Briefing note for NPHET: Study to investigate COVID-19 infection in the Irish population (SCOPI)

13.05.2020

Estimation of population age-specific immunity or past exposure to SARS-CoV-2 is one of the actions in Ireland's National Action Plan in response to COVID-19. The Department of Health National Public Health Emergency Team (NPHET) has asked HSE and HPSC to proceed with plans to undertake a population sero-prevalence study. This work is being carried out jointly by HPSC and NVRL, in collaboration with the Central Statistics Office and Department of Health.

A briefing on this study was provided to NPHET at its meeting on 5th May. The briefing (dated 1st may 2020) provided a summary outline of the study, including the design, sample size, and the proposed timeline for commencement. It also described ongoing North-South collaboration in this work. The protocol is available below.

NPHET requested further information from HSE regarding details of funding for the study. The HSE has agreed to fund the study based on estimated costs of €140,000 per cross sectional survey. There are potentially 3 planned over the next 12 months. An application to the National COVID-19 Research Ethics Committee will be submitted this week. Subject to approval, the aim is to start the study in the next few weeks.

Given the fact that funding has now been secured, we would like to request that NPHET and other key champions within HSE would emphasise to the public the importance of seroprevalence studies in informing the public health response, so that the highest possible response from the public to the call to participate can be obtained.

Study to investigate COVID-19 infection in the Irish population (SCOPI)

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Background

Establishing a national sero-epidemiological unit and serum bank to estimate population age-specific immunity or past exposure to SARS-CoV-2 is listed as one of the actions in Ireland's National Action Plan in response to COVID-19 (1). The Department of Health National Public Health Emergency Team (NPHET) has asked Health Service Executive (HSE) and HSE Health Protection Surveillance Centre (HPSC) to proceed with plans to undertake a population sero-prevalence study. This work is being carried out jointly by HPSC and NVRL, in collaboration with the Central Statistics Office and Department of Health. This document describes our proposal for undertaking a sero prevalence study to fulfil this action.

It is well recognised that many infections due to SARS-CoV-2 are mild and may go under-reported or undiagnosed. In EU/EEA countries with available data up to 8th April 2020, only 32% of diagnosed COVID-19 cases were hospitalised and 2.4% had severe illness (2). In addition, the proportion of infections that are truly asymptomatic is currently unknown. Serological surveillance data avoids the limitations of disease reporting systems for diseases like COVID-19, where under-diagnosis and under-notification of clinical disease can result in significant underestimation of the incidence and prevalence of infection.

With a novel coronavirus, initial seroprevalence in the population is assumed to be negligible due to the virus being novel in origin. Therefore, surveillance of antibody seropositivity in a population can allow inferences to be made regarding the extent and cumulative incidence of infection in the population (3).

Serological data can then be included in mathematical models to produce more accurate simulations of COVID-19 transmission within the Irish population, which could help to estimate the likelihood of a 'second wave' of infection after the initial peak. These models may aid in predicting the impact of public health interventions, such as vaccination and the introduction or removal of social distancing measures, on future disease incidence.

Serosurveillance data would inform decisions regarding which population sub-groups should be prioritised for control measures, such as vaccination, by identifying those sub-groups with little or no immunity to COVID-19. Identifying priority groups for a future vaccination programme would allow for greatest early impact, ensure appropriate allocation of limited resources, and potentially reduce the number of adverse events.

Many European countries have biobanks which facilitate rapid serosurveillance. The need for a serum bank in Ireland was identified in 2009/2010, when questions concerning the susceptibility, or previous exposure, of the population to pandemic influenza (H1N1) 2009 or future similar strains arose. Countries that have established archives of residual serum samples, with ethical approval for sero-epidemiological investigation at a national level in advance of a pandemic, are in a strong position to rapidly conduct these studies in the early stages of a pandemic in order to inform

response measures. Ireland does not currently have the infrastructure to support serosurveillance studies.

However, such a resource is vital to the effective management of future pandemics, and later waves of the current pandemic. The establishment of a permanent biobank in Ireland that can be enabled legally, and established with suitable funding, needs serious consideration now, in parallel with this work.

We have successfully used other methods to perform serosurveys in the past in Ireland, such as the Hepatitis C population prevalence study (4), studies to determine the prevalence of bloodborne viruses amongst Irish prisoners (5) and Phase 2 of the European Sero-Epidemiology Network (ESEN 2), which examined the level of population immunity to a variety of vaccine preventable diseases (measles, mumps, rubella, pertussis, diphtheria, varicella zoster, hepatitis A and hepatitis B)(6).

Having reviewed approaches to sero-epidemiological studies being undertaken internationally, including attending an WHO teleconference on serosurveillance studies on 15th April, and subsequent participation in the ECDC/WHO Europe sero-prevalence collaborative group, our view is that the World Health Organization (WHO) population-based age-stratified sero-epidemiological investigation protocol for COVID-19 virus infection, adapted for use in the Irish population, provides a suitable methodology. In their protocol WHO indicate that each country may need to tailor some aspects of the protocol to align with context-specific factors including public health, laboratory and clinical systems, capacity, availability of resources and cultural appropriateness. The protocol is available at https://www.who.int/publications-detail/population-based-age-stratified-seroepidemiological-investigation-protocol-for-covid-19-virus-infection

The WHO aim is that the studies are carried out using standardised methodology and serological tests, enabling comparison of results between countries, and pooling of results, thereby building international knowledge.

Aims

The aims of this study are:

1. to calculate the anti-SARS-CoV-2 IgG seroprevalence in two areas in Ireland, representing high and low incidence areas, in order to estmate the cumulative exposure to SARS-CoV-2 infection to date, by sex and age group

2. To estimate the fraction of asymptomatic, pre-symptomatic or subclinical infections in the population and by sex and age group

and thus inform future public health responses, including decisions on implementation and lifting of social distancing measures. Repeating this serosurvey at two time points during the pandemic will allow for the evolution of the pandemic in Ireland to be described.

3. To conduct repeat sampling and symptom questionnaires on the subset of the study population who are antibody positive, and who agree to repeat sampling, in order to understand the kinetics of antibody titres/serological markers over time.

Objectives

The study objectives are:

- To measure the prevalence of antibodies to SARS-CoV-2 in a representative sample of the Irish population in two geographically defined areas
- To estimate the age-specific susceptibility to SARS-CoV-2 infection in the population, in order to inform future vaccination policy
- To compare the prevalence of antibodies to SARS-CoV-2 across two geographical areas with high and low incidence of cases of COVID-19 in Ireland, as defined at the time of commencing the study
- To perform the cross-sectional serosurvey at three time points during the pandemic and document the changing patterns in the prevalence of antibody positivity
- To use the data from the repeated serosurveys to inform models predicting the spread of SARS-CoV-2 infection and the impact of social distancing and other control measures
- To examine the relationship between the presence of antibodies to SARS-CoV-2 and the self-reporting of symptoms consistent with COVID-19 or having a previous diagnosis of COVID-19
- For those participants who have antibodies to SARS-CoV-2, to measure serial samples for antibody titres and antibody function over time

Study Design

There are 2 components to the study:

- A cross-sectional prospective study of the Irish population in two geographic areas which will be repeated twice over time in different areas, as determined by the evolution of the pandemic and other logistical factors. For each cross-sectional survey, areas of higher incidence and lower incidence will be chosen**.** The study will be adapted from the WHO protocol, 'Population-based age-stratified sero-epidemiological investigation protocol for COVID-19 virus infection', to suit the Irish context.

- A serial sampling study among the subset of participants who are antibody positive, if they consent to serial sampling at 3 months, 6 months and 12 months**.** At the time of each sample, they will be asked to complete a symptom questionnaire.

Sampling procedure

A random sample of individuals in each of two defined geographic areas (Dublin and Sligo), areas of high and low incidence respectively at the time of commencing the study, will be obtained from the HSE Primary Care Reimbursement Service (PCRS) databases. The locations for the subsequent rounds, one high incidence area and one low incidence area, will be based on the epidemiology at the time.

The Primary Care Reimbursement Service (PCRS) is part of the HSE, and is responsible for making payments to healthcare professionals, like GPs, dentists and pharmacists, for the free or reduced costs services they provide to the public. The PCRS database covers: General Medical Services (GMS), General Practitioner Visit Card (GPVC), Medical cards for children with Domiciliary Care Allowance (DCA) eligibility, Medical cards for children with cancer, GP Visit Card for persons in receipt of Carer's Allowance or Carer's Benefit, Dental Treatment Services Scheme (DTSS), HSE Community Ophthalmic Services Scheme (HSECOSS), Drugs Payment Scheme (DPS), Long Term Illness Scheme (LTI), High Tech Arrangements (HT), High Tech Hub Ordering and Management System, Primary Childhood Immunisation Scheme, Opioid Substitution Treatment Scheme, Immunisations for GMS Eligible Persons, health services that are made available without charge to

persons who have contracted Hepatitis C directly or indirectly from the use of Human Immunoglobulin - Anti D or the receipt within the State of another blood product or blood transfusion. It has approximately 80% population coverage. The methodology unit of the Central Statistics Office (CSO) will supply code to the PCRS statistical unit to select representative samples for each county chosen.

The random sample of persons for the study will be drawn from those on the PCRS databases in the two areas, aged between 12 and 69 years. The rationale for confining sampling to this age group is as follows:

- younger children are not included for practical reasons regarding difficulties in venous blood sampling in children under 12 years of age
- persons 70 years of age and older are in the cocooning group and would not be able to travel to the sample testing centre for blood testing as this poses a health risk for them.

Sample size

Statistical advice has been obtained from the CSO on the appropriate sample size. For the serological part of the study, a sample size of 1,000 in the 12-69 years Sligo population and 1,600 in the 12-69 years Dublin population will be required to calculate overall prevalence rates with the required level of precision.

The numbers invited to participate will be double this number (i.e. 2,000 and 3,200 in Sligo and Dublin respectively) in order to achieve the required sample size, to allow for non-response and for people who will be ineligible due to self-isolating or being ill with COVID-19 at the time of the study..

Participant recruitment and data collection

Each randomly selected individual will be contacted by letter by the HSE HPSC asking them if they would like to take part in the study**.** For children aged 12-17 years, the child's assent, as well as the parent/guardian's consent will be sought. An information leaflet describing the study will accompany the letter. They will also be advised that they may get further information on the study website or by phoning the research team on a helpline. They will be asked to reply, by text, email, or phone call, indicating their interest in the study and providing their phone number. Those indicating an interest in the study will be phoned by a member of the research team.

One reminder letter will be sent by HSE to non-responders after an interval of two weeks from the initial letter.

If they consent to take part in the study, they will be asked to complete a short questionnaire by phone and will also receive an appointment at a time convenient to them to visit the location where blood sampling will be undertaken**.** A unique study ID number will be allocated to each person by HSE HPSC.

Inclusion and exclusion criteria

This study aims to be as representative of the Irish population in the selected areas (Dublin and Sligo in the first round) as possible. Everyone in these areas who is registered on the PCRS system, in the age group 12 to 69 years, and who is selected for the study will be eligible to complete the questionnaire. The invitation letter will include information in several languages to indicate to

recipients that interpretation services are available if required and how to access them. HSE interpretation services will be used to provide information for these individuals.

For health reasons, those who have been advised to 'cocoon' will be excluded from the serological testing component of the study, as travelling to the sample testing locations poses a potential health risk to them. They will be included in the questionnaire aspect of the study. However, if suitable, validated near-patient tests become available that could be administered in the home setting, efforts will be made to include these groups and an amendment to the application for ethical approval will be added in subsequent rounds of the study.

Anyone who has suspected or confirmed COVID-19 at the time of being asked to participate, will be excluded from serological testing, but will be asked to complete the questionnaire.

A person who is restricting movements at the time of the study invitation because they are a close contact of a case of COVID-19 will be excluded from serological testing, but will be asked to complete the questionnaire.

Informed consent

Information about the study, sufficient to allow for informed consent, will be outlined in the patient information leaflet.

Consent will be obtained for sample collection, data processing and sharing of the data internationally with WHO (in an anonymised format).

Verbal consent will be obtained before commencing the telephone questionnaire. This will be recorded by the interviewer and entered into the secure database held within HPSC. Participants will be asked to provide written consent at the blood testing centre. The written consent form will be sent to HPSC, scanned and the electronic record will be held on the secure server within HPSC. Paper copies of the consent form will be securely destroyed by shredding.

Consent will be sought for obtaining and storage of the blood sample for a period of two years for possible further testing if more accurate tests are developed in the interim, as well as for data processing.

For participants aged 12 to 17 years, the consent of the parent or guardian and the assent of the child will be required.

For those with early dementia, mental illness or intellectual disability, a tailored consent form will be used, with the assistance of the HSE assisted decision making programme.

Separate consent will be obtained, from participants who have antibodies to SARS-CoV-2 detected, and who agree to take part in the second study for data collection and processing, at 3, 6 and 12 months, for sample storage for 2 years, and for international sharing of the data with WHO (in an anonymised format)

Sample collection and processing

Sample testing locations will be established by the HSE in the two selected areas where the study is being undertaken. Options for suitable sites are currently under investigation. The sites will not be centres currently used for testing patients for possible current COVID-19 infection.

On arrival at the test centre, the team (administrative personnel and nurse phlebotomists) will confirm that the person is registered as a participant in the study, and will obtain written consent for sampling. Demographic details will be confirmed. A venous serum sample of 10mls will be collected

from each person by the nurse phlebotomist. Arrangements will be made for the participant to receive reimbursement for travel expenses incurred.

Specimens will be transported to the National Virus Reference Laboratory (NVRL) **at** 4 degrees Centigrade for testing using registered couriers. Consent forms will be sent to HSE HPSC where they will be scanned and entered into the secure database. The paper copies will then be securely shredded.

Those participants with detectable antibody to SARS-CoV-2 will also be invited to take part in a follow up study to determine if these antibodies are persistent 3, 6 and 12 months after the initial samples were taken and if they developed symptoms consistent with COVID-19 during this time. They will be asked for consent to take part in this study when results of the first round of testing are available. They will not be provided with the results of these further tests.

Laboratory testing

The SARS-CoV-2 IgG assay to be used by the NVRL will be selected based upon the antigenic targets utilised in the test, review of data generated by the manufacturer and independent assay assessment and also assay verification performed at the NVRL. It is probable, based upon the anticipated numbers for testing, that an automated platform will be used.

The format for the current assays is not suitable for the accurate investigation of SARS-CoV-2 IgG in samples collected "non-invasively" such as oral fluid. However, if a suitable test is identified this approach with be considered and a study amendment will be sought.

Repeat serum samples (at 3 months, 6 months and 12 months) on those who are SARS-CoV-2 IgG positive will be tested.

Retention of biological materials

Samples will be stored in the NVRL for a period of 2 years**.** The serology assays for SARS-CoV-2 are in the early stages of development and it is possible that more sensitive and specific antibody tests and antibody function tests will be developed in the coming months. The retained samples may be retested by the research team during these 2 years. The consent form will specifically ask the participant for consent for their blood sample to be stored in NVRL for up to 2 years, on the understanding that during this time it may be tested again for antibodies and antibody function by the study's research team. After 2 years they will be destroyed.

Data analysis

Response rates and eligibility rates will be calculated. The demographic and other characteristics of the study participants, obtained from the questionnaires, will be analysed and compared to the general population where appropriate to assess their representativeness.

The antibody results, age, sex and geographic area of all participants will be used to calculate an overall prevalence of antibodies to SARS-CoV-2, with a 95% confidence interval, in the sampled populations. This can be used to estimate the number of persons seropositive in the two study population areas. Acknowledging the limitations of having only two geographical areas representing categories of incidence, we will produce corresponding Irish population estimates using weighted analyses. The relationship between the presence of antibodies to SARS-CoV-2 and reported symptoms or previous diagnosis of COVID-19 will be examined.

For participants included in the serial sampling study, we will calculate the proportion for whom antibodies are still detected at each subsequent sampling time point. The relationship between

antibody kinetics and reported symptoms or previous diagnosis of COVID-19 will be examined alongside other participant characteristics such as age.

Reporting of the results

Individual results of the blood test will be provided to participants by letter, explaining that the result is not a diagnostic test, and is meaningful at a population rather than individual level. They will be advised that the presence of antibodies may not equate to immunity from future SARS-CoV-2 infection as further research is required to enhance our understanding of this disease, including the extent to which prior infection confers immunity**.** They will be advised to continue to follow all social distancing and hygiene measures recommended by the government

The potential benefits and harms of providing feedback to individuals were weighed up and on balance it was felt that feedback on presence of Ab to SARS-CoV-2 was appropriate as it would provide the person with knowledge that they had been infected and that it would be carefully explained to the person that the implications of that finding for re-infection was uncertain at this time. Participants will also be given the 'right not to know' and can specify at time of providing consent to participate to not receive their results.

Participants will be advised that they may phone a public health doctor member of the study team if they have queries about the result and will be provided with a contact phone number.

The participant's GP will also be provided with the result, if the participant has agreed to this.

Anonymised results will be shared with NPHET to inform the national pandemic response. In the interests of openness and transparency, a report on the study results will also be shared with the general public, via the HSE and HSE HPSC websites.

The HSE HPSC, through its role as IHR focal point for Ireland, will also share anonymised results with the World Health Organization (WHO) to add to global knowledge on the spread of COVID-19.

A manuscript outlining the study methodology, the results and their interpretation will be submitted for publication in a peer reviewed scientific journal

Those participants with detectable antibody to SARS-CoV-2 will also be invited to take part in a follow up study to determine if these antibodies are persistent 3, 6 and 12 months after the initial samples were taken and if they developed symptoms consistent with COVID-19 during this time. They will be asked for consent to take part in this study when results of the first round of testing are available. They will not be provided with the results of these further tests.

Repeat cross sectional survey

This cross-sectional survey will be repeated twice during the pandemic, with a different sample of participants, from high and low incidence areas. The interval will be determined by the evolution of the pandemic and other logistical factors.

Oversight

A steering group has been established to oversee the design and operation of the study. The membership and terms of reference are set out in Appendix A.

Data processing and safeguards

Using the PCRS database, the HSE HPSC will write to randomly selected individuals, seeking their participation in the study. Those who are interested in participating will be asked to contact the research team at HSE HPSC to indicate their consent to participate and to seek further information if required.

For those who contact the research team, and who give initial verbal consent to participate in the study, information on name, address, sex, age/date of birth, occupation, GP details, and history of symptoms consistent with COVID-19 or a previous diagnosis of COVID-19 will be gathered by phone. This information will be entered and stored in a secure database at HSE HPSC.

Appointments for testing at HSE centres will be organised using the online swiftqueue system. Patients will be allocated a unique study ID. At the testing centres, the staff will have the names, date of birth and study ID numbers of the consenting participants. This information is needed for correctly identifying participants, for the testing procedure and for labelling the serum samples.

The samples, containing the name, date of birth and unique study ID number, and accompanying form containing the same ID, name and date of birth will be sent to NVRL via registered courier.

At NVRL the samples will be processed using the unique study ID, name and date of birth.

NVRL will provide the serology result to HSE HPSC for entry into the secure database using name, date of birth and unique study ID number. If the participant has given consent to receive their test result, the result, and an explanation of how it should be interpreted, will be provided to the participant by letter from HSE on behalf of the study partners. They will also be provided with contact details if they wish to discuss this further with a public health doctor from the research team.

The study database will be located on a HSE HPSC server, with access restricted to designated staff at HSE HPSC. Data management will be guided by the HSE HPSC written Protocols on Record Retention and Data Protection. HPSC is accredited for information security IS0_27001. Data held at NVRL will be managed in accordance with the NVRL Data Protection Policy VI & Data Protection GDPR 2018. All HSE HPSC and NVRL staff and researchers have undertaken data protection training.

Funding

The study is being funded by the HSE, to include the following components:

- A senior manager who will coordinate and facilitate financial and operational aspects
- HSE HPSC coordinated administrative team: Distributing initial letters of invitation and reminder letters, questionnaire administration, data entry into a dedicated database for analysis, collation of results, preparation and distribution of letters communicating results to individual participants
- Test centre teams: Nurse phlebotomists and administrative personnel, PPE for teams
- A reception/appointment system, arrangements for travel expenses for participants, and helpline for queries
- Testing centres with facilities on site – to allow for distancing, completing paperwork, taking bloods

- Consumables for blood taking (sharps bin, packaging for transport, arrangements for transport of specimens to lab)

- Communication team: to advise and input into the development of study materials, engage public support and publicity for the study, and development and operation of the study website

HSE will arrange for indemnity for the study, and liaise with the State Claims Agency to put in place arrangements for cover for compensation in the event of a claim.

Ethics

This proposal is being submitted to the National COVID-19 Research Ethics Committee for ethical approval.

Bias and limitations

The study will not include persons of all ages, as those aged less than 12 years and 70 years and older will be excluded from the study. Those with underlying conditions who are cocooning, or self-isolating for any reason, as specified by the Department of Health, will not be represented in the serological part of the study. Individuals may choose not to participate in the study.

Appendix A:

Study to investigate COVID-19 infection in the population of Ireland (SCOPI)

Steering Group

Terms of reference

1. To provide expertise and advice that will contribute to and strengthen the design of the national population study so that it achieves its purpose
2. To support the project team in preparing for the National Research Ethics Committee submission
3. To advise on financial, legal, and ethical matters related to the study
4. To oversee the implementation of the study
5. To promote and explain the study purpose to external stakeholders
6. To oversee the interpretation and reporting of the findings of the study, and encourage their use to support the public health response to the COVID-19 pandemic

Name		**Body**
Dr Derval Igoe	Specialist in Public Health Medicine (Chair)	HPSC
Dr Cillian de Gascun	Virologist and Director	NVRL
Dr Jeff Connell	Assistant Director, Principal Clinical Scientist	NVRL
Dr Siobhan O'Sullivan	Chief Bioethics Officer	DOH
Dr Mary Keogan	Clinical Lead, National Clinical Programme for Pathology & Consultant Immunologist	HSE Beaumont Hospital
Ms Michele Tait	COVID19 Operations Team, Office of the Chief Operating Officer	HSE
Ms Fiona O'Callaghan	Statistician	Central Statistics Office
Mr Paul Crowley	Senior Statistician	Central Statistics Office
Dr Janice Bailie	Assistant Director R&D	Public Health Agency, Northern Ireland
Professor Frank Kee	Director of UKCRC Centre of Excellence for Public Health Research (NI), Deputy Director	Queens University Belfast

	for the Centre for Public Health	
Dr Margaret O'Sullivan	Specialist in Public Health Medicine	HSE South
Dr Nuala O'Connor	General Practitioner, ICGP GP Lead Advisor Antibiotic Resistance ICGP, GP Lead HSE Antimicrobial Resistance and Infection Control Team, Irish College of General Practitioners	Irish College of General Practitioners
Dr Laura Heavy	Study Coordinator, Specialist Registrar Public Health Medicine	HPSC
Dr Lelia Thornton	Specialist in Public Health Medicine	HPSC
Dr Patricia Garvey	Surveillance Scientist	HPSC
Dr Aoife Colgan	Surveillance Scientist	HPSC

Paula Dempsey: research/surveillance assistant: administrative secretary

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