



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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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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1. KEY CONTACTS

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Committees	<p>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.</p>
Website	<p>https://www.ndm.ox.ac.uk/covid-19-infection-survey</p> <p>Results available on: https://www.ndm.ox.ac.uk/results</p>

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 reflects 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 choice of a minimum of 2m is to reduce risk as much as possible, based on the fact that prevalence may increase again over the coming months and in practice, transmission risk is directly related to actual distance rather than suddenly changing at 1m or 2m, with the choice of thresholds for other activities based on pragmatic as well as scientific justifications. 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 start by inviting 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). To date a mean of 2.1 individuals have been recruited per household. In order to achieve a cohort of ~150,000 individuals sampled at least once a fortnight by October 2020 when the winter season of respiratory infections starts, and monitoring for a possible “second wave” of infections is critical, from the end of July we will scale this up to inviting new groups of around 18,000 households in England, around 1,800 households in Wales, up to 1,800 households in Northern Ireland and around 4,500 households in Scotland approximately every week, targeting recruitment of around 9,000, 900, up to 900, and 2,250 new households per week respectively (total around 13,000 households per week; assuming 50% consent rate; numbers approached will be increased if consent rate is lower to achieve the target enrolment, and ultimately the target of ~150,000 individuals swabbed at least every fortnight in October in England, and ~15,000 in each of Wales and Scotland, and up to 15,000 in Northern Ireland). After October, providing there is no evidence of a second wave, we plan to scale back recruitment. Throughout, we will approach 10-20% of invited households 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 health system 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, Northern Ireland and Scotland, as agreed with the Treasury) The Welsh Government (in-kind contribution) The Department of Health on behalf of the Northern Ireland Government (in-kind contribution) The Scottish Government (in-kind contribution) The Northern Ireland Statistics and Research Agency (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) or Northern Ireland Statistics and Research Agency (NISRA) 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 we will start by approaching approximately 5,000 new households in England, around 500 households in Wales and around 500 households in Northern Ireland 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). From the end of July we will scale this up to inviting new groups of around 18,000 households in England, around 1,800 households in Wales, up to 1,800 households in Northern Ireland and around 4,500 households in Scotland approximately every week, targeting recruitment of around 9,000, 900, up to 900, and 2,250 new households per week respectively (total around 13,000 households per week). The goal is to achieve a cohort of ~150,000 individuals sampled at least once a fortnight by October 2020 in England, and ~15,000 in each of Wales and Scotland, and up to 15,000 in Northern

	<p>Ireland. After October, providing there is no evidence of a second wave, we plan to scale back recruitment. In total recruitment will take place 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.</p> <p>Thus in total, over 12 months, we expect to recruit approximately 380,000 individuals from approximately 180,000 households in England, plus approximately 42,000 individuals and 20,000 households from each of Wales and Scotland, and up to 42,000 individuals and 20,000 households from Northern Ireland.</p>
Planned Study Period	<p>Depending on the consent/assent provided by each individual participant, their involvement may be</p> <ul style="list-style-type: none"> • 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). <p>All participants would have follow-up through available 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 equivalent bodies in Devolved Administrations, and mortality. Consent for this electronic follow-up is required to join the study.</p> <p>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).</p>
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
HCP	Healthcare professional
HRA	Health Research Authority
HSC	Health and Social Care (Northern Ireland)
MHRA	Medicines and Healthcare Products Research Agency
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

Note: All references to the NHS in this protocol also include NHS Wales, the Health and Social Care (HSC) in Northern Ireland, and NHS Scotland.

5. BACKGROUND AND RATIONALEⁱ

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 asymptotically 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 countries⁸). 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 immunoglobulin 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, we will start by recruiting 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 asymptotically, 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, in order to achieve a cohort of ~150,000 individuals sampled at least once a fortnight in England by October 2020 when the winter season of respiratory infections starts, and monitoring for a possible “second wave” of infections is critical, from the end of July we will scale this up to inviting new groups of around 18,000 households in England, around 1,800 households in Wales, up to 1,800 households in Northern Ireland and around 4,500 households in Scotland approximately every week, targeting recruitment of around 9,000, 900, up to 900, and 2,250 new households per week respectively (total approximately 13,000 households per week; assuming 50% consent rate; numbers approached will be increased if consent rate is lower to achieve the target enrolment, and ultimately the target of ~150,000 individuals swabbed at least every fortnight in October in England, and ~15,000 in each of Wales and Scotland, and up to 15,000 in Northern Ireland). After October, providing there is no evidence of a second wave, we plan to scale back recruitment (see

Table 1 below). The same proportions will be approached for blood draws.

Thus in total, over 12 months, we expect to recruit approximately 380,000 individuals from approximately 180,000 households in England, plus approximately 42,000 individuals and 20,000 households from each of Wales and Scotland, and up to 42,000 individuals and 20,000 households from Northern Ireland.

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 asymptotically, 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 thereafter 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. In Phase I and II to date, acceptance of additional visits has been very high and they are therefore follow-up visits are also included in the target of 150,000 individuals sampled every fortnight in England by October 2020 (and equivalently in Devolved Administrations). 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 available data from Public Health England's (PHE's) Second Generation Surveillance System (SGSS) and equivalent national test databases in Wales, Northern Ireland and Scotland 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 all the countries in 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 appropriate government guidance regarding personal protective equipment.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure
<p>Primary Objective</p> <p>To estimate prevalence of symptomatic and asymptomatic SARS-CoV-2 infection in the general population and how this varies over time</p>	<p>Presence or absence of SARS-CoV-2 virus assayed from a nose and throat swab</p>	<p>Every calendar week from the start of the study, with analysis based on the latest test available in the prior 2 weeks</p>
<p>Secondary Objectives</p> <p>To estimate the incidence of new symptomatic and asymptomatic SARS-CoV-2 infection in the general population, and how this varies over time</p> <p>To estimate immunity to SARS-CoV-2 in the general adult population and how this varies over time, as reflected by immunoglobins</p> <p>To estimate the association between prevalence of symptomatic and asymptomatic infection in individual members of households</p> <p>To estimate the association between immunity to SARS-CoV-2 across individual members of households</p>	<p>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)</p> <p>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</p> <p>Presence or absence of SARS-CoV-2 virus assayed from nose and throat swabs taken from different members of the same household*</p> <p>Concentrations and thresholds of IgG to SARS-CoV-2 assayed from blood of different members of the same households*</p>	<p>Every calendar week from the start of the study based on all serial samples to date in those consenting to serial sampling</p> <p>Every calendar week from the start of the study, based on the latest test available</p> <p>Each household visit</p> <p>Each household visit</p>

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure
<p>Exploratory Objectives</p> <p>To assess how prevalence and incidence of symptomatic and asymptomatic infection, and of immunity to SARS-CoV-2 (outcomes) varies by participant characteristics, particularly age, geographical location and time, and for prevalence incidence of symptomatic and asymptomatic infection, how this varies by immunity to SARS-CoV-2</p>	<p>Presence or absence of SARS-CoV-2 virus assayed from a nose and throat swab</p> <p>Presence of SARS-CoV-2 virus in a nose and throat swab, separately in previously negative and previously positive individuals on nose and throat swabs (to estimate re-infection after clearing the virus) and as assessed by immunity determined by IgG to SARS-CoV-2 assayed from blood</p> <p>Concentrations and thresholds of IgG from an ELISA assay for SARS-CoV-2 antibodies assayed from blood</p>	<p>In individual cross-sectional surveys; repeated at each follow-up timepoint in those consenting to serial sampling</p>
<p>To assess how immunity to SARS-CoV-2 affects future use of NHS resources and mortality</p>	<p>Inpatient admissions, outpatient attendances, A&E attendances, consultations with a General Practitioner as collected from available routine electronic NHS health records; overall mortality and cause of death as collected from ONS and relevant national mortality databases</p>	<p>Over the year following each visit; at the final follow-up one year after the last visit of each participant</p>
<p>To compare immunity to SARS-CoV-2 in the general adult population, as reflected by neutralising antibodies and IgG</p>	<p>Concentration of neutralising antibodies to SARS-CoV-2 assayed from blood, categorised according to predefined thresholds¹⁴ as positive or negative</p> <p>Concentrations and thresholds of IgG from an ELISA assay for SARS-CoV-2 antibodies assayed from blood</p>	<p>Specific study visits where neutralising antibody assays performed</p>

* 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 surveys conducted by ONS or the Northern Ireland Statistics and Research Agency (NISRA) 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 present in the household at the enrolment visit and 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, either a “non-contact” visit will be conducted and blood will not be drawn or, if feasible, a “contact” visit will be rescheduled to later in the allowed window when no one is symptomatic, self-isolating or shielding.

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 asymptotically 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). From the end of July, the percentage randomly selected to receive an invitation for blood draw will be increased to 20%, to assess the potential for prior immunity to affect future infection. All households who are approached for blood sampling will be included in the blood sampling cohort 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. They would re-consent in order to provide consent for blood sampling.

Given the scale of Phase II and the fact that it will run across the Devolved Administrations, the lead organisation (IQVIA) will be supported by a number of similarly-qualified data collection organisations (see Section 12). Fieldwork will be managed through a specific call centre, and the number provided on the household's invitation letter and participant information.

Participants who consent to one cross-sectional survey would have just one visit. Participants who consent to serial sampling would have either 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 2,000 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 and NISRA surveys and from databases of addresses held in Devolved Administrations. The ultimate target is to achieve ~150,000 individuals swabbed at least every fortnight in October in England, and ~15,000 in each of Wales and Scotland, and up to 15,000 in Northern Ireland. Sampling will be stratified by geographical location in order to provide more precise regional estimates of incidence and seroprevalence. Where possible, 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.

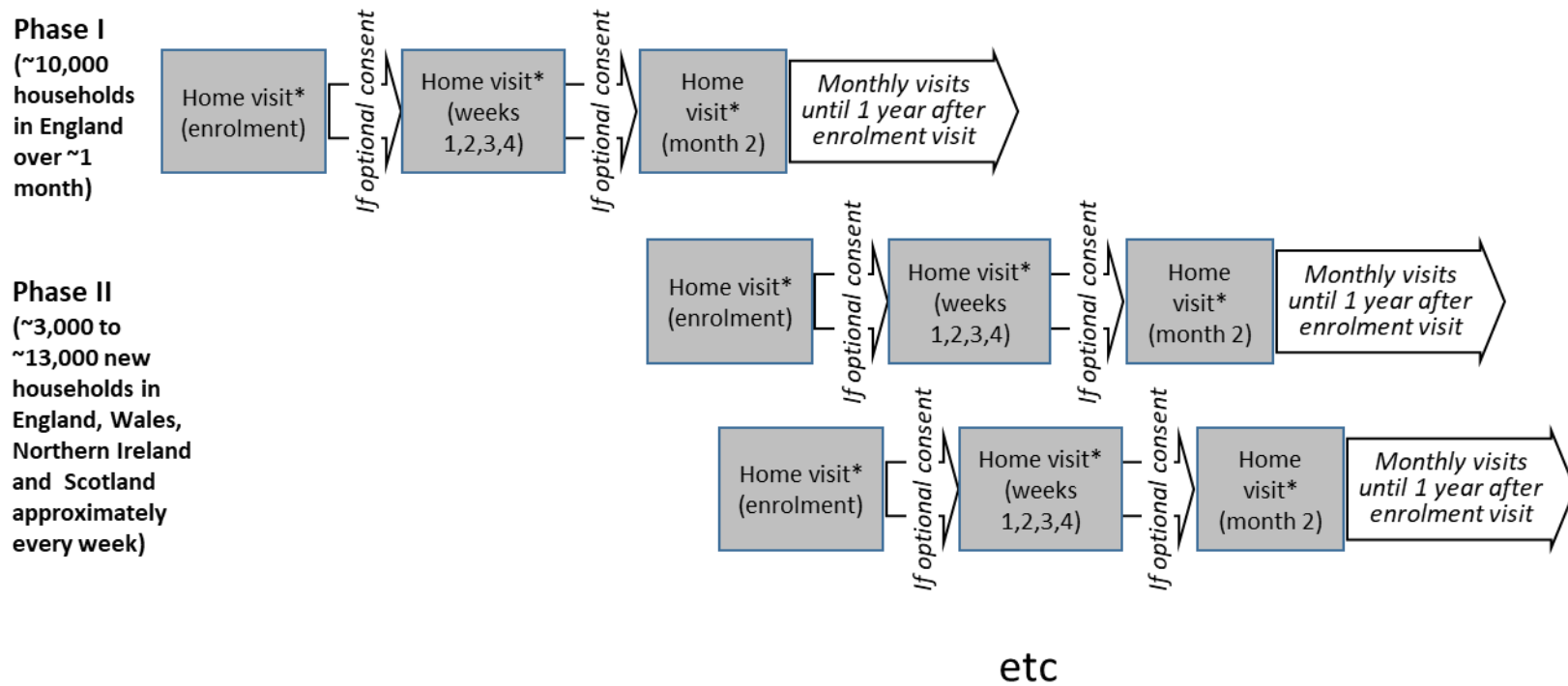
Table 1 Approximate planned recruitment of households in England*

Week starting	Newly recruited households in England (actual or approx planned)	Newly recruited individuals in England (actual or approx planned)
27 April 2020	2523	5483
04 May 2020	3156	7038
11 May 2020	2436	5406
18 May 2020	1365	3092
25 May 2020	442	999
01 June 2020	1163	2526
08 June 2020	2008	4207
15 June 2020	2261	4550
22 June 2020	1778	3622
29 June 2020	1645	3469
06 July 2020	1598	3244
13 July 2020	2500	5388
20 July 2020	2500	5388
27 July 2020	3000	6466
03 August 2020	5000	10776
10 August 2020	7500	16164
17 August 2020	8250	17780
24 August 2020	9000	19397
31 August 2020	9000	19397
07 September 2020	9000	19397
14 September 2020	9000	19397
21 September 2020	9000	19397
28 September 2020	9000	19397
05 October 2020	9000	19397
12 October 2020	9000	19397
19 October 2020	7500	16164
26 October 2020	7500	16164
02 November 2020	5000	10776
09 November 2020	5000	10776
16 November 2020	5000	10776
23 November 2020	5000	10776
30 November 2020	2500	5388
07 December 2020	2500	5388
14 December 2020	2500	5388
21 December 2020	2500	5388
28 December 2020	1500	3233
04 January 2021	1500	3233
11 January 2021	1500	3233
18 January 2021	1500	3233
25 January 2021	1500	3233
01 February 2021	1500	3233
08 February 2021	500	1078
15 February 2021	500	1078
22 February 2021	500	1078
01 March 2021	500	1078
08 March 2021	500	1078
15 March 2021	500	1078
22 March 2021	500	1078
29 March 2021	500	1078
Total enrolled	176602	380292
Average ratio individual: household		2.16

* targets for each of Wales and Northern Ireland are 10% of those shown for England. Target for Scotland is to recruit 2,250 households per week from September, in order to achieve 15,000 individuals sampled every fortnight by October. Targets are approximate and may vary depending on speed of scale-up and other factors, such as consent rates.

Note: Gray shading shows actual data, and white cells current plans. numbers approached given in the main text are based on 50% consent; more will be approached to achieve the numbers recruited above.

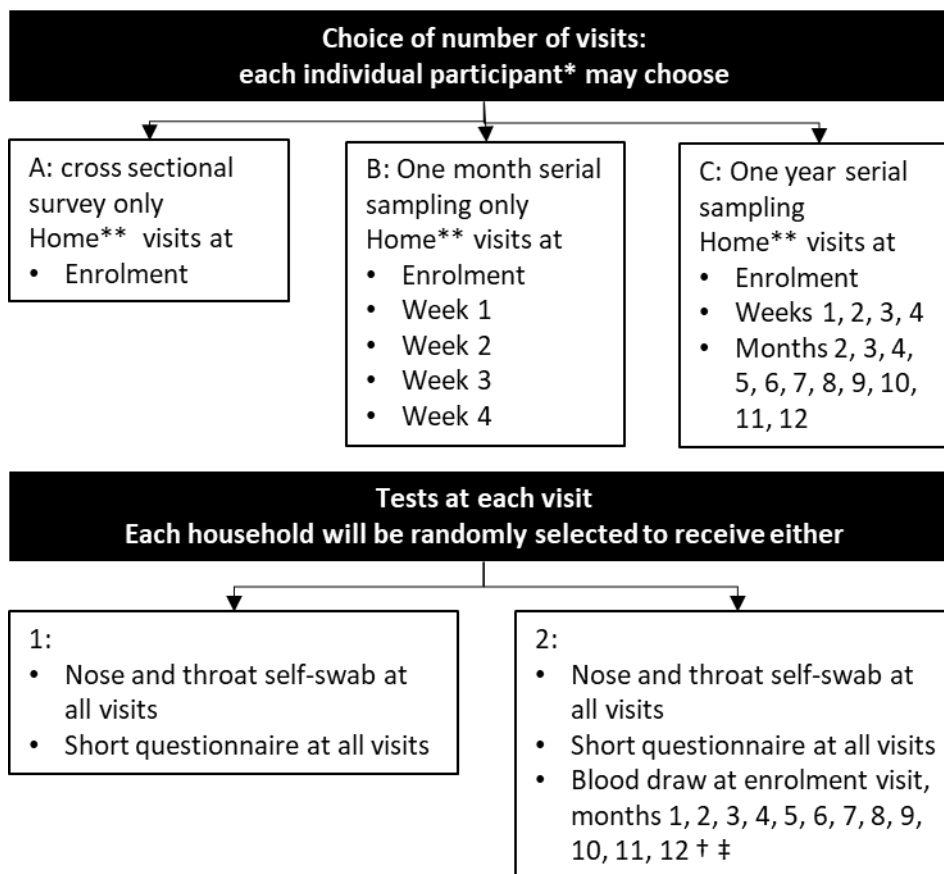
Figure 1 Repeated cross sectional survey design



* 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, between 6,000 and 24,000 invitations will be issued per week (will be increased if consent falls below 50% to achieve targeted recruitment) with continuous recruitment from these issues, 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 or NISRA 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 to 13,000 enrolled households per week in England, Wales, Northern Ireland and Scotland 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. Ultimately the target is to achieve ~150,000 individuals swabbed at least every fortnight in October in England, and ~15,000 in each of Wales and Scotland, and up to 15,000 in Northern Ireland.

Thus in total, over 12 months, we expect to recruit approximately 380,000 individuals from approximately 180,000 households in England, plus approximately 42,000 individuals and 20,000 households from Wales and Scotland, and up to 42,000 individuals and 20,000 households from Northern Ireland.

8.2. Inclusion Criteria

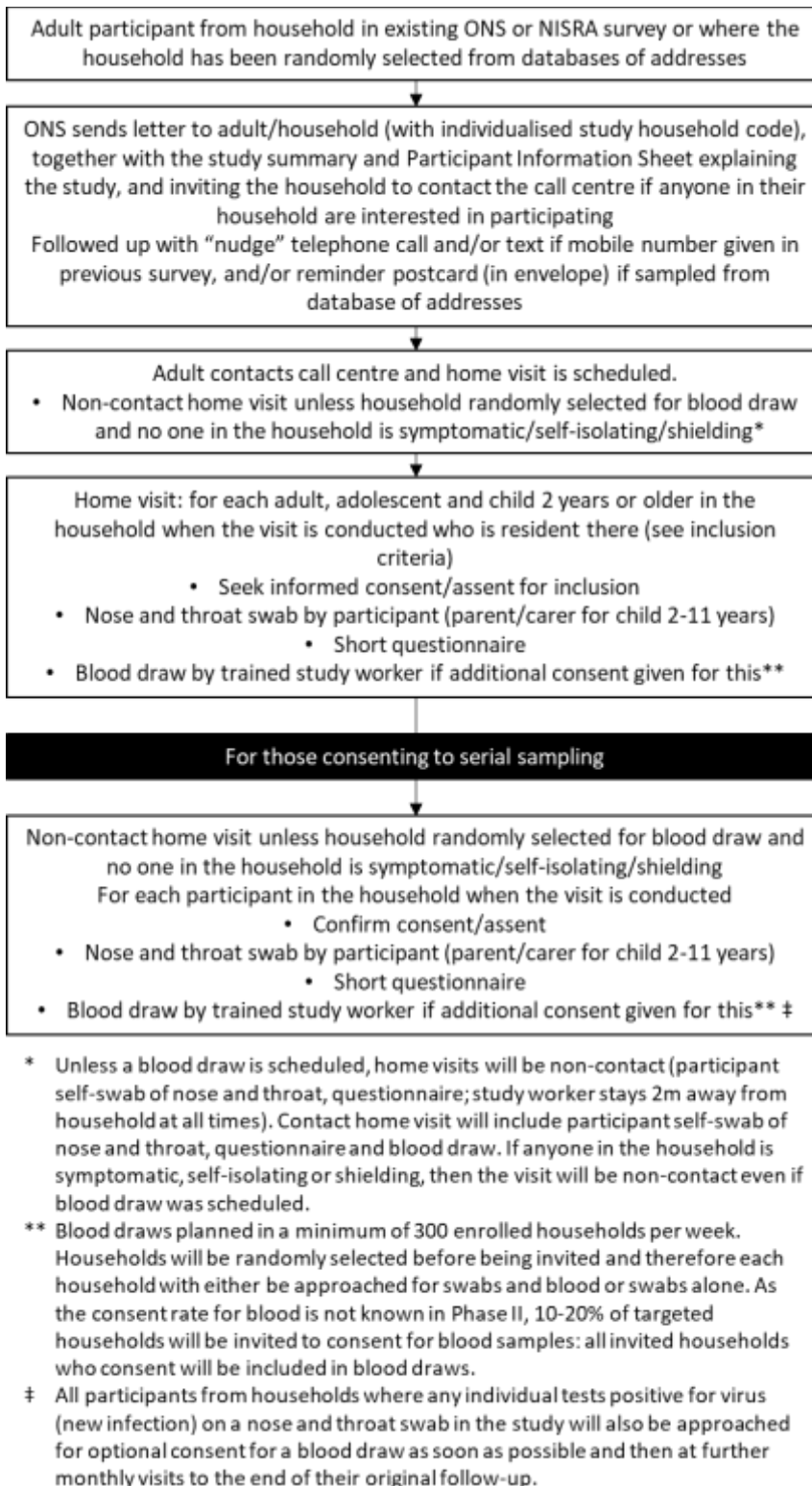
- Adult, adolescent or child aged 2 years or older, male or female
- Currently resident in a household where a household member has participated in an ONS or NISRA Survey and has consented to be approached for future research or where the household has been randomly selected from databases of addresses.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



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 2 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 nose and 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 nose and 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 nose and 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.

* 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 and NISRA surveys, including the ONS 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 5,000 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 4,000 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 and NISRA 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 and/or text reminder following standard practice where contact numbers have been provided through participation in a previous survey. All households, including those sampled through databases of addresses, will receive a postcard reminder (in an envelope to ensure that the households study code remains private). Welsh translations will also be sent to households in Wales. Only the short summary (in leaflet form) and the Participant Information Sheet for adults 16 years and older will be sent with the invitation letter (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 an adult to telephone the call centre if anyone in the household is 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 an adult 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.

In order to minimise risks to participants and study workers, non-contact home visits will be conducted even if a blood draw was planned if anyone in the household reports being symptomatic, self-isolating or shielding on the planned home visit date, and it is not feasible to reschedule the “contact” visit to later in the allowed window when no one is symptomatic, self-isolating or shielding. Non-contact home visits will also be conducted at all other visits where blood is not planned to be drawn. For the purposes of defining when a non-contact visit should take place even if a blood draw was planned, 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 10 days after symptom onset if no fever, nausea/vomiting, or diarrhoea at 10 days or at the end of these symptoms if still have fever, nausea/vomiting, or diarrhoea at 10 days; or for another household member for 14 days from the day the first person started having symptoms. This is not a definition of symptoms in general which differs according to nation, but for the purposes of unified definition of when a non-contact visit should occur across the study. 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 this enrolment home visit, each participant in the household aged 16 years or older must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed. The person who obtains the consent must be suitably qualified and experienced, and have been authorised to do so by IQVIA (responsibility delegated to IQVIA from the

Chief Investigator and Sponsor). An Informed Consent document will be signed; the original paper form will be left at the household with the participant (or parent/carer) and the consent form scanned securely to obtain the research copy.

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.

At the enrolment 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 enrolment visit will be approached for consent/assent. Any individuals who join the household after the enrolment visit will not be included, nor will any individuals who were members of the household at the time of the enrolment visit but not present at the enrolment visit.

Written versions of the Participant Information Sheets will have been provided to the participants together with the original invitation letter (via post) 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: For linking their data and sample results from this study to available 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) 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, Northern Ireland and Scotland 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 name, 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 directly to the participant by letter or via mobile message or email if participant is

happy to provide a mobile number/email in order to receive results (mobile messaging and email provision of results currently being set-up, so letters will be used initially).

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; religion²; occupation (available from ONS or NISRA 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?
- 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 and receive updates on results and news about the study, and receive results by this route (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

² The reason for asking for religion as well as ethnicity is because of the importance of identifying particular communities within whom transmission may be greater or lesser that are not identifiable from ethnicity. Options will follow those planned for the 2021 Census which have been tested for acceptability with the general public. Testing programmes in Pillar 1 and 2 collect both ethnicity and religion and we have been asked that the survey align with these programmes.

- 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 or NISRA survey or the address list from which the household was sampled. 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 in the same way as for the swab test results. The test has shown excellent performance in a comparison with 4 commercially available assays on a large number (>1500) samples;¹⁶ sensitivity and specificity (95% confidence interval, CI) were 99.1% (97.8-99.7%) and 99.0% (98.1-99.5%) respectively, compared with 98.1% (96.6-99.1%) and 99.9% (99.4-100%) respectively for the best commercial assay (Siemens). Submission to the Medicines and Healthcare Products Research Agency (MHRA) is in progress.

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 14 days after the enrolment visit (for example, at the week 1 or 2 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 ± 14 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 2 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 either the National Biosample Centre at Milton Keynes (a Lighthouse Laboratory) or to the Glasgow or Alderley Park (Liverpool) Lighthouse Laboratories, 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>). The reason for using three laboratories is to provide redundancy in case of varying testing burden and ensure coverage across the nations. All use the same testing methodology. Each swab 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 within 24 hours. 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.^{13,17} 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 microneutralisation assay (pMN), as recently used in a study of Scottish blood donors.¹⁴ Residual material (sera and spun cells) will be stored by the University of Oxford in secure facilities.

In all 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.

9.9.2 Return of results

Nose and throat swab and blood test results will be returned directly to the participant by letter or by mobile message or email as described above if they are happy to provide a mobile number/email 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, subsequent swab test results will similarly be returned to participants as will blood test results.

9.9.3 Individuals testing positive on a swab test

As required by law, positive swab test results will also be shared with the relevant personal data (including name, contact details, postcode and ethnicity) with the relevant public health bodies for referral to national systems (Public Health England for referral to the NHS Test and Trace system <https://contact-tracing.phe.gov.uk/>; Public Health Wales for referral to the NHS Wales Test, Trace, Protect system <https://gov.wales/contact-tracing-if-you-have-tested-positive>; the Public Health Agency for referral to the HSC Northern Ireland's Test, Trace, Protect programme <https://www.publichealth.hscni.net/covid-19-coronavirus/testing-and-tracing-covid-19/contact-tracing>; and Public Health Scotland for referral to the NHS Scotland Test and Protect system www.nhsinform.scot/campaigns/test-and-protect). Participants will be informed about this automatic referral of positive swab test results in the Participant Information Sheet, and that by taking part in this survey they agree to this disclosure taking place.

As described above, 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. The individual would be telephoned in order to expedite blood sampling and this would be followed up with a letter. Participants will be informed about this in the Participant Information Sheet.

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 and NISRA 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), 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 records from ONS and equivalent national mortality databases in the Devolved Administrations, 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, Northern Ireland and Scotland 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, and around 21,000 individuals) 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 across England 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 ~1,000 households per month, ~2,100 individuals per month).

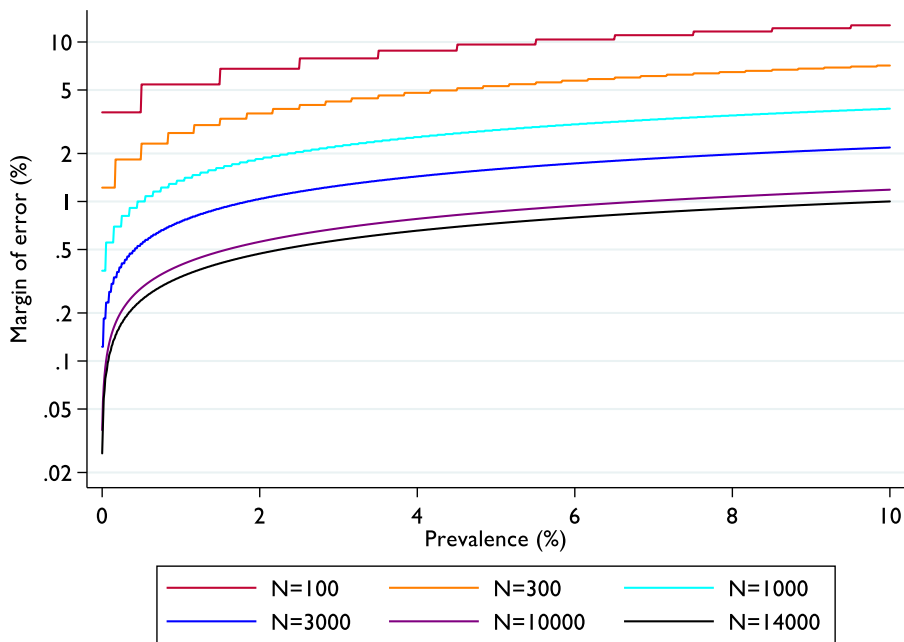
However, a major concern is the ability to monitor regions, rather than England as a whole, by October 2020 when the winter season of respiratory infections starts, and monitoring for a possible “second wave” of infections is critical. Therefore scaling up of recruitment from the end of July is designed to achieve similar numbers regionally as are currently available nationally, ie ~15,000-20,000 individuals swabbed at least once each fortnight in each of the nine government office regions of England and also in each of Wales and Scotland, and up to 15,000 in Northern Ireland (given its smaller overall population). Overall the target is therefore ~150,000 individuals swabbed at least every fortnight in October in England, and ~15,000 in each of Wales and Scotland, and up to 15,000 in Northern Ireland. 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.

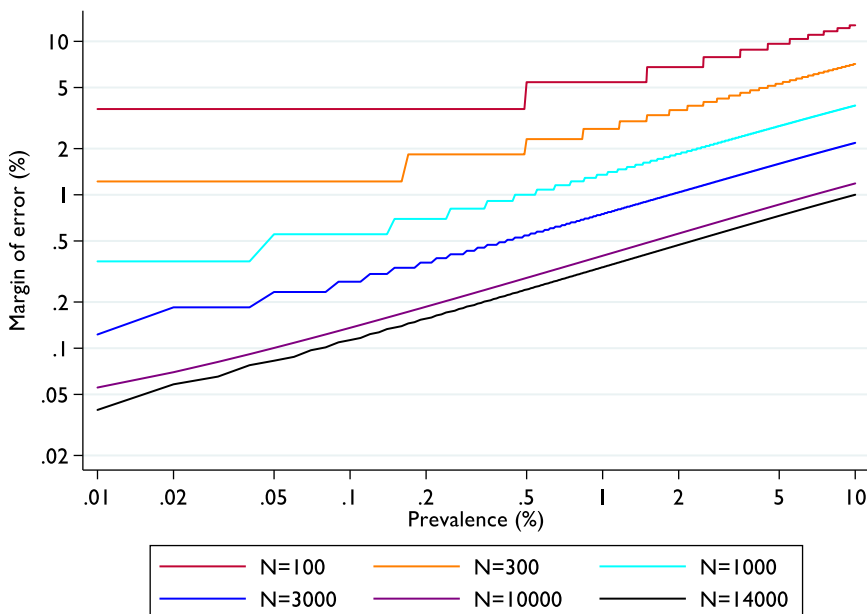
For blood sampling for seroprevalence, 10-20% of those enrolled is considered to provide an acceptable trade-off in terms of precision, given that seroprevalence rates are expected to be higher than infection rates, and so margins of error for the former can be larger than the latter without compromising 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, the Department of Health on behalf of the Northern Ireland Government and the Scottish Government.

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

Each analysis will be restricted to complete cases for the outcomes and exposures considered for that analysis. 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 and NISRA 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, the lead organisation for fieldwork, IQVIA, will sub-contract some of the field work. IQVIA sub-contractors will use the IQVIA Voyager database.

The signed consent forms will be stored in secure facilities for 5 years after the end of the study by IQVIA. 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 a secure data management system (IQVIA Voyager). All study data is stored with bespoke logins and passwords unique to each user (only personnel associated with the programme). Access to the Voyager platform will be granted to an existing or new mobile device only after entering the verification code sent to a mobile phone registered in the users profile.

ONS 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. IQVIA may use Serco to help resource the call centre, through direct access to the IQVIA Voyager database. All will have participant contact details solely in order to undertake this contracted work.

The Lighthouse laboratories at the National Biosample Centre, Milton Keynes, Glasgow, or Alderley Park, Liverpool, will return nose and throat swab results to ONS and IQVIA to communicate results to participants (or their parent/carer, where applicable) via letter, mobile phone or email where they have agreed to this. IQVIA will also send details of positive swab tests to the relevant public health bodies as required by law. IQVIA will already hold the necessary personal details to enable home visits to be arranged. The University of Oxford will return antibody results to ONS and IQVIA, who will pass these onto participants in the same way as swab test results.

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, Northern Ireland and Scotland, 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

Data 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/>. All versions of Voyager are validated and compliant with 21 CFR part 11. Changes to the Voyager system are validated based on IQVIA's internal IT CS_OP_IT029 – System Development Lifecycle and Validation and formally validated as 21 CFR part 11 compliant with within 3 months of release. All health information is backed up within the UK.

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, study updates and return of results 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. All information provided to IQVIA will be shared with ONS, including name and date of birth which are shared for the purposes of linkage to NHS and ONS records, and equivalent national databases in the Devolved Administrations (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 study updates, and these will be shared with the third parties described above that provide these services. IQVIA will carry out a data privacy impact assessment on all personal data they collect to minimise the data protection risk to the study.

Electronic data will be stored on 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 (or parent/carer, for children). 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. Results will be returned directly to participants as these tests are now widely available outside the study, both through the NHS and through commercial companies.

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 directly.

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/>).

As well as providing a continuously updated summary of all the study results published in ONS statistical bulletins and articles to date, and in academic journals, on <https://www.ndm.ox.ac.uk/covid-19/covid->

[19-infection-survey/results](#), we will also email regular study updates and shorter results summaries to participants who are happy to provide an email address for this purpose and to receive vouchers.

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 for this purpose (email can also be used to receive test results and study updates). 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 Department of Health on behalf of the Northern Ireland Government, the Scottish Government, the ONS, the NISRA, 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 platform at IQVIA for a period of 15 years after the end of the study. The only paper based forms are consent forms; any that have not been securely disposed of after being uploaded to Voyager will be stored in a secure off site facility maintained by IQVIA for a period of 5 years after the end of the study.

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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 be 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 study in 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 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 (now Table 2): 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 text 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 (now Table 2): 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)
03	4.0	21 July 2020	Ann Sarah Walker	Sections 2, 3, 5, 6, 8, 11.3, Figure 1, new Table 1: Scale up of recruitment to achieve a target of ~150,000 individuals swabbed at least every fortnight in October in England, and ~15,000 in each of Wales and Northern Ireland in order to monitor for a potential second wave, and increase in percentage approached for blood sampling to 20%.
				Clarifications throughout that electronic record linkage includes the relevant databases from Devolved Administrations and that respondents to both previous ONS and NISRA surveys will be approached
				Section 2: justification for maintaining 2m distancing for study visits regardless of changes in government guidance for other activities
				Section 7, 9.3: clarification that only those present in the household at the enrolment visit are eligible for inclusion in the study (stated elsewhere)
				Section 9.1: clarification that the English NHS guidance quoted in this section is for the purpose of determining whether a visit where a blood draw is planned should be changed from a contact to a non-contact visit instead
				Section 9.9.1, 12: addition of the Glasgow Lighthouse Laboratory as well as the National Biosample Centre (Milton Keynes Lighthouse Laboratory as a testing centre)
				Section 9.9.2, 12: addition of automatic referral of positive swab tests results to the relevant public health bodies as required by law
				Section 9.9.2: clarification around the process of inviting individuals with positive swab tests in the study or elsewhere to undergo blood draws, and also their households
				Section 11.8: clarification regarding the definition of complete case analysis.
04	5.0	25 August	Ann Sarah Walker	Front material, Sections 3, 11.6, 17.1: Clarification that in-kind funding contribution is from the Northern Ireland Department of Health rather than the Northern Ireland Assembly, and that NISRA are also making an in-kind contribution

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
				Sections 2, 3, 5, 7: addition of Scotland to the survey, with the goal of achieving 15,000 individuals swabbed every fortnight by October. As recruitment will not start in Scotland until September, this requires a higher weekly recruitment rate than the other Devolved Administrations.
				Sections 2, 3, 5, 8.1, 11.3: clarification that the scale-up for October 2020 in Northern Ireland will be up to 900 households per week, given low current infection rates in the country and the smaller population size.
				Front material, Sections 7, 9, 9.3, 12: removal of NatCen as joint lead on fieldwork. This was planned earlier in the project and the protocol updated to reflect this. However, contract negotiations were prolonged and ultimately the funder has finally decided to remain with IQVIA as the sole lead. The protocol has therefore been updated to reflect this.
				Section 7, 9.1: option of either rescheduling a “contact” visit to later in the allowed window around a scheduled visit if anyone in the household is symptomatic, self-isolating or shielding if this is feasible, or conducting a “non-contact” visit instead.
				Section 8.2: clarification that inclusion criteria refer to participation in prior surveys conducted by ONS or NISRA as stated elsewhere in the protocol.
				Section 9.1: addition of a reminder postcard following the invitation letter.
				Section 9.1: updated text on duration of self-isolation to follow current guidance (10 days rather than 7 days self-isolation).
				Sections 9.3, 9.3.1, 9.9.2, 12, 13.1, 16.4: results of swab and blood tests will be returned directly to participants either by letter or via mobile message or email (in progress) rather than to the participant’s GP as both these tests are now widely available outside the study, through the NHS and through commercial companies.
				Section 9.3, 11.2, 12: removal of specific references to the Health and Social Care Board in Northern Ireland as a source of data at their request to align with wording for other Devolved Administrations.
				Section 9.6.1: addition of religion to the questions asked as well as ethnicity because of the importance of identifying particular communities within whom transmission may be greater or lesser than those that are not identifiable from ethnicity. Testing programmes in Pillar 1 and 2 collect both ethnicity and religion and we have been asked that the survey align with these programmes.
				Section 9.6.1: clarification that date of birth and postcode will be available from the original NISRA (rather than ONS) survey for some participants (in Northern Ireland).

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
				Sections 9.6.1, 9.9.2, 12, 13.1: antibody (blood) results will be returned to participants in the same way as swab results, since a large-scale evaluation has shown the test used in the study to have very high performance, comparable to the best of 4 commercially available assays tested on >1500 samples.
				Sections 9.6.1, 12.3, 16.6, 16.8: provision of study updates and study results through email, as well as the option to receive test results through email as well as mobile text message (also in the Participant Information Sheet).
				Sections 9.7 and 9.8: extension of the windows around scheduled monthly visits from 10 to 14 days, and extension of the initial window for enrolment blood draw from 10 to 14 days to maximise the number of blood samples obtained.
				Section 9.9.1: clarification that couriering of blood samples to the University of Oxford will happen within 24 hours rather than overnight.
				Sections 9.9.1, 12: addition of the Alderley Park Lighthouse Laboratory at Liverpool as well as the National Biosample Centre (Milton Keynes) and Glasgow Lighthouse Laboratories as testing centres
				Section 9.9.1: Clarification that residual material (sera and spun cells) will be stored by the University of Oxford in secure storage facilities, rather than at the University of Oxford.
				Section 9.9.3: correction of the name of the contact tracing programme in Northern Ireland to "Test, Trace, Protect".
				Sections 12, 20; additional clarifications regarding data capture and storage by IQVIA.