Serological Surveillance of COVID-19 in England

Version	Date	Description of changes
12	30/3/2020	Update to protocol to include new & updated scope of sera collections
13	31/03/2020	Update to protocol to include Frontline HCW study and Army study & update to data management section.
14	02/04/2020	Removal of related protocols as embedded appendices and addition of table identifying related protocols; addition of table of contents; circulated to SSG for comments
15	03/04/2020	Addition of appendix C (samples available from HSE collection); update to data management section; addition of further paediatric hospitals as a source to GOSH section; addition of further HCW survey; update to assay section to reflect assay development group; update to HSE section

Contents

1. Background and rationale

Control of COVID-19 requires the ability to detect asymptomatic and mild infections and thus determine the true number of infections within the general population. The number of true infections within the population is required to understand transmission, to inform control measures such as social distancing and school closures and to provide a denominator for the estimation of severity measures such as infection fatality and infection hospitalisation ratios. The true number of infections can be estimated if the prevalence of immunity of the population prior to, during and after the epidemic are known. This information is provided by serological surveys.

Currently serological methods to diagnose infection are being developed and once validated these assays can be used to provide valuable information to understand the extent of transmission of SARS-CoV-2 and monitor how this changes over time. If this data is available early, it can be used to adjust planning assumptions and help predict the impact upon health and social care services.

The UK undertook a series of influenza sero-surveys during the 2009 pandemic based upon residual blood samples from the HPA National Sero-epidemiology Programme supplemented by samples from chemical pathology labs (1-3). These samples were submitted to HPA and NHS laboratories for routine diagnostic purposes at that time. Although this work delivered critical information on background population seroprevalence and sero-incidence, several issues were raised in post-pandemic reviews (4). These reviews highlighted that, although this information was gathered and published earlier than almost any other country, even earlier availability of this intelligence would have been critical to inform important national policy decisions. The following key recommendations have been made in relation to flu sero-epidemiology and could be applied to the COVID pandemic:

- The Science and Technology Committee (3rd report 2010-11) (5) stated that sero-epidemiological data needs to be available **earlier** in the time course of a future pandemic to help with risk assessment;
- SPI (May 2011 06(07)(01)), JCVI flu sub-committee and the JCVI highlighted the importance of **establishing routine sero-surveillance** for seasonal influenza;
- The CMO-SLG (6) determined that **sero-surveillance is critical to determine population immunity and community infection rates. This data cannot be obtained from other sources and is vital to making modelling predictions of the pandemic**.
- The 2011 UK Influenza Pandemic Preparedness Strategy (7)includes **sero-epidemiology as a key surveillance initiative that will be required at the start of any pandemic, and states that work should be underway to enhance capability in this area based on the H1N1** (2009) influenza pandemic .
- The Hine Report states that **further exploration of population-based surveillance**, such as serology, should be considered (4).

- The SPI-M group recommended that the HPA **strengthen population-based influenza sero-epidemiology,** including collection of key epidemiological information on vaccination status and underlying risk status.
- The PHE influenza programme has identified the development of sampling strategies and methods for establishing representative population surveys as an R and D priority;
- Finally the European Centre for Disease Control and Prevention (**ECDC**) has highlighted the importance of influenza sero-epidemiology, as has **WHO** as part of the Fineberg report (8) into the pandemic response including the need for a proper assessment of severity at national and subnational levels early in a pandemic. **Sero-epidemiology forms a key element of that severity assessment.**

As a result of these recommendations a range of population-based serum banks have been used by PHE for monitoring influenza and other diseases across England.

2. Aims

To set out the requirements to measure the sero-prevalence of SARS-CoV-19 in England during 2020. Specific objectives are to:

1. develop sensitive and specific assays to measure antibodies to SARS-Cov-2 in serum by ELISA and neutralisation assays

2. establish the baseline age-specific prevalence of antibodies to SARS-Cov-2 and cross-reacting antibodies to other coronaviruses and to measure incidence of infection by age during population transmission in England.

3. use the generated data to construct the severity profile of SARS-Cov-2 infections and to parameterise real-time transmission models designed to predict the future behaviour of the virus and the associated likely morbidity in different settings.

3. Surveillance methodology

The project proposes to undertake population-based seroprevalence surveys, involving several thousand individuals across the age-range using sera from before, during and after the COVID-19 outbreak.

Serological analysis of appropriately age stratified and geographically representative samples will provide information on seroprevalence and sero-incidence to set in context other measures of impact of COVID-19 in the UK population, and provide the most accurate measures of population exposure.

The work will consist of three interlinked work-packages: 1) Population surveys 2) Laboratory analysis 3) Statistical and modelling analysis.

4. Governance

This work within PHE will be overseen by the Sero-Epidemiology Steering Group (SSG) (see Appendix A for Terms of Reference). The SSG will report to the Incident Management Team and an Oversight group chaired by the Incident Director. Progress will be monitored at bi-weekly meetings of the steering group. The SEU are providing daily updates to the surveillance cell which is reported in the PHE daily SITREP.

5. Data sources

For population susceptibility, a total of 2,000 existing sera collected prior to the start of circulation of COVID-19 will be required, unless it is determined that there is little evidence of cross-reactivity of developed assays with other coronaviruses and overall specificity is very high, in which case a smaller samples number of baseline samples may be sufficient. This will then be followed by monthly sero-surveys with at least 1000 samples per month to estimate sero-incidence. The complete age range will be represented. The sample will be stratified with 200 for pre-pandemic survey (100 for monthly) specimens in the following age groups (1-4, 5-9, 10-14, 15-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70+). These samples will be tested with highly specific laboratory serological assays (see below). Additional samples from adults (blood donors from NHSBT - plasma) and paediatric samples (Great Ormond Street inpatient and outpatient samples) will be tested using a commercial kit to meet the requirements from SAGE to test 1000 sera per week.

Sero-surveys will be carried out using sera collected via the following sources;

a) PHE Sero-Epidemiology Unit (SEU)

The SEU archive is an opportunistic collection of residual serum samples from routine microbiological testing, submitted voluntarily each year from laboratories throughout England. In 2019, Manchester, Newcastle, Exeter and Leicester laboratories participated in this voluntary collection, with approximately 400 samples received per month. The number of specimens currently available for baseline testing is shown in Appendix B, and to reach a

sample size of 2000 would require testing of samples from June-December 2019. It is anticipated that these laboratories would continue to participate in 2020, however the number of samples expected will be negatively affected due to the COVID-19 situation. 227 samples were received in January, but only 37 in February, and staff time to undertake the additional work required in sending samples to the SEU at the participating laboratories has been identified as a limiting factor. In 2009, chemical pathology laboratories were recruited to contribute to SEU collections and use of this route has been investigated for this study to enable 1000 samples per week to be collected. SEU archive sera are stored at the PHE North West regional laboratory in Manchester and are anonymised and permanently unlinked from any patient identifying information, with only age, gender, date of collection (if available) and contributing laboratory retained.

Progress:. A letter from the Incident Director has been cascaded to All PHLs requesting each laboratory to provide 10-50 serum samples per week. All NHS trusts have also been written to by the Incident Director through a cascade by NHS England to request each NHS laboratory to contribute 10 serum samples a week to the SEU. Trusts have been asked to consider additional sources such as antenatal or haematology samples. Progress is being overseen by the SSG at their bi-weekly meetings.

b) RCGP Research and Surveillance Centre (RSC) _see Separate Protocol/ Appendix D (RCGP)

Residual sera are collected from approximately 100 GP practices across England participating in RCGP Research and Surveillance Centre (RSC) primarily for Influenza surveillance. 10% of the existing participating practices are in London. An original target of 800 sera per month had been agreed with the network of 100 practices. However due to request for scaling up the network of participating practices is being scaled up to 300 practices to provide 900 samples per week. To supplement this PHE working with the RCGP have recruited an additional 30 practices in London who have agreed to contribute sera. This collection mechanism will be used to gain residual sera for COVID-19 sero-surveys. The collection of samples is opportunistic, with samples collected from individuals requiring routine blood testing via their GP, providing a geographically representative dataset for England of individuals aged 10 years and above. This sample will be stratified by age, with 100 samples per age group (10-14, 15-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70+), providing 800 samples per week.

Progress: Collections commenced week beginning 16th March and progress is being reviewed by the SSG with daily updates provided to the PHE SITREP.

c) What's The Story Collection COVID-19__see Separate Protocol/ Appendix D (STORY)

What's The Story COVID-19 will build on an existing national research network and ethically-approved NIHR-funded study to collect childhood and teenage serum samples for near real-

time monitoring of increases in paediatric COVID-19 sero-positivity rates across the UK in 2020 that is representative of the general population. The challenge of obtaining blood samples from representative cohorts of healthy children had already led to the Oxford Vaccine Group, Public Health England and regional partners throughout England establishing the 'What's the STORY (Serum Testing of Representative Youngsters)' network to evaluate antibody levels against vaccine- preventable diseases. This study has commenced, and with additional funding would be expanded to collect 3500 samples throughout 2020, including collection of individual level information on recent respiratory illnesses and relevant medical history.. The region partners are as follows: Oxford, South London/Kent, Yorkshire and Humber, Bristol, Southampton, & Manchester. Further expansion is being investigated to include a potential two further study sites. Postcodes have been selected to be representative of the population according to index of multiple deprivation, although the expanded COVID-19 recruitment will aim to achieve sample size targets by additional advertising for individuals to volunteer to participate in the areas. A total sample size of 3500 participants will be recruited across the seven study sites from healthy individuals up to 25 years, and will comprise of two groups. 2300 participants with 100 in each band with 12 month age bands from 0-22 years, and a 36 month age band from 22-24 years will be recruited to be representative of their test site region based on post code and associated index of material deprivation (IMD), while the method of recruitment of a further 1200 participants, recruited equally over the ages 0-4, 5-9, 10-14 and 15-19 years (i.e. 300 per age group), will be less restrictive based on postcode.

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

Progress: Weekly updates on numbers recruited by region and age break down are being sent to the SSG.

d) Pertussis serology

Pertussis serology testing is undertaken on patients presenting with persistent cough (>2 weeks duration). Residual sera of patients with suspected pertussis can be used to test for COVID-19. This testing is offered at the pertussis reference laboratory at Colindale for all age groups across England, providing good geographical representation. Although all age groups can be tested, those with suspected pertussis are predominately adolescents and adults. This collection of samples will provide approximately 1300 samples per month, but may also be affected by the COVID19 outbreak. These samples can be contributed directly to the SEU archive, together with the result of pertussis testing.

Progress: The impact of COVID19 outbreak on number of samples submitted is being clarified and will be monitored by the SSG.

e) ESCAPE study __see Separate Protocol/ Appendix D (ESCAPE)

This study is a longitudinal seroepidemiological survey of PHE and NHS employees, with repeated collection of blood (and potentially oral fluid samples) from approximately 1000 staff on a monthly basis for a period of six months. In addition to a monthly blood sample, volunteers answer a short questionnaire at each time point regarding history of respiratory illness in the past month. Initial data collected includes age, gender, whether the participant has direct patient contact and the number (and age groups) of household contacts. Initial collections will be carried out at PHE sites in Colindale, Porton and Manchester. A key value of this study is the repeated sampling of the same individuals over time and to distinguish frontline clinical from laboratory and administrative staff.

Progress to date: Ethical approval has been received and recruitment has commenced at both PHE Colindale and PHE Manchester. Recruitment progress will be monitored by the SSG.

f) NHS Blood and Transport (NHSBT)

Blood donors represent a nationwide sample of healthy adult volunteers, but excludes people with a history of recent illness/infection (in the last 14 days). Provision of blood donor samples to supplement existing samples above is being investigated based on numbers available from other sources. An initial 1000 samples (age, gender and postcode stratified) from NHBST in London will be used for initial testing using a commercial kit at the request of SAGE. This will be followed up with a 1000 samples per week from London and other geographical regions to be tested with the commercial kit at Porton. Accompanying data likely to be available will be sample date, and patient age, gender and postcode (stem).

Progress to date: Discussions are in progress and will be monitored by the SSG.

g) Great Ormond Street Hospital (GOSH) (see Separate Protocol/ Appendix D (GOSH)

GOSH is a tertiary specialist children's hospital but has also adapted during the pandemic to host inpatients and staff from other London hospitals so it currently has a broad spectrum of patients aged from 0 days through to 18 years. GOSH has in place a system for storing and using, where relevant, residual blood and/or tissue taken during routine investigation of patients. A generic consent system is also in place for parents and or the children to consent to residual material from their investigations being de-identified and made available for research. For the PHE seroprevalence surveys, GOSH is identifying samples irrespective of consent, on a daily basis, that could be shipped to PHE. They consist of both plasma (mostly EDTA left over from full blood counts) and serum samples with a minimum volume of 0.5ml. Sample tubes will be identified with a unique identifier prior to shipment and this in turn is linked to a minimal de-identified data set which includes gender, month/year of birth and postcode stem. Identified samples will exclude those that originate from children with an underlying immune deficiency or children who are recovering from a transplant. It is anticipated that there will be approximately 100 samples per week from children under the

age of 16 from London and the South East. Samples will be sent on a twice weekly basis to PHE Manchester. This workstream is currently being expanded to 7 (and possibly more) paediatric hospitals/departments.

Progress to date: Recruitment will be monitored by the SSG.

h) Frontline NHS workers at 4 London Hospitals __see Separate Protocol/ Appendix D (londonCOVID)

This study is a longitudinal seroepidemiological survey of NHS staff working in a clinical setting at four London hospitals, with repeated collection of blood from at least 500 staff on a fortnightly basis for a period of six months. In addition to a fortnightly blood sample, volunteers answer a short questionnaire at each time point regarding history of respiratory illness since the last blood test. Initial data collected includes age, gender, whether they have direct contact with patients and details of clinical role. A key value of this study is the repeated sampling of the same individuals over time. A separate similar study is being recruited at UCLH/Liverpool.

Progress to date: Recruitment will be monitored by the SSG.

i) armyCOVID: surveillance of army personnel __see Separate Protocol/ Appendix D (armyCOVID)

In March 2020, a case of COVID-19 was confirmed in a soldier at the Household Cavalry Mounted Regiment in London where around 300 soldiers, their family and civilians reside. This resulted in self isolation of 29 close contacts. In order to better understand the transmission dynamics of SARS-CoV-2, Public Health England (PHE) is working with the Household Cavalry Mounted Regiment to conduct surveillance of staff and residents within the barracks. Volunteers will be asked to complete a short questionnaire and provide nose/throat swabs and blood samples that will be tested for SARS-CoV-2 and antibodies against SARS-CoV-2 at PHE. It is aimed to collect two blood samples from soldiers, their family members and civilians approximately one month apart. Initial data collected includes age, gender, history of respiratory illness and the number (and age groups) of household contacts. A key aim of the study is to study COVID transmission in a small community.

Progress to date: Recruitment will be monitored by the SSG.

j) Other Potential Sources of Sera

The Health Survey for England (HSE) is a stratified random probability sample of private residences, with serum samples collected from participating household members aged 16 years and older. This is a geographically representative sample, and is usually carried out monthly. The HSE has been paused due to the COVID19 pandemic since the middle of March, but could potentially provide baseline sera (see Appendix C) if needed depending on required sample sizes and available SEU collections (see section a) and may resume in June. The normal collection size is 300 samples per month, and it has been decided to request 1000

baseline samples from this source due to the strength of sampling design from October 2019 – January 2020.

UK Biobanks are a further source of samples but are currently also only able to provide retrospective samples, and further collections are likely to be impacted by the COVID19 pandemic. The Wellcome Trust are in contact with the UK Biobanks about prospective collections. PHE are in contact for potential future collaboration if needed. Antenatal sera are another possible source which is being explored by the SSG through collaboration with academic partners at Imperial College who have established a network of laboratories across England who are willing to provide antenatal sera (from booking bloods) on a weekly basis throughout the epidemic (see Separate Protocol/ Appendix D (ANTENATAL).

5.1 Sample size and precision

The precision (95%CI) of incidence estimates based on simple subtraction of prevalence, based on approximately 1,000 samples, collected from 8 age groups, are shown in Tables 1a-b. Note that in practice incidence and cumulative prevalence will be modelled statistically over time which will mean greater precision that that shown, as will increases above 1000 samples per month (95% CIs become ~30% narrower if sample size is doubled). For prevalence, the precision based on 100 and 200 samples in each age group is shown in table 1c. "For example using the method of Baguelin (2), assuming a 10% increase in cumulative infection rate for a given age group across a 5 month period, no prior knowledge of the propensity to consult and a seroconversion probability of 80%, 1000 samples per month would provide a precision of 2% (measured as the difference between the upper and lower bounds of the credibility interval)."

For prevalence, the precision based on 100 and 200 samples in each age group is shown in table 1c.

Table 1: Incidence percentages and 95% CI for different number of samples per age group

(a) Comparison to baseline from a specific month

Prevalence at specific month (n=100)	**Baseline prevalence (n=200)**		
	0%	**5%**	**10%**
5%	5 (0.7,9.3)		
10%	10 (4.1,15.9)	5 (-1.6,11.6)	
15%	15 (8.0,22.0)	10 (2.4,17.6)	5 (-3.1,13.1)
20%	20 (12.2,27.8)	15 (6.6,23.4)	10 (1.1,18.9)
30%	30 (21.0,39.0)	25 (15.5,34.5)	20 (10.1,29.9)

40%	40 (30.4,49.6)	35 (24.9,45.1)	30 (19.5,40.5)
50%	50 (40.2,59.8)	45 (34.7,55.3)	40 (29.4,50.6)

(b) Comparison between consecutive months for monthly incidence

Prevalence the following month (n=100)	**Prevalence in one month (n=100)**					
	0%	**5%**	**10%**	**15%**	**20%**	**25%**
5%	5 (0.7,9.3)					
10%	10 (4.1,15.9)	5 (-2.3,12.3)				
15%	15 (8.0,22.0)	10 (1.8,18.2)	5 (-4.1,14.1)			
20%		15 (6.1,23.9)	10 (0.2,19.8)	5 (-5.5,15.5)		
25%			15 (4.7,25.3)	10 (-1,21)	5 (-6.6,16.6)	
30%				15 (3.6,26.4)	10 (-1.9,21.9)	5 (-7.4,17.4)
35%					15 (2.8,27.2)	10 (-2.6,22.6)
40%						15 (2.2,27.8)

(c) precision of prevalence estimates (95%CI) for n=100 and n=200

Prevalence	N=100	N=200
0	0.0,3.6	0.0,1.8
5	1.6,11.3	2.4,9.0
10	4.9.17.6	16.2,15.0
15	8.6,23.5	10.4,20.7
20	12.7,29.2	14.7,26.2
25	16.9,34.6	19.2,31.6
30	21.2,40.0	23.7,36.9
40	30.3,50,3	33.2,47.1
50	39.8,60.2	42.9,57.1

Note that the sample size calculations shown are based on a binary serological classification of positive or negative based on an appropriate cut-point.

Additional sera will be tested using a commercial kit to meet the requirements from SAGE to test 1000 sera per week as part of a complementary work stream.

6. Sample requirements (see Separate Protocol/ Appendix D (LAB))

Spun samples from sending laboratories are preferred, if possible. However whole blood can be received and spun at the receiving PHE centre.

For sample volume:

- serum: an optimal sample volume is at least 2 mL; the minimum acceptable volume is 200uL
- whole blood: an optimal sample volume is at least 7 mL; the minimum acceptable volume is 1mL

If samples are unseparated, then they should be no older than 7 days due to haemolysis; if refrigerated as serum, these can be sent up to 4 weeks after they are spun. If frozen they can be sent after any duration.

Sequential samples from the same patient can be sent but will need to be linked through unique identifiers.

Whole blood tubes should be red topped Vacutainers of 3 to 15 mL volume.

Serum vials should be rigid polypropylene with a screw-cap with O-ring seal, ideally a Sarstedt™ 2mL tube.

6.1 Sample Transfer

All contributions of samples to the archive must be sent in secure, appropriately-labelled packaging. Samples can be sent at room temperature or at 4°C (or frozen with appropriate freezer packs in an appropriate container), with DX the preferred mode of transport or courier where frozen samples are being sent. The timing of sending of samples is up to customer choice e.g. daily, small batches, weekly batch. As packaging and shipping is an additional burden, weekly batches may be easiest to coordinate.

A printed list of samples or a box plan should also accompany all sample shipments.

6.2 Data accompanying sample submission

Contributing laboratories will be requested to submit samples with an anonymised ID, together with details including age, sex and the first three or four characters of the postcode e.g. NW13 on an accompanying spreadsheet by email.

Upon receipt of a shipment of samples, the samples will be checked against the sample information provided, and confirmation and/or notes of discrepancies will be notified to the contributing laboratory by email or telephone. Full contact of the person (s) to whom queries can be directed will be requested. Data will be stored on a password-protected Excel spreadsheet and made available only to key laboratory and surveillance team members within the organisation.

6.3 Sample management

All samples will be sent to the SEU at PHE Manchester for sample management and recording of associated demographic data. Samples will be aliquoted into two parts and one half retained at PHE Manchester/SEU. The other half will be processed and distributed as required to testing laboratories. NHS, PHLL, RCGP, residual pertussis and ESCAPE samples will be added directly to the SEU collection. GOSH, STORY and NHSBT samples will be stored as separate collections. Minimal accompanying demographic data will be month and year of birth, gender and region (submitting laboratory and/or stem postcode).

7. Serological analysis

A sub-group of the SSG has been set up to look at assay suitability for the sero-epidemiology work streams. Assays in use or in validation include the Euroimmun kit ELISA assay using the Gemini robot at PHE Porton, for large scale testing, as well as other ELISA and antibody neutralising tests at the Respiratory Virus Unit (RVU) at PHE Colindale and at PHE Porton. Assays used for testing of serum collections for the sero-epidemiology surveillance will be discussed by the SSG and other oversight groups, and may include testing of a subset of samples with multiple assays.

8. Data Management

Collection of samples is being co-ordinated by the SEU and a data management group has been formed to discuss flow back of data. It is not currently known whether the outputs of the assays will be quantitative or qualitative, and what units might be used. It is aimed to collate all outputs from testing in a central database to be stored at a shared drive location to be identified, to allow comparison between testing streams and document oversight. Feedback pathways to submitting laboratories will also be decided.

9. Statistics and modelling

9.1 Descriptive analysis

A cut off for seropositivity will be determined following assay development and testing (see Separate Protocol/ Appendix D (INDAT). It is important to assess the antibody data generated in initial mixture models to assess whether the assay cut-offs are appropriate and to enable estimates of seroprevalence based on both applying a cut-off and based on a mixture modelling approach. Mixture models may also enable identification of a third distribution consisting of individuals transitioning to positivity due to a recent infection. The optical density data will be log-transformed, and the density distribution examined by plotting the histogram. If there is evidence visually of 2 or more distributions and if these do not clearly separate from one another then mixture modelling (normal mixtures initially) will be used to estimate the means, standard deviations and proportions falling into each mixture (which give seroprevalence). This will be done allowing prevalence (proportion in each mixture) to vary by age, but with the same mean and SD for the mixtures in each age group. The mixtures will also be used to identify the best assay cut-off to optimise the theoretical sensitivity and specificity based on the fitted distributions (or provide least biased estimates of prevalence – although this would depend on the prevalence itself).

Descriptive statistics will describe the population sampled, numbers of samples and give the sero-prevalence and sero-incidence estimates (with 95%CI) for samples taken in each month week by age group and by region. A weighted overall estimate will also be calculated allowing for the sampling fractions by age and region. This will also enable estimation of numbers of infection when combined with ONS population data. In addition, geometric mean titres and reverse cumulative distribution (RCD) curves will be calculated with 95% CI's.

The prevalence by age with 95% CI will be calculated using both the cut-off approach and, if necessary, the mixture modelling approach (which might also have an estimate of a third distribution of those transitioning – although this distribution if it exists may be difficult to identify).

This initial analysis will help inform how the antibody data should be used in mathematical models and whether a simple cut-off approach is appropriate (and if so how the estimated sensitivity / specificity could be adjusted for in such models if they do not use the quantitative data). It will also inform how the descriptive analysis of seroprevalence by age/region should best be done.

The descriptive analysis initially planned is to estimate seroprevalence by age and region as well as overall and a sampling weight adjusted overall analysis. When more than one time is available the descriptive incidence will be based on change on prevalence.

Descriptive analyses will also cover how representative the populations sampled maybe of the general population and the likely time point that positivity may relate to based on whether or not individuals that have been recently symptomatic are likely to be included in the population sampled. This, along with the seroprevalence results themselves will inform how and if results from different serosurveys can be combined.

9.2 Statistical and mathematical modelling of cumulative incidence

Statistical models of temporal trends in sero-positivity across age groups and regions will be fitted to the cumulating data (cumulative incidence). Two proposed methods are as follows:

a. fractional polynomial logistic regression

b. Baguelin et al method (2). Weekly Incidence is estimated using a likelihood approach by combing data from 3 data sources as follows: i) the seroprevalence data (which is used at an individual level based on actual dates of samples); ii) information on the temporal distribution of cases as estimated from laboratory/clinical surveillance; iii) information on the seroconversion interval in cases (obtain from data on blood samples taken at different times since onset).

Data in these analyses would need to be appropriately weighted according to age/regional sampling rates.

9.3 Models of epidemic spread

Models for real time prediction of epidemic spread have been developed during 2009 (2) (10)(see above)). Serological data is fundamental to ensuring that modelled estimates of the epidemic are correctly scaled to provide a reliable estimate of the numbers of infections occurring in the population. These data provided information on the “baseline” age-specific susceptibility before the epidemic. Also, in conjunction with other surveillance data collected during the epidemic and indirectly related to incidence of infection (e.g. GP consultations, positivity data), these data have been shown to be crucial in the reconstruction of the incidence of infection by age group and region. These models will be used together with future available data on different aspects of the disease (e.g. hospitalisations) to provide real time estimates, of infections and forecasts of the likely future course of the epidemic. The ability of these models to track incidence of infection in a timely fashion and to provide reliable projections depends crucially on the prompt availability of valid serological data, which, as the epidemic evolves, informs the scale of the pandemic. We, therefore, aim to establish a system of rapid handling of routine serological data, including data extraction, transfer and analysis.

9.4 Proposed outputs

- A sero-surveillance pandemic COVID-19 data-set use in real-time models.
- Temporal estimates of population susceptibility and sero-incidence due to COVID-19
- A report or publication to disseminate findings.

10. Ethical approval

a. SEU - PHE has ethical approval (05/Q0505/45) for the collection and use of unlinked and anonymised residual serum samples in cross-sectional antibody prevalence studies for the surveillance of population immunity to vaccine preventable diseases of public health importance and the collection has been extensively used for this purpose.

b. RCGP RSC - this work is Health Protection and therefore falls under Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002 the existing agreement with PHE. Therefore, no further legal basis is required. The implications of this are that verbal consent (as now for virology samples) is all that is required for virological and serological samples. This has been confirmed by email with PHE's Caldicott Guardian's Office.

c. COVID-19: Coronavirus STORY - use of collected serum for COVID-19 sero-epidemiology is possible under the ethical approval for 'What's the STORY' (REC Ref 19/LO/1040; IRAS 263097), in parallel to submission of substantial amendments to increase the study sample size and modify recruitments methods to enable an even and sustained recruitment rate.

d. GOSH has a generic consent system in place for parents and or the children to consent to residual material from their investigations being de-identified and made available for research. The Electronic Patient Record (EPIC) has a field that indicates if generic consent has been given so samples and tissue can be stored and then requested by researchers with ethics approval for research projects.

11. Timelines and milestones

Key milestones for the work are highlighted below and the associated timelines in Table 4. Collection of samples has already commenced through the different sources identified and will be reviewed by the SSG. Collection will continue through the epidemic and for some months post pandemic. Collections will cease on advice of SSG.

Table 4: Project timelines

Month 0	Month 1	Month 2-7	Mont
▪ Convene Steering Group ▪ Initiate request for sample collection	▪ Collect and analyse residual sera pre-season	▪ Collect and analyse residual sera monthly ▪ Undertaken statistical and mathematical analysis	▪ Undertake fina sero-survey

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Appendix A: Sero-epidemiology Steering Group TOR

Public Health England

Protecting and improving the nation's health

Sero-epidemiology Steering Group

Terms of Reference

1. Purpose

Severity assessment for COVID-19 will require the detection of asymptomatic and mild infections and the determination of the true number of infections within the general population. The number of true infections can be determined if the prevalence of immunity of the population prior to, during and after the epidemic are known.

The Sero-epidemiology Steering Group will provide oversight of PHE's sero-epidemiology work for COVID-19. The Group will oversee the establishment and monitoring of a population-based seroprevalence survey in England. This work will be used to inform our understanding of the extent of transmission of SARS-CoV-2, to monitor how this changes over time, and to ensure that information is available to facilitate timely adjustment to the Government's planning assumptions.

2. Core terms of reference

The SSG shall:

- oversee sero-epidemiology of COVID-19 during the epidemic;
- ensure the collection of appropriately representative (age stratified, geographic) serum samples across England;
- work with the Assay Development Group to ensure relevant samples are available for testing in a timely manner; and
- work in close collaboration with SPI-M to ensure timely data availability to inform modelling.

3. Accountability

The SSG will report to the Incident Management Team.

4. Reporting Methods

The work of the SSG will be reported by the Chair to the IMT on a weekly basis.

The work of the SSG regarding sero-epidemiology will be reported back to WHO as required.

5. Membership

The SSG consists of the following core members:

- Gayatri Amirthalingam (Chair)
- Mary Ramsay
- Kevin Brown
- Liz Miller
- Miles Carroll
- Bassam Hallis
- Maria Zambon
- Nick Andrews
- Andre Charlett
- Simon de Lusignan
- Ray Borrow
- Ezra Linley
- Meera Chand
- Charlotte Gower
- Colin Brown
- Samreen Ijaz

Additional members may be invited to complement the expertise of the SSG.

6. Working Methods

The DIWG will meet initially twice a week, and at least once a week once systems are in place.

The secretariat for the SSG will be provided by the JCVI Secretariat.

7. Document History

To be reviewed annually.

Version	Reason for change	Agreed	Date of review
V1.0	First draft	23 March 2020	
V1.1	Second draft	26 March 2020	

Appendix B: SEU samples available for baseline testing

Month	Total Samples	Cumulative Number of Samples prior to Jan 2020
December 2019	**13**	**13**
November 2019	**63**	**76**
October 2019	**285**	**361**
September 2019	**349**	**710**
August 2019	**503**	**1213**
July 2019	**660**	**1873**
June 2019	**289**	**2162**
May 2019	**787**	**2949**
April 2019	**547**	**3496**

Appendix C: Stored serum from the Health Survey for England

Collected between November 2019 and March 2020 (n=1395), by age and region. Individuals were selected using probability sampling methods. Actual numbers are likely to be c.4% lower (due to insufficient residual serum).

Count

		Date of nurse visit - month					Total
		November 2019	December 2019	January 2020	February 2020	March 2020	
(D) Age 16+ in ten year bands	16-24	16	5	14	12	14	61
	25-34	42	28	35	42	24	171
	35-44	61	44	53	50	28	236
	45-54	74	34	60	63	33	264
	55-64	62	39	57	81	41	280
	65-74	70	34	49	59	30	242
	75+	48	15	24	30	24	141
Total		373	199	292	337	194	1395

Region * Date of nurse visit - month Crosstabulation

Count

		Date of nurse visit - month					Total
		November 2019	December 2019	January 2020	February 2020	March 2020	
Region	North East	38	17	26	29	14	124
	North West	46	19	45	50	18	178
	Yorkshire and The Humber	38	17	31	40	19	145
	East Midlands	46	10	32	18	6	112
	West Midlands	35	22	34	33	37	161
	East of England	48	23	26	48	30	175
	London	41	33	31	39	24	168
	South East	64	43	38	53	22	220
	South West	17	15	29	27	24	112
Total		373	199	292	337	194	1395

HSE blood samples are taken by a trained nurse in the respondent's own home. The samples are then posted that day or the following day (or up to two days later if taken on a Saturday) to the laboratory (RVI, Newcastle), where they are spun, analysed, and any remaining serum is frozen and stored at -40ºC. For most of the time during transit the samples are at room temperature.

Appendix D: List of Related Protocols

Code	Study Protocol Title	Protocol File Name	Current Version no
RCGP	Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC), Public Health England (PHE) and the Specialist Microbiology Network (SMN): extended community virological and serological surveillance at the time of the emergence of a novel coronavirus (SARS-CoV-2)	RCGP_RSC_SMN_protocol PHE_extended_surveillance_COVID_2020 v6.docx	6
STORY	Sero-epidemiological survey of England in 2019/2020_What's the STORY (Serum Testing of Representative Youngsters)	What's the STORY protocol V4.0/04_03-2020.pdf	4
ESCAPE	Enhanced SeroIncidence for COVID-19 Antibodies among PHE and NHS staff	seroCOVID protocol version 1.2 dated 22march2020.pdf	1.2
GOSH	National Age Stratified Population Seroprevalence – Great Ormond Street Hospital	GOS_PHE_Age-Stratified COVID seroprevalence v1.pdf	1
ARMY	COVID-19 surveillance among army personnel in a London barracks	armyCOVID2.pdf	1.0
NHS	Seroincidence for COVID-19 Antibodies among frontline NHS staff	londonCOVIDprotocol2_clean.doc	1.0
ANTENATAL	Using routinely collected antenatal booking serum to assess the COVID-19 outbreak in England in women aged 18-45	COVID 19 seroprevalence in maternal booking serum MRC call NIHR text.doc	
LAB	PHE Serosurveillance Programme during COVID-19 pandemic: Protocol for participating laboratories and centres	20200327-20.30h PHE Serosurveillance Programme during COVID-19 pandemic – Protocol V01.00.docx	1
INDAT	Initial analysis of COVID-19 assay data to assess cut-offs and the potential use of mixture models to determine seroprevalence	Initial analysis of COVID-19 assay data to assess cut-offs and the potential use of mixture models to determine seroprevalence.pdf	1