Title:
Seroprevalence of SARS-Cov-2 Antibodies in Children

Short title:
Seroprevalence of SARS-Cov-2 Antibodies in Children

Protocol

Version: 10.0
5th January
2022

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Study Funding:
Royal Belfast Hospital for Sick Children – Charitable funds and
Queen's University Belfast – Soft funds

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GLOSSARY

CE-IVD	Conformite Europeene In Vitro Diagnostics
COVID-19	COrona Virus Disease 2019
CRF	Case Report Form
LAMP	Loop mediated isotherm AMPlification
NHS	National Health Service
PCR	Polymerase Chain Reaction
POC	Point-of-care
PICU	Paediatric Intensive Care Unit
PCR	Polymerase Chain Reaction
PPE	Personal Protective Equipment
RBHSC	Royal Belfast Hospital for Sick Children
SARS-CoV-2	Severe Acute Respiratory Syndrome CoronaVirus 2

PROTOCOL SUMMARY

Full title:	RAPid diagnostics, antibody testing and host response in children with CovID-19 (RAPID-19)
Short title:	RAPID-19
Rationale:	Very little is known regarding the symptoms and signs of Covid-19 disease in children. In particular we do not know how many children are asymptomatic carriers of the SARS-CoV-2 virus and what the symptoms and signs of mild Covid-19 disease are. We need to understand the pattern of immunological (e.g. cytokine) response is in children who experience mild versus severer disease. We also need to develop a rapid accurate point of care (POC) test for SARS-CoV-2 virus. We have an opportunity to complete this research rapidly in Northern Ireland and because we are 2-3 weeks behind mainland UK in the development of the COVID-19 epidemic we are ideally suited to this. In the midst of this rapidly evolving pandemic we have designed this pragmatic study to start addressing the above issues.
Study type:	Prospective cohort study
Population:	1) Healthy children (between 2 and 15 years of age) of healthcare professionals (n=1000+/- 10%). 2) Children up to 15 years of age admitted to the Royal Belfast Hospital for Sick Children with confirmed Covid-19 disease (n=10 to 30) and children admitted with confirmed other serious infections (n=10 to 30)
Study sites:	Royal Belfast Hospital for Sick Children (RBHSC, a large tertiary children's hospital in Northern Ireland) and additional UK sites. The Ulster Independent Clinic (a private hospital that has offered free support to the study)
Study duration per participant:	12 months (maximum)

Description of intervention:

Healthy cohort:

Daily symptom diary if/when unwell:

Week 0:

- Blood test (5ml) to measure antibodies indicating previous infection, cytokine baseline and proteomic, and transcriptomic baseline.

When/if develop symptoms:

- Nasal and throat swabs to assess for current infections with SARS-CoV2.
- Blood test (5ml) to measure antibodies indicating previous infection, cytokine response and proteomic, and transcriptomic response (where possible).

Week 8:

- Blood test (5ml) to measure antibodies indicating previous infection, cytokine response and proteomic, and transcriptomic response.
- Crevicular fluid swab to measure antibodies

4 to 6 months:

- Blood test (5ml) to measure antibodies indicating previous infection, cytokine response and proteomic, and transcriptomic response.
- Crevicular fluid swab to measure antibodies and/or to perform viral testing

10 to 12 months – Only for individuals with antibodies detected at one of the three previous clinic appointments, Testing timed at 10 to 12 months.

- Blood test (5ml) to measure antibodies indicating previous infection, cytokine response and proteomic, and transcriptomic response.
- Survey data to record any interim Covid-19 infections/exposure and any Covid-19 vaccinations received.

Admitted cohort:

- Review of medical notes to record symptoms.
- Residual blood samples to measure antibodies, assess the host cytokine response, proteomic, and transcriptomic response to infection. If no residual specimen then consent sought for a single blood test (5ml) to measure antibodies indicating previous infection, cytokine response and proteomic, and transcriptomic response.
- Daily blood spot (2 drops of blood). Taken via a finger prick. To monitor the cytokine response. Timed, where possible, with any routine blood tests.
- At 4 weeks and 8 weeks a single blood test (5ml) to measure antibodies indicating previous infection, cytokine response and proteomic, and transcriptomic response.

Primary Outcome measures:

- Diagnostic test accuracy of a rapid diagnostic test for SARS-CoV2
- SARS-CoV2 nasal swab PCR-positivity in healthy children of healthcare professionals.
- IgM and IgG positivity in healthy children of healthcare professionals at recruitment, at 8 weeks and at 4 to 6 months
- To correlate clinical symptoms with infection and seroconversion to SARS-CoV2 in healthy children of healthcare professionals
- IgM and IgG positivity to SARS-CoV2 at recruitment, at 4 weeks and at 8 weeks in children hospitalised with COVID-19

Secondary Outcome measures:

- To correlate clinical symptoms with swab PCR positivity in children
- Host cytokine response, proteomic and transcriptomic response in severe disease

BACKGROUND INFORMATION

Introduction

Coronaviruses are non-segmented positive-stranded RNA viruses with a roughly 30 kb genome (1). The majority of coronaviruses cause disease in a specific host species but some have infected humans by cross-species transmission. This process has led to a number of severe outbreaks of human disease including severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2012 (1).

From December 2019 a novel infection "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) was identified in the Wuhan region of China. The infection was identified as the causal factor in a growing number of severe cases of pneumonia (1). This disease was subsequently named coronavirus disease 2019 (COVID-19) by WHO. SARS-CoV-2 has been shown to cause severe disease similar to the previous SARS coronavirus from 2003. Severe disease is associated with pneumonia and damage to vital organs including lung, heart, liver, and kidney (1). Pneumonia is the leading cause of mortality in children worldwide but very little is known regarding the disease process in children.

- **We do not know - why so many children exhibit mild disease, or why some children suffer severe disease and die.**
- **We need an accurate rapid point of care diagnostic test to diagnose SARS-CoV-2 infection (the cause of COVID-19).**

Point-of-care (POC) testing

A rapid POC test for SARS-CoV-2 is essential. With such a potentially fatal disease confirming the diagnosis early will allow for prompt and appropriate therapy. A rapid test would also allow for early cohorting of children thereby improving flow through the emergency department. Finally rapid testing could support the wider fight against Covid-19 through quicker contact tracing and isolation.

The research team in Belfast have a lot of experience of using Loop-mediated isothermal AMPlification (LAMP) for the rapid diagnosis of serious infections in children and have been involved with the development of LAMP testing for Meningococcal Disease, invasive E.coli infection Group B Streptococcal disease (2,-4). There now exists a CE marked commercially available LAMP rapid test for SARS-CoV-2 that can be performed with minimal equipment within 30 minutes (Figure1). The test can be performed using a single throat or nasal swab.

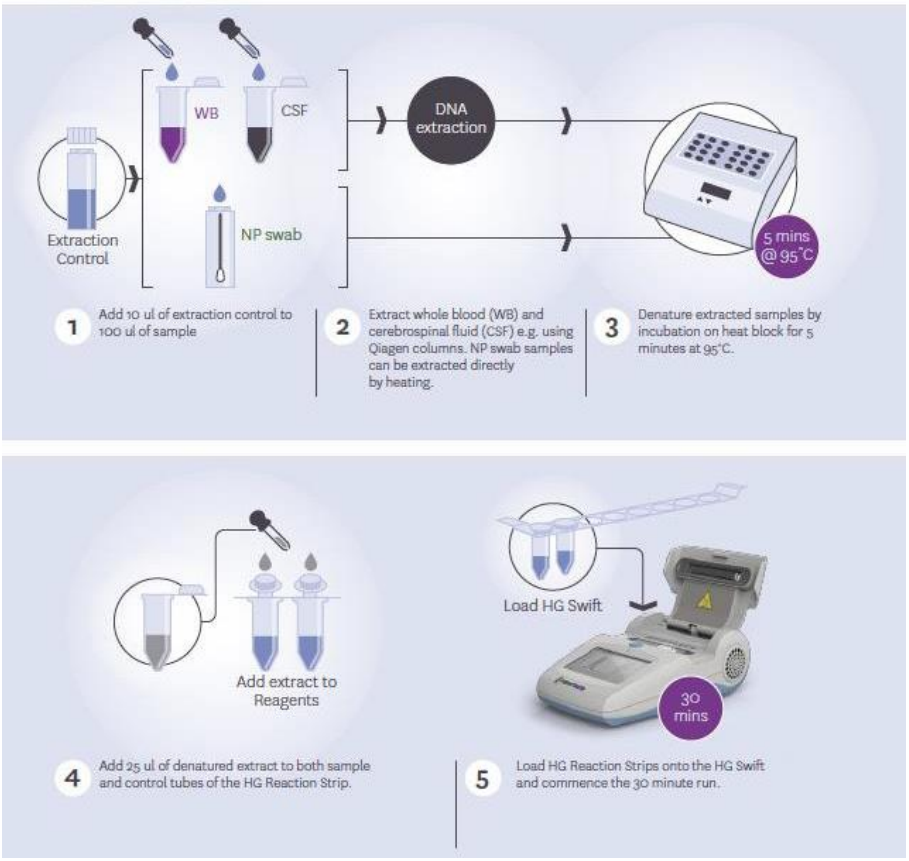

Figure 1: Schematic of

Disease process

Very little is known regarding the symptoms and signs of Covid-19 disease in children (1). In particular we do not know how many children are asymptomatic carriers of the SARS-CoV-2 virus and what the symptoms and signs of mild Covid-19 disease are. We also do not know why some, previously well, children develop severe disease. Research is required to understand the symptoms and signs of infection, the spectrum of disease and the host immune response in those with severe disease. We intend to compare the host immune response in children with mild.moderate and severe Covid-19 disease and compare that to the immune response in children with other serious infections.

Rationale for the study

This RAPID-19study aims to improve our understanding of how Covid-19 affects healthy children. By following children of healthcare workers we have an opportunity to follow children as they acquire Covid-19 and develop immunity. During this time we will be able assess the performance of antibody tests and rapid diagnostics. These tests are vital in the fight against Covid-19. We have chosen to study children of healthcare workers as we feel this group is a highest risk of contracting the infection during the current social distancing measures. We intend to study the seroprevalence of SARS-Cov2 in populations in Northern Ireland and mainland UK. The purpose for this is that Northern Ireland is currently seeing very low transmission rates whereas mainland UK is seeing much higher rates. By recruiting children from both Northern Ireland and mainland UK we can better understand how the timing of different social distancing measures affects transmission.

In addition to the main cohort (children of healthcare workers) we intend to recruit children with known Covid-19 admitted to the RBBHSC. We expect that severe disease and admission to hospital will be an uncommon event for most children and we expect only 1 or 2 children of the (100-120) healthcare workers to be admitted for treatment. By following admitted children we have an opportunity to research the full spectrum of disease from minor illness through to moderate and severe disease. By following a range of severities we can gain an insight into

the different cytokine proteomic, and transcriptomic responses. This will provide insight into prognostication and potential therapeutics. We need to begin this research immediately as part of a national pandemic response. We believe Northern Ireland is approximately 2-3 weeks behind mainland UK in the development of the COVID-19 epidemic and we have a short window of opportunity to begin this study. If we delay the start of this project by more than a few days we will potentially lose that opportunity.

Objectives/Outcome

Primary Objectives:

- Diagnostic test accuracy of a rapid diagnostic test for SARS-CoV2
- SARS-CoV2 nasal swab PCR-positivity in healthy children of healthcare professionals.
- IgM and IgG positivity in healthy children of healthcare professionals at recruitment, at 8 weeks and at 4 to 6 months
- To correlate clinical symptoms with infection and seroconversion to SARS-CoV2 in healthy children of healthcare professionals
- IgM and IgG positivity to SARS-CoV2 at recruitment, at 4 weeks and at 8 weeks in children hospitalized with COVID-19

Secondary Objectives:

- To correlate clinical symptoms with nasal swab PCR positivity in children
- Host cytokine response, proteomic and transcriptomic response in severe disease

STUDY DESIGN

Population

1) Healthy children (between 2 and 15 years of age) of healthcare professionals. (n=1000+/-10%) Healthy children defined as children not currently receiving antibiotics, not admitted to hospital within the last seven days, not receiving immunosuppressive drugs and never diagnosed with a malignancy or chronic disease affecting the immune system, kidneys, heart or lungs.
2) Children aged 15 years and under admitted to the Royal Belfast Hospital for Sick Children with confirmed Covid-19 disease (n=10 to 30) and children admitted with other serious infections (n=10 to 30)

Recruitment of healthy children
Healthy children of healthcare workers will be identified by the use of internal websites and email. In all instances informed consent will be obtained prior to including children in the study. We intend to recruit approximately 1000+/- 10% healthy children. Potential participants will be provided with a participant information sheet and consent form. This will be followed up with a telephone conversation to answer any questions. Completed consent forms will be stored securely within the University or at the participating NHS site.

Consent/assent form completion
Wherever possible the child will be included in the consent/assent process. We will ask parents to involve their children with consent discussions at home using the age-appropriate information sheets provided.

If a child turns 16 during the follow up period they will be invited to provide consent using the appropriate consent form. If they decline consent they will be withdrawn from the study.

Withdrawal of Consent
The parent is free to withdraw consent at any time without providing a reason and without being subject to any resulting detriment. The rights and welfare of the patients will be protected and the quality of medical care will not be adversely affected if they decline to participate in the study the principle investigator (or their deputy) will maintain a record of all those that withdraw consent to participate in the study.

Recruitment of unwell children with Covid-19

Children with Covid-19 admitted to the RBHSC for emergency treatment will be identified by clinical staff in the ED and a member of the research team will screen them for inclusion. We intend to recruit between 10 and 30 patients with Covid-19 and a matched population of between 10 and 30 patients with other serious infections. Data regarding the clinical status of the child will be recorded by the research team and residual blood samples, that would otherwise be discarded, will be stored. At the earliest appropriate opportunity consent will be sought to use the data and stored samples. This process is known as research without prior consent (RWPC) and the research team have experience of utilising this approach for previous emergency research (5-7). Research without prior consent in children has been shown to be appropriate and well accepted by parents when conducted in emergency situations and when information and opportunities for consent are offered at an appropriate time (5-7). Unwell children **WILL NOT UNDERGO ANY ADDITIONAL PHLEBOTOMY EVENTS OR SWABBING** beyond usual care without prior consent.

Based on the best practice guidance for performing research without prior consent a member of the research team will check with the relevant ward staff that the participant is stable and that timing is appropriate before approaching the parent (8). If the participant's condition has not stabilised additional time will be allowed before approaching parent. A member of the ward team would explain the nature of the study and invite the parent to talk with a researcher. A member of the research team will explain to parents the reasons why informed consent cannot be sought in emergency care research. These discussions will occur at a convenient time for the family and via telephone to prevent spread of Covid-19.

A member of the research team will also discuss with the parent the:

- Objectives
- Risks and inconveniences of the study
- Conditions under which it is to be conducted
- Emphasise that participation in the study is voluntary and that the participant may withdraw from the study at any time and for any reason.

The parent will be sent a link for the patient information and consent forms. Upon reviewing the documents, all participants will be given opportunity to ask any questions that may arise, have

the opportunity to discuss the study with their surrogates and have time to consider the information prior to agreeing to participate. These steps will occur via telephone where possible.

Consent/assent form completion
Wherever possible the child will be included in the consent/assent process. We will ask parents to involve their children with consent discussions in hospital. When a consent form is completed it will be stored, securely and electronically, on University servers. Paper copies of the consent forms will be available as a backup option.

When a child turns 16 during the study they will be invited to provide consent again at the enxt clinic visit. They will only remain in the study if consent is provided.

Death prior to consent being sought
This is likely to be a rare occurrence. If a participant dies before consent has been sought, the site principle investigator (or nominated deputy) will obtain information from clinical colleagues and establish the most appropriate practitioner to notify parents of the research involvement. Consent can be sought from parents following the death of their child at the most appropriate time point. However, it is at the discretion of the clinical staff to determine if this is appropriate for each individual family. It maybe that it is not appropriate for consent to be obtained. If the clinical team deem an approach inappropriate then the child will be excluded from the study. If an approach is deemed appropriate then a researcher will call the family, provide study information and provide a link to the participant information sheet and consent forms.

Discharge/transfer prior to consent being sought
If a child is discharged prior to consent being obtained then the child will be excluded from the study.

Consent declined
If research without prior consent is declined the child's data will not be included. The site principle investigator (or nominated deputy) will maintain a record of all instances of declined consent.

Withdrawal of consent

The parent is free to withdraw consent at any time without providing a reason and without being subject to any resulting detriment. The rights and welfare of the patients will be protected and the quality of medical care will not be adversely affected if they decline to participate in the study. The site principle investigator (or their deputy) will maintain a record of all those that withdraw consent to participate in the study.

ASSESSMENTS AND PROCEDURES

Table 1: Study assessments/procedures

Assessment/procedure	Well children	Unwell children
Consent discussion	In advance via telephone for well children. .	At the earliest appropriate opportunity
Assessment of eligibility criteria	In advance to attending initial clinic appointment (via telephone).	Screening performed by clinical staff with eligibility confirmed by the research team
Swabs	When unwell Crevicular Fluid Swabs if/when available and if practical at that site.Can be performed at routine clinic appointment.	All admitted children
Phlebotomy	• Weeks 0 and 8 and again at between 4 and 6 months and 12 months • If/when unwell if possible	Residual blood stored pending consent. Consent also sought for additional phlebotomy as inpatient and again at 4 to 6 months.
Finger prick blood tests	Only if phlebotomy fails	Daily during admission.
Data collection	Symptom diaries when unwell. Notes review if admitted.	By research team using a notes review and additional history taken during consent discussion.

Phlebotomy, swabs and finger pricks

All procedures will be performed by trained paediatric healthcare professionals, with at least three years paediatric experience, wearing appropriate protective personal equipment. To minimise any distress we intend to make use of and topical anaesthetic creams. For both swabs and blood tests the parent can choose not to have the test performed at any point.

Crevicular Fluid

Crevicular fluid swabs involve collecting saliva on a small mouth swab that is placed next to the gums. This is far less uncomfortable than throat or nasal swabs. Where available we want to utilize this method instead of throat/nasal swabbing. We wish to offer routine swabs at week 8 and at 6 months for viral PCR and/or antibody testing. The importance of this is that if crevicular fluid proves reliable for antibody testing then this could be used as an alternative to painful blood tests in young children.

Adverse events

Any adverse events will be recorded. The most likely adverse events relate to additional phlebotomy. All phlebotomy will be performed by experienced healthcare professionals and any complications (such as slight bruising) will be managed with appropriate first aid and analgesia In the exceptionally unlikely event of a more significant adverse event the child will be assessed by non-research team members at the Royal Belfast Hospital for Sick Children Emergency Department.

Additional testing

All residual specimens will be made available for, appropriate, further analysis relating to Covid-19 including validation of other rapid diagnostic tests, antibody and immunity testing and further development of biomarkers of infection/prognosis.

Background sero-prevalence/Cross-reactivity with other seasonal coronaviruses

The background sero-prevalence of IgM and IgG positivity to SARS-CoV2 will be determined from residual samples of children with blood taken for non-infective reasons (n=150 to 300). These will be collected in a fully anonymised from the Royal Victoria Hospital laboratory and/or participating NHS sites in mainland UK. Consent to perform this testing will not be sought.

Serum/plasma collected during the study will undergo testing for other seasonal coronaviruses as part of the antibody response assessment.

Potential risks/benefits

The RAPID-19 study involves performing additional phlebotomy events on well and healthy children. This has the potential to cause distress. This will be minimised by the use of topical anaesthetic creams. Rarely the phlebotomy may cause harm through local bruising. To minimise this all phlebotomy will be performed by experienced healthcare professionals with at least three years paediatric experience. Any complications arising from phlebotomy will be recorded. The RAPID-19 study also involves additional swabbing of healthy children. This is a low risk intervention with no expected harms but can cause some minor distress. For both swabs and blood tests the parent can choose not to have the test performed at any point.

There are no benefits for the participants in this study.

STATISTICAL CONSIDERATIONS

The study population will be described in terms of demographic characteristics, clinical symptoms and signs, parenteral antibiotic use, admission to hospital, admission to intensive care and survival using descriptive statistics. The performance of the rapid test (index) will be compared to laboratory PCR (reference standard) with sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) (with 95% confidence intervals) reported.

The clinical features, cytokine response, proteome and transcriptome will be described for unwell, admitted children. The cytokine, proteomic and transcriptomic response will be compared between healthy children and those with severe disease.

The sample size for this study is a pragmatic one that allows for the study to be completed in a timely way whilst also being likely to provide insights into the disease process and accuracy of clinical tests.

ETHICAL CONSIDERATIONS & RISK ASSESSMENT

Consenting Issues

During the Covid-19 pandemic there is a need for social distancing and this poses a number of challenges with obtaining consent. It is essential that social distancing is maintained and as such we will perform consent discussion via the telephone and seek written consent electronically where possible. This will minimise face-face contact and spread of infection through the use of paper documents. For those healthy children recruited to the study there will be time to obtain prior informed consent.

For those admitted with severe Covid-19 disease the process will be more complicated. We wish to evaluate a rapid test for the diagnosis of Covid-19 and also to monitor the host response during the infection. It is vital that we collect clinical data from the onset of the infection and that we store vital residual specimens before they are discarded. Due to the urgency of treating severe Covid-19 it would not be appropriate for researchers to delay urgent care and we will instead seek consent at the earliest appropriate opportunity. This is in-line with best practice guidance and our experience of other previously successful trials (5-8). If consent is declined the collected clinical data will be permanently deleted and any stored residual samples destroyed as planned by the NHS site they are stored at. No additional procedures, such as phlebotomy/nasal swabs/finger pricks will take place without prior consent.

Additional procedures
The phlebotomy, finger scratches and swabs will involve some distress for children. This will be minimised by having these procedures performed by experienced paediatric doctors and nurses (a least three years paediatric training). A topical anesthetic cream will be offered for blood tests.).

Risks to researchers
The risk to researchers will be minimised by minimising face-face discussions with family members and by avoiding handling of potentially hazardous materials where possible. All procedures and specimen handling will be performed wearing appropriate personal protective equipment (PPE).

Case report forms (CRF)
Data will be recorded on an electronic CRF using a numerical reference number that can be linked back to the original patient if required. The CRF will only include clinical data pertinent to the study. Examples include basic demographic data such as age, gender and clinical data such as current symptoms of infection. The symptom CRFs will be completed online by parents.

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exception that medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

Providing information regarding antibody testing
Results of antibody testing will be disseminated at future clinical meetings. A guide to interpreting results will be produced to guide families as to how to interpret test results. Following the final 6 month appointment those children with newly identified antibodies will have their results sent to them via post.

Ethical approval
The study protocol, including the participant information sheets and consent/assent forms and all other relevant study documentation will be submitted for review by the Research Ethics Committee (REC).

FINANCIAL ARRANGEMENTS
This study has been supported by the Royal Belfast Hospital for Sick Children charitable funds and Queen's University with donations of £23,000

PUBLICATION

The results will be analysed and published as soon as possible. High impact journals will be targeted as will academic meetings with the aim disseminating the key-learning around Covid-19 affecting children.

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