**“ADAPT-C” Sub-Study:**

**Community-based cohort of people tested for COVID-19**

*A sub-study to the “ADAPT COVID-19 Study: A prospective, observational cohort study at St Vincent’s Hospital Sydney” protocol*

**ADAPT-C**

**Protocol version: 1**

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**Sponsor: St Vincent’s Hospital Sydney**

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**Summary**

|  |  |
| --- | --- |
| **Study Title** | “ADAPT-C” Sub-Study: Community-based cohort of people tested for COVID-19  *A sub-study to the “ADAPT COVID-19 Study: A prospective, observational cohort study at St Vincent’s Hospital Sydney” protocol* |
|  |  |
| **Objectives** | Primary: To establish three negative control community-based cohorts of people tested for SARS-CoV-2, to enable evaluation of SARS-CoV-2 serological assays and long-term COVID-19 illness. |
| **Study design** | Prospective and retrospective cohort study |
| **Planned sample size** | 150 patients (50 each cohort) |
| **Selection criteria** | Patients with nasopharyngeal swab respiratory viral panel testing |
| **Study procedures** | Blood collection and Questionnaires |
| **Statistical considerations** | Sample size calculation: 150 patients  Analysis plan: Descriptive statistics will be summarised by median (IQR) and counts (%-total). Differences between groups will be compared using the Student’s T test for continuous variables and the Chi-Square test for categorical variables. Logistic regression analysis will be performed to measure the association between continuous predictors and binary outcome variables. |
| **Study duration** | 12 months of longitudinal follow-up |

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# BACKGROUND

## Disease Background

In December 2019, there were a series of unexplained cases of severe pneumonia reported in Wuhan, Hubei Province China. In January 2020, the World Health Organisation (WHO) declared the disease an international public health emergency. In February 2020, the International Committee on Taxonomy of Viruses formally named the disease COVID-19 and the causative agent SARS-CoV-2. Covid-19 has rapidly spread around the world and to date (28th May 2020) there are 5.8 million confirmed cases in 184 countries that have caused 360,000 deaths (1). In Australia there are currently 7,155 cases and 103 deaths.

### Etiologic Agent and Epidemiology

SARS-CoV-2 is a coronavirus and belongs to the β-coronavirus cluster of the Coronaviridae subgenus botulinum (2). It is regarded as a zoonotic coronavirus disease including SARS and Middle East respiratory syndrome (MERS). SARS-CoV-2 is a chimeric bat virus (3-5). SARS-CoV-2 remains viable in aerosol for up to 3 hours. It is more stable on plastic and stainless steel than on copper and cardboard – viable virus was detected up to 72 hours after application to these surfaces (6).

SARS-CoV-2 infection was reported to increase by 31.4 times over a 14-day period in China (7). The estimated case fatality rate was 2.84%. The median age of death was 75 years, the median time from first symptom to death was 14 days with a male:female ratio for death was 3.25:1 (7-10). In another study, the median age of patients infected with SARS-CoV-2 was 59, of which 56% were males with an average incubation period of 5.2 days (11). Wu et al. estimated a transmission rate of infected individuals to be 30% and a case fatality rate of 14% (12).

### Symptoms and Complications

Following infection with COVID-19, patients may suffer pulmonary and extra-pulmonary manifestations that may result in death and disability. The most common presenting symptoms include fever (Temperature > 38 degrees), cough, myalgias (13). Huang et al. report dyspnoea in 55% patients. A smaller number demonstrated expectoration, headaches, haemoptysis and diarrhoea. Pathology tests demonstrated leucopenia in 25% and lymphocytopenia in 63%. AST is elevated in 37% patients. Elevated high-sensitive troponin was detected in 12% patients. Subpleural, peripheral ground glass opacities were detected in 98-100% patients. Huang et al. reported that the most common complications in patients with SARS-CoV-2 were acute respiratory followed by anaemia, myocardial injury and secondary infections (13).

Many patients (>80%) with COVID-19 may only have mild or mild-moderate disease and will not require hospitalisation or intervention, however a significant number of individuals will need respiratory support and a small number of these will require ventilation. The spectrum of COVID-19 disease in the Australian population is unknown given the uncertainties in the data emerging from other countries and the variability in testing and case ascertainment. The degree to which the long term effects of COVID-19 will vary by disease presentation is also unknown.

The long-term effects of respiratory infections on lung function, exercise capacity, emotional and economic well-being are becoming more widely recognised for respiratory pathogens (including tuberculosis) but are not known for Covid-19 infection. Immediate and long-term psychological impacts of Covid-19 infection are also under investigation in various populations world-wide (Zhang, IJERPH 31 March 2020, Nguyen, JCM 27 March 2020) and have not yet been characterised in the Australian setting. The neurocognitive impact of COVID-19 is as yet undescribed.

### Disease Stages and presentation

SARS-CoV-2 infection may divided into 3 stages (8):

Stage 1: An asymptomatic incubation period with or without detectable virus. A recent report showed that the median duration of viral shedding in COVID-19 was 20 days in patients with severe illness and could be as long as 37 days (14)

Stage II: Non-severe symptomatic period with the presence of virus

Stage III: Severe Respiratory symptomatic stage with features of Acute Respiratory Distress Syndrome (ARDS)

Further, there are potentially three broad categories of clinical illness:

1. Mild disease. These patients are only mildly asymptomatic (or asymptomatic) and have a short duration respiratory illness consisting of fever, fatigue and upper respiratory tract symptoms. These patients are managed in the community and make up 80-90% of current COVID-19 cases
2. Moderate disease. These patients have significant symptoms suggestive of lower respiratory tract involvement and often require hospital admission for oxygen and supportive care. They tend to be older with a range of co-morbidities. They constitute 10-15% of COVID-19 cases
3. Severe disease. A small proportion of patients (1-5%) will have significant disease requiring intensive care support and ventilation. The illness is characterised by features of ‘cytokine storm’ and often multi-organ failure. Respiratory support is prolonged and in a proportion of these patients the illness is fatal.

It is likely that many clinical outcomes will vary considerably across the disease spectrum but as yet these are largely uncharacterised.

### Diagnosis, Prevention and Treatment

SARS-CoV-2 is diagnosed by respiratory viral swab with the COVID-19 reverse-transcriptase polymerase chain reaction (RT-PCR). Empiric antibiotics have been prescribed to prevent secondary bacterial infections. Patients with intractable hypoxaemic respiratory failure require lung-protective invasive mechanical ventilation. Remdesivir has been associated with symptoms resolution in a case study (15). In hospitalized adult patients with severe COVID-19, no benefit was observed with lopinavir-ritonavir treatment beyond standard care (16). The efficacy of investigational drugs such as hydroxychloroquine and Favipiravir needs to be verified by clinical trials. The role of high dose IVIg remains to be clarified. The role of a soluble ACE2 receptor remains to be clarified. No SARS-CoV-2 vaccine has been successfully developed. Strategies to control the spread of infection include early diagnosis, reporting and isolation. For individuals, protective measures including social distancing, personal hygiene may reduce the community transmission of SARS-CoV-2 (17).

### Mechanisms of Disease and Adaptive Immune Response

Zhao et al. demonstrated that angiotensin-converting enzyme 2 (ACE2) is the receptor for SARS-CoV-2 infection (18). In the normal human lung, ACE2 is expressed on type I and type II alveolar epithelial cells. 83% of type II alveolar cells have ACE2 expression. Higher ACE2 expression is observed in men and individuals of Asian ancestry. Of note, nasal epithelial cells, specifically goblet cells and ciliated cells, have the highest expression of ACE2 within all of the lung epithelial cells analysed (Sungnak et al. Publication pending). Binding of SARS-CoV-2 on ACE2 causes an elevated expression of ACE2 which is injurious to alveolar cells. The receptor binding-ability of SARS-CoV-2 is 10-20 times stronger than at of SARS-CoV (19). The severe form of SARS-CoV-2 infection, acute respiratory distress syndrome (ARDS), is thought to be mediated by a dysregulated immune cytokine production. Strikingly, ACE2 is an interferon-stimulating (IFS) gene in human epithelial cells. SARS may exploit IFN-driven up-regulation of ACE2, a key tissue-protective mediator during lung injury, to enhance infection (Ziegler et al. Publication pending 2020). Highly immunogenic monocyte-derived FCN1+ macrophages represent the predominant macrophage subset in bronchoalveolar lavage fluid (Liao et al. 2020 pre-print). The formation of tissue resident, highly expanded clonal CD8+ T cells was detected in patients with mild symptoms without an exaggerated immune response. Early histologic assessment of patients with SARS-CoV-2 demonstrated oedema, proteinaceous exudate, focal alveolar cell hyperplasia with a patchy inflammatory cellular infiltration and multinucleated giant cells (20). SARS-CoV-2 appears to evolve in vivo after infection with a range of 1-4 intra-host variants (21).

## Rationale for Performing the Study

There is pressing urgency to better understand the pathogenesis and physiologic consequences of COVID-19. The aim of the ADAPT study is to increase scientific knowledge regarding the immune and pathophysiologic consequences of COVID-19 infection. The aim of the ADAPT-C sub-study is to create SARS-CoV-2 negative control cohorts to the ADAPT study and enable development of serological assays to manage the disease burden of SARS-CoV-2.

# STUDY OBJECTIVES

## Primary Objective

To establish three negative control community-based cohorts of people tested for SARS-CoV-2, to enable evaluation of SARS-CoV-2 serological assays and long-term COVID-19 illness.

## Secondary Objectives

* To evaluate cross-reactivity of SARS-CoV-2 serological assays with other respiratory viral infections, particularly other coronaviruses
* To determine sensitivity and specificity of SARS-CoV-2 serological assays, including at different timepoints following infection
* To determine whether mild-moderate COVID-19 illness is associated with prolonged quality of life impairment, including a post-viral fatigue syndrome
* To determine whether mild-moderate COVID-19 illness is associated with psychological effects

# STUDY Design

## Design

A prospective and retrospective cohort study of patients who have undergone nasopharyngeal swab respiratory viral panel (RVP) testing at St Vincent’s Hospital Sydney and Bondi Beach pop-up clinic who test negative for COVID-19 infection. Three cohorts will be established.

Cohort C (n=50): COVID-19 negative, other coronavirus positive

Cohort D\* (n=50-100): COVID-19 negative, respiratory viral panel negative, no known epidemiological risk factor for COVID-19 infection

Cohort E (n=50): COVID-19 negative, respiratory viral panel negative, known epidemiological risk factor for COVID-19 infection (close contact of known COVID-19 case, overseas travel in 2 weeks prior to testing date)

\*Cohort D will be age, gender and temporally matched (within 2 weeks) to ADAPT COVID positive patients.

## Number of Participants

The study is anticipated to enrol up to 150 subjects, however, this number may be re-evaluated depending on the curve of the epidemic and funding sources.

## Number of Sites

This is a single centre cohort study. All recruitment and sample collection will occur at St Vincent’s Hospital Sydney. Samples will be transferred to the St Vincent’s Centre for Applied Medical Research laboratory for further analysis and storage.

## Duration

Each patient shall be followed for a period of 12 months from the time of RVP testing. The study will run for 2 years in total.

# Participant section

## Inclusion Criteria

1. Age ≥ 18 years
2. SARS-CoV-2 negative nasopharyngeal swab RVP test
   1. Cohort C: RVP positive for other non-SARS-CoV-2 coronavirus
   2. Cohort D: No documented respiratory pathogens on RVP and **no known** epidemiological link to COVID-19 case OR epidemiological risk factor including overseas travel or cruise ship
   3. Cohort E: No documented respiratory pathogens on RVP and **a known** epidemiological link to COVID-19 case OR epidemiological risk factor including overseas travel or cruise ship
3. Able to provide informed consent

## Exclusion Criteria

1. Unable or unwilling to provide consent
2. Documented SARS-CoV-2 test previously

# STUDY Outline

## Schedule of Assessments

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Assessment / Procedure** | **Screening** | **Follow-up** | | |
| **Study weeks**  **(Visit name)** | **0**  **(ENR)** | **4**  **(FU1)** | **16**  **(FU2)** | **48**  **(FU3)** |
| **Study Days** | **0** | **28** | **112** | **336** |
| ***Visit Window (Days)*** | ***+2*** | ***-7 to +28*** | ***+/- 56*** | ***+/- 28*** |
| Informed consent | X |  |  |  |
| Demographics | X |  |  |  |
| Medical history | X |  |  |  |
| Medication review | X | X | X | X |
| Clinical review | X | X | X | X |
| HRQOL measures (SPHERE, IES, EQ-5D, Depression Scale) |  | X | X | X |
| **Research sample collection** | | | | |
| 2 x 8.5mL SST Gold tubes for serum | X | X | X | X |
| 1 x 10mL EDTA Purple tube for plasma | X | X | X | X |
| 4 x 9mL ACD Yellow tubes for PBMCs2 | X | X |  |  |
| Dry blood spot1 | X | X | X | X |

1. May be self-collected
2. Optional

## Study Procedures

The following information will be collected for all participants in an electronic Case report Form (eCRF).

|  |  |
| --- | --- |
| Demographic details | DOB, gender, ethnicity, source of income, level of education |
| Clinical details | Co-morbidities, date of symptom onset and resolution, presenting symptoms, risk factors, medications including recent antibiotics |
| RVP | Results, date of testing |
| Blood sampling | 27mLs blood collected in SST and EDTA tubes (and an optional 36mLs in ACD tubes) will be taken at each time point in the study to create a biobank of samples suitable for COVID-19 related immunovirological research, and serological assay evaluation. |
| Dried blood spot sampling | A dried blood spot (DBS) will be collected at each time point (in comparison to phlebotomy sampling). DBS can be self-collected by participants at home if required. DBS will be mailed to participant with instructions on self-completion using standard educational materials developed for the use of DBS in HIV and HCV research. |
| Health-Related Quality of Life (HRQoL)measures | Study subjects will be asked to complete standardized HRQoL questionnaires at pre-specified follow-up timepoints. Survey instruments have been selected for general health measures, response to a major event and for psychological outcomes as follows:   * Depression Scale * Impact of Events Scale * SPHERE * EQ-5D Functional Impact of Illness |

## Recruitment Procedure

The Infectious Diseases (ID) clinical service will identify patients with a negative SARS-CoV-2 nasopharyngeal swab result from the St Vincent’s Hospital Sydney pathology laboratory. A member of the study team will then contact potentially eligible patients (e.g. not excluded based on age) who will be listed on the Study Screening Log under Cohort C, D or E dependent on their RVP testing results and epidemiological risk.

For Cohort D, a list of potential participants (RVP negative with no epidemiological risk factor) will be generated. Participants will be matched to participants in Cohort A/B (within main ADAPT study) on age (within 5 years), gender, and timing of swab test criteria (within 1 week).

## Informed Consent Process

Potential participants will be contacted via phone by one of the study team and invited to attend the clinic if they agree to participate. Participants will be given full information about the study and the chance to ask questions. Written consent will then be obtained and will be documented in the medical records. A copy of the consent form will be given to the participant.

## Enrolment Procedure

The participant will be enrolled into the study after the informed consent process has been completed and the participant has met all inclusion criteria and none of the exclusion criteria. The participant will receive a study unique identifying number and this will be documented in the participant’s medical record, the eCRF and on all study documents.

# TISSUE CoLLECTION/ BIOBANKING

This research project involves the collection of blood for storage, testing and analysis for research purposes. Multiple blood collections (of 27 – 63mL) will occur throughout the study with the first being on entry to the study. Blood samples will be transferred to the St Vincent’s Centre for Applied Medical Research for storage.

This research project involves the establishment of a tissue bank and involves the storage of blood for future research. Not all potentially beneficial future research can be known at any one time, as the need for future research is determined by ongoing developments in the field. Any future research projects using these samples and/ or data will be reviewed and approved by the Human Research Ethics Committee prior to commencement. Consent for the use and transfer of samples for future research will be obtained.

Blood samples will be stored at the St Vincent’s Centre for Applied Medical Research until they are used up or are no longer viable. St Vincent’s Centre for Applied Medical Research will record all biospecimen storage in the secure ORACLE database, BIMS.

Blood samples will be individually re-identifiable with a unique study number form. Patient privacy and confidentiality will be maintained. All attempts will be made to limit the identifiable and re-identifiable coding converters. With respect to the use of tissue for future research, this matter would be overseen by the St Vincent’s Hospital Sydney HREC.

The custodian of the blood samples is St Vincent’s Hospital Sydney.

## Analysis of biobank

The analysis of bloods collected as part of this study may occur at a variety of locations depending on the specific questions of interest. This analysis will include, but not be limited to, a range of cellular and molecular techniques to evaluate cross-reactivity of SARS-CoV-2 serological assays with other respiratory viral infections, particularly other coronaviruses, and to determine sensitivity and specificity of SARS-CoV-2 serological assays, including at different timepoints following infection.

# adverse events

This research does not involve any interventional treatments or procedures, so there will be no recording or reporting of Adverse Events.

## Data Safety and Monitoring Board

Not applicable

## Early Termination

In the unlikely event that this study is terminated early, the Principal Investigator (or one of the Co-investigators if PI is unavailable) will notify the participants and the HREC in writing, and compile a final study report.

# ethics committee/regulatory approval

The Principal Investigator is responsible for obtaining ethical approval for the protocol and Participant Information and informed Consent Form in compliance with local regulatory requirements prior to entering any participant in the study.

This study shall be conducted in accordance with the ethical principles laid out in the Declaration of Helsinki (most current issued version) and the National Statement on Ethical Conduct in Research Involving Humans (most current issued version).

# OUTCOMES AND FUTURE PLANS

The results of this study will be presented in both abstract(s) form and manuscript(s) form for publication in scientific journals.

# STATISTICAL CONSIDERATIONS

Descriptive statistics will be summarised by median (IQR) and counts (%-total). Differences between groups will be compared using the Student’s T test for continuous variables and the Chi-Square test for categorical variables. Logistic regression analysis will be performed to measure the association between continuous predictors and binary outcome variables. Will intend to account for potential bias by running multivariate logistic and Cox Regression models by adjusting models for the presence of absence of confounding variables.

# Data collection, source documents and record retention

## Data management

Clinical data will be collected on a study-specific electronic case record form (eCRF). The Principal Investigator will be responsible for ensuring the data collected are complete, accurate and recorded in a timely manner.

Specimens and associated data will be linked via the unique study ID number at the time of collection. Only the treating physician will be able to link the name and contact details of participants to the study ID. These data will not be disclosed to any researchers outside of the study personnel and will remain confidential. A password protected data file containing the coded database will be accessible only to the investigators named in this ethics application. Upon the completion of the study, the collected data will be collated and published with no identifying data attached. Remaining data will be archived within the research database. The data will be password protected.

The Principal Investigators and the institutions where the study is being conducted will permit study-related monitoring, audits, and ethics committee reviews providing direct access to source documents.

## Confidentiality and Storage and Archiving of Study Documents

Study data will be stored during and after completion of the study in a collaborative database at St Vincent’s Hospital Sydney (RedCap). It will be stored in a re-identifiable manner. Data access will be achieved through a secure process – only investigators in the study will be provided access to use, disclose and re-use the data.

All data stored will be kept for a minimum of 15 years as per ICH GCP, from the date of publication, in accordance to the minimum recommended period for retention of research data stated in section 2.1.1 of the NHMRC Code for Responsible Conduct of Research (22). After this period, electronic data will be permanently deleted, and paper documents will be securely shredded.

# Other study documents

Patient Case Report Form (eCRF)

Patient Questionnaires – EQ5D, SPHERE, Depression Scale, IES.

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