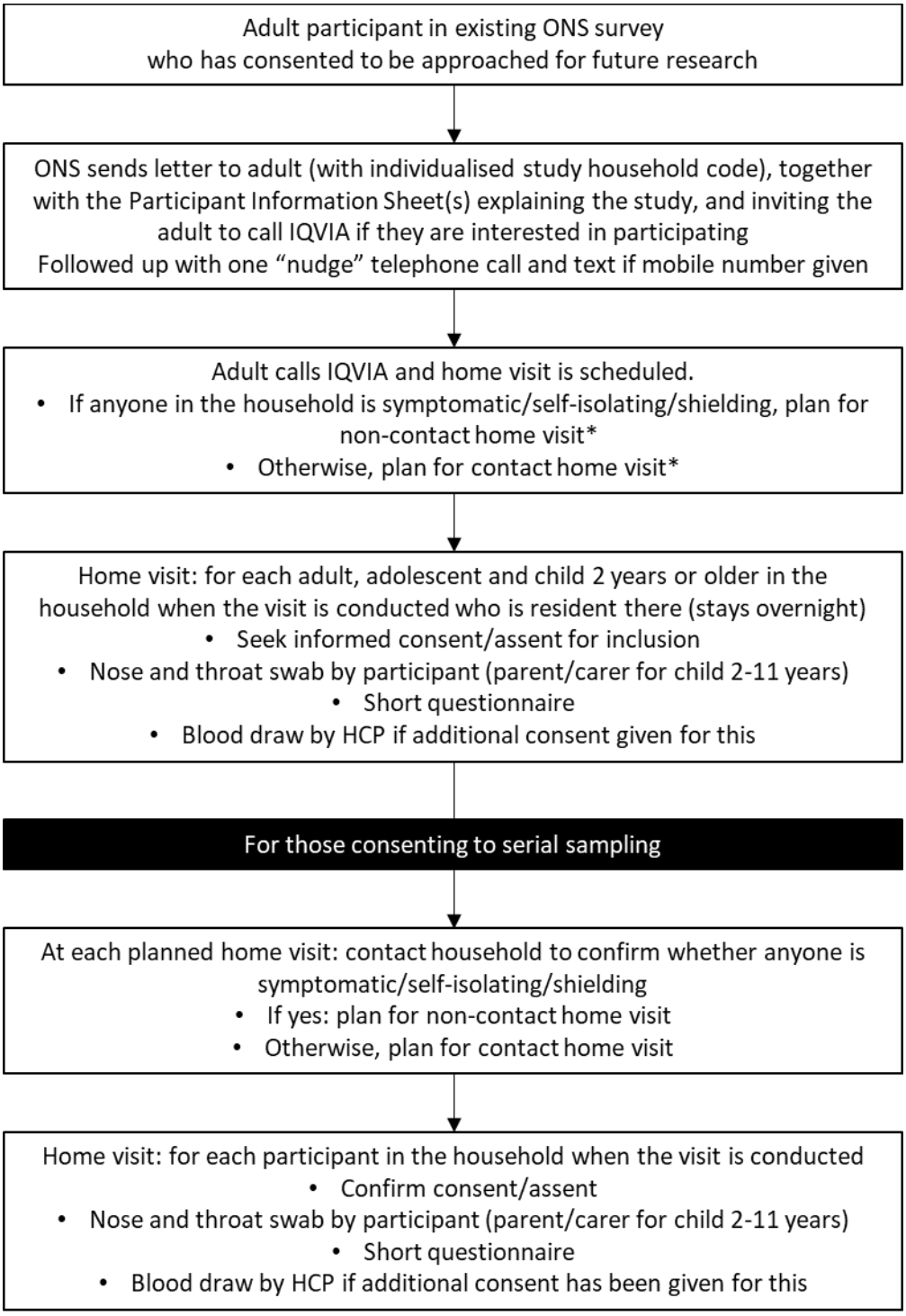
- Healthy adult, adolescent or child aged 2 years or older, male or female
- Currently resident in a household where a household member has participated in an ONS Survey and has consented to be approached for future research. 'Currently resident' is defined according to 2011 Census definitions:
    - A 'resident' is defined as a person who typically stays overnight in the address at least 4 nights out of 7
    - A 'household' is defined as one person living alone; or a group of people (not necessarily related) living at the same address who share cooking facilities and share a living room or sitting room or dining area
- If 16 years or older: Participant is willing and able to give informed consent for participation in the study.
- If 2-15 years at last birthday: A parent/carer is able to give informed consent for participation in the study; those aged 10 years and older should also provide assent.

8.3. Exclusion Criteria

There are no exclusion criteria.

9. PROTOCOL PROCEDURES

Figure 3 Flow diagram



* Home visits are defined as contact (participant self-swab of nose and throat, questionnaire, blood draw if participant has consented for this) or non-contact (participant self-swab of nose and throat, questionnaire; HCP stays 2m away from household at all times). Non-contact visits are based on the status of the household at the planned visit date: if anyone in the household is symptomatic, self-isolating or shielding, then the visit will be non-contact.

Note: only individuals present in the household at the original enrolment visit and who originally provided consent/assent will be included in the serial sampling. Any individuals who join the household after the enrolment will not be included. Any individuals who originally consented to serial sampling and leave the household will be considered withdrawn from the study.

Table 1 Schedule of investigations for each new cohort (recruited each month, see Figure 1)

	Initial letter from ONS	Telephone contact with IQVIA	Enrolment home visit*	Week 1, 2, 3 home visit	Week 4/month 1, months 2-12 home visit
All participants					
Participant Information Sheet(s)	X				
Eligibility screen		X			
Informed consent/assent			X		
Participant throat self-swab (done by parent/carer for child 2-11 years)			X		
Short questionnaire			X		
Blood draw by HCP if participant 16 years or older and provides consent (see Figure *2*)			X*		
If consent provided for visits at weeks 1, 2, 3					
Informed consent/assent confirmed				X	
Participant throat self-swab (done by parent/carer for child 2-11 years)				X	
Short questionnaire				X	
If consent provided for visit at week 4/month 1 or subsequent monthly visits (see Figure *2*)					
Informed consent/assent confirmed					X
Participant throat self-swab (done by parent/carer for child 2-11 years)					X
Short questionnaire					X
Blood draw by HCP if participant 16 years or older and provides consent (see Figure *2*)					X*

* Home visits are defined as contact (participant self-swab of nose and throat, questionnaire; blood draw if consented and relevant timepoint) or non-contact (participant self-swab of nose and throat, questionnaire, no blood draw regardless of consent; study health workers stay 2m away from household at all times)

9.1. Recruitment

Households will be recruited from existing and ongoing ONS surveys, including their Opinions COVID-19 Survey. This survey is a wave 6 of the Labour Force Survey and recruits one adult per household across the UK to ask non-medical questions about the impact of SARS-CoV-2. The survey is voluntary and is conducted in compliance with the Code of Practice for Official Statistics. As part of this survey, participants indicate whether they are happy to be approached for future research and those who have indicated that they are willing will be approached for recruitment into this study.

As of 18 April 2020, approximately 5000 adults from across the UK have agreed to be approached for future research from this survey. Phase I will approach all these adults in England for feasibility reasons relating to initial availability of study health workers, together with other households identified from the Labour Force Survey who have similarly agreed to be approached for future research. Recruitment into the Opinions COVID-19 Survey is continuing, with approximately 4000 adults being recruited per month for the next two months. Phase II currently plans to take a similar approach to sampling depending on the results from Phase I (see Section 5, Study Design, above), including participants in the devolved nations.

In Phase I, ONS will send a letter to all targeted adults, explaining the nature of the study, together with the main adult and adolescent 16 years and older Participant Information Sheet(s) and will follow this up with one telephone call following standard practice. Only the sheet for adults and those 16 years and older will be sent, since the point of contact is an adult and it will not be known whether there will be children or adolescents in the household. This includes relevant information for parents/carers about any children in the household. Additional age-appropriate information will be provided at home visits where appropriate.

Each targeted adult will be assigned a unique household code at the point their household is selected to be approached for the study: this code will be used on all subsequent study correspondence. (After recruitment, a suffix will be used indicate different household members (A, B, C etc) who will be uniquely identified by their date of birth (required for linkage to NHS/ONS records as well as unique identification of individuals within each household).) The invitation letter will ask the targeted adult to telephone IQVIA if they or anyone in their household are interested in taking part. One or multiple members of the household may participate, regardless of whether the originally targeted adult chooses to participate, but those outside the household are not eligible. A similar approach is planned for Phase II.

When the targeted adult telephones IQVIA, any immediate questions will be answered and a home visit from study health workers will be arranged. Verbal consent will be obtained for this home visit, and documented. Home visits will be of two types

- At a contact home visit, participant(s) aged 12 years and older will self-swab their nose and throat (methods currently being successfully used in those 12 years and older at drive through testing centres) and study health workers will administer a short questionnaire (details below). For children aged 2-11 years, the parent/carer will self-swab the child (minimising risk to study health workers) and will complete the questionnaire on behalf of the child. If on the initial telephone call, the targeted adult indicates that any adult in the household aged 16 years above is potentially interested in donating blood, this visit will be conducted by a HCP trained to draw blood (see Table *1* above).
- At a non-contact home visit, the participant(s) will self-swab their nose and throat and study health workers will administer the short questionnaire (same procedures as above for children aged 2-11 years); study health workers will stay 2m away from household at all times, passing the necessary equipment to the participant(s).

Non-contact home visits will be conducted if anyone in the household is symptomatic, self-isolating or shielding on the planned home visit date. Symptoms will be as defined by current NHS guidance (https://www.nhs.uk/conditions/coronavirus-covid-19/symptoms-and-what-to-do/), specifically a high temperature or a new, continuous cough. Self-isolation will also be as defined by current NHS guidance https://www.nhs.uk/conditions/coronavirus-covid-19/self-isolation-advice/, specifically for an individual 7 days after symptom onset if no fever at 7 days or end of fever if still have fever at 7 days; or for another household member for 14 days from the day the first person started having symptoms. The study health workers will bring all the recommended personal protective equipment (PPE) to these home visits.

Full consent (and assent where relevant) will be taken at this enrolment home visit (see below).

9.2. Screening and Eligibility Assessment

There is no maximum duration between receiving the invitation letter and recruitment. The time will depend on participant convenience and availability of study health workers, but will be as short as possible in order to maintain the serial survey design. In the case of late response, the household will be assigned to the following cross-sectional survey for analysis.

9.3. Informed Consent

Verbal consent for the home visit will be obtained during the telephone call in which the appointment is made.

At the home visit, each participant in the household aged 16 years or older must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed. The person who obtains the consent must be suitably qualified and experienced, and have been authorised to do so by IQVIA (responsibility delegated to IQVIA from the Chief Investigator and Sponsor). An Informed Consent document will be signed, with one copy given to the participant (or parent/guardian) and the other retained by IQVIA. In the case of a non-contact visit, study health workers will have each participant complete consent form and then scan it securely to obtain the research copy. The original paper form will be left at the house.

The same process will be followed to obtain consent from a parent/carer for participation of a child or adolescent aged 2-15 years, and for assent from older children and adolescents aged 10-15 years. Age-appropriate information will be provided at the home visit.

Each potentially eligible household member may choose to participate or not to participate individually – all those who consent/assent will be included, but not every member of the household is required to consent/assent. Only those individuals present in the household at the time of the visit will be approached for consent/assent. Any individuals who join the household after the enrolment will not be included.

Written versions of the Participant Information and Informed Consent will be presented to the participants in the original invitation letter detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason, including at the initial home visit, and with no obligation to give the reason for withdrawal. Information will also be presented verbally at the home visit or during the telephone call to make the home visit appointment.

Consent will include consent

- Required: To provide a small amount of additional data on questionnaires (see below).
- Required: To inform their GP of their participation and for their nose and throat swab results to be returned to their GP (see below, stated in the Participant Information Sheet(s)).
- Required: For linking their data and sample results from this study to data already held by ONS (because this is where we will obtain geographic data from, and to obtain overall mortality and cause of death) and to NHS records for 12 months from their last home visit (in order to assess the impact of results gained from the study on future healthcare utilisation). It will be stated in

the Participant Information Sheet(s) that this linkage will require the study to hold name, address, sex and date of birth.
- Optional: Blood sampling in those 16 years and older (where requested)
- Optional: For any leftover material from blood samples taken at the study visits (see below) to be saved for future better tests relating to SARS-CoV-2.
- Optional: To repeated home visits to collect the same samples and information, see **Figure 2** for options.

The Participant Information Sheet will have been posted to the household with the original invitation letter, ensuring that households have adequate time to consider whether they wish to call IQVIA to discuss participation in the study. Age appropriate documentation will be brought to the visit for children. It is not possible to give potential participants unlimited time to consider the study at the home visit where blood is drawn. However, they will have had the opportunity to cancel the appointment at any time between the original telephone call and the home visit.

Each potentially eligible household member will be recorded as either having consented/assented to the study or not. For those who do not consent/assent, the reason will be recorded if the person is willing to provide this, and their age in years.

Any individual household member who assented to the study at enrolment but attains 16 years during the study will be consented individually at the first study visit after their 16th birthday.

9.4. Enrolment

The study is not randomised and there is no intervention.

Participants will be enrolled at the first home visit.

9.5. Blinding and code-breaking

There is no blinding and there is no intervention in this study.

9.6. Description of study intervention(s), comparators and study procedures (clinical)

There is no intervention in this study and hence no comparator either.

9.6.1. Description of study procedure(s)

At each study visit, each participant aged 12 years or older will be provided with a self-swabbing kit, and asked to take their own nose and throat swab. These kits are identical to those currently being used successfully for self-swabbing at the SARS-CoV-2 drive through testing centres in those aged 12 years and older. Parents/carers will be asked to take the swab from children aged 2-11 years, after first taking their own swab so they can be confident that it is not painful. The study health workers will explain and demonstrate the technique to each participant in the household. The self-swabbing kit includes viral transport media which the swab is placed directly into. This will again be labelled with the unique household study code, date of sampling and participant suffix (A, B, C etc) and month and year of birth. Results from this accredited test will be returned to the participant's General Practitioner for them to discuss with the participant.

The study health workers will ask each participant (including those under 16 years old) a short set of specific questions based on those recommended by the WHO,[15] namely

- Date of birth (required for unique participant identification and for linkage to NHS/ONS records); gender; ethnicity; occupation (available from ONS for the adult targeted in the original letter, but not for the rest of the household)
- Is the participant currently symptomatic, self-isolating or shielding? (whilst this determines the type of visit at the household level, we need to record it for each participant)
- Do they have any of the following symptoms today (yes/no for each of fever, muscle ache (myalgia), fatigue, sore throat, cough, shortness of breath (dyspnea), headache, nausea/vomiting, abdominal pain, diarrhoea, loss of taste, loss of smell)
- Have they been in contact with someone that they definitely know (based on a diagnostic test) was infected with Covid-18/SARS-CoV-2? Yes/No
    - If yes, date of last contact
    - If yes, was this someone in their own household or someone outside their household
- Have they been in contact with someone that they suspect (no diagnostic test) was infected with Covid-19 SARS-CoV-2? Yes/No
    - If yes, date of last contact
    - If yes, was this someone in their own household or someone outside their household
- Do they think/know they have been infected by SARS-CoV-2? Yes/No
    - If yes, date first symptoms and what symptoms (yes/no for each of fever, muscle ache (myalgia), fatigue, sore throat, cough, shortness of breath (dyspnea), headache, nausea/vomiting, abdominal pain, diarrhoea, loss of taste, loss of smell)
    - If yes, did they contact the NHS about this (suspected) SARS-CoV-2 infection? Yes/No
        - If yes, were they tested? Yes/No
        - If yes, were they positive/negative?
        - If yes to contacting NHS, were they hospitalised?
- Name and address of GP (to return results of nose and throat swabs)

Household postcode (required for geospatial analyses) will be available from the original ONS survey. At a household level, the number and ages in months of any children under 2 years who are normally resident in the household (as per 2011 Census definition) will also be recorded, as will the number and age (years) of any individual not present when the visit was conducted. Household size will thus be available from this data together with the record of who consented/assented or not at the home visit (with ages, see section 9.3 above). This information will be used in analysis of transmission, to account for the fact that these individuals are not sampled within the study design.

For those participants who provide additional consent (**Figure 2**), 5ml venous blood will be drawn by the study HCP from each participant in the household aged 16 years of older into a BD Vacutainer™ SST™ II Advance Tube for both antibody assays. The tube will be barcoded and labelled with the unique household study code, date of sampling and participant suffix (A, B, C etc) and month and year of birth (not personally identifiable). Results from these antibody tests will not be returned to participants (stated in the Participant Information Sheet(s)) because these assays are currently research tests not approved by the Medicines and Healthcare Products Research Agency.

9.7. Baseline Assessments

The procedures above will be conducted at the baseline home visit, according to whether it is a contact or non-contact home visit.

9.8. Subsequent Visits

Households from which one or more participants consent to serial sampling will be visited approximately 1, 2, 3, and 4 weeks later (within a ±3 day window to allow for participant convenience and study health workers availability), and then (depending on consent, **Figure 2**) two months after the enrolment visit and every month thereafter for one year (within a ±10 day window to allow for participant convenience and study health workers availability). One home visit will be made to each household at each of these timepoints, and all consenting participants in the household at the time of the home visit will be included – additional visits will not be made if one or more participant happens not to be present at the time of an individual visit. Such participants may however be included at subsequent visits.

Subsequent visits will be scheduled through IQVIA contacting the participant to make arrangement for a visit by the study health workers, and determining whether this will be a contact or a non-contact visit based on whether anyone in the household is symptomatic, self-isolating or shielding on the planned home visit date.

Consent/assent from each participant will be confirmed, and the procedures in Table *1* above will be conducted on all consenting/assenting participants.

9.9. Sample Handling

9.9.1 Sample handling for study purposes

The nose and throat swab will be couriered directly to the National Biosample Centre at Milton Keynes, where it will be tested for the presence of SARS-CoV-2 using reverse transcriptase polymerase chain reaction (RT-PCR) in an accredited test as part of the national testing programme. Residual material will be discarded.

Blood tubes will be kept in a cool bag during the day, and then couriered to the University of Oxford overnight. Serum will be tested by research staff at the University of Oxford for antibodies using a novel ELISA for immunoglobulins IgG and IgM, based on tagged and purified recombinant SARS-CoV-2 trimeric spike protein.[13,16] Antibody binding to the S protein is detected with ALP-conjugated anti-human IgG or anti-human IgM. Serum will also be tested using neutralisation assays. These neutralisation assays use a lentiviral construct which expresses SARS-Cov2 S protein, and are tested in a cell-based system described as a pseudotype microneutalisation assay (pMN), as recently used in a study of Scottish blood donors.[14] Residual sera will be stored at the University of Oxford.

In both laboratories, assay results will be returned to ONS identified only by the unique household study code, date of sampling and participant suffix (A, B, C etc) and month and year of birth. Antibody results will be returned as the quantitative optical density readings for the ELISA assay and as positive/negative together with a half maximal inhibitory concentration in the positive group for the neutralisation assay through either a secure FTP site or an encrypted and password protected file. Nose and throat swab results will be returned as positive/negative and cycle threshold (CT) value. Throat swab results will be returned to the participant's GP for discussion with the participant. This be done through IQVIA who will already hold personal details for participants.

9.10. Early Discontinuation/Withdrawal of Participants

During the course of the study, a participant may choose to withdraw from future study procedures. Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely. They may also withdraw consent for continued storage of their blood samples. Alternatively, they may lose the capacity to consent during the study. Finally, participants may withdraw from the study simply because they leave the household which was originally sampled. Each participant has the right to withdraw from the study at any time; individual participant withdrawal will not mean others in the household are automatically withdrawn, each participant will make their own individual decision. Data obtained up to the point of consent withdrawal will be kept and used in analysis and this is explained in the Participant Information Sheet(s).

Participants who wish not to continue participation in some or all parts of the study will therefore be offered the following options, and the type of withdrawal recorded on the case record form.

1) Participants may withdraw from active follow-up (i.e. future study procedures) and further communication but allow the study team to continue to access their ONS and NHS records. Residual serum samples would be kept for future research.

2) Participants can withdraw from the study but permit data and samples obtained up until the point of withdrawal to be retained for use in the study analysis, and any residual serum samples to be used for future research. No further data or samples would be collected after withdrawal.

3) Participants can withdraw completely from the study and withdraw their samples collected up until the point of withdrawal. The data already collected would be used in the analysis, but samples would be destroyed if not already analysed and any residual serum samples already being stored would also be destroyed.

Participants who lose capacity to consent during the study will be withdrawn from active follow-up (option 1). Participants who withdraw for any reason will not be replaced.

9.11. Definition of End of Study

The end of Phase I of the study is the date of the last home visit of the last participant targeted for Phase I. The end of Phase II of the study is the date of the last home visit of the last participant targeted for Phase II.

10. SAFETY REPORTING

There are no interventions in this study, and the only procedures are a standard blood draw performed by study HCP and a participant self-swab using a methodology which is being used widely at drive through testing centres across the country. Therefore, there is minimal safety risk to participants and safety reporting is not applicable.

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here. The initial analysis of Phase I will follow this plan. For Phase II, details will be fully described in a statistical analysis plan that will be written and finalised before any analysis beyond that described below takes place.

11.2. Description of the Statistical Methods

For the primary outcome, the proportion of individuals with symptomatic and asymptomatic infection (based on RT-PCR of nose and throat swabs) will be summarised according to age at last birthday (2-4, 5-11, 12-17, 18-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75+ years) and geographical region in each cross-sectional survey. Depending on numbers, analyses will also consider gender and ethnicity. Proportions will be calculated adjusting for clustering within household using marginal estimates obtained after fitting random effects logistic models (random effect per household), incorporating sampling weights for both the original ONS surveys, each individual cross-sectional survey and for non-response to this survey. Association between different household members will be estimated from the correlation parameters within this model. Simple proportions based on the single adult targeted by the original ONS survey will also be estimated, as will household-clustering adjusted proportions without survey sample weights. A smooth continuous relationship with age will be estimated using mixed generalised additive models.

Similar methods will be used to estimate proportions with immunity defined (i) based on the optical density readings from the ELISA assay for IgG and IgM antibodies versus the thresholds proposed in its initial evaluation,[13] namely 0.07 for IgM and 0.4 for IgG (3 and 5 standard deviations above the negative mean respectively) (ii) based on the neutralisation assays using thresholds defined based on studies of negative controls in and predefined dilution curve statistics[14] (secondary outcomes). We will also consider the proportions with recent infection as defined by relative levels of IgG and IgM antibodies,[13] and the proportions with previous infection as defined by antibodies but no previous symptoms.

Random effects linear regression models will also be generated for results from each cross-sectional survey based on absolute optical density readings for each antibody (potentially log-transformed depending on the distribution) in relation to time since onset of first symptoms, with those not reporting symptoms treated as an additional category (random effect per household – may be omitted depending on model fit). Additional factors considered in these models will include age, gender and ethnicity. Similar models will be fit to the continuous measures output from the neutralisation assays, which is a half maximal inhibitory concentration for positive results.

It is not anticipated that sufficient information will be available from the original Phase I cross-sectional survey to construct (Bayesian and non-Bayesian) spatiotemporal models (for example, mixed generalised additive models can also incorporate geographical effects). Ultimately however, these cross-sectional models will be included to estimate the impact of both calendar time and geographical proximity on seroprevalence as measured by the different immunity assays. We anticipate that two analyses will be performed. The first model will be a mixed effects model that accounts for the survey design using survey weights but ignores any spatial correlation. The second model will be a (Bayesian) spatiotemporal model, accounting for both spatial correlation and the complex survey design. In this model, individual- and area-specific factors will be used in the model to predict the seroprevalence in areas from which no

seroprevalence data has been collected. Additional models will consider weighting for non-response. Following best practice recommendations, we will test different types of models (for example, additive vs non-additive models, various types of (non)adaptive smoothing, etc) and chose those with the best fit to the data.

Through linkage to NHS records, we also aim to determine the impact of immunity and symptomatic/asymptomatic infection status on healthcare usage, in particular inpatient admissions, A&E attendances and general practitioner consultations. Through linkage to ONS records, we aim to determine the impact of immunity and symptomatic/asymptomatic infection status on mortality and cause of death.

11.3. Sample Size Determination

The target sample size for Phase I (around 11,000 enrolled households) was determined based on a conservative assumption that all members of the same household have the same infection status, and therefore each household should only be counted as one unit in the sample size calculation. If infection status varies within households, this will increase precision around our estimates.

The precision (margin of error) that various sample sizes provide around various estimates of infection rates (and seroprevalence) is illustrated in

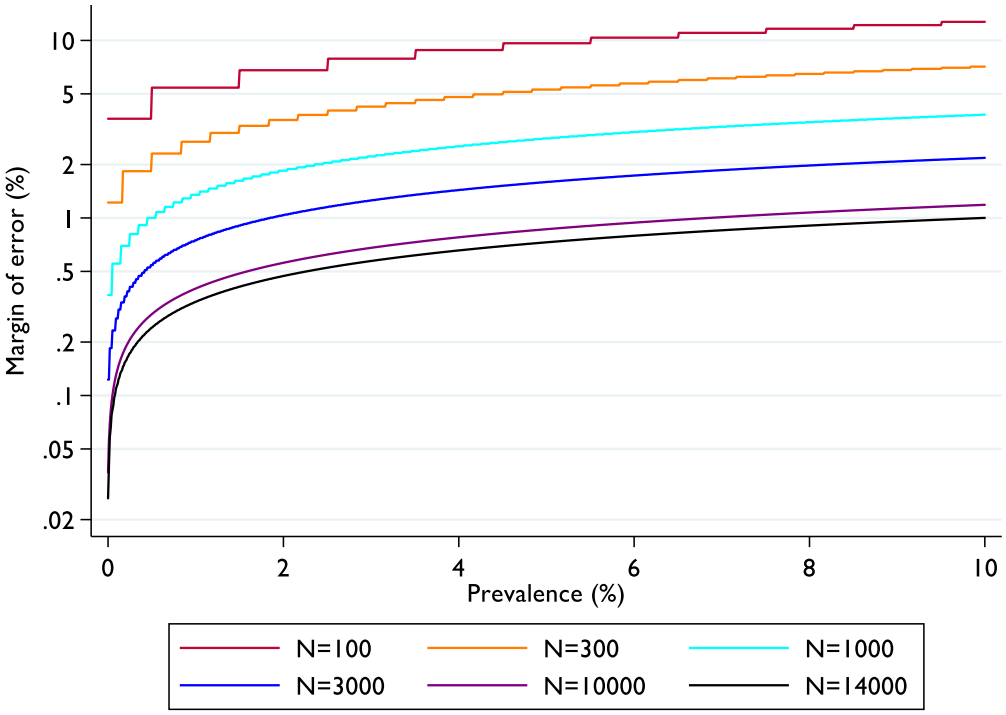
Figure *4* below, together with the precision for smaller sample sizes, which should be achieved for specific regions and/or groups defined by other characteristics such as age. For a given prevalence p and sample size N, the expected margin of error corresponds to the expected width of the 95% confidence interval associated with the point estimate of p obtained using an exact binomial test. On balance, around 11,000 participants in Phase I, and each subsequent cross-sectional survey wave is considered to provide sufficient precision overall, particularly at lower prevalence rates which may be expected at earlier cross-sectional surveys, as well as the possibility of assessing evidence for variation within smaller but very important subgroups. Targeting 11,000 enrolled households based on a 50-60% response rate to the initial 20,000 invitations to participate would also provide good precision if in fact fewer households respond (say 10,000).

For blood sampling for seroprevalence, 1000 enrolled households is considered to provide an acceptable trade-off in terms of precision, given that seroprevalence rates are expected to be higher than infection rates, and so margins of error for the former can be larger than the latter without compromising decision-making.

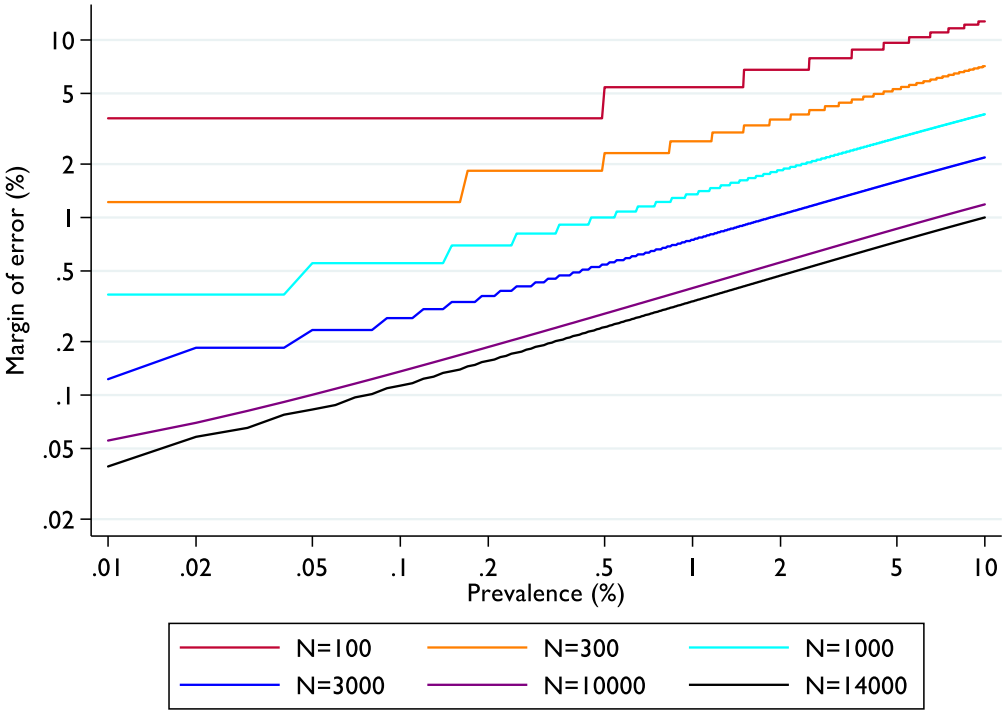
The same sample size is currently planned for each cross-sectional survey in Phase II, based on the same justification.

Figure 4 Impact of sample size on precision for various estimates of prevalence

(a) With prevalence on an absolute scale



(b) With prevalence on a log scale to highlight the impact at low prevalences



Note: straight lines indicate where the denominator does not allow more accurate estimation: eg out of 100 individuals, all true prevalences of under 0.5% correspond to 0/100 individuals.

11.4. Analysis populations

All enrolled participants will be included in analyses, which will adjust for clustering by household. Secondary analyses will be restricted to adults targeted by ONS in the original approach letter.

11.5. Decision points

Analyses will be conducted after each cross-sectional survey, in order to inform the UK's response to the SARS-CoV-2 pandemic. Results will be available to all organisations involved in conducting the research. Decisions regarding subsequent cross-sectional surveys (and any necessary protocol amendments) will be made by the study management group (see section 13.3 below). Decisions will be reached by consensus wherever possible.

11.6. Stopping rules

There are no formal stopping rules for futility, efficacy or lack of power. The final decision to terminate the study will be made by the Department for Health and Social Care.

11.7. The Level of Statistical Significance

A nominal significance level of 5% will be used; however, results will be interpreted based on their 95% confidence intervals rather than using a rigid threshold approach.

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

Analyses will be restricted to complete cases. Missing assay data is expected to be extremely rare, as study health workers will oversee the participant self-swabbing of nose and throat and ask the specific additional questions at the home visit, and study HCP will take blood. The RT-PCR test for virus is being used as a diagnostic and hence has extremely high performance. Sufficient sera will be obtained to re-run the immunological assays in case of initial assay failure. For similar reasons we do not anticipate that spurious data will be obtained.

Standard inverse probability weighting methods will be used to weight observed data back to a representative UK population, based on response to the initial ONS letter in adults originally targeted, their characteristics compared with those to whom the original invite to participate in the ONS surveys, and those characteristics vs the general UK population.

11.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Deviations from the original statistical plan or the statistical analysis plan will be described and justified in the analysis reports.

12. DATA MANAGEMENT

The plan for the data management of the study are outlined below. There is not a separate Data Management document in use for the study.

The signed consent forms will be stored in a locked room at 3 Forbury Place, 23 Forbury Road, Reading, RG1 3JH during the active phase of the study and for 5 years after the end of the study in a secure off site facility maintained by IQVIA. Questionnaire data will be identified only by the household code, a suffix to indicate different household members (A, B, C etc) and the participant's month and year of birth (not personally identifiable). Date of birth, name and address will be held separately using a hierarchically structured database, so that only individuals with appropriate permissions (e.g. arranging home visits) can access it. The questionnaire data will be directly entered onto the IQVIA Voyager, data management system. All study data is stored in secure Voyager with bespoke logins and passwords unique to each user (only IQVIA personnel associated with the programme). Access to the Voyager platform is via recognised equipment and confirmation process in place if accessed via unknown equipment. Passwords are of high complexity and are required to be changed regularly.

ONS sometimes shares selected information with their service providers to help run studies. Sodexo will be responsible for sending voucher compensation. APS and GovDelivery will assist with communication for recruitment. Both will have participant contact details solely in order to undertake this contracted work.

The National Biosample Centre will return nose and throat swab results to ONS, who will pass these onto IQVIA to communicate results to GPs. IQVIA already hold the necessary personal and GP details to enable home visits to be arranged. In order to reduce burden on participants and reduce duplication of effort, we will ask participants for consent to retrieve information from ONS and NHS Digital, to obtain information about their utilisation of NHS services (including Inpatient admissions, outpatient attendances, consultations with a general practitioner, A&E admissions), their ONS mortality status to link to their immunity and infection status. Linkage to NHS records will be done through ONS.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' data are obtained. These include, but are not limited to, hospital records and laboratory records. As the electronic case record form (eCRF) is the site of the original recording of the questionnaire data for this study (i.e. there is no other written or electronic record of data), eCRF entries will be considered source data. All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by their household code, participant suffix, month and year of birth, and not by name.

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

All data capture by IQVIA will be entered on the Voyager platform and uses the robust salesforce.com platform relies on salesforce security measures https://trust.salesforce.com/en/. The system is validated

and compliant with 21 CFR part 11. The platform is also GxP validated. IQVIA has an internal SOP 29 SDLC – System Development Lifecyle and Validation which is reviewed and maintained their IT security team.

The participants will be identified by a unique household code and participant suffix in the database storing questionnaire data. The participant's name, address and contact details, and date of birth will be included in IQVIA voyager platform but this information is primarily for the purposes of communication with participants. Name and date of birth will be shared with ONS for the purposes of linkage to NHS and ONS records, but will not be shared with any third party involved in the study. IQVIA will carry out a data privacy impact assessment on all personal data they collect to minimise the data protection risk to the study.

Electronic data will be stored on IQVIAs Voyager CRM and will remain active for the duration of the study. Participants' identifiable data will then be removed and the data will be archived within the platform to be retained for a period of 5 years.

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.

13.1. Risk assessment

No formal risk assessment is required. The study involves recruiting individuals without symptoms who will be asked to to self-swab their throat and nose and optionally provide a blood sample taken by a study HCP. Further participation in repeated visits to collect the same samples is based on consent of the participant. The main burden of participating in the study is the time taken for the home visit. There is minimal risk of harm to any patient from participating in the survey since it does not include any intervention. The diagnostic test for the presence of virus from the nose and throat swab will be conducted by an accredited laboratory and will be returned to the participant's GP so that they can explain this to the participant. Individual participant results of the immunity assays will not form part of patient care or interfere with routine diagnostic testing, and these results will not be released to the participant or their GP given their experimental nature.

13.2. Study monitoring

No GCP monitoring will be undertaken. As described above, there are minimal risks posed to patients by this observational and non-interventional study. The only data items are either retrieved directly from electronic records (that is, are source documents in their own right against which no monitoring is possible) or are participant responses to a questionnaire which will be completed by study health workers with the participant present and for which the eCRF forms the source document. The inclusion criteria are extremely simple – they will be recorded on the single study case record form. The only study procedures are completing the questionnaire and taking samples – absence of sample by definition means that research procedures were not followed.

13.3. Study Committees

Oversight will be provided by a study management group, including investigators named above as representatives of participating organisations and the key collaborators, and chaired by the Chief Investigator.

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 trial 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 Chief Investigator, 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

Following Sponsor approval the protocol, informed consent form, Participant Information Sheet(s) will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions 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. Other Ethical Considerations

The main study-specific ethical consideration is the inclusion of children; other adult vulnerable participants and participants who are unable to consent for themselves are not eligible. Children are critically important to estimates of both infection status and seroprevalence, and obtaining reliable estimates in this population is essential for informing ongoing school closures amongst other decisions.

At this stage, there is no possibility that the testing will result in incidental findings that would be serious and medically actionable, as only SARS-CoV-2 antibodies will be analysed in the blood sample. Results of the RT-PCT on the nose and throat swab will already be returned to the participant's GP.

16.5. Reporting

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

16.6. Transparency in Research

As the study is non-interventional it will not be registered on a clinical trials site. It will be registered on HRA Summaries (https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/).

16.7. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal

data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.8. Expenses and Benefits

A small compensation (£50 voucher) will be offered to each consenting/assenting participant (including child participants) for each completed enrolment home visit (contact or non-contact) to reflect their time and inconvenience. For each subsequent completed serial sampling home visit, each participant will be offer a £25 voucher. The total compensation per participant would therefore be £50 for a single visit, £150 for five visits over one month and £425 for 16 visits over one year.

17. FINANCE AND INSURANCE

17.1. Funding

Funding is provided by the Department of Health and Social Care. In-kind support is provided by the ONS, the University of Oxford (in particular through the Oxford National Institutes of Health Research (NIHR) Biomedical Research Centre and the NIHR Health Protection Research Unit in Antimicrobial Resistance and Healthcare Associated Infections in collaboration with Public Health England [NIHR200915]) and Public Health England.

17.2. Insurance

The University 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).

17.3. Contractual arrangements

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

18. PUBLICATION POLICY

The Investigators and other relevant representatives of the collaborating organisations will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study funding as detailed in Section 17.1 above. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the study.

20. ARCHIVING

Electronic data for the study will be de-identified and archived in the voyager CRM platform at IQVIA for a period of 15 years after the end of the study. The only paper based forms are the consent forms, which will be stored in a secure off site facility maintained by IQVIA for a period of 5 years after the end of the study.

21. REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; **382**(8): 727-33.
2. World Health Organisation. Coronavirus disease (COVID-19) Situation Dashboard; https://covid19.who.int/. 2020 (accessed 17 April 2020.
3. World Health Organisation. WHO announces COVID-19 outbreak a pandemic;Available from: http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic. 2020 (accessed 31 March 2020.
4. Sjodin H, Wilder-Smith A, Osman S, Farooq Z, Rocklov J. Only strict quarantine measures can curb the coronavirus disease (COVID-19) outbreak in Italy, 2020. *Euro Surveill* 2020; **25**(13).
5. Prem K, Liu Y, Russell TW, et al. The effect of control strategies to reduce social mixing on outcomes of the COVID-19 epidemic in Wuhan, China: a modelling study. *Lancet Public Health* 2020.
6. Public Health England. Guidance and standard operating procedure COVID-19 virus testing in NHS laboratories; https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/guidance-and-sop-covid-19-virus-testing-in-nhs-laboratories-v1.pdf., 2020.
7. Konrad R, Eberle U, Dangel A, et al. Rapid establishment of laboratory diagnostics for the novel coronavirus SARS-CoV-2 in Bavaria, Germany, February 2020. *Euro Surveill* 2020; **25**(9).
8. Lazzerini M, Putoto G. COVID-19 in Italy: momentous decisions and many uncertainties. *Lancet Glob Health* 2020.
9. To KK, Tsang OT, Leung WS, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis* 2020.
10. Wikramaratna P, Paton RS, Ghafari M, Lourenco J. Estimating false-negative detection rate of SARS-CoV-2 by RT-PCR. *MedRvix* 2020; **https://www.medrxiv.org/content/10.1101/2020.04.05.20053355v2**.
11. Li Z, Yi Y, Luo X, et al. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. *J Med Virol* 2020.
12. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; **579**(7798): 270-3.
13. National COVID Testing Scientific Advisory Panel. Antibody testing for SARS-CoV-2 using ELISA and lateral flow immunoassays. *MedRvix* 2020.
14. Thompson C, Grayson N, Paton R, et al. Neutralising antibodies to SARS coronavirus 2 in Scottish blood donors - a pilot study of the value of serology to determine population exposure *MedRvix* 2020; **https://www.medrxiv.org/content/10.1101/2020.04.13.20060467v1**.
15. World Health Organisation. Population-based age-stratified seroepidemiological investigation protocol for COVID-19 virus infection; https://www.who.int/publications-detail/population-based-age-stratified-seroepidemiological-investigation-protocol-for-covid-19-virus-infection [accessed 17 April 2020], 2020.
16. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 2020; **367**(6483): 1260-3.

22. APPENDIX: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made