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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Funder: Department of Health and Social Care (funding the survey in England, Wales, Northern Ireland and Scotland, as agreed with the Treasury)

Chief Investigator Signature: 

The investigators have no potential conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be

disclosed to anyone other than the Sponsor, the Investigator Team, Health Research Authority, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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Study Clinical Experts	Professor Tim Peto Professor Chris Conlon Dr David Eyre Dr Philippa Matthews Dr Nicole Stoesser (contact via the Chief Investigator)
Committees	A study management group will provide oversight, including investigators named above as representatives of participating organisations, a representative of the Devolved Administrations, the Chief Investigator, and with an independent Chair.
Website	https://www.ndm.ox.ac.uk/covid-19/covid-19-infection-survey Results available on: https://www.ndm.ox.ac.uk/covid-19/covid-19-infection-survey /results

2. LAY SUMMARY

The COVID-19 pandemic has had, and continues to have, a profound impact across the UK. This study aims to find out how many people are still getting the infection and how many are likely to have had the infection, even if they haven't realised it at the time. This is particularly important as more people start getting vaccinated against COVID-19. Although the vaccine works very well, it is not 100% protective, and it is necessary to monitor how well it works in the real-world.

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 and give some protection against future infection. Getting vaccinated against COVID-19 is another way that people can get antibodies that can protect them against getting 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, or has developed antibodies against it after getting vaccinated.

In this study we want to find out how many people of different ages across the UK have COVID-19 over time, particularly as people start going back to work or school, and as more and more people get vaccinated, 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 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 ask everyone aged 2 years or older in each randomly selected 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 a randomly selected subset of these enrolled households to also give a sample of blood. At the start of the study, this was taken from a vein by a trained nurse, phlebotomist or healthcare assistant, but now we are moving towards it being taken by a fingerprick by the participant themselves so that all visits can happen without study workers and participants needing to come into close contact (<2m). Where an adult in the household is already giving blood, from September 2021 we will also ask children and young people aged 5-15 years whether they would be happy to give a sample of blood. We will take swabs from all households, whether anyone is reporting symptoms or not. At the start of the study, we did not take blood from a vein from anyone in a household where someone had symptoms compatible with COVID-19 infection, or was currently self-isolating or shielding, to make sure that study workers stay at least 2m away from them at all times. Now study staff will be able to maintain recommended distancing at all study visits, so blood can be collected by fingerprick at every visit, including in households where anyone has symptoms or is currently isolating/shielding. 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.

In April 2020, we began 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). Around 2,000 of these households (500 per week) were asked to give blood. After this, in Phase II we invited 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 from October 2020 onwards 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 scaled 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). **Ultimately the swab target is to achieve ~150,000 individuals with swab test results at least every fortnight from October 2020 onwards in England, ~9,000 in Wales, ~5,000 in Northern Ireland and ~15,000 in Scotland (~179,000 total across the UK)** (absolute numbers reflecting the relative size of the underlying populations)**.** To January 2021, we approached 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. From February 2021, we asked a representative sample of those already recruited to the study but only giving swabs to also give blood at their monthly visits, and for everyone giving blood samples to stay in the study until April 2022. **The blood target is to achieve up to ~125,500 adults 16 years and older with blood test results every month in England, and up to ~7,500, ~4,500 and ~12,500 per month in Wales, Northern Ireland and Scotland (~150,000 in total across the UK)** (absolute numbers reflecting the relative size of the underlying populations). This is to monitor how vaccination affects immunity at both the population and the individual level. For those aged 5-15 years, the target is to achieve 25% uptake of the invitation to participate in fingerprick blood testing, corresponding to +4,000 children aged 5-9 years and ~7,000 older children/adolescents aged 10-15 years, and to a total of ~5,500 blood test results every month (sampling those 5-15 years every other month).

From April 2021 onwards, we will maintain the targets for both swab results per fortnight and blood results per month above through to April 2022 by

- inviting everyone who is currently active in the study to remain on monthly follow-up visits until April 2022 (additional consent)

- inviting additional households who are only giving swabs at their monthly visits to additionally give blood by fingerprick at these visits until April 2022 (additional consent)
- until January 2022 continuing to invite new households to join the study and have follow-up visits up until April 2022 in order to replace participants who stop follow-up or supplement current numbers in order to maintain targets despite possible missed visits.

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	ISRCTN21086382
Sponsor	University of Oxford Joint Research Office 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 swab target is to achieve a cohort of ~150,000 individuals providing swab test results at least once a fortnight from October 2020 onwards in England, ~9,000 in Wales, ~5,000 in**

	Northern Ireland and ~15,000 in Scotland (total 179,000 across the UK) (absolute numbers reflecting the relative size of the underlying populations)**.** Numbers approached will be increased if the consent rate is lower to achieve the target enrolment. In total, to achieve this, to 12 April 2021, we recruited 371,996 individuals from 182,007 households in England, plus 23,461 individuals from 11,957 households in Wales, 12,687 individuals from 6,311 households in Northern Ireland and 32,206 individuals from 17,936 households in Scotland. To January 2021, between 10-20% of those recruited also provided blood samples as well as swab samples, with the remainder giving swabs only. From February 2021, we asked a representative sample of those already recruited to the study but only giving swabs to also give blood at their monthly visits, and for everyone giving blood to stay in the study until April 2022. **The blood target is to achieve up to ~125,500 adults 16 years and older with blood test results every month in England, and up to ~7,500, ~4,500 and ~12,500 per month in Wales, Northern Ireland and Scotland (~150,000 in total across the UK) through to April 2022** (absolute numbers reflecting the relative size of the underlying populations). Where an adult in the household is already giving blood, from September 2021 we will also ask children and young people aged 5-15 years whether they would be happy to give a sample of blood. For those aged 5-15 years, the target is to achieve 25% uptake of the invitation to participate in fingerprick blood testing, corresponding to ~4,000 children aged 5-9 years and ~7,000 older children/adolescents aged 10-15 years, and to a total of ~5,500 blood test results every month (sampling those 5-15 years every other month). From April 2021 onwards, we will continue to maintain the targets for both swab results per fortnight and blood results per month above through to April 2022 by • inviting everyone who is currently active in the study to remain on monthly follow-up visits until April 2022 (additional consent) • inviting additional households who are only giving swabs at their monthly visits to additionally give blood by fingerprick at these visits until April 2022 (additional consent) • until January 2022, inviting new households to join the study and have follow-up visits up until April 2022 in order to replace participants who stop follow-up or supplement current numbers in order to maintain targets despite possible missed visits.
Planned Study Period	Depending on the consent/assent provided by each individual participant, their involvement may be • for one home visit only (cross-sectional survey) • for five home visits (cross-sectional survey then optional to repeat visits every week for the next month) • for at least 6 home visits (cross-sectional survey then optional to repeat visits every week for the next month and then monthly through to April 2022. 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.

	The total study duration is 3.25 years (1.75 year recruitment of participants (see below), serial sampling for recruited participants to April 2022), one year additional follow-up after the end of serial sampling through existing electronic records from the final serial sampling timepoint) plus 3 months closeout.
Planned Recruitment period	24 April 2020 to 31 January 2022 (1.75 years)
Planned study duration	24 April 2020 to 31 July 2023 (3.25 years)
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
DHSC	Department of Health and Social Care
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
RGEA	Research Governance, Ethics and Assurance University of Oxford
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 RATIONALE[i]

The first cases of infection with a novel coronavirus, subsequently designated SARS-CoV-2 (commonly called COVID-19), emerged in Wuhan, China on 31st December 2019.[1] Despite intensive containment efforts, there was rapid international spread and by 17 April 2020, SARS-CoV-2 had caused over 2 million confirmed infections and 140,000 reported deaths globally.[2] A global pandemic was declared by the World Health Organisation (WHO) on 12th March 2020.[3]

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

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

For these reasons, attention has turned to the potential for antibody testing to provide data to support individual or population-level release from lock-down and inform mathematical models to predict the future trajectory of the pandemic, as well as supporting diagnosis of individuals with a clinical COVID syndrome. In contrast to RT-PCR, assays that reliably detect antibody responses specific to SARS-CoV-2 could contribute to diagnosis of both acute infection (via rises in IgM and IgG levels) and identify those who have been exposed and recovered with or without symptoms (via persisting IgG).[11] Receptor-mediated viral entry to the host cell occurs as a result of the interaction between the unique and highly conserved trimeric SARS-CoV-2 spike (S) glycoprotein and the ACE2 cell receptor.[12] This S protein is the primary target of specific neutralising antibodies, and serology assays for SARS-CoV-2 therefore typically seek to identify these antibodies (see Figure 1 in [13]). Within this study we plan to use an antibody assay for the anti-spike IgG immunoglobin in all participants with blood draws; we will also assay neutralising antibodies directly in a subset of participants with blood draws. From February 2021, we will combine this anti-spike assay with an anti-N (nucleocapsid) assay to try to distinguish between those with immunity due to natural infection (expected to be anti-S and anti-N positive) and vaccination (expected to be anti-S positive, anti-N negative because the vaccines produce antibodies to spike only).

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

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 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 asymptomatically, based on diagnostic RT-PCR performed on a nose and throat swab collected by the participant (self-swabbing) or by a parent/carer from participants aged 2-11 years, and self-reported symptoms. Numbers approached will be increased if the consent rate is lower to achieve the target enrolment. In approximately 300-600 enrolled households per week (1,200-2,400 households per month; 10-20%, including 100-200 households per month from each of Wales and Northern Ireland), a trained healthcare professional (HCP) will also collect venous 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 from October 2020 onwards when the winter season of respiratory infections starts, and monitoring for a possible “second wave” of infections is critical, from the end of July 2020 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). **Ultimately the swab target is to achieve ~150,000 individuals with swab test results at least every fortnight from October 2020 onwards in England, ~9,000 in Wales, ~5,000 in Northern Ireland and ~15,000 in Scotland (total 179,000 across the UK)** (absolute numbers reflecting the relative size of the underlying populations) (see *Table 1* below for initial planned recruitment). The same proportions will be approached for blood draws.

However, additional critically important questions remain about onward transmission and waning immunity in individuals who are positive, whether such individuals can be re-infected symptomatically or asymptomatically, and about incidence of new infection in individuals without prior exposure. Incorporating nested serial sampling of consenting individuals can efficiently provide estimates of these outcomes in different subgroups. We will therefore also serial sample individuals from these cross-sectional surveys who provide additional consent 1, 2, 3 and 4 weeks (1 month) after their first enrolment visit (counted as week 0); if further consent is provided, we will continue this sampling at 2 months and every month therafter for 12 months from their first home visit to assess this over the longer term. Infection (nose and throat swab) will be assessed at every visit and immunity (antibodies) every month. 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 from October 2020 onwards (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.

However, in order to monitor the impact of vaccination on both immunity and infection, from February 2021, we will ask a representative sample of those already recruited to the study but only giving swabs to also give blood at their monthly visits, and for everyone giving blood samples to stay in the study until April 2022 (i.e. to have additional visits beyond their original 12 month study period). Blood will initially either be taken through a venous blood draw as previously or through a capillary blood draw (fingerprick) done by the participant. From protocol v9.0, all blood draws will be capillary so that all visits can be conducted without any contact. **The blood target is to achieve up to ~125,500 adults 16 years and older with blood test results every month in England, and up to ~7,500, ~4,500 and ~12,500 per month in Wales, Northern Ireland and Scotland (~150,000 in total across the UK) through to April 2022** (absolute numbers reflecting the relative size of the underlying populations)**.** Where an adult in the household is already giving blood, in order to monitor the impact of immunity as well as infection in younger individuals, from September 2021 we will also ask children and young people aged 5-15 years whether they would be happy to give a sample of blood. See Section 9.4.3 for rationale and details. For those aged 5-15 years, the target is to achieve 25% uptake of the invitation to participate in fingerprick blood testing, corresponding to ~4,000 children aged 5-9 years and ~7,000 older children/adolescents aged 10-15 years, and to a total of ~5,500 blood test results every month (sampling those 5-15 years every other month).

In total, from 24 April 2020 to 12 April 2021, we recruited 371,996 individuals from 182,007 households in England, plus 23,461 individuals from 11,957 households in Wales, 12,687 individuals from 6,311 households in Northern Ireland and 32,206 individuals from 17,936 households in Scotland.

From April 2021 onwards, we will continue to maintain the targets for both swab results per fortnight and blood results per month above through to April 2022 by

- inviting everyone who is currently active in the study to remain on monthly follow-up visits until April 2022 (additional consent)
- inviting additional households who are only giving swabs at their monthly visits to additionally give blood by fingerprick at these visits until April 2022 (additional consent)
- until January 2022, inviting new households to join the study and have follow-up visits up until April 2022 in order to replace participants who stop follow-up or supplement current numbers in order to maintain targets despite possible missed visits.

The reason for following already recruited participants for longer, rather than only recruiting new participants, is the importance of assessing the duration of protection provided by vaccination and previous infection against new infection. Power to do this is maximised by having longer higher quality survey follow-up, including SARS-CoV-2 tests regardless of symptoms and antibody data, on the same individuals, rather than recruiting large numbers of new participants whose SARS-CoV-2 history is unknown or much less clearly documented (e.g. only symptomatic testing for current infection through national testing programmes, and no prior antibody test data).

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 venous blood samples (before protocol v9.0); visits where blood is not being drawn from a vein, including all visits from protocol v9.0 onwards) may be conducted by other trained individuals to ensure HCP are not diverted from the NHS. Before protocol v9.0, visits will also be split into two types, contact visits and non-contact visits. Non-contact visits will be performed unless a venous blood draw is scheduled, and to households where anyone is currently symptomatic/self-isolating/shielding (detailed definitions below). From protocol v9.0, all visits will be non-contact. 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
Primary Objective To estimate prevalence of symptomatic and asymptomatic SARS-CoV-2 infection in the general population and how this varies over time	Presence or absence of SARS-CoV-2 virus assayed from a nose and throat swab	Every calendar day from the start of the study, with analysis based on continuous time and the latest test available in the prior 2 weeks
Secondary Objectives		
To estimate the incidence of new symptomatic and asymptomatic SARS-CoV-2 infection in the general population, and how this varies over time	Presence of SARS-CoV-2 virus in a nose and throat swab, separately in previously negative and previously positive individuals (to estimate re-infection after clearing the virus)	Every calendar day from the start of the study based on all serial samples to date in those consenting to serial sampling
To estimate immunity to SARS-CoV-2 in the general adult population and how this varies over time, as reflected by anti-S and anti-N immunoglobins	Optical density readings for anti-S(spike) and anti-N(nucleocapsid) IgG from a ELISA assay for SARS-CoV-2 antibodies assayed from blood, categorised according to predefined thresholds based on pre-pandemic plasma as positive or negative	Every calendar day from the start of the study, with analysis based on continuous time and the latest test available in the last month
To estimate the association between prevalence of symptomatic and asymptomatic infection in individual members of households	Presence or absence of SARS-CoV-2 virus assayed from nose and throat swabs taken from different members of the same household*	Each household visit
To estimate the association between immunity to SARS-CoV-2 across individual members of households	Concentrations and thresholds of IgG to SARS-CoV-2 assayed from blood of different members of the same households*	Each household visit

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure
Exploratory Objectives To assess how prevalence and incidence of symptomatic 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, both natural and following vaccination	Presence or absence of SARS-CoV-2 virus assayed from a nose and throat swab Presence of SARS-CoV-2 virus in a nose and throat swab, separately in previously negative and previously positive individuals on nose and throat swabs (to estimate re-infection after clearing the virus), as assessed by immunity determined by IgG to SARS-CoV-2 assayed from blood, and by vaccination status and time from vaccination Concentrations and thresholds of IgG from an ELISA assay for SARS-CoV-2 antibodies assayed from blood	In individual cross-sectional surveys; repeated at each follow-up timepoint in those consenting to serial sampling
To assess how immunity to SARS-CoV-2 affects future use of NHS resources and mortality	Inpatient admissions, outpatient attendances, A&E attendances, consultations with a General Practitioner as collected from available routine electronic NHS health records; overall mortality and cause of death as collected from ONS and relevant national mortality databases	Over the year following each visit; at the final follow-up one year after the last visit of each participant
To compare immunity to SARS-CoV-2 in the general adult population, as reflected by neutralising antibodies and IgG	Concentration of neutralising antibodies to SARS-CoV-2 assayed from blood, categorised according to predefined thresholds[14] as positive or negative Concentrations and thresholds of anti-S and anti-N IgG from an ELISA assay for SARS-CoV-2 antibodies assayed from blood	Specific study visits where neutralising antibody assays performed

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

7. STUDY DESIGN

The overall study design is repeated cross-sectional surveys of representative households across the UK, identified either by one adult from the household having participated in existing 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 from their first study visit to assess these outcomes over the longer term. The choice of participating once at enrolment, weekly for the first month, or weekly for the first month and then monthly will be made at the enrolment visit; participants will not be offered the option to extend if they initially choose weekly visits for one month only.

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 venous blood draw is scheduled, a “contact” visit will take place where the study worker enters the household. However, in order to reduce the need to rely on trained HCP to conduct blood draws when they may be needed elsewhere in the NHS, blood for the antibody test may be drawn either from a vein by a study worker or from a capillary via a fingerprick by the participant, since the antibody tests being used in this study have similar performance regardless of source of blood. Self-fingerprick has been successfully used with these antibody assays (which require very small sample volumes) in very large numbers in the UK BioBank serology study (https://www.ukbiobank.ac.uk/media/zusjljce/ukb_serologystudy_report_month2_final-1.pdf). If anyone in the household is symptomatic, self-isolating or shielding on the date of a home visit date where a venous blood draw is planned, either a “non-contact” visit will be conducted with a fingerprick blood draw by the participant or without any blood draw; alternatively, a “contact” visit may be rescheduled to later in the allowed window when no one is symptomatic, self-isolating or shielding. In

order to remove the need for study workers to enter participants' homes and to make all home visits "non-contact", thus further reducing transmission risks to study workers and participants, from protocol v9.0, venous blood draws will be phased out and all participants on venous blood draws will be offered the options of moving to capillary blood draws or only taking swabs (no blood) for their remaining study visits.

At every visit (contact or non-contact), all participants will take a self-swab of their nose and throat and complete a short questionnaire. The self-swab can be done by those aged 12 years and older and is currently being successfully used in drive through testing centres; those 2-11 years will be swabbed by their parent/carer. The swab is the same size as that used routinely in paediatric practice and there is no modification to the technique needed. Self-swabbing minimises the risk to study workers of contracting SARS-CoV-2 from an asymptomatically infected individual. In a subset of households, optional consent will also be sought for adults aged 16 years or older to have a blood draw. In the first cross-sectional survey (Phase I, see below), the invitation to undergo additional blood sampling was sent to those sampled from the ONS Opinions COVID-19 Survey for practical reasons and to enable future data linkage to more detailed data on reported self-isolation behaviours. In subsequent surveys, of the 6,000 households invited to participate each week (24,000 per month), approximately 600-1200 households per week (2,400-4,800 per month; 10%-20%; including 200-400 households per month from each of Wales and Northern Ireland) will be randomly selected to receive an invitation for adults aged 16 years and older in the household to have a blood draw, as well as for all individuals 2 years and older to self-swab, targeting enrolment of a minimum of 300 households per month for blood sampling (10% of the target enrolment; including at minimum 50 households per month from each of Wales and Northern Ireland). From the end of July 2020, the percentage randomly selected to receive an invitiation for blood draw was increased to 20%, to assess the potential for prior immunity to affect future infection. In order to monitor the impact of vaccination on both immunity and infection, from February 2021, we will ask a representative sample of those already recruited to the study but only giving swabs to also give blood at their monthly visits, and for everyone giving blood samples to stay in the study until April 2022 (i.e. to have additional visits beyond their original 12 month study period). **The blood target is to achieve up to ~125,500 adults 16 years and older with blood test results every month in England, and up to ~7,500, ~4,500 and ~12,500 per month in Wales, Northern Ireland and Scotland (~150,000 in total across the UK) through to April 2022.** 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 to provide blood samples will be adjusted based on opt-in rates. 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**. Where an adult in the household is already giving blood, from September 2021 we will also ask children and young people aged 5-15 years whether they would be happy to give a sample of blood. For those aged 5-15 years, the target is to achieve 25% uptake of the invitation to participate in fingerprick blood testing, corresponding to ~4,000 children aged 5-9 years and ~7,000 older children/adolescents aged 10-15 years, and to a total of ~5,500 blood test results every month (sampling those 5-15 years every other month).

In order to contribute additional information to analyses of how immunity after infection changes over time, 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 reconsent in order to provide consent for blood sampling. For participants recruited under protocol 6.0 and later, consent for blood draws after testing positive on a nose and throat swab within the study will be sought at enrolment, to avoid needing to reconsent individuals after they test positive on a nose and throat swab.

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 at least 6 study visits over one year (enrolment; weeks 1, 2, 3, 4; then every month subsequently). The precise duration of follow-up would depend on when the participant was recruited and what they consented to – however, participants who agreed to monthly visits can withdraw permanently at any time and can also miss individual visits. From protocol v9.0, the majority of participants agreeing to multiple follow-up visits after one month would have monthly visits through to April 2022. However, if some participants recruited before protocol v9.0 choose not to provide optional consent for follow-up through to April 2022, they would be followed for a maximum of 12 months (as the original consent form specified participation for a maximum of 12 months). Participants newly recruited under protocol v9.0 would be followed up monthly until April 2022, which would be between 3 and 9 months, depending on specific date of recruitment. 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. **For assessment of current infection, the swab target is to achieve ~150,000 individuals with swab test results at least every fortnight from October 2020 in England, ~9,000 in Wales, ~5,000 in Northern Ireland and ~15,000 in Scotland (total 179,000 across the UK)** (absolute numbers reflecting the relative size of the underlying populations)**.** For assessment of immunity, **the blood target** (as of February 2021) **is to achieve up to ~125,500 adults 16 years and older with blood test results every month in England, and up to ~7,500, ~4,500 and ~12,500 per month in Wales, Northern Ireland and Scotland (~150,000 in total across the UK) through to April 2022** (also giving paired swab samples at the same timepoints) (absolute numbers reflecting the relative size of the underlying populations). For those aged 5-15 years, the target is to achieve 25% uptake of the invitation to participate in fingerprick blood testing, corresponding to ~4,000

children aged 5-9 years and ~7,000 older children/adolescents aged 10-15 years, and to a total of ~5,500 blood test results every month (sampling those 5-15 years every other month). From April 2021 onwards, we will maintain the targets for swab results per fortnight and blood results per month above through to April 2022 by

- inviting everyone who is currently active in the study to remain on monthly follow-up visits until April 2022 (additional consent)
- inviting additional households who are only giving swabs at their monthly visits to additionally give blood by fingerprick at these visits until April 2022 (additional consent)
- until January 2022, continuing to invite new households to join the study and have follow-up visits up until April 2022 in order to replace participants who stop follow-up or supplement current numbers in order to meet targets despite possible missed visits.

Initial sampling for recruitment 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. Sampling will also take into consideration local non-response rates to ensure those recruited remain regionally representative as much as possible. Those approached to provide blood samples from enrolment were selected completely at random from the initial recruitment invitation letters. To ensure that the expanded cohort providing blood samples is representative of the different regions, has the greatest possible power to investigate the impact of ethnicity, and places the least burden on participants, invitations to households to join the blood cohort after recruitment will be randomly selected stratified by sub-regional geographical area, but proportionately increased in households where anyone reports coming from an ethnic group other than White. Only households where anyone originally consented to repeated follow-up for longer than one month will be approached for consent for additional blood sampling. Sampling will also be proportionately adjusted to take into consideration non-response rates to the invitation to provide additional blood samples by factors including sub-region and age, to ensure those providing blood samples remain representative as much as possible.

Table 1 Original planned recruitment of households in England* †

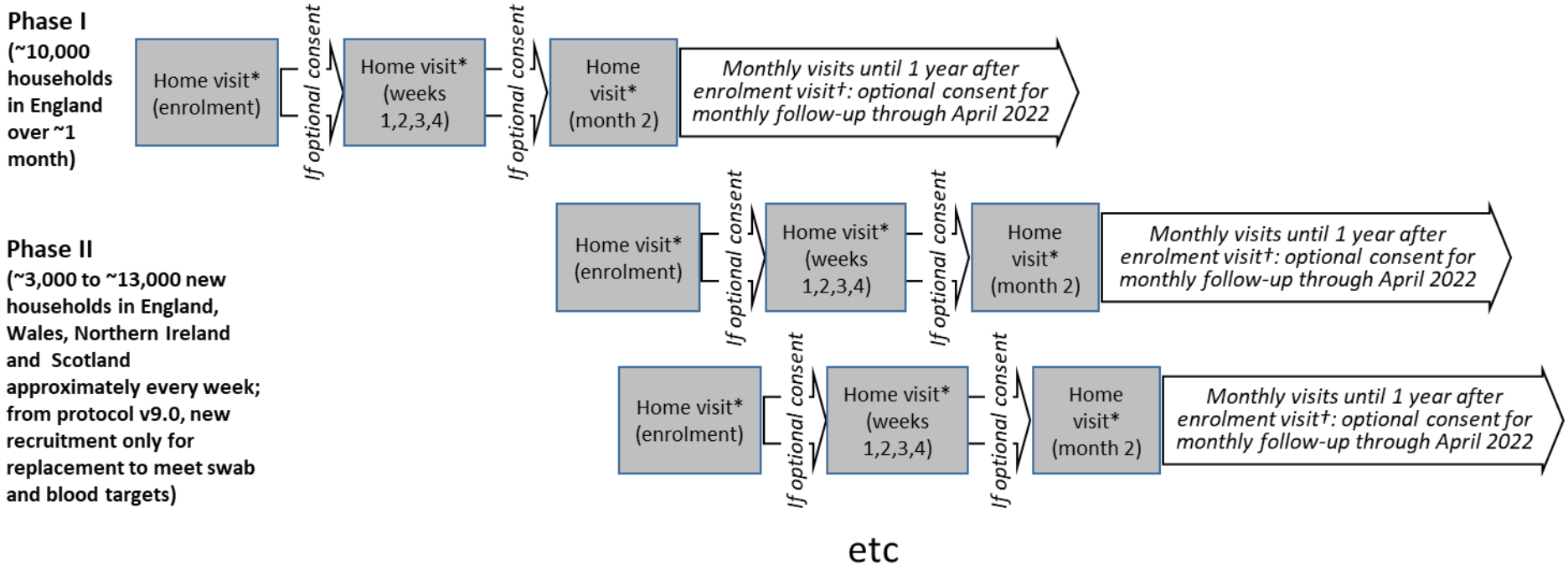
Week starting	Newly recruited households in England (actual or approx planned)	Newly recruited individuals in England (actual or approx planned)
27 April 2020	2523	5483
04 May 2020	3156	7038
11 May 2020	2436	5406
18 May 2020	1365	3092
25 May 2020	442	999
01 June 2020	1163	2526
08 June 2020	2008	4207
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 from October 2020 onwards. Targets are approximate and may vary depending on speed of scale-up and other factors, such as consent rates.

† After April 2021, to maintain the targets for swab results per fortnight and blood results per month above through to April 2022, we will invite already recruited participants to remain in follow-up through April 2022, with either swabs or swabs and fingerprick blood tests, and we will continue to invite new households to join the study.

Note: Gray shading shows data to July 2020, and white cells plans thereafter. 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

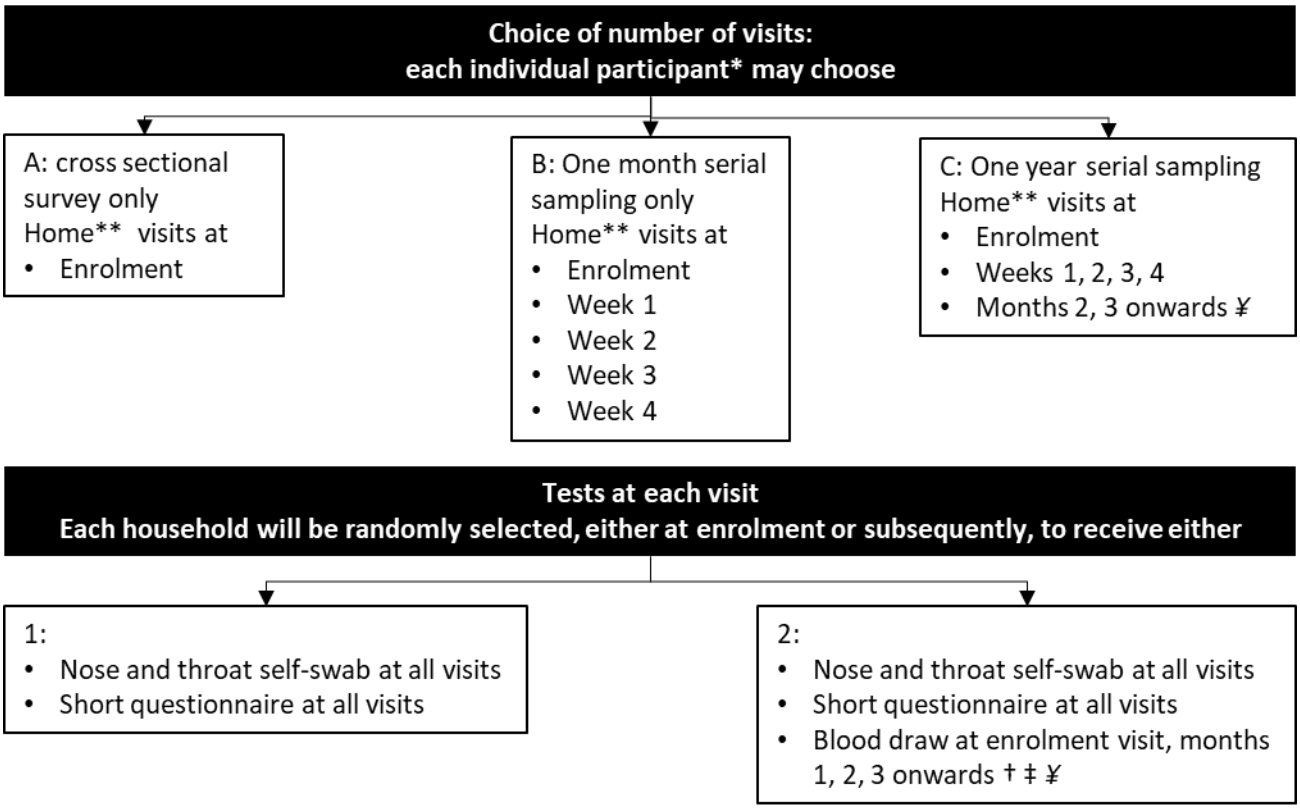


* Unless a venous blood draw is scheduled, home visits will be non-contact (participant self-swab of nose and throat, questionnaire; study worker stays 2m away from household at all times; capillary blood draw if participant has been randomly selected for blood draw and consented). Contact home visit will include participant self-swab of nose and throat, questionnaire and venous blood draw (only up to protocol v8.0 – phased out from protocol v9.0).

† Participants will be asked for consent to continue monthly follow-up visits to April 2022 (consent forms through protocol v6.0 specified participation for 12 months only, so additional consent is required).

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 venous 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; capillary blood draw if participant has been randomly selected for blood draw and consented). Contact home visit will include participant self-swab of nose and throat, questionnaire and venous blood draw (only up to protocol v8.0 – phased out from protocol v9.0). If anyone in the household is symptomatic, self-isolating or shielding, then the visit will be non-contact even if venous blood draw was scheduled.

† Up to and including protocol v10.0, 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. From protocol 11.0, those aged 5-15 years in households where at least one adult is already providing fingerprick blood samples may provide consent for optional blood draw every other month.

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

¥ Participants will be asked for consent to continue monthly visits to April 2022 (consent forms through protocol v6.0 specified participation for 12 months only, so additional consent is required).

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 swab target is to achieve ~150,000 individuals with swab test results at least every fortnight from October 2020 onwards in England, ~9,000 in Wales, ~5,000 in Northern Ireland and ~15,000 in Scotland (total 179,000 across the UK) (absolute numbers reflecting the relative size of the underlying populations). The blood target is to achieve up to ~125,500 adults 16 years and older with blood test results every month in England, and up to ~7,500, ~4,500 and ~12,500 per month in Wales, Northern Ireland and Scotland (~150,000 in total across the UK) (absolute numbers reflecting the relative size of the underlying populations). For those aged 5-15 years, the target is to achieve 25% uptake of the invitation to participate in fingerprick blood testing, corresponding to ~4,000 children aged 5-9 years and ~7,000 older children/adolescents aged 10-15 years, and to a total of ~5,500 blood test results every month (sampling those 5-15 years every other month).

In total, from 24 April 2020 to 12 April 2021, we recruited 371,996 individuals from 182,007 households in England, plus 23,461 individuals from 11,957 households in Wales, 12,687 individuals from 6,311 households in Northern Ireland and 32,206 individuals from 17,936 households in Scotland.

After April 2021, we will maintain the targets for swab results per fortnight and blood results per month above by

- inviting everyone who is currently active in the study to remain on monthly follow-up visits until April 2022 (additional consent)
- inviting additional households who are only giving swabs at their monthly visits to additionally give blood by fingerprick at these visits until April 2022 (additional consent)
- until January 2022, continuing to invite new households to join the study and have follow-up visits up until April 2022 in order to replace participants who stop follow-up or supplement current numbers in order to maintain targets despite possible missed visits.

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.

8.4. Blood sampling

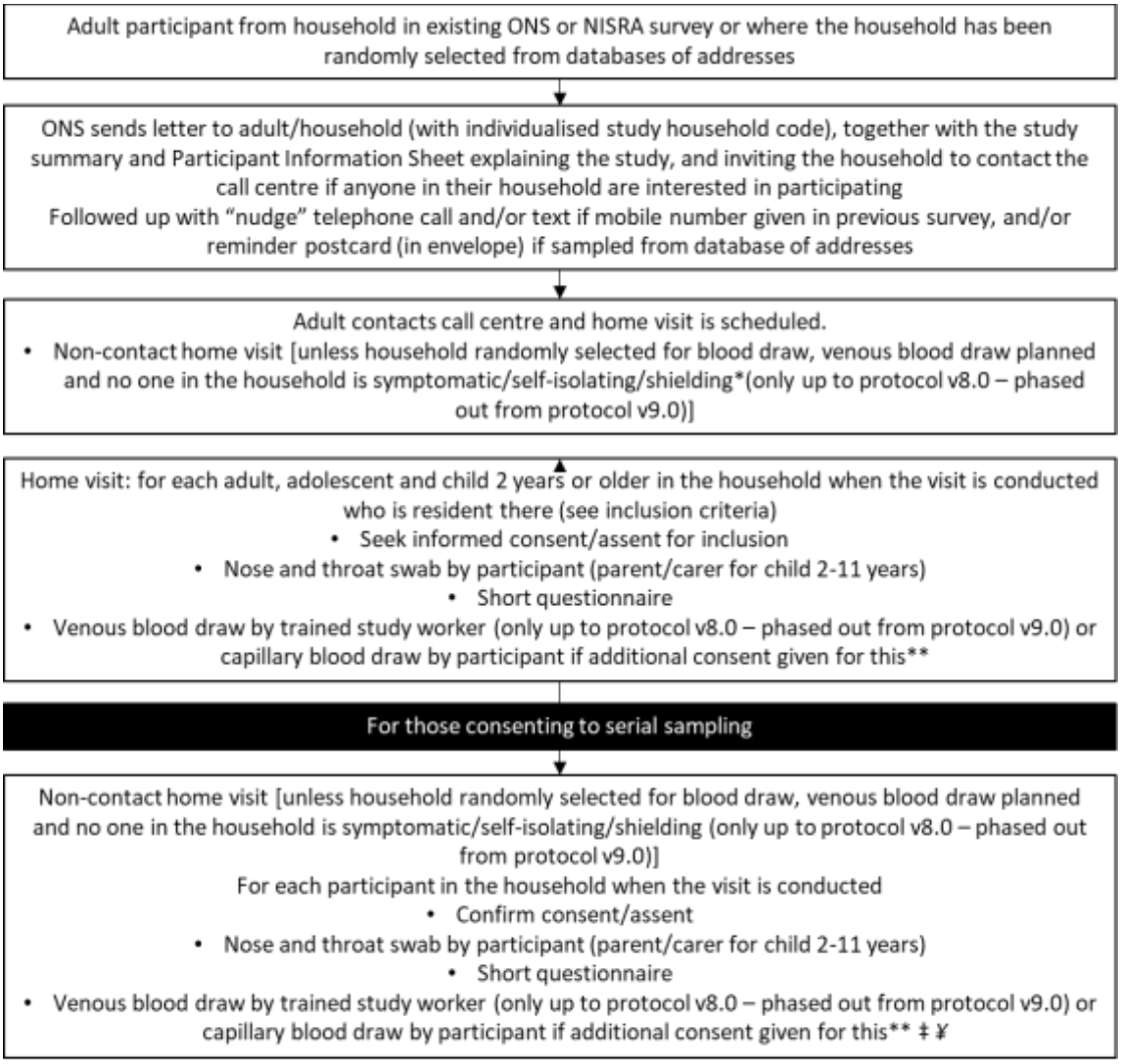
Those approached for blood sampling from recruitment will be a random sample of invited addresses.

Those aged 16 years and older approached for optional additional blood sampling after recruitment will be restricted to those households where at least one person gave consent for follow-up beyond 1 month, in order to monitor antibody positivity over time. Households which have ceased active follow-up will also not be eligible to be approached for optional additional blood sampling and extended follow-up.

Those aged 5-15 years approached for optional additional blood sampling after recruitment will be restricted to those households where at least one adult is currently providing fingerprick blood samples. No child or young person aged 5-15 years will be approached to provide blood samples at household recruitment.

9. PROTOCOL PROCEDURES

Figure 3 Flow diagram



* Unless a venous 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; capillary blood draw if participant has been randomly selected for blood draw and consented). Contact home visit will include participant self-swab of nose and throat, questionnaire and blood draw (only up to protocol v8.0 – phased out from protocol v9.0). If anyone in the household is symptomatic, self-isolating or shielding, then the visit will be non-contact even if venous blood draw was scheduled.

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

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

¥ Participants will be asked for consent to continue these monthly visits to April 2022 (consent forms through protocol v6.0 specified participation for 12 months only, so additional consent is required).

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	Tele-phone contact with call centre †	Enrol-ment home visit*	Week 1, 2, 3 home visit	Week 4/ month 1, months 2-¥ home visit	Alternate months 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			
Venous blood draw by HCP (phased out from protocol v9.0) or capillary blood draw by participant 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	
Venous blood draw by HCP (phased out from protocol v9.0) or capillary blood draw by participant if participant is 16 years or older and provides consent, and is either in a household randomly selected for blood sampling (starting from recruitment or subsequently), or is from a household where a participant has had a positive nose and throat swab in the study (see Figure 2)					X*	
Capillary blood draw by participant or parent/carer if participant is 5-15 years and consent (and assent) is provided, and is in a household where one or more adults are already giving capillary blood monthly						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; venous blood draw if consented and relevant timepoint) (phased out from protocol v9.0) or non-contact (participant self-swab of nose and throat, questionnaire; capillary blood draw if participant has been

randomly selected for blood draw and consented but no venous blood draw regardless of consent; study workers stay 2m away from household at all times).
¥ Participants will be asked for additional consent to continue monthly visits to April 2022.

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 or are available via the address list from which households are sampled. 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. The invite letter will direct participants to a website where some additional translations will be available. 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.
    - If the household has been selected for blood draw, blood may be taken from a capillary (fingerprick) by the participant (aged 16 years or older) at a non-contact home visit.
- At a contact home visit, the same procedures will be followed but the study worker will enter the home to take blood from a vein. Contact visits will be phased out in protocol v9.0, and all participants who have previously had venous blood draws offered the option to move to capillary blood draws or continue to just take nose and throat swabs. This is to avoid study workers having to enter participants' homes and to reduce any risk of transmission.

In order to minimise risks to participants and study workers, non-contact home visits will be conducted even if a venous 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 either draw blood from a capillary fingerprick or 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 venous blood is not planned to be drawn. For the purposes of defining when a non-contact visit should take place even if a venous 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. The choice of participating once at enrolment, weekly for the first month, or weekly for the first month and then monthly will be made at the enrolment visit; participants will not be offered the option to extend if they initially choose weekly visits for one month only.
- Optional: For the study to approach them in future with details of other ethically approved research studies or other programmes approved by DHSC (or equivalent in Devolved Administrations) for them to consider for potential participation (see below). (A list of DHSC (or equivalent) approved programmes is maintained on the study website with further details for participants.)
- Optional: if originally approached for swab tests only, to provide swab and blood tests if any member of their household tests positive on a swab test (as described in Section 7 above).

The reason for asking whether individuals would be happy to be approached in future for other ethically approved research studies or other programmes run by the NHS (or equivalent in Devolved Administrations) is because several other studies are trying to recruit individuals, for example, for human genetic studies led by Genomics England (https://www.genomicsengland.co.uk/covid-19/) or to potentially donate convalescent plasma within the NHS (or equivalent in Devolved Administrations). However, if participants indicate that they are happy to be approached for future ethically approved research or other programes run by the NHS (or equivalent in Devolved Administrations) (optional consent), this study would forward to them information about other studies/programmes for their consideration. This information would also be maintained on the study website.

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 (whether at recruitment or subsequently).

Participants will be enrolled at the first home visit.

9.4.1. Post enrolment recruitment into providing monthly blood samples and extending follow-up in those providing blood samples to April 2022 (protocol version 7.0)

A random sample of 10-20% households has been approached for consent to provide blood samples from the point of recruitment for the duration of their follow-up in the study. However, larger numbers are required to assess the impact of vaccine rollout on population level immunity (see Section 11.3 below). Therefore from February 2021, a randomly selected sample of already enrolled households who are currently providing swab but not blood samples, and where at least one person originally provided consent for 12 months' follow-up, will be invited to additionally provide blood samples at their monthly visits and extend their follow-up through to April 2022. This will be optional, and will be on an individual basis in those aged 16 years and older, but will be for both components (follow-up to April 2022 and monthly blood draws). Those aged 16 years or older who do not provide consent for this optional blood sampling will remain on monthly follow-up for 12 months from the original household recruitment date with swabs only. If anyone in the household provides additional consent, then parents/carers of anyone aged under 16 years in the household will be approached for consent to extend follow-up to April 2022 only for these individuals (to ensure that the household continues follow-up together).

At the same time, those households who were approached for blood draws from enrolment, and where one or more person has already consented to blood draws from enrolment, will be approached for optional consent to extend their monthly follow-up to April 2022. This is because the original consent form for these participants specified the duration of study participation as one year. Similarly, if anyone in the household provides additional consent, then parents/carers of anyone aged under 16 years in the household will be approached for consent to extend follow-up to April 2022 only for these individuals (to ensure that the household continues follow-up together). From May 2021 (protocol v9.0), venous blood draws, and more specifically the contact home visits required to conduct them, will be phased out, and all participants who have previously had venous blood draws offered the option to move to capillary blood draws or continue to just take nose and throat swabs.

The reason for not consenting will be recorded if the participant is willing to provide one, but this is not required. Regardless of consent, study participants may refuse a blood draw at any individual visit according to their preference at that visit.

As consent to be approached in future for other ethically approved research studies or other programmes run by the NHS (or equivalent in Devolved Administrations) (see Section 9.3 above) was only added for all participants, regardless of positivity, in protocol v6.0, this option will be sought from all those being approached about additional blood draws and extended follow-up until April 2022.

Selected households will receive an invitation letter explaining the additional blood draws and visits. This may be sent by email where participants have provided email addresses to receive vouchers and information about the study; participants without email addresses will be sent the invitation by post. Anyone who is willing to consent can do so either by informing their study worker at their next scheduled visit or by contacting the call centre. They will then be asked to sign an additional consent form at their next scheduled visit, before any blood is drawn.

9.4.2. Post enrolment recruitment into extending follow-up in those only providing swab samples to April 2022

In order to maintain swab targets through April 2022, from May 2021, we will approach all participants providing swab samples only and who originally agreed to 12 months follow-up for consent to extend their monthly visits to April 2022. This will be optional, and will be on an individual basis for each participant (i.e. is not dependent on agreement of the whole household). This is because the original consent form for these participants specified the duration of study participation as one year. The reason for not consenting will be recorded if the participant is willing to provide one, but this is not required. Regardless of consent, study participants may refuse any individual visit according to their preference.

As consent to be approached in future for other ethically approved research studies or other programmes run by the NHS (or equivalent in Devolved Administrations) (see Section 9.3 above) was only added for all participants, regardless of positivity, in protocol v6.0, this option will be sought from all those being approached about extended follow-up until April 2022.

Selected households will receive an invitation letter explaining the additional blood draws and visits. This may be sent by email where participants have provided email addresses to receive vouchers and information about the study; participants without email addresses will be sent the invitation by post. Anyone who is willing to consent can do so either by informing their study worker at their next scheduled visit or by contacting the call centre. They will then be asked to sign an additional consent form at their next scheduled visit.

9.4.3. Post enrolment recruitment into providing monthly blood samples for those aged 5-15 years

Through protocol version 10.0, fingerprick blood testing for antibodies in the survey was done only in those aged 16 years and older. However, as schools re-opened in Autumn 2021, positivity rates were 1.41% the week ending 27 August 2021 compared with 0.05% the week ending 25 August 2020. COVID-19 vaccinations were recommended only for those 12-15 years with long-term health conditions leaving them at higher risk of serious illness from COVID-19 or living with someone at higher risk of serious illness, meaning the majority of school age children remained unvaccinated. However, positivity rates are far higher in school age children than adults, leaving key questions relating to the degree of immunity school-aged children might already possess due to higher previous rates of natural infection and how much this might mitigate effects of return to school on positivity rates, and hence onward transmission, within this critical age group. For example, despite historically higher positivity rates in children, between September-December 2020, 13% of both students and staff in eighteen schools in six regions in the sKIDsPLUS study were SARS-CoV-2 sero-positive[15]. In March 2021, 13% of primary and 17% of secondary school pupils tested positive for SARS-CoV-2 antibodies in the ONS Schools Infection Survey, although this varied between 5% and 28% across secondary school pupils in different areas[16]. In the same survey, in June 2021, 25% of primary school staff and 23% of secondary school staff tested positive for SARS-CoV-2 antibodies[17] (pupil data not yet available). How antibody prevalence in children relates more

generally to antibody prevalence in adults in the same household and adults in the same communities is unknown, particularly in a general population representative sample.

From protocol v11.0, the option for their child to participate in fingerprick blood testing for SARS-CoV-2 antibodies will be offered to parents of children aged 5-15 years already enrolled in the survey, where at least one adult in the household is themselves already providing fingerprick blood samples. This is to ensure that the parent/carer providing consent for the child has a clear understanding of the procedure and what it means to provide the fingerprick blood sample. Consent from the parent/carer will be to provide a fingerprick sample every other month (i.e. not monthly as for adult participants) in order to estimate how antibody levels change over time in children and adolescents, in the same way as adults. Children will be asked for their verbal assent for the blood draw and any dissent will always be respected. Regardless of initial consent/assent, participants aged 5-15 years may refuse a blood draw at any individual visit according to their preference at that visit, and/or their parent/carer may refuse on their behalf. Those aged 5-15 years for whom consent is not provided for this optional blood sampling will remain on monthly follow-up for swabs only. The reason for not consenting and assenting will be recorded if the participant is willing to provide one, but this is not required.

As all visits are non-contact with the study worker staying at least 2m away at all times, the parent/carer will take the fingerprick sample for the child, using the same instructions as they use themselves (adolescents may take the sample themselves following the fingerprick guide) (see Section 9.6.1 below). The sampling kits for adults and children are identical, except that a paediatric lancet will be available for children who need it (adolescents may prefer to use the adult lancet depending on age and body size). Fingerprick samples will be processed using exactly the same methods and assay as for adult participants (see Section 9.9 below), and antibody results will be returned in the same way as for adult participants (see section 9.9.2 below). One important reason for using identical testing methods is to ensure comparability in antibody positivity results across the age range, rather than using a different test in those 5-15 years from those 16 years and older. Use of identical methods and assays will mean the data are directly comparable. In contrast, saliva antibody tests used in the ONS Schools Infection Survey have an estimated sensitivity of only 80%[16], meaning methods of analysis firstly need to make adjustments for this and secondly also need to account for different positivity thresholds. The minimum blood volume marked on the tube is 250μL, although the laboratory are able to process samples down to 200μL, but this provides a quantitative antibody level as well as a positive/negative result. This is essential moving forwards in the pandemic as it provides the flexibility to look at higher antibody levels which appear likely to be needed to neutralise different variants. This is also a major limitation of point of care lateral flow antibody tests, which do require smaller blood volumes, but each use their own individual threshold and again have much poorer sensivity. For example the FORTRESS assay used in adults in the REACT study had sensitivity 84% and specificity 99% for PCR-confirmed cases/pre-pandemic sera (compared with >99% for the assay currently used in adults in the survey[18]), again leading to the same challenges with analysis as saliva based tests.

Support for fingerprick testing with a quantitative assay comes from a large online public engagement study (n=4,290) carried out in June 2020 by REACT[19]. Key findings from their Executive Summary were

- There is high willingness among parents/carers to perform finger-prick antibody testing on children, even if just for research purposes.

- Young people also showed high willingness to be tested to see if they've had COVID-19, although to a slightly lesser extent than parents/carers.
- Overall preference was for the test to be performed at home by the parent or young person.
- Whilst 59% chose “saliva test (spit into tube)” as their preferred test approach, “finger-prick test” was the second most common choice (25%) and further comments suggested preference was generally for whichever test is more accurate.

We have also discussed parent/carer supervised/performed fingerprick testing with highly experienced research nurses from the Oxford Vaccine Group and they confirm that it would be a feasible and acceptable approach.

Therefore, households where at least one adult participant is already providing fingerprick samples and where one or more children/adolescents aged 5-15 years are participating in the survey will receive an invitation letter explaining the additional blood draws. By definition this will be at a post-enrolment visit. This invitation may be sent by email where participants have provided email addresses to receive vouchers and information about the study; any participants without email addresses will be sent the invitation by post. Any parent/carer who is willing to provide consent for their child/adolescent can do so by informing their study worker at their next scheduled visit. They will then be asked to sign an additional consent form at their next scheduled visit, before any blood is drawn. Children will be asked for their verbal assent for the blood draw at this visit and any dissent will always be respected. Children and young people who attempt the blood draw will receive a sticker as a “thank you”.

However, reflecting the fact that uptake is unknown, invitations will be sent using a phased approach. We will first sent invitations to all adults aged 24 years or older in around 1,100 eligible households focussed around specific geographic regions (to facilitate additional studyworker training) and targeting invitation letters to as even a spread of around 1,000 approached children between 5-15 years as possible (taking into account non-response/missed visits). Assessment of feasibility of proceeding across all eligible households would be based on the number of fingerprick tests attempted and antibody test results obtained per child/adolescent in whom consent was sought (so incorporating both parent/carer consent and ability to provide a blood sample of sufficient volume to run the test successfully). This outcome would be modelled by age from 5-15 years, and separately in those 5-9 and 10-15 years. If test results are obtained in <5% in either age group, then no further households would be approached for recruitment. Age ranges or age groups with >25% test results and >50% agreeing to do the test again in future (see below) would proceed to full implementation. For rates between 5 and 25% the funder would take a decision about proceeding to full implementation based on exact rates and association with age, and anticipated future participation. If a decision is made not to proceed, then any households invited into the pilot who have not yet had a study visit (e.g. due to dates not being convenient/personal preference) would not be subsequently approached.

In addition to the two quantitative outcomes (consenting and finger prick test attempted/approached, valid blood test result/approached), we would also record the parent/carers views on acceptability of fingerprick testing for each child approached, specifically regarding whether or not the test was completed successfully, how easy or hard they found the test, and how often in future would they be willing to try fingerprick testing again (including a never option), as well as any free text comments regarding the pilot. As this feedback would be sought only within the pilot, it will either be recorded on the main study database (depending on time needed to develop this) or using a separate survey tool

(Smart Survey) to the main study database. On Smart Survey, child participants would be identified only by their age in years at last birthday, sex, and pseudonymised household identifier (no personal identifiable information).

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 directly to the participant (see Section 9.9.2 below).

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.[20]

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); sex; ethnicity; 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 (including high temperature), 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, trouble sleeping, loss of appetite/eating less than usual, runny nose/sneezing, noisy breathing (wheezing), 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?
    - If yes, do they think that they are suffering from "long COVID" and with what symptoms? How is this limiting their activities?

- Mobile telephone number for participant to be informed directly of their swab test results, or those of their children in future (results will be returned by the study 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 (including high temperature), muscle ache (myalgia), fatigue, sore throat, cough, shortness of breath (dyspnea), headache, nausea/vomiting, abdominal pain, diarrhoea, loss of taste, loss of smell, trouble sleeping, loss of appetite/eating less than usual, runny nose/sneezing, noisy breathing (wheezing), other symptoms) or since the last visit, or otherwise consider that they currently have COVID-19
- Have they recently been in contact with someone that they definitely know (based on a positive test) or suspect (no positive test) was infected with COVID-19 at the time of contact? Yes/No for each type of contact and for each
    - If yes, date of last contact
    - If yes, was this someone in their own household or someone outside their household
- Working status (employed, not working, retired, student etc) and work location (at home, outside of home etc), including number of days per week usually spent working outside the home or at school/nursery, and mode of transport to get to work/school/nursery
- Healthcare and social care contacts including currently working in health/social care in roles which primarily directly interact with patients/residents/clients or not, recently visited hospital or residential/nursing care home
- Contacts with other individuals inside the household (eg social distancing within the household) and outside the household, including through work, school/nursery, shopping, exercise etc including duration and number of individuals, how easy they find it to maintain social distancing and use of face coverings or masks
- Do they have long-term health problems, and do these limit their activities?
- Current smoking status.
- Have they recently travelled abroad? If yes, to which countries?
- Have they received or been offered a vaccine against COVID-19? If yes, type, number of doses, dates.
- Have they received a vaccine against influenza? If yes, date.

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**), blood will be drawn in one of two ways. Where a trained HCP is available to conduct a visit, 5ml venous blood will be drawn by the study HCP from each participant in the household aged 16 years or older into a BD Vacutainer™ SST™ II Advance Tube. Venous blood draws will be phased out from protocol v9.0 so that study workers do not have to enter participants' homes. Alternatively 0.5ml blood will be collected from a capillary via fingerprick by the participant (or the participant's parent/carer for those aged 5-15 years) into a Greiner MiniCollect® tube, which will then be placed into a larger carrier tube to facilitate logistics. Both methods will be used at first to provide flexibility in terms of availability of trained HCP for the study given other pressures in healthcare provision associated with the pandemic. Initially venous blood draw would continue to be carried out in households receiving venous blood draw from recruitment, and households currently only doing swab tests would start blood draws using fingerpricks (hence remaining with non-contact visits). Subsequently households receiving venous blood draws would be offered fingerprick, reducing the need for contact visits. This will be done by email where participants have provided email addresses to receive vouchers and information about the study; participants without email addresses will be sent this invitation by post. Individuals who are not able to conduct the fingerprick test, or would prefer not to, can either only take nose and throat swabs at their remaining study visits or may choose to withdraw.

All the materials required for the fingerprick will be pre-packaged into a standard kit by Thermofisher, including contact-activated lancets, alcohol and saline wipes, plasters and instruction sheets. This kit will generally be provided to the participant as part of the study visit. However, in order to improve study logistics and reduce the amount of time that participants have to spend with study workers (albeit at non-contact visits with social distancing) kits may also be posted to participants with instructions to self-administer the fingerprick test once the study worker has telephoned on the day of the visit to confirm the visit. This would only be done after at least one visit from a study worker where a fingerprick was performed. The fingerprick test would therefore only be done on the day of the study visit, and the study worker would collect it at the visit where they collect the questionnaire data and supervise the swabbing.

Each tube (or carrier 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 the antibody test for anti-spike (S) protein will be returned to participants in the same way as for the swab test results. The test for anti-spike (S) protein has shown excellent performance in a comparison with 4 commercially available assays on a large number (>1500) samples;[21] 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). The test is now CE marked by the Medicines and Healthcare Products Research Agency (MHRA). Performance is similar on capillary and venous blood drawn from the same individual, and capillary blood draws have been successfully used with this assay in the large UK Biobank serology study ((https://www.ukbiobank.ac.uk/media/zusjljce/ukb_serologystudy_report_month2_final-1.pdf)). From February 2021, samples will also be tested for antibodies against the N (nucleocapsid) protein, rather than just the S protein, on the same sample as part of the single automated workflow. This should enable antibody responses to be categorised as against S only (compatible with vaccination) or against S and N (compatible with natural infection). Because anti-S is common to protection from both vaccination and natural infection, anti-S results will be returned to participants, but anti-N will not.

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). If key participant characteristics are not collected at the baseline assessment in error, these may either be elicited at a follow-up visit or by a phone call from IQVIA. Emails given by participants (e.g. to receive vouchers) that are recorded incorrectly will also be corrected by a phone call from IQVIA.

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, and then (depending on consent, **Figure 2**) two months after the enrolment visit and every month thereafter through to April 2022. To allow for participant convenience and study workers availability, visits should occur within equidistant windows around scheduled study timepoints, that is within a ±3 day window for the first three weekly visits, within a window of [-3,+16] days around the week 4 visit, or within a ±15 day window around the visits from months 2 onwards. 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 venous blood sampling is planned, or household preference. From protocol v9.0, contact visits will be phased out and subsequently all visits will be non-contact.

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 wherever possible. Serum or plasma will be tested by research staff at the University of Oxford for antibodies using a novel quantitative ELISA for immunoglobulins IgG, based on tagged and purified recombinant SARS-CoV-2 trimeric spike protein in a high throughput assay.[13,22] Antibody binding to the S protein is detected with ALP-conjugated anti-human IgG. This assay was originally developed by the University of Oxford, but has achieved CE marking for use with both venous and capillary blood and is now being marketed in collaboration with Thermo Fisher Scientific as the OmniPATH Combi SARS-CoV-2 IgG Spike ELISA. In parallel the same sample will be tested for antibodies against the N (nucleocapsid) protein, as part of the same automated workflow. The platform is capable of processing very small sample volumes often encountered with finger lance capillary sampling. Serum from a subset of samples will also be tested using neutralisation assays. These neutralisation assays use a lentiviral construct which expresses SARS-Cov2 S protein, and are tested in a cell-based system described as a pseudotype microneutalisation assay (pMN), as recently used in a study of Scottish blood donors.[14] Any residual material (sera and spun cells) will be stored by the University of Oxford in secure facilities; it is not expected that there will be substantial residual material following capillary blood sampling, but any remaining sample will be stored and assay plates will be stored temporarily to enable assays to be re-run if necessary (e.g. if quality control issues are identified). Any residual material collected and stored in the study that, following analysis for the study, has been clearly identified as being of no further use, may be released to other researchers for use in COVID-19 related research projects, providing consent has been provided for samples to be stored and used in future research (explicitly requested, see Section 9.3).

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 assays 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

At minimum, nose and throat swab and blood test results will be returned directly to the participant through the study by email or by letter if they do not want to provide an email address for this purpose (or do not have an email address). 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.

As currently required by law (Public Health Regulations (2010)), 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).

The 2010 Regulations have been amended in England to require that, in addition to positive cases, indeterminate, negative and void test results must be reported by laboratories to identify the causative

agents for COVID-19 (including antibody and swab test results) (in place from 23 November 2020). The required items of personal data (minimum dataset) for each sample taken will be shared with the national testing programmes as required, also to enable immediate movement of positive results into the national tracing systems (see Section 12). National tracing systems will then immediately and automatically notify participants of positive results. Participants will be informed about this automatic referral of a limited set of personal data to be linked to test results in the Participant Information Sheet, and that by taking part in this survey they agree to this disclosure taking place. In addition, all results will be returned directly to the participant by email or letter, as described above.

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. For participants recruited under protocol 6.0 and later, consent for blood draws after testing positive on a nose and throat swab within the study will be sought at enrolment, to avoid needing to reconsent individuals. In other cases, individuals 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. The study team may also withdraw a household for unreasonable behaviour in exceptional circumstances, for example, repeatedly touching study workers at non-contact visits despite being requested to maintain social distancing or being verbally abusive.

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.

De-identified data obtained up to the point of consent withdrawal will be kept and used in analysis for all participants who withdraw, regardless of type of withdrawal (described below) 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 have the following options, and the type of withdrawal recorded.

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

2) Participants can withdraw from active follow-up (i.e. future study procedures) and further communication and also request their personal identifiable information be removed so that their study records cannot be linked to ONS and NHS records for future electronic follow-up. De-identified data and samples obtained up until the point of withdrawal would 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. Personal identifiable information would be removed so that their study records cannot be linked to ONS and NHS records for future electronic follow-up.

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 specifically replaced; rather ongoing recruitment will be to maintain the overall swab and blood targets described above, accounting for both withdrawals and intermittent missed visits without withdrawal. 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 venous blood draw performed by study HCP (phased out from protocol v9.0), a participant fingerprick blood draw using methods which have been widely used in other serology studies and for commercial antibody testing, 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.

However, any serious adverse event **which is considered related to any of the study procedures** will be reported to the Sponsor. A serious adverse event is defined as any untoward medical occurrence that

- Results in death
- Is life-threatening (with a real, not hypothetical, risk of death at the time)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Has a real, not hypothetical, risk of one of the above

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

10.1. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the Health Research Authority (HRA) report of serious adverse event form (see HRA website).

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, Bayesian dynamic spatiotemporal multi-level regression with post-stratification (MRP) will be used to investigate changes in positivity rates over calendar time.[23,24] Potential spatial correlation between neighbouring areas is taken into account using a "BYM2" specification. Time will be allowed to vary in a non-linear fashion by using a first-order autoregressive term for time. Space-time, and space-age interactions will be included to allow the positivy over time to vary by age and age group. This spatiotemporal MRP is an extension of the spatial MRP method developed by Gao et al.[25] In extensive simulations, Gao et al found that bias was significantly reduced when using a BYM2 specification compared to a non-spatial independent identically distributed specification. Attenuation in absolute bias was most apparent with small sample sizes. Even when simulating outcome data as a multivariate independent normal, BYM2 spatial prior produced nearly same posterior estimates as independent identically distributed prior, indicating that the BYM2 spatial prior does not force spatial structure when it is not present.

The reason for using MRP as the primary method is because it allows probabilistic assessment of relatively rapid changes in positivity. MRP consists of two steps. First, a multilevel regression model is used to generate the outcome of interest as a function of (socio)demographic and geographic variables. Next, the resulting outcome estimates for each demographic-geographic respondent type are poststratified by the percentage of each type in the actual overall population. In several empirical and simulation studies MRP was superior at both the national and regional levels to classical survey weighted and unweighted approaches, including when using small sample sizes.[24,26] Factors included in the main models - besides time, space, and a space-time interaction described above – will be sex, age, ethnicity and an age-time interaction. Whether additional interactions are needed will be determined based on the Watanabe-Akaike information criterion.

In addition, 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 (as both categorical and continuous variables) and other responses to the short questionnaire. These factors will also be considered in multi-level regression models, similar to the main model over continuous time described above.

Similar spatiotemporal MRP methods will be used to estimate proportions over time 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. 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, sex and ethnicity.

Incidence will be calculated directly using similar Bayesian dynamic multi-level regression models (Poisson log link) 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 thin plate splines as above.

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.

More information about the methods used in analysis can be found on https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/methodologies/covid19infectionsurveypilotmethodsandfurtherinformation#14-day-estimates.

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

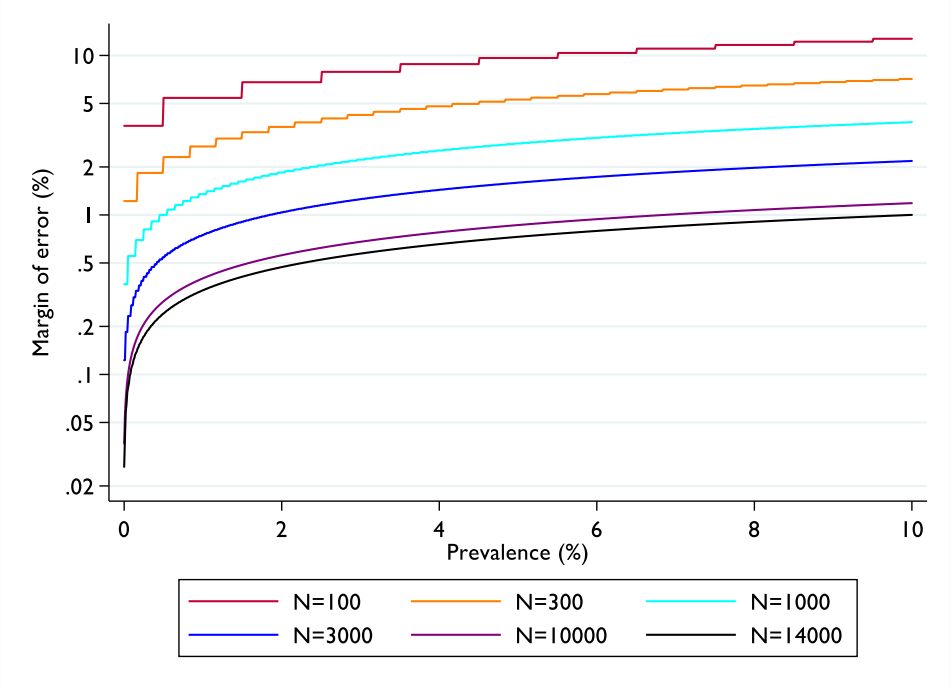
for variation within smaller but very important subgroups, including regions and Devolved Administrations (each targeting ~1,000 households per month, ~2,100 individuals per month).

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 2020 is designed to achieve similar numbers regionally as were originally available in England as a whole in Phase I, ie ~15,000-20,000 individuals with swab test results at least once each fortnight in each of the nine government office regions of England and also proportionate samples in Wales, Scotland, and Northern Ireland. Overall the swab target is therefore ~150,000 individuals with swab test results at least every fortnight in October in England, ~9,000 in Wales, ~5,000 in Northern Ireland and ~15,000 in Scotland (total 179,000 across the UK) (absolute numbers reflecting the relative size of the underlying populations). 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.

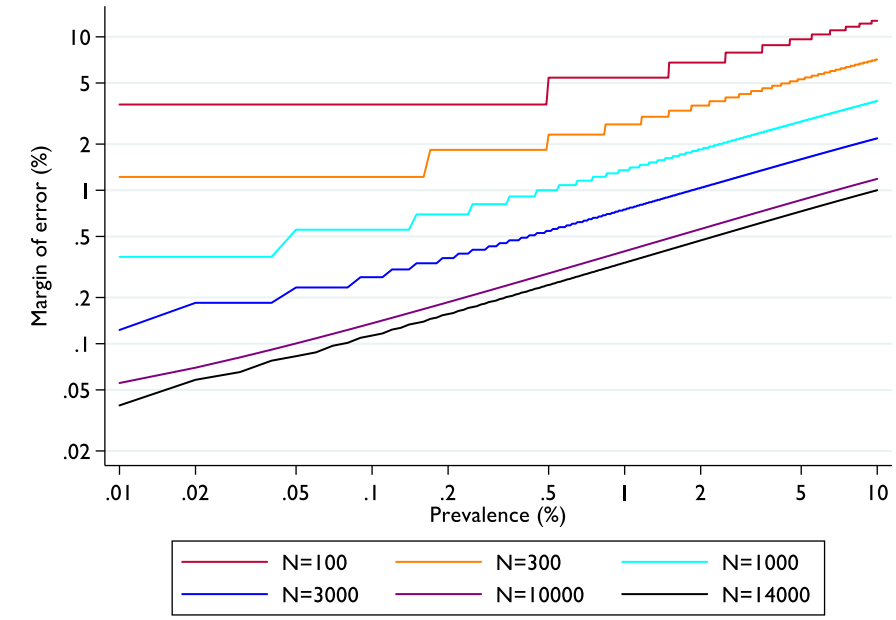
For blood sampling for seroprevalence, 10-20% of those enrolled providing blood samples from recruitment was considered to provide an acceptable trade-off in terms of precision, given that seroprevalence rates are expected to be higher than infection rates, and so margins of error for the former can be larger than the latter without compromising decision-making. However, in order to assess the impact of vaccination, larger numbers are needed. The total blood target of ~125,500 adults 16 years and older sampled every month in England for approximately one year through to April 2022 (allowing time for scale-up in additional recruitment to blood sampling) is designed to provide estimates of immunity within different regions (~10,000-15,000 per month) with a margin of error below 2%, and within different age groups over 16 years within regions (~2,000 per month) with margins of error below 5% (Figure 4(c)). For those aged 5-15 years, the target is to achieve ~5,500 blood test results every month. This will achieve a margin of error below 3% across the UK.

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

(a) With prevalence ranging from 0 to 10% on an absolute scale

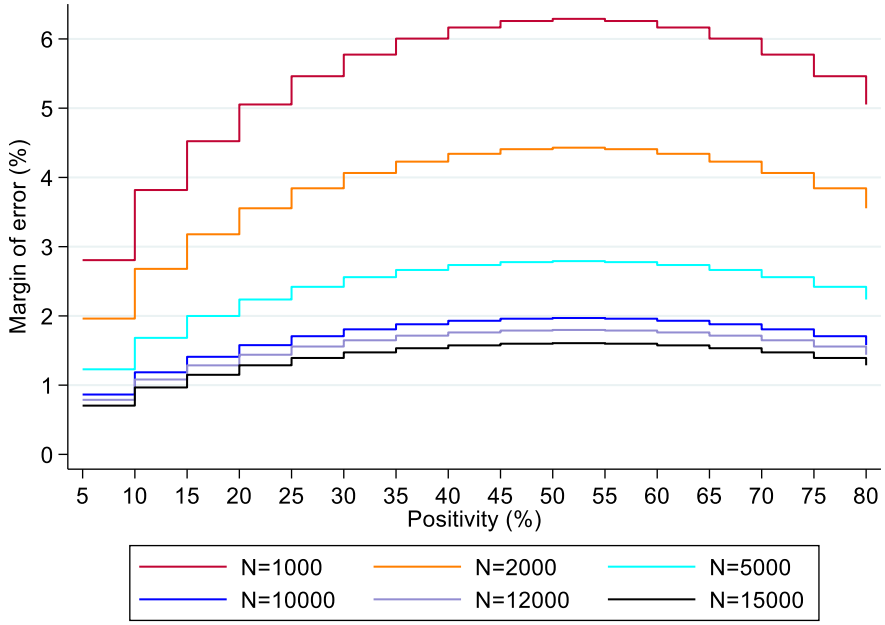


(b) With prevalence ranging from 0 to 10% on a log scale to highlight the impact at low prevalences



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.

(c) With prevalence ranging from 5 to 80% on an absolute scale



11.4. Analysis populations

All enrolled participants will be included in analyses, which will adjust for clustering by household wherever possible. Secondary analysis will also be conducted de-duplicating to one individual per household, for example 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/covid-19/covid-19-infection-survey/results and published by ONS) 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 region and age, with additional analyses by sex, ethnicity, occupation, region and symptoms as examples. 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, participant capillary blood draw, and ask the specific additional questions at the home visit, and study HCP will take venous blood (phased out from protocol v9.0). 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 or post-stratification 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 gratned 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 (through to July 2021) and Capita (from July 2021) to help resource the call centre, through direct access to the IQVIA Voyager database. The NHS Business Services Authority will return test results to participants by email. Eight Days will print test result letters for those participants not wishing to receive results by email. All will have participant contact details solely in order to undertake this contracted work. The companies involved in the survey may sub-contract out specific services but any sub-contractors will be bound by the same duty of confidentiality and security arrangements.

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 or email. At present IQVIA will also send the relevant minimum set of personal data for participants with positive swab tests to the relevant public health bodies as required by law. To enable compliance with the 2010 Regulations in England (in force from 23 November 2020) which require all test results relating to COVID-19 to be reported to public health bodies (positive/negative/Void), IQVIA will send the required minimum set of personal data for all visits where a swab was taken to the national testing programmes as required by law. The Lighthouse laboratories will also return nose and throat swab results directly to the national testing programmes as required by the regulations, identified by their study barcode. All results will also be returned directly to participants by IQVIA using a letter printed by Eight Days or email through the NHS Business Services Authority where participants have provided an email address to receive study test results through. In order to do this, IQVIA will send test results, along with the participant's name, email address and month and year of birth to the NHS Business Services Authority who will issue the results to participants via email, in the same way as results from the national testing programme. 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, and to public health bodies in the required format.

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 for England, and through the equivalent national bodies in the Devolved Administrations.

For the pilot study of antibody finger prick blood testing in those aged 5-15 years old, a small amount of feedback on the parent/carer experience of attempting finger prick blood testing in their child will be sought. This will either be recorded on the main study database (depending on time needed to develop this) or on a separate survey tool (Smart Survey) to the main study database. On Smart Survey, child participants would be identified only by their age in years at last birthday, sex, and pseudonymised household identifier (no personal identifiable information).

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 from the survey 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 Lifecyle and Validation and formally validated as 21 CFR part 11 complaint 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 to arrange visits, and email address for vouchers, study updates and return of results if participants are willing to provide this, 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 all information will not be routinely shared with other third parties 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. Participants name, email and month and year of birth will be provided to NHS Business Services Authority to issue test results via email where participants are willing to receive their test results this way, and to Eight Days to issue test results by letter otherwise. The companies involved in the survey may sub-contract out specific services but any sub-contractors will be bound by the same duty of confidentiality and security arrangements.Some IQVIA offices are located outside the UK, therefore IQVIA will sometimes need to process information outside the European Economic Area. Such transfers will only take place within IQVIA with appropriate safeguards in place to ensure the confidentiality and security of personal information, and participants will be informed about this in the information sheet. 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 identifiable 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).

Parent/carer experience of antibody finger prick blood testing in those aged 5-15 years old in the pilot study will either be recorded on the main study database (depending on time needed to develop this) or on a separate Smart Survey database, given the very limited number of households involved and the small number of questions. Smart Survey are hosted in the UK, hold ISO 27001 and Cyber Essentials Plus (CE+) certification, have been formally assured by ONS as part of their assurance process and approved for use in other ONS surveys.

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 themselves via fingerprick or from a vein by a study HCP (phased out from protocol v9.0). 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 at the start of the protocol as representatives of participating organisations, a representative of the Devolved Administrations, the Chief Investigator and an independent Chair (Professor Sir David Spiegelhalter).

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

The study is registered on ISRCTN, http://www.isrctn.com/ISRCTN21086382. The protocol and participant information sheets are available on https://www.ndm.ox.ac.uk/covid-19/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 results 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. This includes any additional visits after 12 months for those invited to extend follow-up for additional monthly visits through to April 2022. 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; those consenting to additional monthly visits up to April 2022 would receive £425 plus or £25 for each extra visit up to April 2022 (total depending on date of original household enrolment).

Children and young people aged 5-15 years who attempt a blood draw for finger prick testing will receive a sticker as a "thank you".

17. FINANCE AND INSURANCE

17.1. Funding

Funding for the survey in England, Wales, Northern Ireland and Scotland 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 approached per week, targeting ~2,500, 250 and 250 being enrolled respectively.
				Sections 3, 5, 9.3, 9.6.1, 11.2: clarification that results of tests for COVID-19 infection done within the NHS and held within Public Health England (PHE) and equivalent national test databases in Wales and Northern Ireland will also be linked into the studyin order to accurately ascertain infection status outside of the study/study visits (was in the version 1.0 Participant Information Sheet).
				Sections 5, 6: clarification that neutralising antibodies will not now be done on all participants with blood drawn in the study (since this is highly labour intensive), but may be done on a subset to triangulate with results from the main high-throughput assay used. Correspondingly in section 6, neutralising antibodies also therefore moved to an "Other" exploratory outcome. Further, IgG will be assayed on all participants using a high-throughput version of the referenced assay, since IgM adds little information.
				Sections 5, 7: clarification that non-contact visits will be performed wherever possible to reduce risks to participants and study workers.
				Sections 5, 7, 9: addition of approach for consent for for blood draw in any individual who tests positive for virus (new infection) during the study as quickly as possible after their positive test and then at monthly visits to contribute additional information to analyses of how immunity after infection changes over time

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
				Section 6: timepoints where outcome measures evaluated amended to weekly over calendar time, reflecting results as presented on https://www.ndm.ox.ac.uk/results. Objectives section reordered to clarify which timepoints go with which outcomes, but no changes (other than moving neutralising antibodies to an "other" exploratory outcome as described above.
				Section 7: clarification that in Phase II, between 10-20% of households will be randomly selected to be approached for consent for blood draws, targeting a minimum of 300 households enrolled per week undergoing blood draws (exact consent rate is unknown).
				Section 9.1, Table 1 (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 tesxt if they are happy to provide mobile phone numbers, as well as being returned to the GP by letter or email. Results of blood tests will be returned once the assay is approved by the MHRA (submission currently in preparation). We would like to seek approval to do this now so we can implement without delay when the system is finalised.
				Section 9.6.1: Minor changes to the questions being asked on the questionnaire, including adding domains about recent contacts outside the home. Section reordered into questions asked once at enrolment with only changes elicited at follow-up and questions asked explicitly at each follow-up.
				Section 9.6.1: clarified that swab and blood samples are primarily identified by a unique sample barcode linked to the participant's unique study number on the database.

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
				Section 9.6.1: addition of option to be approached about further research if participant tests positive for COVID-19.
				Section 9.7: Clarified that the enrolment visit blood draw can be delayed if needed, at any time up to the first serial sampling visit (including its time window).
				Section 9.9: Clarification that residual material from blood samples are stored for consistency with the Participant Information Sheet and Informed Consent Form which referred to storing leftover blood sample.
				Section 11.2 Update to statistical analysis methods to reflect ongoing analysis results summarised on https://www.ndm.ox.ac.uk/results
				Section 11.5: Clarified that interim analyses will be conducted at least twice a month in order to inform the UK's response to the pandemic, in response to suggestion from the REC.
				Section 11.8: Clarified that regular checks for data quality will be run, in response to suggestion from REC
				Section 12: addition of NatCen as a second key collaborator and lead organisation, given the scale of Phase II and the need to conduct the study across the Devolved Administrations. Changes throughout this section to clarify data management with a second lead organisation.
				Section 12.1 Clarification that name is collected on the household CRF for the purposes of linkage, to make consistent with other parts of the protocol and the Participant Information Sheet
				Section 12.1: addition of mobile telephone numbers if participants wish to receive results by text, and of email addresses if they wish to receive incentive vouchers by email (can be posted instead) and clarification that email addresses will be shared with the third parties named in 12.1 who provide the vouchers.
				Section 13: removed "GCP" from the first sentence for consistency with Section 13.2 which clearly states that no GCP monitoring will be performed.
				Section 16.8: Clarification that participants have the option of receiving vouchers more quickly if they provide an email address.
MA01 (non-notifiable)	2.1	17 June 2020	Ann Sarah Walker	Sections 7, 9, Table 1 (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
SA02	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)
SA03	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.
SA04	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 withing whom transmission may be greater or lesser 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.

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
				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).
				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.
SA05	6.0	20 November 2020	Ann Sarah Walker	Title page, and Sections 3 and 16.6: addition of ISCRTN number (also a condition of NIHR granting the survey Urgent Public Health status)
				Contacts: updated ONS representatives
				Contacts: added details of Study Clinical Experts
				Contacts and Section 13.3: addition of a representative of the Devolved Administrations and an independent Chair to the Study Management Group (the latter as a condition of NIHR granting the survey Urgent Public Health status).

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
				Sections 6, 11.2: update of timing of analyses and statistical methods to reflect the fact that models assessing a continuous relationship between positivity and incidence and calendar time are used as the primary analysis, with models based on categorising time a secondary analysis.
				Sections 7, 9.3, 9.9.2: For households invited to provide nose and throat swabs only, additional optional consent will be sought at enrolment for additional blood samples if anyone in their household tests positive on a nose and throat swab (in order to avoid reconsenting them later on – information about this already in the participant information sheet).
				Section 9.1: clarification that a single "nudge" telephone call may be made to addresses where a telephone number is available through either participation in previous surveys or the address list via which households were sampled.
				Section 9.1: addition of a website hosting translated participant materials.
				Section 9.3: extension of optional consent for other research studies to other programmes approved by DHSC (or equivalent in Devolved Administrations) (e.g. convalescent plasma).
				Section 9.6.1: addition of questions around long COVID
				Section 9.7: addition of phone call to elicit missing participant data.
				Section 9.8: clarification around visit windows being equidistant.
				Sections 9.9.2, 12: amendment of methods for returning results to participants given changes to the Public Health Regulations (2010) in England (in process for Devolved Administrations) to require all results (positive/negative/void) of any laboratory test (swab or blood) to be returned to public health bodies, not just positive tests. Until these regulations are in place, only positive swab results will be passed onto public health bodies in the relevant nations as per protocol v5.0 and all results will continue to be provided to participants by letter. Once regulations are in place, notification of swab test results will be via the national reporting systems linked to national tracing programmes.
				Section 9.10: clarification of different options around withdrawal from the study.
SA06	7.0	1 February 2021	Ann Sarah Walker	Sections 2, 6: clarification that survey remains important to monitor infection rates as increasing numbers of people get vaccinated and that vaccination is an important participant characteristic to be considered in analyses.
				Sections 2, 3, 5: removal of plans to rapidly decrease recruitment in the absence of a "second wave" of infection in October 2020

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
				Sections 2, 5, 7, 8, 9, 11, 16: approach for consent from individuals from enrolled households currently providing swabs only to provide optional blood samples at monthly visits and for monthly visits to be extended to April 2022, in order to monitor vaccine rollout. Approach for optional consent for individuals from households already providing blood samples to extend follow-up to April 2022 (because the original consent form specified a 12 month study participation). The target is to achieve up to ~125,000 people giving blood samples every month in England, and up to ~7,500, ~5,500 and ~12,000 per month in Wales, Northern Ireland and Scotland (~150,000 in total across the UK) through to April 2022.
				Sections 2, 5, 7, 9, 10, 11.8, 13.1: addition of the option for blood to be obtained from participant fingerprick (capillary) rather than only venous blood draw, to avoid the need to rely on trained HCP who may be needed in other parts of the NHS and to allow the ability to obtain blood if individuals in the house are symptomatic, self-isolating or shielding.
				Sections 5, 6, 9.6, 9.9.1: extension of the antibody assays to measure antibodies against both S (spike) and N (nucleocapsid) proteins on the same sample within the same automated workflow. Only anti-S results will be returned to participants (as in previous protocol versions) since both natural infection and vaccination produce these antibodies.
				Section 9.6.1: clarification that questions about vaccination include both the offer and receipt, and also the type of vaccine, number of doses and dates if vaccinated.
				Section 11: updates to statistical analysis since the survey has now reached sufficient size that spatiotemporal models can be fitted (originally presented as a future aspiration in Phase I).
				Section 12.3: addition of possibility of data processing by IQVIA outside the EEA as they are a worldwide organisation. This had always been in the participant information sheet, but had been omitted from the protocol in error.
MA02	7.0	05 April 2021	Ann Sarah Walker	Updates to the instruction sheet for participants for capillary blood which will be sent ahead of the visit.
MA03	8.0	9 April 2021	Ann Sarah Walker	Lay summary, Synopsis, Sections 5, 7, 8.1: Extension of recruitment from 23 April 2021 to 31 July 2021 and study duration to 31 July 2023. We will continue to invite new households to join the study in order to maintain the stated targets for swab results per fortnight and blood results per month.

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
SA08	9.0	29 April 2021	Ann Sarah Walker	Lay summary, Synopsis, Sections 5, 7, 8.1, 9.4.2, 16: From April 2021 onwards, we will maintain both the targets for swab results per fortnight and blood results per month above through to April 2022 by • inviting everyone who is currently active in the study to remain on monthly follow-up visits until April 2022 (additional consent) • inviting additional households who are only giving swabs at their monthly visits to additionally give blood by fingerprick at these visits until April 2022 (additional consent) • continuing to invite new households until January 2022 to join the study in order to replace participants who stop follow-up and to supplement current numbers in order to meet targets despite possible missed visits.
				Sections 7, 9, 11, 13: phasing out of venous blood draws so that blood is only taken from fingerprick tests, meaning that study workers never enter participants' homes. Participants on venous blood draws will receive the option of moving to capillary blood draws or only taking swabs for the rest of their study visits.
				Section 11: clarification of targets for swabs and bloods, and addition of reference to the Methods article on the ONS website.
MA04	9.1	12 May 2021	Ann Sarah Walker	Section 12: Change from Serco to Capita to help resource the call centre from July 2021.
SA09	10.0	22 July 2021	Ann Sarah Walker	Section 9.9.2, 12: removal of text option for returning study test results, removal of results return through NPEx (which is being phased out of the national testing programme processes) and transitioned to the NHS Business Services Authority) and implementation of results return via email, with letters remaining for those who do not have or do not wish to provide an email to receive test results (and clarification of sub-contracting arrangements to enable this).
				Sections 9.6.1, 11.2: clarification that case record forms collect sex rather than gender. Removal of religion (no longer collected).
				Section 10: addition of standard further detail for safety reporting.
SA09	11.0	13 September 2021	Ann Sarah Walker	Sections 2, 3, 5, 7, 8.1: Amendment of country-level adult blood targets for England, Northern Ireland and Scotland to reflect the Barnett formula (same overall target of 150,000 antibody test results per month) and clarification that, as per sample size section, all targets relate to test results being obtained.
				Sections 2, 3, 5, 7, 8.1: Addition of targets for blood test results in those aged 5-15 years (~5,500 antibody test results per month).

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
				Section 7, 9.3: clarification that the choice of participating once at enrolment, weekly for the first month, or weekly for the first month and then monthly will be made at the enrolment visit; participants will not be offered the option to extend if they initially choose weekly visits for one month only.
				Section 9.4.3, 16.8 (plus brief statement in other sections where fingerprick testing is mentioned): Addition of optional fingerprick blood tests for antibody levels to those aged 5-16 years; implementation starting with a pilot including collection of a small number of questions relating to parent/carer experience either on the main study database (depending on time needed to develop this) or on a separate survey tool, Smart Survey. If Smart Survey is used, only pseudonymised identifiers (household identifier, age in years, sex) would identify child participants. Participating children would receive a sticker as a thank you.
				Section 9.6.1: Addition of questions about flu vaccination and other respiratory virus related symptoms to the questionnaire.
				Section 9.9.1: Clarification regarding use of stored serum samples.
				Section 12: details regarding the Smart Survey tool and its certification and assurance.