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Alberta Childhood COVID-19 Cohort (AB3C) Aim 3: Longitudinal Sero-Epidemiology Study First Interim Report January 31, 2021

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First Interim Report January 31, 2021

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On behalf of the AB3C Investigators and Staff

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Introduction

The AB3C study has three primary aims:

1. Establish a prospective cohort study of all children in Alberta tested for or diagnosed with confirmed or probable COVID-19 infection. (Funded by Alberta Children's Hospital Research Institute (ACHRI))
2. Conduct a detailed multiomic precision-medicine evaluation of some children in Alberta with confirmed or probable COVID-19 infection, as well as some healthy controls. (Funded by Genome Alberta)
3. Evaluation of the adaptive immune response to SARS-CoV-2 virus in children will be conducted measuring the antibody response against COVID-19 in children with and without clinically apparent confirmed or probable COVID-19 infection in a longitudinal sero-epidemiology study over two years. (Funded by Alberta Health and ACHRI)

The AB3C study has received research ethics and operational approval from the University of Calgary's and Alberta Health Services' Conjoint Health Research Ethics Board (CHREB). This report describes the results of the enrolment and first of four visits for Aim 3.

Methods

Study Population and Research Visits

All study participants were children under the age of 18 years, residing primarily in the Calgary Zone served by Alberta Health Services. Two distinct study groups were enrolled.

Group 1 included children with confirmed or probable COVID-19 infections, as defined by Alberta Health. These children were identified by Alberta Health Services. The families of all children identified from March to July 2020 were sent a letter of information about the study by AHS, with an invitation to contact the study team if interested. In addition an agent of AHS, a Clinic Clerk from the Infectious Diseases Clinic, Alberta Children's Hospital (ACH), called the families of these children, as well as children diagnosed with COVID-19 after July 2020, to invite the children to participate and provide information and electronic consent forms. All interested families were invited to participate.

Group 2 included children whose families expressed interest in the study through responding electronically to a study announcement posted on the ACHIEVE Research Team's Facebook page. Study staff then contacted families to provide information and electronic consent forms. Children in this group may have had a negative PCR test for COVID-19, or may have never been tested during 2020. As there were more families than needed who expressed interest to participate, possible participants were randomly selected for contact, from age stratified groups to ensure that the age distribution of participants would be similar to the age stratification of Albertan children with confirmed or probably COVID-19 infections.

For both groups, electronic consent was obtained from the parents of all participating children (or directly from mature minors). Appointments were booked for in-person visits to the Pediatric Infectious Diseases Research Clinic at ACH for venous blood sampling.

The study visits took place from July 30 to November 18, 2020 with 98% of visits taking place from August 1 to October 31. Clinics were conducted on any day of the week, including weekends and there were 20 to 70 visits at each clinic. The target for enrollment was 1000 children.

Survey – Demographic and Clinical Information

The parents of all children under 14, and all children aged 14 and above, completed an online survey that included questions on demographic features, health history and behaviours related to public health measures during the COVID-19 pandemic. This survey was completed shortly after the research clinic visit. The survey was adapted from the core data elements document from the COVID-19 Immunity Task Force.

Serology – Laboratory Methods

During the study visit, experienced pediatrics phlebotomists collected blood samples in the Pediatric ID Research Clinic. Up to 4 mL of venous blood was collected in a gold-top serum separator tube (SST). The samples were sent to the Calgary APL-Public Health Laboratory for SARS-CoV-2 antibody testing.

The Abbott ARCHITECT i System, which detects IgG antibodies against the nucleocapsid protein of SARS-CoV-2 was used on all specimens. From the product monograph: *"This assay is an automated, two-step immunoassay for the qualitative detection of IgG antibodies to SARS-CoV-2 in human serum and plasma using chemiluminescent microparticle immunoassay (CMIA) technology… The resulting chemiluminescent reaction is measured as a relative light unit (RLU)… The ARCHITECT i System calculates the calibrator mean chemiluminescent signal from 3 calibrator replicates and stores the result. Results are reported by dividing the sample result by the stored calibrator result…"*which is expressed as the sample/calibration (S/C) index. Samples with an index value of ≥1.40 were considered positive and samples with an index value of <1.40 were considered negative. On the basis of some literature suggesting that samples with index values of 0.80 – 1.39 may actually be positive, we described samples with S/C index values in this range as "possible" positives.

In addition, the DiaSorin LIAISON® SARS-CoV-2 S1/S2 IgG test was performed on some samples. These samples included: all children with known prior confirmed (PCR-positive) or probable COVID-19 infections; and all children with positive or possibly positive Abbott serology tests. The DiaSorin test detects IgG antibodies against the binding (S1) and fusion (S2) spike proteins of SARS-CoV-2 and positive or negative results appear to correlate well with the

presence or absence of neutralizing antibodies against SARS-CoV-2. From the US FDA Emergency Use Authorization (EUS) statement: *"An indirect chemiluminescence immunoassay (CLIA) technology is used; this involves a two stage reaction. In the first stage antibodies to SARS-CoV-2 present in the sample bind with SARS-CoV-2 recombinant S1 and S2 antigens coated on the well. During the second incubation the antibody conjugate reacts react with IgG to SARS-CoV-2 already bound to the solid phase… a flash chemiluminescence reaction is thus induced. The light signal… is measured… as relative light units (RLU) and is indicative of the presence of IgG to SARS-CoV2 in calibrators, samples or controls."* The results are expressed as arbitrary units (AU)/mL and samples with a value of ≥15.0 were considered positive and samples with a value of <15.0 were considered negative.

Data Management and Analysis

All demographic and survey information from each participant has been entered in a University of Calgary Licensed REDCap® database. Statistical analysis has been performed with STATA®.

Results

A total of 1032 children were enrolled and 1023 completed Visit 1 (V1).The remaining 9 children could not be scheduled by the time of the final V1 clinic, but will be invited for the second visits. Of all 1032 enrolled, 994 (96.3%) completed the survey.

There were 114 children in Group 1 and 112 completed V1. Of these, 93 had confirmed COVID-19 infections with positive PCR tests from respiratory swabs and 88 of them had blood collected during V1. Another 19 children had probable COVID-19 infections and had blood collected during V1. There were 2 additional children with probable COVID-19 infections who did not attend V1 but who completed the survey.

There were 918 children in Group 2 and 916 completed V1. There were 2 additional children with confirmed COVID-19 infections who did not attend V1 but who completed the survey.

The descriptive results from most survey items, comparing Group 1 and Group 2, are presented in Tables 1 and 2. Some results are still being reviewed and not presented.

Of the children who completed V1, serology results are available for 1019/1023 children (99.6%), with 2 samples mislabeled (from 2 siblings) and blood not successfully collected from 2 other children. The Abbott test was performed on all samples. The DiaSorin test was performed on all children with known prior confirmed (PCR-positive) or probable COVID-19 infections and all children with positive or possibly positive Abbott serology tests. Partial serology results are provided below. All numbers are subject to final confirmation.

Table 1. Demographic and Clinical Features of Group 1 and Group 2 in 2020

Demographic and Clinical Features	**Group 1** Confirmed or Probable COVID-19 (n=114)	**Group 2** Healthy (n=918)	**P value**
Age, median (IQR), y	10.6 (6.5-14.6)	9.8 (5.8-13.1)	
Age group in years, N (%)			0.028
- <1	1 (0.9)	22 (2.4)	
- 1-4	19 (16.7)	161 (17.5)	
- 5-9	32 (28.1)	292 (31.8)	
- 10-14	36 (31.60	341 (37.2)	
- 15-17	26 (22.8)	102 (11.1)	
- Sub-Total	114 (100)	918 (100)	
Female gender at birth, N (%)	46 (45.5)	451 (50.9)	0.302
Sub-Total	101 (88.6)	885 (96.4)	
Indigenous status yes N (%)	4 (3.0)	28 (3.2)	0.680
Sub-Total	101 (88.6)	878 (95.6)	
Ethnicity, N (%)			<0.000
- White	59 (57.9)	820 (92.9)	
- South Asian	18 (17.7)	17 (1.9)	
- Chinese	7 (6.9)	12 (1.4)	
- Black	3 (2.9)	2 (0.2)	
- Other	6 (5.9)	10 (1.1)	
- No Answer	9 (8.9)	22 (2.5)	
- Sub-Total	102	883	
No. of residents in household, median (IQR)	4 (4-5)	4 (4-5)	0.063
COVID-19 test (nasal/throat swab), N (%)	87 (84.5)	417 (47.6)	<0.000
Sub-Total	103	876	
No. of COVID-19 tests, median (IQR)	1 (1-2)	1 (1-2)	0.744
Chronic medical conditions), N (%)			
- Asthma	8 (7.0)	96 (10.5)	0.250
- Immune Suppressed	0	16 (1.7)	0.156
- Chronic Neurological Disorder	1 (0.9)	11 (1.2)	0.763
- None	88 (77.2)	596 (64.9)	0.009
- Sub-Total	97 (85.1)	719 (78.3)	
Regular family physician, N yes (%)	98 (96.1)	861 (97.2)	0.173
Influenza vaccination in last year, N yes (%)	56 (54.4)	554 (62.5)	0.110

Table 2. Activities and Behaviours of Group 1 and Group 2 in 2020

Activities and Behaviours	**Group 1** Confirmed or Probable COVID-19 (n=114)	**Group 2** Healthy (n=918)	**P value**
Travel history since January 2020, N (%)			0.631
- National	23 (76.7)	403 (80.3)	
- International	7 (23.3)	99 (19.7)	
- Sub-Total	30 (26.3)	502 (54.7)	
Frequency of behaviours since March 2020, N (%) reporting Often or Always vs Never, Rarely or Occasionally, N (%)			
- Wore a mask in public places	62 (60.2)	394 (44.5)	0.002
- Practiced physical distancing in public places	67 (65.2)	452 (51.1)	0.007
- Avoided crowded places/gatherings	65 (63.7)	459 (51.9)	0.024
- Avoided common greetings	63 (61.8)	419 (47.5)	0.006
- Limited contact with people at higher risk (e.g., an elderly relative)	64 (62.8)	420 (47.4)	0.003
- Self-isolated because you thought you were infected with COVID-19	46 (45.1)	87 (9.9)	<0.000
- Self-quarantined because you may have been exposed to COVID-19, but did not show symptoms	39 (39.0)	53 (6.0)	<0.000
Household member COVID-19 test positive	84 (81.6)	32 (3.8)	<0.000
Hospitalization of household member with COVID-19	11 (11.3)	1 (0.2)	<0.000

Serology Results Group 1

There were 88/93 children with **prior confirmed PCR+ SARS-CoV-2** infections who were tested and all were tested with both Abbott and DiaSorin:

- 67/88 (76.1%) were Abbott positive and 12/21 (57.1%) of Abbott negative samples were DiaSorin positive. Therefore 79/88 (89.8%) were Abbott **or** DiaSorin positive.

Within the 21 Abbott negative samples a signal/cutoff (s/c) ratio a possibly positive value of 0.80-1.39 was recorded in 8/21 (38.1%). Of these, 1/7 (14.3%) samples collected <90 days after the positive PCR test was possibly positive, compared with 7/14 (50.0%) samples collected ≥90 days after the positive PCR test (P<=0.112 for difference).

The number of days from prior PCR+ SARS-CoV-2 test to serology test was determined for 88 children:

- 33/40 (82.5%) collected <90 days after the positive PCR test were Abbott positive and
- 34/48 (70.8%) collected ≥90 days after the positive PCR test were Abbott positive (P<0.001 for difference).

There were 19 children with **prior probable COVID-19** infections had serology tests with Abbott +/-DiaSorin:

- 8/19 (42%) were Abbott positive and 3/11 Abbott negative samples were DiaSorin positive. Therefore 11/19 (58%) were Abbott or DiaSorin positive.

Serology Results Group 2

There were 911/919 children without known prior COVID-19 infections who had serology tests with Abbott:

- 3/911 were Abbott positive (0.3%, 95% CI 0.1%, 1.0%).
- Of the 908 Abbott negative samples the s/c ratio was possibly positive (0.8 – 1.4) in 6/911 (0.7%) of samples.

Interim Conclusions

1. We successfully achieved (and exceeded) our target of recruiting 1000 children in total.

2. It was difficult to recruit children with confirmed or probable prior COVID-19 infections as very few families with such children volunteered through the social media advertising. Contacting families of these children through letters sent by AHS and phone calls made by an agent of AHS was partly successful but laborious, time consuming and expensive. Also, children in this group were more likely to cancel or not attend appointments.

3. There were few difference in demographic and clinical characteristics between Group 1 children (confirmed or probable prior COVID-19 infections) and Group 2 children (healthy children). The most notable difference was in ethnicity, with 42% of Group 1 children being non-White, compared with 7% of Group 2 children.

4. Children in Group 1 were considerably more likely to report practicing behaviours to reduce SARS-CoV-2 virus transmission than children in Group 2. However we do not know if these behaviours were practiced differently before or after the diagnosis of COVID-19 infections in Group 1 children or their family members. The survey will be revised for subsequent visits to ensure that the timing of symptoms is noted.

5. The sensitivity of the Abbott test in children with known prior positive SARS-CoV-2 PCR test was low (76.1%). When the second test (DiaSorin) was also performed, the combined sensitivity was improved (89.8%) but still less than ideal. The Abbott test was less sensitive when performed ≥90 days after COVID-19 infection (70.8%) than when performed <90 days after COVID-19 infection (82.5%).

6. The SARS-CoV-2 antibody seropositivity rate in children without known COVID-19 infections was very low in this survey (0.3%, 95% CI 0.1%-1.0%), but reflected the period of the modest first wave of the COVID-19 pandemic in Alberta.

7. A revised survey has been created before the start of the second visits. The second visits will start on February 10, 2021.

8. New versions of the both the Abbott and DiaSorin assays, as well as other assays, are being evaluated by APL-Public Health and will be implemented in a new diagnostic algorithm for use for the subsequent visits in the AB3C study. It is anticipated that all

Visit 1 samples will eventually be retested according to the new algorithm which will facilitate clear comparison between the results of the first and subsequent surveys.