Study Title: Incidence of COVID-19 (SARS-CoV-2) infection and prevalence of immunity to COVID-19 (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 for National Statistics Survey

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Chief Investigator:	Professor Ann Sarah Walker Professor of Medical Statistics and Epidemiology Modernising Medical Microbiology Research Group, University of Oxford sarah.walker@ndm.ox.ac.uk 01865 851180
Operational Director and Government Liaison	Iain Bell Deputy National Statistician and Director General for Population and Public Policy Office for National Statistics iain.bell@ons.gov.uk
Investigators:	Professor Sir Ian Diamond National Statistician Office for National Statistics ian.diamond@ons.gov.uk Peter Benton Director - Population and Public Policy Operations Office for National Statistics peter.benton@ons.gov.uk

Professor Sir Jeremy Farrar (study clinical lead)
Wellcome Trust
j.farrar@wellcome.ac.uk

Professor Sir John Bell
University of Oxford
regius@medsci.ox.ac.uk

Professor John Newton
Public Health England
john.newton@phe.gov.uk

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

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 the survey in England, Wales and Northern Ireland, as agreed with the Treasury)

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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Chief Investigator	Professor Ann Sarah Walker Professor of Medical Statistics and Epidemiology Modernising Medical Microbiology, University of Oxford Microbiology Research, Level 7 John Radcliffe Hospital, Oxford, OX3 9DU sarah.walker@ndm.ox.ac.uk Tel: 01865 851180
Sponsor	University of Oxford Joint Research Office 1st floor, Boundary Brook House Churchill Drive, Headington Oxford OX3 7GB Tel: 01865 616480 ctrg@admin.ox.ac.uk
Funder(s) (including in-kind support)	Department of Health and Social Care (funding the survey in England, Wales and Northern Ireland, as agreed with the Treasury) 39 Victoria Street London, SW1H OET The Welsh Government (in-kind contribution) Knowledge and Analytical Services, Cathays Park Cardiff, CF10 3NQ The Northern Ireland Assembly (in-kind contribution) Parliament Buildings Ballymiscaw, Stormont Belfast, BT4 3XX Office for National Statistics (in-kind contribution) 1 Drummond Gate, Pimlico London, SW1V 2QQ University of Oxford (in-kind contribution through the Biomedical Research Centre and the Health Protection Research Unit, Director Ann Sarah Walker as above) Dr Vasiliki Kiparoglou, Chief Operating Officer Oxford Biomedical Research Centre, Oxford vasiliki.kiparoglou@ouh.nhs.uk Tel: 01865 572308 Public Health England (in-kind contribution, including through the Health Protection Research Unit) 61 Colindale Avenue London NW9 5EQ

Key Collaborator	Helena Jordan, Medical Solutions Lead, UK and Ireland IQVIA IES UK LIMITED 3 Forbury Place 23 Forbury Road Reading, RG1 3JH Tel: 0118 450 1229 Helena.jordan@iqvia.com
Key Collaborator	Gillian Prior, Director of Surveys, Data and Analysis The National Centre for Social Research (NatCen) 35 Northampton Square, London, EC1V 0AX Gillian.Prior@natcen.ac.uk
Statistics and Design	Professor Ann Sarah Walker (contact details as above) Peter Benton (contact details as above) Dr Julie Robotham Public Health England 61 Colindale Avenue London, NW9 5EQ Julie.Robotham@phe.gov.uk Dr Koen Pouwels Health Economics Research Centre Nuffield Department of Population Health, University of Oxford Richard Doll Building, Old Road Campus Oxford, OX3 7LF koen.pouwels@ndph.ox.ac.uk Dr Thomas House School of Mathematics University of Manchester Manchester M13 9PL thomas.house@manchester.ac.uk
Committees	A study management group will provide oversight, including investigators named above as representatives of participating organisations and the key collaborators, and chaired by the Chief Investigator.
Website	https://www.ndm.ox.ac.uk/covid-19-infection-survey Results available on: https://www.ndm.ox.ac.uk/results

2. LAY SUMMARY

The COVID-19 pandemic has had, and continues to have, a profound impact across the UK. This study aims to find out how many people are still getting 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. The main test used to diagnose COVID-19 uses a swab taken from someone's nose and throat. Once an individual has recovered from the infection, the virus cannot be found any longer. 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 – with other infections, this is what helps them avoid getting the same infection again, although we do not yet know whether the same is true for COVID-19. 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 find out how many people of different ages across the UK have COVID-19 now, particularly as people start going back to work or school, 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 the coming months – 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 20,000 households to participate with an assumed 50% opt-in rate, and a target enrolment of 10,000 households (2,500 per week over around one month). We will ask 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 workers. We will ask adults aged 16 years or older from around 2,000 of these enrolled households (500 per week) 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 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.

After this, in Phase II we will invite new groups of around 5,000 households in England, around 500 households in Wales and around 500 households in Northern Ireland approximately every week, targeting recruitment of around 2,500, 250 and 250 new households per week respectively (total 3,000 households per week; assuming 50% consent rate; numbers approached will be increased if consent rate

is lower to achieve the target enrolment). We will approach 10-20% to also give a sample of blood. 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 COVID-19 **(**SARS-CoV-2) infection and prevalence of immunity to COVID-19 (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 the survey in England, Wales and Northern Ireland, as agreed with the Treasury) The Welsh Government (in-kind contribution) The Northern Ireland Assembly (in-kind contribution) 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 either participated in Office for National Statistics (ONS) surveys or in households that have been randomly selected from databases of addresses.
Sample Size	Phase I will start with 20,000 households in England being approached for the initial cross-sectional survey and approximately 10,000 households being recruited over approximately one month (around 2,500 per week). All consenting/assenting adults, adolescents and children aged 2 years and older within each enrolled household will be recruited (approximately 21, 000 individuals from approximately 10,000 households). In Phase II approximately 5,000 new households in England, around 500 households in Wales and around 500 households in Northern Ireland will be approached approximately every week in new cross-sectional surveys, targeting enrolment of around 2,500, 250 and 250 new households per week respectively (total ~3,000 households per week/~12,000 households per month; assuming 50% consent rate) for one year after the start of Phase I (12 month recruitment period in total for Phase I and II). Numbers approached will be increased if the consent rate is lower to achieve the target enrolment. Thus in both Phases, over 12 months, we expect to recruit approximately 300,000 individuals from approximately 142,000 households.
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 five home visits (cross-sectional survey then optional to repeat visits every week for the next month)

	• for 16 home visits (cross-sectional survey then optional to repeat visits every week for the next 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 for one year from their final study visit to assess use of healthcare, results from tests for COVID-19 infection done within the NHS, and mortality. 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
MHRA	Medicines and Healthcare Products Research Agency
NatCen	National Centre for Social Research
NHS	National Health Service
NISRA	Northern Ireland Statistics and Research Agency
ONS	Office for National Statistics
PHE	Public Health England
PPE	Personal protective equipment
REC	Research Ethics Committee
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
SGSS	Second Generation Surveillance System
SOP	Standard Operating Procedure
WHO	World Health Organisation

5. BACKGROUND AND RATIONALE[i]

The first cases of infection with a novel coronavirus, subsequently designated SARS-CoV-2 (commonly called COVID-19), 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 healthcare 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 pandemic, 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 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 an antibody assay for the IgG immunoglobin in all participants with blood draws; we will also assay neutralising antibodies directly in a subset of participants with blood draws.

In this study, we aim to address crucial unknowns regarding the extent of transmission and ongoing rates of infection in the UK. We will use a repeated cross-sectional survey design. In Phase I, we will invite approximately 5,000 households from England to participate every week with an assumed 50% opt-in rate, and a target enrolment of 2,500 households, providing a cohort of approximately 10,000

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

population-representative households in the first month. In Phase II, over the next 11 months we will recruit new cohorts of approximately 2,500 households per week from England (approximately 10,000 each month) together with approximately 250 households per week from Wales and 250 households per week from Northern Ireland (each approximately 1,000 each month; total households across all regions approximately 3,000 per week and 12,000 per month) 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. Numbers approached will be increased if the consent rate is lower to achieve the target enrolment.In approximately 300-600 enrolled households per week (1,200-2,400 households per month; 10-20%, including 100-200 households per month from each of Wales and Northern Ireland), a trained healthcare professional (HCP) will also collect blood to estimate seroprevalence using 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 enrolment visit (counted as week 0); if further consent is provided, we will continue this sampling at 2 months and every month therafter for 12 months from their first home visit to assess this over the longer term. Infection (nose and throat swab) will be assessed at every visit and immunity (antibodies) every month. We will also approach anyone with a positive test for virus (i.e. new infection) in the study to undergo a blood draw as quickly as possible after their positive test and then at monthly visits to contribute additional information to analyses of how immunity after infection changes over time.

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 to NHS data for one year after the last study visit for each participant to estimate the impact on the NHS and future requirements, to data from Public Health England's (PHE's) Second Generation Surveillance System (SGSS) and equivalent national test databases in Wales and Northern Ireland to ensure that we have information on other tests for SARS-CoV-2, and to ONS and relevant national mortality 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 forward.

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. Non-contact visits will be performed unless a blood draw is scheduled, and to households where anyone is currently symptomatic/self-isolating/shielding (detailed definitions below). Study workers will follow NHS guidance regarding personal 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	Every calendar week from the start of the study, with analysis based on the latest test available in the prior 2 weeks
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 (to estimate re-infection after clearing the virus)	Every calendar week from the start of the study based on all serial samples to date 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 from a ELISA assay for SARS-CoV-2 antibodies assayed from blood, categorised according to predefined thresholds based on pre-pandemic plasma as positive or negative	Every calendar week from the start of the study, based on the latest test available
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*	Each household visit
To estimate the association between immunity to SARS-CoV-2 across individual members of households	Concentrations and thresholds of IgG to SARS-CoV-2 assayed from blood of different members of the same households*	Each household visit

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 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 (to estimate re-infection after clearing the virus) Concentrations and thresholds of IgG from an ELISA assay for SARS-CoV-2 antibodies 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 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 of each participant
To compare immunity to SARS-CoV-2 in the general adult population, as reflected by neutralising antibodies and IgG	Concentration of neutralising antibodies to SARS-CoV-2 assayed from blood, categorised according to predefined thresholds[14] as positive or negative Concentrations and thresholds of IgG from an ELISA assay for SARS-CoV-2 antibodies assayed from blood	Specific study visits where neutralising antibody assays performed

* estimated from statistical random effects models, see Section 11.

7. STUDY DESIGN

The overall study design is repeated cross-sectional surveys of representative households across the UK, identified either by one adult from the household having participated in existing ONS surveys and providing consent for future contact regarding research or by the household being randomly selected from a commercially available source such as AddressBase, which is maintained by the Ordnance Survey, or equivalent databases including in the Devolved Administrations. This will ensure that the sample remains representative in terms of the country throughout its duration and also facilitate proportionate increases where there is evidence of increasing prevalence in Phase II, as described below.

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 because it is essential to understand prevalence and incidence of symptomatic and asymptomatic infection in children, particularly to inform regarding continuation of school closures.

These cross-sectional surveys will be repeated over time, recruiting new households each week, 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) after their enrolment visit (week 0) 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 thereafter 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. Wherever possible, in order to reduce risks to participants and study workers, home visits will be “non-contact” visits where study 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. Where a blood draw is scheduled, a “contact” visit will take place where the study worker enters the household. However, if anyone in the household is symptomatic, self-isolating or shielding on the date of a home visit date where a blood draw is planned, a “non-contact” visit will be conducted and blood will not be drawn.

At every visit (contact or non-contact), all participants will take 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 workers of contracting SARS-CoV-2 from an asymptomatically infected individual. In a subset of households, 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 was 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. In subsequent surveys, of the 6,000

households invited to participate each week (24,000 per month), approximately 600-1200 households per week (2,400-4,800 per month; 10%-20%; including 200-400 households per month from each of Wales and Northern Ireland) will be randomly selected to receive an invitation for adults aged 16 years and older in the household to have a blood draw, as well as for all individuals 2 years and older to self-swab, targeting enrolment of a minimum of 300 households per month for blood sampling (10% of the target enrolment; including at minimum 50 households per month from each of Wales and Northern Ireland). All households who are approached for blood sampling will be included if anyone in the household is willing to provide consent for blood draws, and blood will be drawn from all participants in the households selected for blood sampling who are willing to provide blood, so the precise percentage randomly selected to receive this invitation will be adjusted based on opt-in rates in Phase II. If participants consent 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**.

In order to contribute additional information to analyses of how immunity after infection changes over time, and reflecting the fact that prevalence of infection is low (as expected) during the study to date, the household of any participant with a positive nose and throat swab for virus during the study (either from a study sample or from a test result linked to study data from national databases) would also be approached for consent for a blood draw as quickly as possible after the first positive test in the household and then at subsequent monthly visits to the end of their participation. Each individual participant within these households would make their own decision about agreeing to these additional blood draws or not, but the entire household would be approached.

Given the scale of Phase II and the fact that it will run across the Devolved Administrations, two different organisations (IQVIA and NatCen) will lead on fieldwork. The volume of fieldwork means they will each be supported by a number of similarly-qualified data collection organisations (see Section 12). Each household will be managed by one lead organisation only; IQVIA will manage all households randomly selected for blood draw and IQVIA and NatCen will share the management of households not randomly selected for blood draw. Each household will be allocated to one lead organisation before they are invited to participate in the study. Each organisation will manage fieldwork through their own specific call centre, and the specific number for each will be provided on the household's invitation letter and participant information. Any NatCen-managed household where a participant has a positive nose and throat swab during the study and agrees to give blood would move from NatCen to IQVIA management. They would reconsent with IQVIA, in order to provide consent for blood sampling.

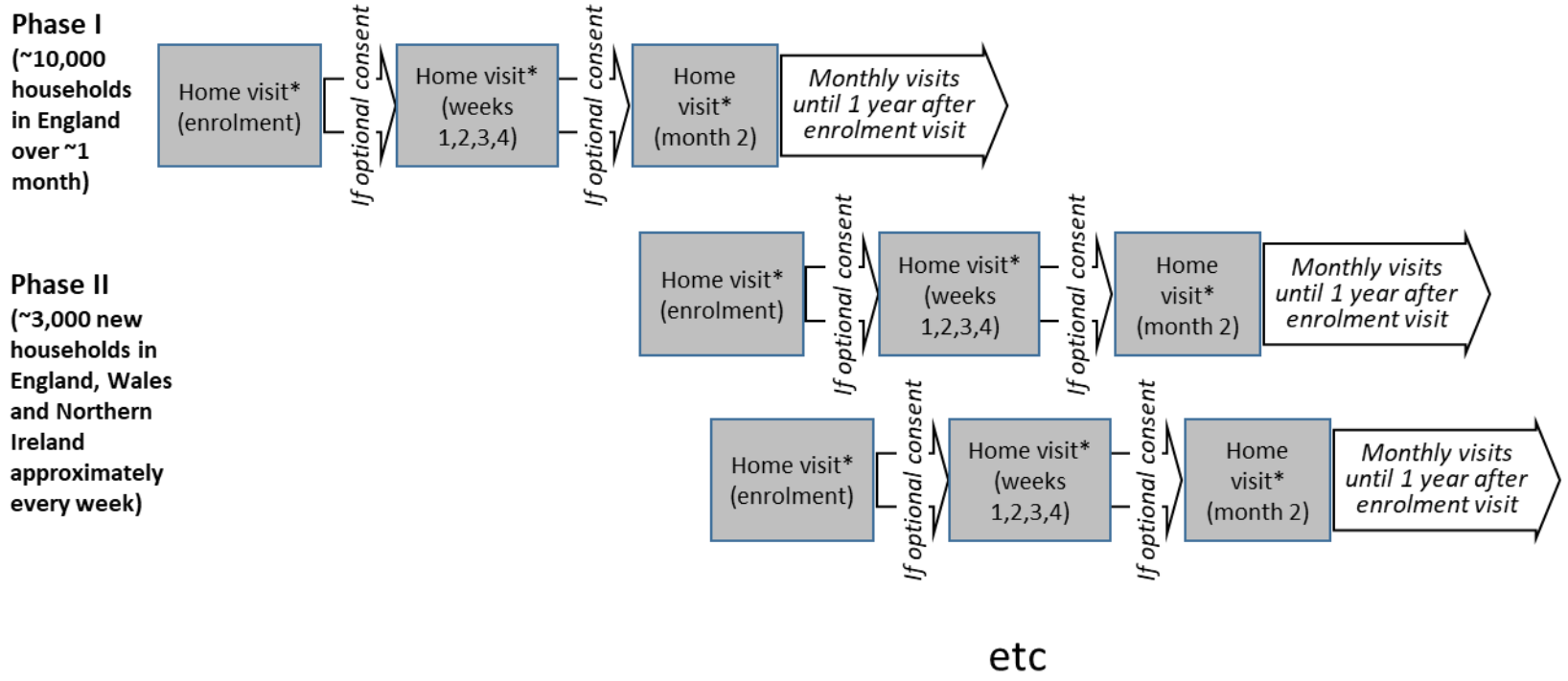
Participants who consent to one cross-sectional survey would have just one visit. Participants who consent to serial sampling would have either have five study visits over one month (enrolment, weeks 1, 2, 3, 4) or 16 study visits over one year (enrolment; weeks 1, 2, 3, 4; then every month from 2 to 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 approach to 20,000 households from England in Phase I, aiming to enrol 10,000 households (approximately 2,500 per week over one month), 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% response rate. All eligible participants in these households who consent to serial sampling will be included in the serial sampling component, and approximately 2000 households from the ONS Opinions

COVID-19 survey who were approached for consent to the blood draw will be included in that component.

In Phase II, sampling will be from households who have participated in ongoing and further ONS surveys and from databases of addresses. Sampling will be stratified by geographical location in order to provide more precise regional estimates of incidence and seroprevalence. Sampling will also be stratified by ethnicity to ensure sufficient numbers for appropriate representation in final weighted estimates of prevalence. During Phase II, sampling may be proportionately increased in regions or occupations or other groups with any evidence of increasing prevalence, in order to provide greater certainty regarding the probability of increasing infection rates as opposed to sampling variation.

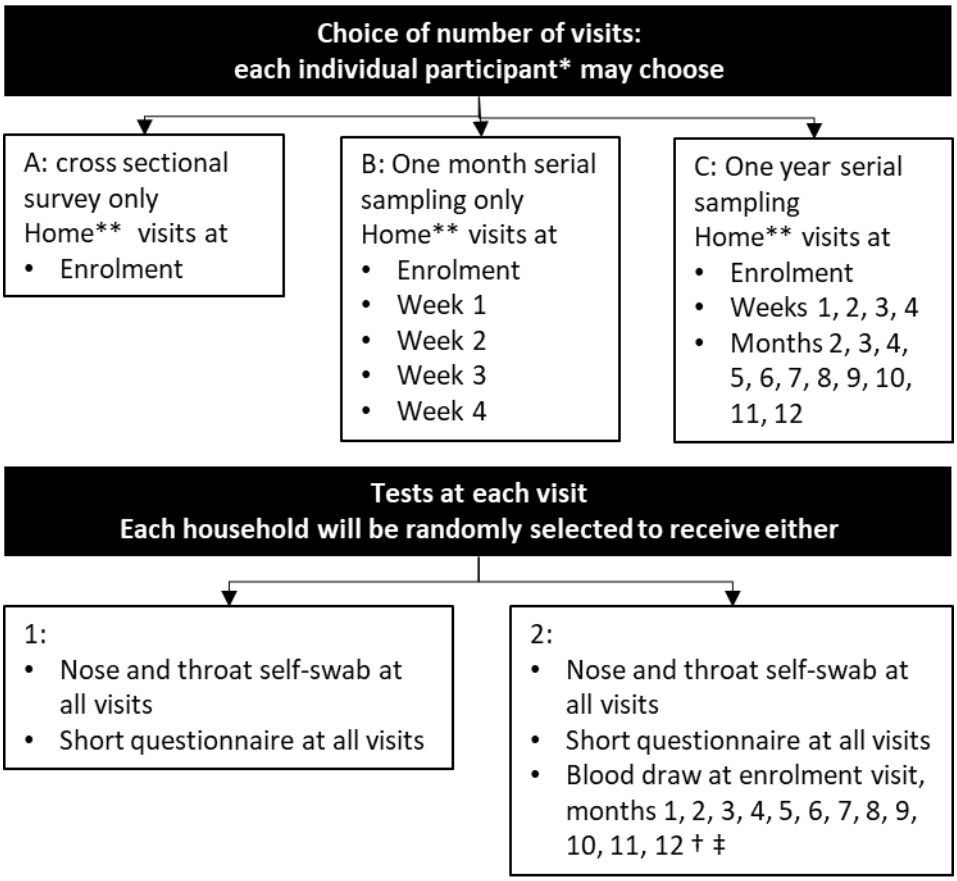
Figure 1 Repeated cross sectional survey design



* Unless a blood draw is scheduled, home visits will be non-contact (participant self-swab of nose and throat, questionnaire; study worker stays 2m away from household at all times). Contact home visit will include participant self-swab of nose and throat, questionnaire and blood draw.

Note: in Phase I a single invitation letter was sent simultaneously to 20,000 households, with households then enrolled at ~2,500 per week for 4 weeks. In Phase II, approximately 5,000 invitations will be issued per week with continuous recruitment from these isseus, hence Phase II is shown on multiple lines.

Figure 2 Serial sampling frequency and tests



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

** Unless a blood draw is scheduled, home visits will be non-contact (participant self-swab of nose and throat, questionnaire; study worker stays 2m away from household at all times). Contact home visit will include participant self-swab of nose and throat, questionnaire and blood draw. If anyone in the household is symptomatic, self-isolating or shielding, then the visit will be non-contact even if blood draw was scheduled.

† Blood draw in those aged 16 years and older. 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.

‡ All participants from households where any individual tests positive for virus (new infection) on a nose and throat swab will also be approached for optional consent for a blood draw as soon as possible and then at further monthly visits to the end of their original follow-up.

Note: in Phase I, selection of households to be approached for blood draw was based on previous participation in one of the surveys from which households were drawn. This is random with respect to household.

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 either participated in an ONS Survey and has consented to be approached for future research or where the household has been randomly selected from databases of addresses.

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 in England, inviting 20,000 households to participate with an assumed 50% opt-in rate, and a target enrolment of around 10,000 households, around 2,500 per week over one month (expect ~21,000 individuals).

In Phase II, the target is to recruit all adults, adolescents and children aged 2 years or older from a new set of approximately 3,000 enrolled households per week in England, Wales and Northern Ireland (expect ~25,000 individuals) for 11 months (total 12 months from the start of Phase I) (Figure 1). Numbers approached will be increased if the consent rate is lower than 50% in order to achieve this target enrolment.

8.2. Inclusion Criteria

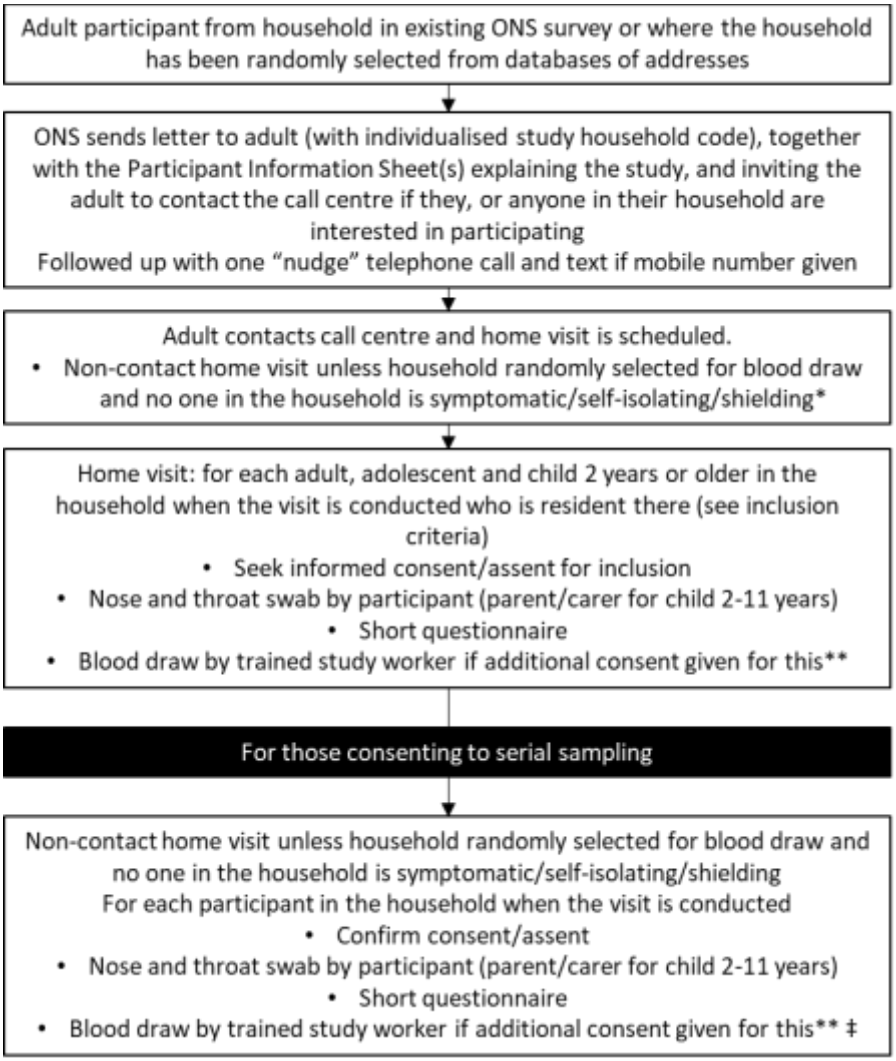
- Adult, adolescent or child aged 2 years or older, male or female
- Currently resident in a household where a household member has participated in an ONS Survey and has consented to be approached for future research or where the household has been randomly selected from databases of addresses. 'Currently 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



* Unless a blood draw is scheduled, home visits will be non-contact (participant self-swab of nose and throat, questionnaire; study worker stays 2m away from household at all times). Contact home visit will include participant self-swab of nose and throat, questionnaire and blood draw. If anyone in the household is symptomatic, self-isolating or shielding, then the visit will be non-contact even if blood draw was scheduled.

** Blood draws planned in a minimum of 300 enrolled households per week. Households will be randomly selected before being invited and therefore each household with either be approached for swabs and blood or swabs alone. As the consent rate for blood is not known in Phase II, 10-20% of targeted households will be invited to consent for blood samples: all invited households who consent will be included in blood draws.

‡ All participants from households where any individual tests positive for virus (new infection) on a nose and throat swab in the study will also be approached for optional consent for a blood draw as soon as possible and then at further monthly visits to the end of their original follow-up.

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 week, see Figure 1)

	Initial letter from ONS	Telephone contact with call centre †	Enrolment home visit*	Week 1, 2, 3 home visit	Week 4/month 1, months 2-12 home visit
All participants					
Participant Information Sheet(s) (including Welsh translation for households in Wales)	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 is in a household randomly selected for blood sampling, is 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 is 16 years or older and provides consent, and is either in a household randomly selected for blood sampling, or is from a household where a participant has had a positive nose and throat swab in the study (see Figure 2)					X*

† A contact email will be available for those unable to telephone (eg due to hearing or speech impairment). Each household's invitation letter and participant information sheet will have the specific call centre number for either IQVIA or NatCen.

* 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 workers stay 2m away from household at all times).

9.1. Recruitment

Households will be recruited from databases of addresses (Phase II) and existing and ongoing ONS surveys, including their Opinions COVID-19 Survey in Phase I. This survey is 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 Phase I of 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 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 at least May and June 2020. Given its size and scale, Phase II will extend this approach to sampling, by continuing to recruit individuals who have indicated that they are willing to be approached about future studies from other ONS surveys and also include participants in the Devolved Administrations, and also by selecting households randomly from a commercially available source such as AddressBase, which is maintained by the Ordnance Survey, or equivalent databases including in the Devolved Administrations. This will ensure that the sample remains representative in terms of the country throughout its duration and also facilitate proportionate increases where there is evidence of increasing prevalence.

In both phases, ONS will send a letter to all targeted households, explaining the nature of the study, together with the main Participant Information Sheet and a short summary of the study and will follow this up with one telephone call following standard practice. Welsh translations will also be sent to households in Wales. Only the short summary and the Participant Information Sheet for adults 16 years and older will be sent (and not other Participant Information Sheets), since the point of contact from previous surveys is an adult or the household as a whole in Phase II and it will not be known whether there will be children or adolescents in the household. This Participant Information Sheet 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 household will be assigned a unique code at the point they are selected to be approached for the study: this code will be used on all subsequent study correspondence. (After recruitment, different household members who consent to participation will be uniquely identified by a pseudonymised study number.) The invitation letter will ask the targeted adult to telephone the call centre if they or anyone in their household are interested in taking part. A contact email will be available for those unable to telephone (eg due to hearing or speech impairment). 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.

When the targeted adult or anyone else from the household telephones the call centre, any immediate questions will be answered and a home visit from a study worker will be arranged. Verbal consent will be obtained for this home visit, and documented. Home visits will be of two types

- At a non-contact home visit, the 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 in Phase I) and study workers will administer the short questionnaire (details below). For children aged 2-11 years, the parent/carer will self-swab the child (minimising risk to study workers) and will complete the questionnaire on behalf of the child. Study workers will stay 2m away from household at all times, passing the necessary equipment to the participant(s). In practice in Phase I, non-contact visits have either been conducted at the doorstep, or the study worker has telephoned the household from their car for the majority of

the visit, coming to the doorstep only to pass over consent/assent forms (enrolment only) and the self-swabbing materials, with the choice left to the individual participants in the household. Given its acceptability and the fact that the information collected in the study has a low risk for confidentiality (the questions about health are about COVID-related symptoms now and in the past), a similar approach will be used in Phase II.

- At a contact home visit, the same procedures will be followed but the study worker will enter the home to take blood.

Non-contact home visits will be conducted if anyone in the household reports being symptomatic, self-isolating or shielding on the planned home visit date, and at all other visits where it is possible to do so in order to minimise risks to participants and study workers. 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, or loss or change to sense of taste and/or smell. 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 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 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 analysed according to the date the household was enrolled (first study visit).

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 or NatCen (responsibility delegated to IQVIA or NatCen from the Chief Investigator and Sponsor). An Informed Consent document will be signed; either the original paper form will left at the household with the participant (or parent/carer) and the consent form scanned securely to obtain the research copy or one physical copy will be left with the participant (or parent/carer) and one kept as the research copy (eg using carbon copies). Where a participant tests positive and agrees to provide blood samples, they will be transferred to IQVIA management and will reconsent (see also Section 7).

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 visit will not be included.

Written versions of the Participant Information Sheets will be presented to the participants together with 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: If they are registered with a GP, for the study 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). Individuals who are not registered with a GP may still join the study.
- Required: For linking their data and sample results from this study to data already held by ONS and relevant national mortality databases (because this is where we will obtain geographic data from, and to obtain overall mortality and cause of death), to NHS records (and equivalent national databases in Devolved Administrations such as the Health and Social Care in Northern Ireland) for 12 months from their last home visit (in order to assess the impact of results gained from the study on future healthcare utilisation) and to PHE and equivalent national test databases in Wales and Northern Ireland from the beginning of 2020 to 12 months from their last home visit to ensure that we have information on other tests for SARS-CoV-2. It will be stated in the Participant Information Sheet that this linkage will require the study to hold address, sex and date of birth.
- If household selected for blood sampling: Optional: Blood sampling in those 16 years and older (where requested)
- If household selected for blood sampling: 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.
- Optional: If they test positive for COVID-19 (swab or antibody), for the study to approach them in future with details of other ethically approved COVID-19 research studies for them to consider for potential participation (see below)

The reason for asking whether individuals would be happy to be approached in future for other ethically approved COVID-19 related research studies if they test positive for COVID-19 is because several other studies are trying to recruit individuals with mild or asymptomatic infection, for example, for human genetic studies led by Genomics England (https://www.genomicsengland.co.uk/covid-19/). A very small percentage of participants in this study will have infection and therefore it is not feasible to take, for

example, blood for human DNA analysis in all participants. However, if participants indicate that they are happy to be approached for future ethically approved research if they test positive, this study would forward to them information about other ethically approved studies for their consideration.

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 to discuss participation in the study. Age appropriate documentation will be brought to the visit for adolescents and children. It is not possible to give potential participants unlimited time to consider the study at the home visit. 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

There is no intervention.

Whether a household is approached for blood sampling is randomly allocated.

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 (one swab from the nose and throat). These kits are identical to those currently being used successfully for self-swabbing in those aged 12 years and older at the drive through testing centres and in Phase I. 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 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 be labelled with a unique barcode (for this sample) linked directly to the participant's unique study number on the study database, date of sampling and month and year of birth. Results from this accredited test will be returned to the participant's General Practitioner (GP) (if they are registered with them) by secure NHS email or letter. We will also ask whether the participant is happy to provide a mobile number in order to send results directly to the participant by mobile message in the near future (currently in progress).

The study 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]

The following questions will be asked at enrolment, with only changes (where relevant) being elicited at any follow-up visits:

- Date of birth (required for unique participant identification and for linkage to NHS/ONS/PHE records and those from relevant databases in Devolved Administrations); gender; ethnicity; occupation (available from ONS for the adult targeted in the original letter, but not for the rest of the household)
- Do they think/know they have been infected by COVID-19? 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), chest pain, headache, nausea/vomiting, abdominal pain, diarrhoea, loss of taste, loss of smell, other symptoms)
    - If yes, did they contact the NHS about this (suspected) COVID-19 infection? Yes/No
    - If yes, were they tested? Yes/No
        - If tested, were they positive/negative/test failed/results not yet received?
    - If yes, were they hospitalised Yes/No?

- Name and address of GP (to inform of participation and return results), if registered with a GP
- Mobile telephone number if participant would like to be informed directly of their swab test results, or those of their children in future (results will be returned identified by month and year of birth only (not person-identifiable))
- Email if participant would like to receive vouchers for participation directly (see Section 16.8)

The following questions will be asked at each follow-up visit (including the enrolment visit):

- Is the participant currently symptomatic or self-isolating? If self-isolating is this because of symptoms in self or others in the household
- 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, other symptoms) or since the last visit, or otherwise consider that they currently have COVID-19
- Have they recently been in contact with someone that they definitely know (based on a positive test) or suspect (no positive test) was infected with COVID-19 at the time of contact? Yes/No for each type of contact and for each
    - If yes, date of last contact
    - If yes, was this someone in their own household or someone outside their household
- Working status (employed, not working, retired, student etc) and work location (at home, outside of home etc), including number of days per week usually spent working outside the home or at school/nursery, and mode of transport to get to work/school/nursery
- Healthcare and social care contacts including currently working in health/social care in roles which primarily directly interact with patients/residents/clients or not, recently visited hospital or residential/nursing care home
- Contacts with other individuals inside the household (eg social distancing within the household) and outside the household, including through work, school/nursery, shopping, exercise etc

including duration and number of individuals, how easy they find it to maintain social distancing and use of face coverings or masks
- Do they have long-term health problems, and do these limit their activities?
- Current smoking status?
- Have they recently travelled abroad? If yes, to which countries?
- Have they received a vaccine against COVID-19?

Household postcode (required at the level of outward portion and first number of the inward portion 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 in households randomly selected for blood draws 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 a unique barcode (for this sample) linked directly to the participant's unique study number on the study database, date of sampling and month and year of birth (not personally identifiable). Results from these antibody tests will be returned to participants once the assay has been approved by the Medicines and Healthcare Products Research Agency (MHRA) (submission planned; stated in the Participant Information Sheet) in the same way as for the swab test results.

9.7. Baseline Assessments

The procedures above will be conducted at the enrolment home visit, according to whether it is a contact or non-contact home visit. If it is not possible for blood to be drawn at the enrolment visit, it may be drawn up to 10 days after the enrolment visit (for example, at the week 1 visit (allowing the window below) if the participant has consented to further follow-up; any time within this window is allowed if the participant prefers an additional 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 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 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 the call centre contacting the participant to make arrangement for a visit by the study workers, or directly with the household's study worker, 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, or whether blood sampling is planned, or household preference.

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 sent directly to the National Biosample Centre at Milton Keynes, using packaging and transport in accordance with Category B transportation regulations (https://www.gov.uk/government/publications/wuhan-novel-coronavirus-guidance-for-clinical-diagnostic-laboratories/laboratory-investigations-and-sample-requirements-for-diagnosing-and-monitoring-wn-cov-infection). At Milton Keynes, 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, based on tagged and purified recombinant SARS-CoV-2 trimeric spike protein in a high throughput assay.[13,16] Antibody binding to the S protein is detected with ALP-conjugated anti-human IgG. Serum from a subset of samples 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 material (sera and spun cells) will be stored at the University of Oxford.

In both laboratories, assay results will be returned to ONS identified only by the unique barcode and date of testing. 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) values.

Throat swab results will be returned to the participant's GP as described above. In the near future, we will also return results directly to participants by text message if they are happy to provide a mobile number for this (currently in progress). The Participant Information Sheet will contain standard advice that the entire household need to isolate if anyone tests positive. After the enrolment visit, IQVIA or NatCen will email or write to the GP informing them that the participant has been enrolled in the study and providing the enrolment swab results. Subsequent swab test results will similarly be returned to GPs and participants as will blood test results once the assay has been approved by the MHRA.

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 or even die (since there is no age limit on participation). Finally, participants may withdraw from the study simply because they leave the household which was originally sampled – it is the physical household location that is sampled so if they move, their participation finishes. 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.

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. If a participant dies, immediate visits will be cancelled, and the household will be written to, asking them to call the call centre if they would like to restart visits, but that otherwise we will not make further contact. This provides family members with the freedom to make their own personal decision about further participation.

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 (or parent/carer swab of a child) 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. There is no formal Statistical Analysis Plan.

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) based on the latest result in the last two weeks will be summarised approximately every calendar week from the start of the study, overall and by geographical region. Proportions will be calculated incorporating sampling weights for the original ONS surveys, this survey and for non-response to this survey, with 95% confidence intervals estimated using the Korn-Grauberd method which allows for the low anticipated positivity rates. We will use Bayesian methods in sensitivity analyses assessing the impact of plausible ranges of test sensitivity and specificity on results, incorporating both the assay performance and the fact that participants are self-swabbing. Associations between various predictors and ever testing positive for infection vs never testing positive will be estimated using unweighted proportions and Fisher's exact tests with multivariable logistic regression models to adjust for confounding. Factors considered will include sex, ethnicity, age at last birthday (2-11, 12-19, 20-49, 50-69, 70+ years) and other responses to the short questionnaire. Multi-level regression with post-stratification will be used to investigate changes in positivity rates by these different factors over calendar time. 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 based on the optical density readings from the ELISA assay for IgG antibodies versus the threshold defined in comparison with pre-pandemic plasma. As immunity is generally considered to persist, all previous results will be considered for analyses rather than just restricting to tests done in the last 2 weeks. We will also estimate the proportions with previous infection (as defined by antibodies) but no previous symptoms.

Random effects linear regression models will also be generated for the absolute optical density readings (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.

Incidence will be calculated using standard Poisson models based on total time at risk in the study in those negative on their nose and throat swab at enrolment through to their last negative test or their first positive test. Time at risk will be divided by calendar day; a smooth continuous relationship with calendar date will be estimated using natural cubic splines.

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 (and equivalent national databases in Devolved Administrations such as the Health and Social Care Board in Northern Ireland), 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. Through linkage to records from PHE and equivalent national test databases in Wales and Northern Ireland on other tests for SARS-CoV-2, we will ensure that we obtain as accurate as possible associations between infection and immunity.

11.3. Sample Size Determination

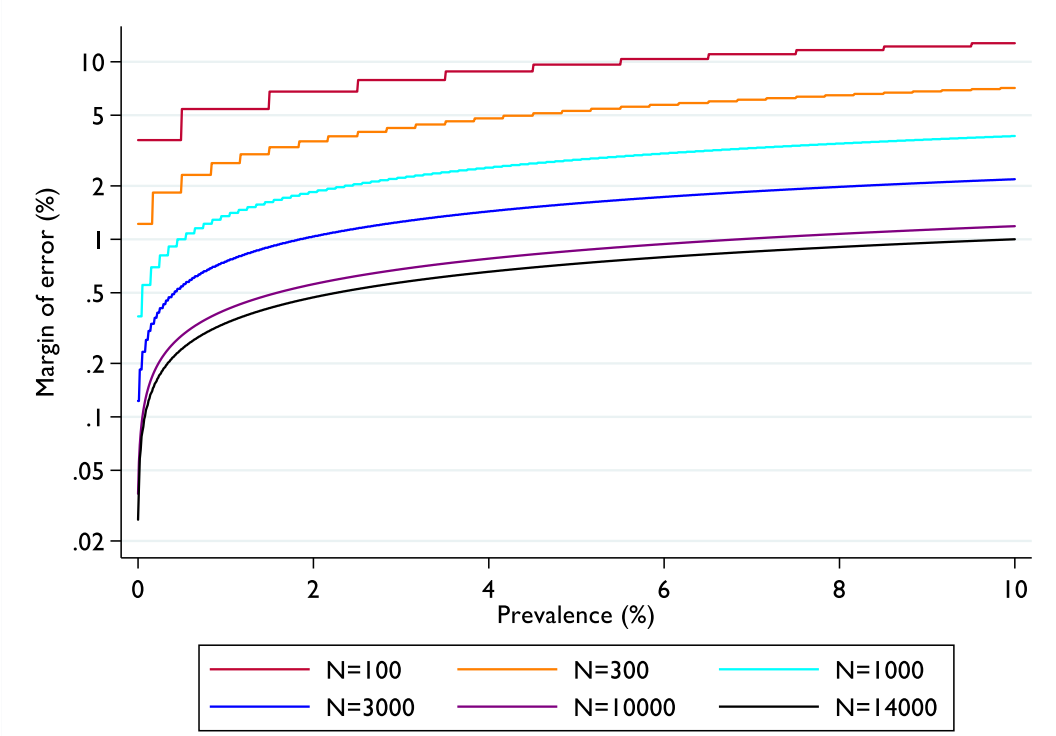
The target sample size for Phase I (around 10,000 households enrolled over one month) was determined based on a conservative assumption that all members of the same household have the same infection status, and therefore each household should only be counted as one unit in the sample size calculation. 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 10,000 households in Phase I (around 21,000 individuals), and around 12,000 households (25,000 individuals) each subsequent month (3,000 per week) in Phase II, 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, including regions and Devolved Administrations (each targeting ~1000 households per month, ~2,100 individuals per month). Sampling may be increased in regions or occupations with any evidence of increasing prevalence, in order to provide greater certainty regarding the probability of increasing infection rates as opposed to sampling variation.

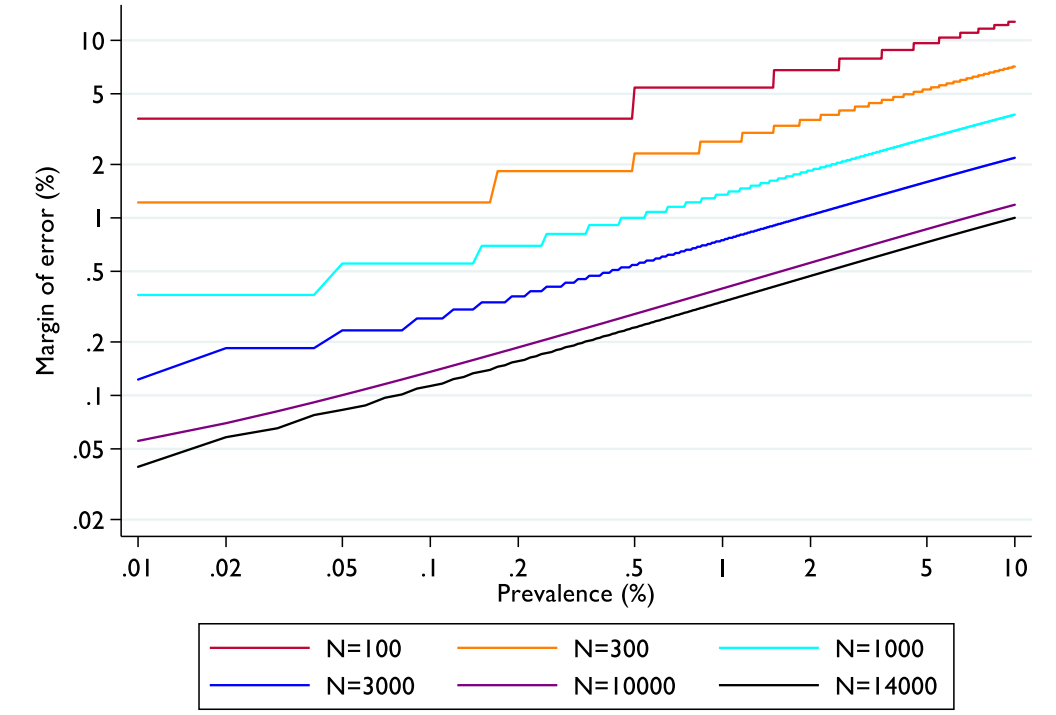
For blood sampling for seroprevalence, a minimum of 1200 enrolled households per month (300 per week) is considered to provide an acceptable trade-off in terms of precision, given that seroprevalence rates are expected to be higher than infection rates, and so margins of error for the former can be larger than the latter without compromising decision-making.

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. A secondary analysis will also be conducted de-duplicating to one individual per household restricting to adults targeted by ONS in the original approach letter.

11.5. Decision points

Interim analyses will be conducted at least twice a month by statisticians and analysts from the ONS, the University of Oxford and Devolved Administrations (results summarised on https://www.ndm.ox.ac.uk/results) in order to inform the UK's response to the SARS-CoV-2 pandemic. These interim analyses will follow a standardised format, and will particularly consider prevalence in key subgroups defined by age, sex, ethnicity, occupation, region and symptoms. 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 of Health and Social Care following appropriate consultation and agreement with the Welsh Government and the Northern Ireland Assembly.

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 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.

Regular checks for data quality will be run on the small amount of predominantly self-reported data collected (see section 9.6.1). Standard range checks and plausibility checks will be run on all data fields as part of routine data processing for interim analyses. For participants agreeing to serial sampling, consistency between visits will also be checked. Given the short-time scales of the study visits, last observation carried forward and backward will be used to impute any missing data.

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 statistical plan above 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.

Given the scale of Phase II and the fact that it will run across the Devolved Administrations, two different organisations (IQVIA and NatCen) will lead on fieldwork. In order to cover the volume of fieldwork, both organisations will sub-contract some of the field work. IQVIA sub-contractors will use the IQVIA Voyager database. NatCen will sub-contract some fieldwork to Kantar Public, Ipsos-MORI, ONS and the Northern Ireland Statistics and Research Agency (NISRA) who may have their own secure databases in their own system, but all built to provide the same study data to a common format. Each lead organisation will take responsibility for specific sub-groups of the sample so that each household will be managed by one lead organisation only. Each lead organisation will manage fieldwork through their own specific call centre, and the specific number for each will be provided on the household's invitation letter.

The signed consent forms will be stored in secure facilities for 5 years after the end of the study by IQVIA or NatCen for their respectively households. Questionnaire data will be identified only by the household and participant code. Date of birth, name and address will be held separately using a hierarchically structured database or equivalent form of access-controlled network structure, so that only individuals with appropriate permissions (e.g. arranging home visits) can access it. The questionnaire data will be directly entered onto the each organisation's secure data management system (IQVIA Voyager, NatCen Blaise/Unicorn Intelligence). All study data is stored with bespoke logins and passwords unique to each user (only personnel associated with the programme). Access to each platform is via recognised equipment and confirmation process in place if accessed via unknown equipment.

ONS, NatCen and IQVIA sometimes share selected information with their service providers to help run studies. Sodexo (contracted by ONS) will be responsible for sending voucher compensation. HH Global and GovDelivery (contracted by ONS) will assist with communication for recruitment. UK Geographics (contracted by NatCen) will divide the NatCen households into regional clusters for study workers, including from their sub-contracted organisations. Both IQVIA and NatCen may use Serco to help resource the call centre (although in the case of IQVIA this will be done through access to the IQVIA Voyager database). All 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, NatCen and IQVIA to communicate results to their GP (if registered) by letter or secure email to an NHS email address and in the near future to participants (or their parent/carer, where applicable) via mobile phones where they have agreed to this. NatCen and IQVIA will already hold the necessary personal and GP details to enable home visits to be arranged. However, at present IQVIA has the ability to contact GPs and NatCen to send mass text messages, and therefore, to enable return of results to GPs/participants as quickly as possible, at present the necessary personal and GP details to facilitate this will be shared between IQVIA and NatCen. The University of Oxford will return antibody results to ONS, who will pass these onto IQVIA and NatCen for return to participants once the test is approved by the MHRA.

In order to reduce burden on participants and reduce duplication of effort, we will ask participants for consent to retrieve information from ONS, NHS Digital and PHE and equivalent national databases in Wales and Northern Ireland (the Health and Social Care Board, Business Services Organisation (which holds data from the Health and Social Care Trusts in the data warehouse), and NISRA (mortality data), to

obtain information about their utilisation of NHS services (including inpatient admissions, outpatient attendances, consultations with a general practitioner, A&E admissions), their mortality status to link to their immunity and infection status and other tests for SARS-CoV-2. Linkage to NHS and test 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. Paper versions of the CRF will be available in case of failure of electronic systems. On all study-specific documents, other than the signed consent and primary household form, the participant will be referred to by their household code, participant study number, month and year of birth, and not by name. Name is required to be captured on the primary household form (where consent is documented) as this is needed for linkage, as stated in the Participant Information Sheet.

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

For IQVIA managed households, data capture will be entered on the IQVIA Voyager platform. This uses the robust salesforce.com platform and 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. For NatCen managed households, all data will be collected in compliance with the requirements of ISO27001 and only organisations certified to this standard will be allowed to support NatCen.

The participants will be identified by a unique household code and participant study number in the database storing questionnaire data. The participant's name, address and contact details, including mobile telephone number for return of results and email address for vouchers if participants are willing to provide these, and date of birth will be included in each database 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 (ONS already holds household address), but will not be shared with any third party involved in the study. Email addresses will be returned to ONS for provision of incentive vouchers, and these will be shared with the third parties described above that provide these services. IQVIA and NatCen will carry out a data privacy impact assessment on all personal data they each take the lead on collecting to minimise the data protection risk to the study.

Electronic data will be stored on each database and will remain active for the duration of the study. Participants' identifiable data will then be removed and the data will be archived within each platform to be retained for a period of 5 years. This is under the joint data controllership of the University of Oxford

and ONS. The University of Oxford will not process or retain any personal data. It is definitionally a data controller as sponsor of this research. ONS sets out in its privacy information its scope of processing, including for secondary purposes (https://www.ons.gov.uk/aboutus/transparencyandgovernance/dataprotection).

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, relevant regulations and standard operating procedures.

13.1. Risk assessment

No formal risk assessment is required. The study involves recruiting individuals at low risk in the community (rather than in a healthcare setting) who will be asked 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 discuss this with the participant, as well as to the participant themselves in the near future (or parent/carer, for children) if they are happy to provide a mobile phone number for this. Individual participant results of the immunity assays will not form part of patient care or interfere with routine diagnostic testing, and these results will be released to the participant and their GP following approval by the MHRA.

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 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 any relevant 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 and assent form, Participant Information Sheets and summary 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, either directly in the near future or through their 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. The protocol and participant information sheets are available on https://www.ndm.ox.ac.uk/covid-19-infection-survey. 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) wherever it is possible to do so, with person-identifiable information required for linkage held in an access-controlled structure. 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 offered a £25 voucher. Vouchers can be posted to participants, but we will offer them the option of receiving the vouchers more quickly by email if they are happy to provide an email address (purely for this purpose). 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 for the survey in England, Wales and Northern Ireland is provided by the Department of Health and Social Care, as agreed with the Treasury. In-kind support is provided by the Welsh Government, the Northern Ireland Assembly, 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 academic publications arising from the study. Authors on academic publications will acknowledge that the study funding as detailed in Section 17.1 above. Authorship of academic publications will be determined in accordance with the International Committee of Medical Journal Editors 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 database platforms at IQVIA and NatCen for a period of 15 years after the end of the study. The only paper based forms are consent forms, which will be stored in a secure off site facility maintained by IQVIA ot NatCen (for their respective households) 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
SA01	2.0	9 June 2020	Ann Sarah Walker	Title amended to include "COVID-19" at the request of the Research Ethics Committee, also Section 3 (Synopsis)
				P1: Jeremy Farrar formally named as clinical lead
				P2,6, Section 3: Additional in kind funding from the Devolved Administrations
				P7: additional key collaborator NatCen; resulting change of reference to IQVIA to 'call centre' to accommodate both organisations leading different parts of the fieldwork.
				Sections 2, 3, 5: amendment of recruitment in Phase I to ~5,000 households from England being approached per week and ~2,500 being enrolled rather than ~20,000/~10,000 per month for logistic reasons. In Phase II ~5,000 households from England, ~500 from Wales and ~500 from Northern Ireland will approached per week, targeting ~2,500, 250 and 250 being enrolled respectively.
				Sections 3, 5, 9.3, 9.6.1, 11.2: clarification that results of tests for COVID-19 infection done within the NHS and held within Public Health England (PHE) and equivalent national test databases in Wales and Northern Ireland will also be linked into the studyin order to accurately ascertain infection status outside of the study/study visits (was in the version 1.0 Participant Information Sheet).
				Sections 5, 6: clarification that neutralising antibodies will not now be done on all participants with blood drawn in the study (since this is highly labour intensive), but may be done on a subset to triangulate with results from the main high-throughput assay used. Correspondingly in section 6, neutralising antibodies also therefore moved to an "Other" exploratory outcome. Further, IgG will be assayed on all participants using a high-throughput version of the referenced assay, since IgM adds little information.
				Sections 5, 7: clarification that non-contact visits will be performed wherever possible to reduce risks to participants and study workers.
				Sections 5, 7, 9: addition of approach for consent for for blood draw in any individual who tests positive for virus (new infection) during the study as quickly as possible after their positive test and then at monthly visits to contribute additional information to analyses of how immunity after infection changes over time

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
				Section 6: timepoints where outcome measures evaluated amended to weekly over calendar time, reflecting results as presented on https://www.ndm.ox.ac.uk/results. Objectives section reordered to clarify which timepoints go with which outcomes, but no changes (other than moving neutralising antibodies to an "other" exploratory outcome as described above.
				Section 7: clarification that in Phase II, between 10-20% of households will be randomly selected to be approached for consent for blood draws, targeting a minimum of 300 households enrolled per week undergoing blood draws (exact consent rate is unknown).
				Section 9.1, Table 1: clarification that blood draws are done only in those within the blood sampling target, and that the telephone contact is made with the call centre (number provided on original invitation letter as two organisations will lead different parts of the fieldwork given the scale of Phase II).
				Section 9.1, 9.6.1: removal of participant suffix as a method for identifying participants, who are instead identified by a unique pseudonymised study number.
				Section 9.3: minor clarification to wording around scanning of the original paper copy of the consent form to obtain the research copy.
				Section 9.3: Added that a short summary of the study will be sent with invitation letter and the main Participant Information Sheet, and removed Informed Consent Form (included incorrectly here in v1.0 and was not consistent with Section 9.1).
				Section 9.6.1, 9.9.1, 12, 13, 16.4: At the suggestion of the REC we are actively in the process of setting up the ability to return results of nose and throat swabs directly to participants by tesxt if they are happy to provide mobile phone numbers, as well as being returned to the GP by letter or email. Results of blood tests will be returned once the assay is approved by the MHRA (submission currently in preparation). We would like to seek approval to do this now so we can implement without delay when the system is finalised.
				Section 9.6.1: Minor changes to the questions being asked on the questionnaire, including adding domains about recent contacts outside the home. Section reordered into questions asked once at enrolment with only changes elicited at follow-up and questions asked explicitly at each follow-up.
				Section 9.6.1: clarified that swab and blood samples are primarily identified by a unique sample barcode linked to the participant's unique study number on the database.

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
				Section 9.6.1: addition of option to be approached about further research if participant tests positive for COVID-19.
				Section 9.7: Clarified that the enrolment visit blood draw can be delayed if needed, at any time up to the first serial sampling visit (including its time window).
				Section 9.9: Clarification that residual material from blood samples are stored for consistency with the Participant Information Sheet and Informed Consent Form which referred to storing leftover blood sample.
				Section 11.2 Update to statistical analysis methods to reflect ongoing analysis results summarised on https://www.ndm.ox.ac.uk/results
				Section 11.5: Clarified that interim analyses will be conducted at least twice a month in order to inform the UK's response to the pandemic, in response to suggestion from the REC.
				Section 11.8: Clarified that regular checks for data quality will be run, in response to suggestion from REC
				Section 12: addition of NatCen as a second key collaborator and lead organisation, given the scale of Phase II and the need to conduct the study across the Devolved Administrations. Changes throughout this section to clarify data management with a second lead organisation.
				Section 12.1 Clarification that name is collected on the household CRF for the purposes of linkage, to make consistent with other parts of the protocol and the Participant Information Sheet
				Section 12.1: addition of mobile telephone numbers if participants wish to receive results by text, and of email addresses if they wish to receive incentive vouchers by email (can be posted instead) and clarification that email addresses will be shared with the third parties named in 12.1 who provide the vouchers.
				Section 13: removed "GCP" from the first sentence for consistency with Section 13.2 which clearly states that no GCP monitoring will be performed.
				Section 16.8: Clarification that participants have the option of receiving vouchers more quickly if they provide an email address.
MA01 (non-notifiable)	2.1	17 June 2020	Ann Sarah Walker	Sections 7, 9 (Table 1): clarification that IQVIA will manage all households randomly allocated to be invited for blood draws and a proportion of households not randomly allocated to be invited for blood draws, for reasons of operational efficiency.

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
02	3.0	1 July 2020	Ann Sarah Walker	Synopsis, Sections 7, 8, 9.1,, Figure 1; addition of random sampling from available databases of addresses given the larger sample numbers in Phase II, in order to ensure that the sample remains representative in terms of the country throughout its duration and also facilitate proportionate increases where there is evidence of increasing prevalence in Phase II (already included I protocol v0)