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Evaluation of commercial SARS-CoV-2 serological assays in Canadian public health laboratories

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ABSTRACT

The COVID-19 pandemic has led to the influx of immunoassays for the detection of antibodies towards severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into the global market. The Canadian Public Health Laboratory Network Serology Task Force undertook a nationwide evaluation of twelve laboratory and 6 point-of-care based commercial serological assays for the detection of SARS-CoV-2 antibodies. We determined that there was considerable variability in the performance of individual tests and that an orthogonal testing algorithm should be prioritized to maximize the accuracy and comparability of results across the country. The manual enzyme immunoassays and point-of-care tests evaluated had lower specificity and increased coefficients of variation compared to automated enzyme immunoassays platforms putting into question their utility for large-scale sero-surveillance. Overall, the data presented here provide a comprehensive approach for applying accurate serological assays for longitudinal sero-surveillance and vaccine trials while informing Canadian public health policy.

1. Introduction

On December 31st 2019, Chinese officials confirmed dozens of cases of pneumonia with an unknown cause. By January 7th 2020, the cause of the outbreak was determined to be a novel coronavirus termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease (COVID-19). The outbreak of SARS-CoV-2 has evaded containment efforts and has spread worldwide with over 78 million infections and 1.7 million deaths as of December 2020 (Dong et al. 2020). Canada has taken proactive measures to prevent community transmission; however, over 500,000 cases and over 14,000 deaths have been confirmed across the country to date. Long-term care homes have been particularly affected by the SARS-CoV-2

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pandemic with >80% of deaths occurring in those settings (Holroyd-Leduc and Laupacis 2020).

Serological assays have been developed in response to the ever-growing pandemic in the hopes of providing widespread testing, which may determine the magnitude of community transmission (Bonelli et al. 2020; Charlton et al. 2020; Lassaunière et al. 2020; Theel et al. 2020a). However, the development of humoral responses can take anywhere from several days to weeks following infection to develop. Additionally, some studies suggest that up to 40% of asymptomatic infections may become seronegative in the convalescent phase, further complicating the role of serology in the diagnosis of COVID-19 (Long et al. 2020b). The critical window for detection of SARS-CoV-2 infection remains the symptomatic period when antibody testing is, by its nature, insensitive, making PCR based methodologies the preferred diagnostic tool of acute SARS-CoV-2 infection (LeBlanc et al. 2020).

Antibodies to SARS-CoV-2 are believed to target the viral nucleocapsid or spike proteins and spike protein is believed to be the main target of neutralizing antibody responses (Prévost et al. 2020; Long et al. 2020a). Cross-reactivity with other circulating human coronaviruses particularly in the nucleocapsid region may hinder serological assays as a diagnostic tool (He et al. 2004; Khan et al. 2020). In the absence of definitive data on the duration of antibody responses and their utility as a correlate of protection, SARS-CoV-2 serological assays are currently limited to sero-surveillance studies, outbreak cluster analysis, and as an aid in diagnosing rare COVID-19 related disorders such as multi-inflammatory syndrome in children (MIS-C) (Bryant et al. 2020; Theel et al. 2020b).

There are two types of commercial serological platforms/assays currently available, which include laboratory and point-of-care (rapid cassettes) based tests. The laboratory-based assays are further categorized as being implemented on high-through-put chemiluminescent platforms (CLIA) or medium-through-put enzyme immunoassays (EIA). With the rapid development of serological tests and the extensive number of assays available for testing in the North American market, the Canadian Public Health Laboratory Network Serology Task Force conducted a nationwide evaluation of SARS-CoV-2 serological assays in order to better inform serological testing in Canada.

2. Methods

The Canadian Public Health Laboratory Network conducted a nationwide evaluation of SARS-CoV-2 serological assays. Common sample criteria were applied across the study in order to generate comparable data. All specimens analyzed for sensitivity were confirmed positive for SARS-CoV-2 RNA by RT-PCR targeting the nucleocapsid or envelope gene from nasopharyngeal swabs. Patient results were stratified into groups by symptom onset including 0-7, 8-14, >14, or >21 days. Pre-outbreak samples utilized for specificity were collected prior to December 1, 2019 (Canada's first reported case was January 25, 2020) (maximum 240 specimens). Cross-reactivity was evaluated using serum samples from patients who tested positive by PCR for other common respiratory infections including within 6 weeks postsymptom onset: influenza A (n = 25), influenza B (n = 15), respiratory syncytial virus (n = 5), adenovirus (n = 9), rhinovirus (n = 13), and human coronaviruses (n = 30), 229E (n = 1), OC43 (n = 4), HKU1 (n = 5), and NL63 (n = 7). In addition, sera positive for antibodies to syphilis (n = 39), Epstein-Barr virus IgM/IgG (n = 22), parvovirus IgM/IgG (n = 2), cytomegalovirus IgM/IgG (n = 39), human immunodeficiency virus 1 (n = 19), hepatitis A/B/C virus IgM (n = 51), herpes simplex virus (n = 8), varicella zoster virus (n = 9), rubella (n = 12), measles (n = 4), mumps (n = 10), rabies (n = 25) toxoplasma (n = 3) and other autoimmune disorders, such as, rheumatoid arthritis (n = 51) were included in the panel as these specimens often result in cross-reactivity. Also, specimen's positive for anti-nuclear antibody (n = 31) and anti-double stranded DNA (n=18) were included. Serology testing was conducted using the manufactures' instructions for the following CLIA/EIA tests: Architect SARS-CoV-2 IgG (Abbott, Chicago, IL, USA), BioRad SARS-CoV-2 IgM, IgG or Platelia Total (Bio-Rad Laboratories, Hercules, CA, USA), Liaison SARS-CoV-2 IgG (DiaSorin, Saluggia, Italy), EDI Novel Coronavirus COVID-19 IgM or IgG (Epitope Diagnostics Inc., San Diego, CA, USA), Euroimmun SARS-CoV-2 IgA or IgG (EUROIMMUN, Lubeck, Germany), VITROS Anti-SARS-CoV-2 IgG or Total (Ortho-Clinical Diagnostics, Raritan, NJ, USA), Elecsys Anti-SARS-CoV-2 Total (Roche, Basel, Switzerland). EIA based tests were performed using an automated Dynex platform in all laboratories with the exception of a one being performed manually. Several point-of-care rapid cassettes were also evaluated which included: Artron IgM/IgG, Biocan IgM/IgG, BioEasy IgM/IgG, Biolidics IgM/IgG, BTNX IgM/IgG, and NADAL IgM/IgG. Each province provided aggregate data for each test, which allowed analysis of overall sensitivity and specificity across the country. Additionally, there were limited lot numbers available resulting in all laboratories using the same lot number for their respective test. Overall sensitivity and specificity values were calculated by combining aggregate results from each individual public health laboratory. In addition, the coefficient of variation was calculated to measure variability between the reported sensitivity and specificities for the respective laboratories. Sensitivity and specificity analyses were calculated using Graphpad Prism v6. Positive predictive values for individual and combined testing algorithms were calculated as previously described (Bryant et al. 2020).

3. Results

3.1. Laboratory-based SARS-CoV-2 serological assays

Twelve different laboratory-based CLIA/EIA serological tests were evaluated for sensitivity and specificity in order to develop a serological testing algorithm for use by the provinces for sero-surveillance and the diagnosis of rare COVID-19 related disorders. Of the twelve assays evaluated, only four were licensed by the Medical Devices Branch (MDB) of Health Canada at the time of this study for use in Canada including the Abbott, DiaSorin, Roche, and Ortho-Clinical tests (https://www.canada.ca/en/health-canada). All four of these tests are implemented on high-volume instrumentation capable of processing hundreds of specimens per hour. All serological assays irrespective of manufacturer were relatively insensitive when serum samples were collected less than 7 days post-symptom onset [range: 25.0% – 67.9%] (Table 1 and Supplemental Fig. 1). Sensitivity improved considerably for all tests when specimens were assayed >14 days post-symptom onset [range: 55.9% – 96.7%]. The Abbott IgG, DiaSorin IgG, Roche total and Ortho-Clinical total tests achieved sensitivities >14 days postsymptom onset of 90.2%, 85.0%, 86.6%, and 94.0% respectively. While individually the Euroimmun IgA and IgG test achieved 92.8% and 91.2% sensitivity, respectively, combining the two assays improved the sensitivity to 96.7% >14 days postsymptom onset.

Given that specificity is a key metric in establishing positive predictive value (PPV) in low prevalence settings, clinical specificity and cross-reactivity serum panels were compiled by each provincial laboratory including pre-December specimens and specimens known to be reactive for antibodies to non-SARS-CoV-2 respiratory infections across the country. The Abbott, DiaSorin, Roche, and Ortho-Clinical test kits achieved 99.0% to 100.0% specificity, while the manual EIA test kits generally achieved lower specificity [range; 84.7% – 98.6%]. Aggregate test results where more than one laboratory evaluated a particular platform were used to estimate the variability associated with performing these tests on a national scale (Table 2). The Euroimmun IgA test showed the least variation between laboratories when overall sensitivity was considered (7.8% CV) while the BioRad IgM test was the most variable (26.8%). The variation in reported overall specificities

Table 1
Performance characteristics of commercial laboratory serological assays for SARS-CoV-2.

Manufacturer / Assay	Isotype	SARS-CoV-2 PCR-Positive Patients															Negative Samples (Pre Dec 2019)			Cross-Reactivity Samples			# Prov. Labs
		<7 d			7-14 d			>14 d			>21 d			All time points									
		Neg	Pos	Sens.	Neg	Pos	Sens.	Neg	Pos	Sens.	Neg	Pos	Sens.	Neg	Pos	Sens.	Neg	Pos	Spec.	Neg	Pos	Spec.	
Auto (CLIA)																							
Abbott[T]	IgG	69	36	34.3	37	88	70.4	30	274	90.1	22	262	92.3	140	444	76.0	240	2	99.2	453	4	99.1	6
DiaSorin[T]	IgG	84	34	28.8	68	82	54.7	33	186	84.9	58	197	77.3	166	377	69.4	219	3	98.6	395	3	99.2	6
Ortho[T]	Total	62	36	36.7	26	90	77.6	12	187	94.0	7	182	96.3	101	354	77.8	88	0	100.0	286	1	99.7	3
Ortho	IgG	72	24	25.0	46	54	54.0	19	155	89.1	16	152	90.5	140	272	66.0	88	0	100.0	284	3	99.0	3
Roche[T]	Total	57	24	29.6	35	92	72.4	45	292	86.6	33	251	88.4	137	408	74.9	98	0	100.0	271	0	100.0	4
Manual (EIA)																							
BioRad	IgM	32	18	36.0	34	67	66.3	56	71	55.9	38	17	30.9	128	158	55.2	124	1	99.2	216	4	98.2	4
BioRad	IgG	21	24	53.3	20	72	78.3	19	90	82.6	17	38	69.1	62	192	75.6	122	3	97.6	201	15	93.1	4
BioRad	Comb.	21	24	53.3	19	72	79.1	17	92	84.4	15	40	72.7	58	194	77.0	122	3	97.6	201	15	93.1	4
BioRad Platelia	Total	58	43	42.6	25	29	53.7	32	85	72.6	26	72	73.5	115	125	52.1	45	3	93.8	195	4	98.0	2
Epitope Diagnostics	IgM	23	23	50.0	25	63	71.6	22	72	76.6	18	38	67.9	76	160	67.8	100	0	100.0	162	8	95.3	4
Epitope Diagnostics	IgG	22	24	52.2	17	78	82.1	18	89	83.2	16	52	76.5	58	198	77.3	110	2	98.2	209	10	95.4	5
Epitope Diagnostics	Comb.	16	30	65.2	15	73	83.0	10	84	89.4	10	46	82.1	42	194	82.2	98	2	98.0	139	13	91.4	4
Euroimmun	IgA	17	36	67.9	17	86	83.5	11	141	92.8	12	109	90.1	50	308	86.0	162	13	92.6	247	61	80.2	5
Euroimmun	IgG	35	29	45.3	43	73	62.9	18	187	91.2	10	127	92.7	97	338	77.7	173	2	98.9	294	11	96.4	5
Euroimmun	Comb.	17	36	67.9	17	86	83.5	5	147	96.7	4	117	96.7	39	319	89.1	162	13	92.6	268	64	80.7	5

[T]Health Canada Approved, [Neg] Negative, [Pos] Positive, [Sens] Sensitivity, [Spec] Specificity

between laboratories was considerably smaller (<5% CV), with the exception of the Euroimmun and Epitope Diagnostics test kits.

3.2. Point-of-care SARS-CoV-2 serological assays

The Serology Task Force also evaluated six commercially available point-of-care cassettes in order to determine their feasibility for large-scale sero-surveillance in areas where laboratory testing poses logistical challenges. Similar to CLIA/EIA based assays, rapid cassettes were also relatively insensitive with samples collected less than 7 days postsymptom onset (Table 3) ranging from 34.1 – 74.2%. Sensitivity was drastically improved when specimens were assayed >14 days postsymptom onset with the Artron test cassette achieving 95.3% sensitivity while the BioEasy cassette achieved the lowest reported sensitivity of 80.0%. The specificity of the cassettes varied considerably with the BTNX cassette achieving 89.3% overall specificity while the Biocan cassette performed the best with 99.6% overall specificity. The variability (Table 4) in the reported overall sensitivity between laboratories ranged from as high as 30.6% (BioEasy) to as little as 4.6% (Artron v2) with the majority of variability associated with acute specimens. The variation in reported specificities between laboratories ranged from 0.4% (Biocan) to 8.5% (BTNX).

4. Discussion

This study was designed to evaluate the analytical performance of commercial SARS-CoV-2 serological test kits / platforms in clinical laboratories across Canada. In addition, these data represent testing that occurred in multiple provincial public health laboratories from over six provincial jurisdictions making it one of the most comprehensive national data sets to date. Indeed, a total of twelve different CLIA/EIA laboratory based assays as well as six different point-of-care rapid cassettes were evaluated for the detection of SARS-CoV-2 antibodies. Overall, the sensitivity of laboratory-based assays was quite variable less than 7 days post-symptom onset underscoring the limitation of serological testing for clinical diagnosis of acute SARS-CoV-2 infection. While the IgM assays tended to have improved sensitivity during acute infection compared to IgG, and the Euroimmun IgA

Table 2
Variability of commercial laboratory serological assays for SARS-CoV-2.

Manufacturer / Assay	Isotype	SARS-CoV-2 PCR-positive patients										Overall specificity		# Prov. labs
		<7 d		7-14 d		>14 d		>21 d		All time points				
		Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	
Auto (CLIA)														
Abbott[T]	IgG	41.5	41.3	75.6	18.5	90.8	6.7	94.8	6.2	82.3	15.6	98.9	1.3	6
DiaSorin[T]	IgG	36.6	43.6	57.0	23.4	90.2	11.3	85.2	14.4	71.7	18.1	99.0	1.0	6
Ortho[T]	Total	43.7	55.3	77.0	3.4	94.0	6.4	96.7	3.2	79.3	11.4	99.7	0.4	3
Ortho	IgG	30.3	61.4	53.3	6.6	89.7	13.0	91.7	8.0	68.3	15.7	99.3	1.2	3
Roche[T]	Total	43.0	65.1	77.0	20.8	85.5	10.3	87.0	8.2	78.3	20.4	100.0	0.0	4
Manual (EIA)														
BioRad	IgM	42.0	39.8	68.8	27.6	56.3	31.7	43.8	51.6	56.3	26.8	98.8	1.4	4
BioRad	IgG	59.3	16.9	82.0	12.3	85.0	18.0	78.8	32.1	78.8	16.2	94.1	2.6	4
BioRad	Comb.	59.3	16.9	82.5	11.0	86.3	15.9	73.3	34.3	79.8	14.7	94.1	2.6	4
BioRad Platelia	Total	41.0	58.6	81.0	0.0	90.0	0.0	91.0	0.0	77.5	11.9	97.3	1.0	2
Epitope Diagnostics	IgM	59.8	32.1	77.0	23.5	81.3	16.2	65.3	38.8	74.5	21.5	94.8	6.9	4
Epitope Diagnostics	IgG	58.3	26.1	88.6	13.4	89.0	14.5	80.0	30.6	84.6	16.2	95.1	3.7	5
Epitope Diagnostics	Comb.	74.3	27.3	87.0	11.2	92.0	10.7	78.3	32.8	86.5	12.7	90.6	9.2	4
Euroimmun	IgA	62.8	22.8	84.0	11.2	89.0	12.2	91.0	11.4	85.8	7..75	84.6	7.9	5
Euroimmun	IgG	48.8	23.2	63.8	32.0	88.6	6.7	91.2	6.9	78.6	21.5	97.3	1.6	5
Euroimmun	Comb.	62.8	22.8	84.0	11.2	94.8	6.8	93.0	13.0	89.4	8.4	84.6	6.9	5

[T] Health Canada Approved, [%CV] Coefficient of variation.

Table 3
Performance characteristics of commercial point-of-care (rapid cassette) serological assays for SARS-CoV-2.

Manufacturer / Assay	Isotype	SARS-CoV-2 PCR-Positive Patients															Negative Samples (Pre Dec 2019)			Cross-Reactivity Samples			# Prov. Labs
		<7 d			7-14 d			>14 d			>21 d			All time points									
		Neg	Pos	Sens.	Neg	Pos	Sens.	Neg	Pos	Sens.	Neg	Pos	Sens.	Neg	Pos	Sens.	Neg	Pos	Spec.	Neg	Pos	Spec.	
Artron v2.	IgM/IgG	8	23	74.2	9	51	85.0	10	202	95.3	9	125	93.3	27	276	91.1	35	1	97.2	85	3	96.6	2
Biocan	IgM/IgG	54	28	34.1	29	79	73.1	30	185	86.0	24	120	83.3	113	292	72.1	59	0	100.0	209	1	99.5	3
BioEasy	IgM/IgG	7	8	50.0	8	20	56.0	1	9	80.0	0	1	100.0	16	37	58.0	36	0	100.0	23	2	92.0	2
Biolidics	IgM/IgG	3	7	70.0	4	20	83.3	2	23	92.0	0	10	100.0	9	50	84.7	59	2	96.7	0	0	0.0	2
BTNX	IgM/IgG	47	41	46.6	20	104	83.9	14	222	94.1	7	147	95.5	81	367	81.9	108	1	99.1	177	33	84.3	4
NADAL	IgM/IgG	41	27	39.7	17	61	78.2	13	181	93.3	9	155	97.0	71	269	79.1	45	0	100.0	170	8	95.5	2

[Neg] Negative, [Pos] Positive, [Sens] Sensitivity, [Spec] Specificity

Table 4
Variability of commercial point-of-care (rapid cassette) serological assays for SARS-CoV-2.

Manufacturer / Assay	Isotype	SARS-CoV-2 PCR-Positive Patients										Overall Specificity		# Prov. Labs
		<7 d		7-14 d		>14 d		>21 d		All time points				
		Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV	
Artron v2.	IgM/IgG	74.0	1.9	85.5	17.4	96.0	3.0	93.0	0.0	92.0	4.6	95.5	6.7	2
Biocan	IgM/IgG	44.3	57.6	75.7	19.8	88.3	9.5	83.0	5.1	75.7	19.0	99.8	0.4	3
BioEasy	IgM/IgG	55.0	12.9	78.0	39.9	90.0	15.7	100.0	0.0	74.0	30.6	98.0	2.9	2
Biolidics	IgM/IgG	70.0	20.2	86.5	22.1	95.0	7.4	100.0	0.0	87.5	12.1	98.0	2.9	2
BTNX	IgM/IgG	59.0	39.8	82.8	12.0	93.8	4.1	96.7	3.0	83.8	12.0	92.2	8.5	4
NADAL	IgM/IgG	42.5	25.0	78.0	5.4	93.5	2.3	94.5	3.7	79.5	8.0	96.0	1.9	2

[%CV] Coefficient of variation.

reaching 67.9% sensitivity, these assays also suffered from increased cross-reactivity and generally poorer specificity (Table 2). Early diagnosis <14 days post-symptom onset is a key factor in immediate public health interventions such as patient isolation and contact tracing to limit community transmission. However, the sensitivity of these assays improved with time following the onset of symptoms, specifically, >14 days postsymptom onset. Importantly, all four serological tests licensed by the MDB of Health Canada consistently achieved specificity values exceeding 99% which is a key metric when cross-reactivity can occur with other circulating human coronaviruses in low COVID-19 prevalence settings.

The majority of the rapid cassettes achieved between 90 and 100% specificity; however, in a low prevalence setting they would not achieve the necessary PPV that would be required for implementing large-scale, sero-surveillance testing. Examination of lot-to-lot variability of all COVID serological testing platforms is needed. In addition, our studies of rapid test cassettes made use of serum as opposed to capillary blood which is the preferred specimen for these particular test kits. A recent study demonstrated that various sample sources can have profound effects on serological test results indicated further validation of these platforms is needed (Flower et al. 2020).

Given the current low estimated prevalence in some jurisdictions across Canada a two-tiered orthogonal algorithm should be considered when conducting sero-surveillance studies, or rare diagnostic testing (Skowronski et al. 2020). The PPV of any single test at an estimated prevalence of 1% for example, would be as high as 43.4% for the Abbott IgG CMIA and as low as 11.3% for the BioRad EIA (Fig. 1). In contrast, when combining some of the top-performing assays such as those produced by Abbott and DiaSorin or Abbott and Ortho-Clinical at a prevalence of 1%, PPVs significantly improve to 98.1% and 99.8% respectively.

We recognize that the variability analysis between laboratories was not based on overlapping specimens measured by each respective laboratory. A national panel is currently being constructed in order to measure the variance on a national scale for multiple platforms. However, our data represent a comprehensive sampling of COVID-19 sera from across the country, and while sensitivity varied considerably for specimens collected before 14 days postsymptom

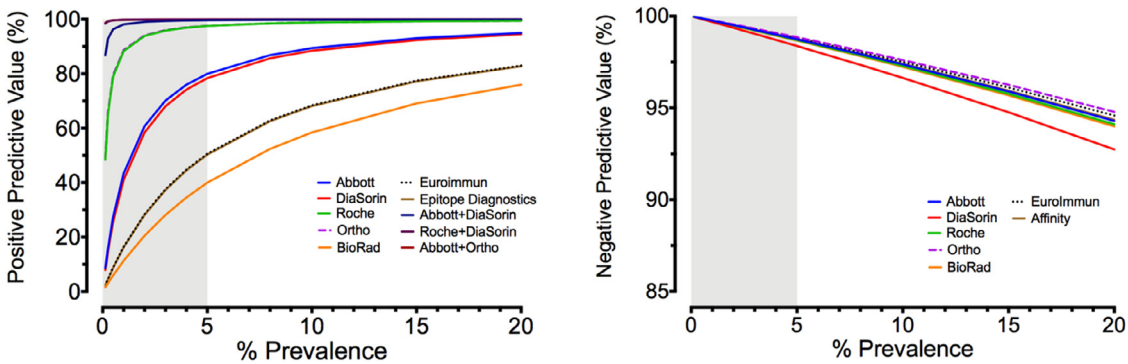

Fig. 1. Performance of individual and combined commercial serological assays for SARS-CoV-2 infection. he positive and negative predicative value of individual and combined assays were plotted based on estimated prevalence rates using the sensitivity and specificity characteristics of each serological test.

onset, sensitivity and reproducibility between laboratories markedly improved >14 days post-symptom onset.

A consideration of utmost importance in implementing serological testing for SARS-CoV-2 infection is that antibodies have yet to be shown to provide immunity to reinfection. In fact, a recent study has reported that antibodies diminish considerably 2-3 months following infection, making the value of reporting individual results contentious in regards to immune status or protection (Long et al. 2020b). The use of serological testing for SARS-CoV-2 may provide some insight into cases where late presentation (2 weeks post-symptom onset) occurs outside the window of detection offered by molecular nasopharyngeal testing. In these cases, documenting seroconversion using an acute and convalescent specimen could be considered. Studies with semi-quantitative serological assays documenting increases in signal between specimens should also be considered as a strategy for identifying recent or recurrent infections. In addition, virus neutralization assays must also be performed to better understand the possible correlates of protection and how their results may align with the serological assays / platforms assessed in this study. Moreover, serological testing may become helpful in understanding the etiology of multi-system inflammatory syndrome in children (MIS-C) (Perez-Toledo et al. 2020; Riollano-Cruz et al., 2021). Finally, a key role for serological testing will be its use in understanding the spread of SARS-CoV-2 infection across the country, informing evidence-based public health policy decisions that affect all aspects of Canadian society and health.

Credit statement

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Declaration of competing interest

The authors declare no competing interests.

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Supplementary materials

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