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COVID-19: A YEAR LATER

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Contact the Editorial Office

phac.ccdr-rmtc.aspc@canada.ca
613.301.9930

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The cover image illustrates a paved street with red tape labelled COVID-19 criss-crossing across the image, with the number 2021 with an arrow pointing forward through the red tape. Image from Adobe Stock (https://stock.adobe.com/images/covid-19-in-2021-is-ahead-asphalt-road-with-road-markings-yellow-warnings-tapes-labeled-covid-19-and-number-2021-of-the-year-with-covid-19-to-the-2021-year/382865864)

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Practical guidance for clinical laboratories for SARS-CoV-2 serology testing

Carmen Charlton[1,2,3]*, Jamil Kanji[1,2,4], Vanessa Tran[5,6], Julianne Kus[5,6], Jonathan Gubbay[5,6], Carla Osiowy[7], Jason Robinson[8], Inna Sekirov[9], Michael Drebot[7], Todd Hatchette[10], Derek Stein[11,12], Nadia El-Gabalawy[7], Amanda Lang[13], Lei Jiao[10], Paul Levett[11], Heidi Wood[7], Christian Therrien[14], L Robbin Lindsay[7], Muhammad Morshed[9], Jessica Forbes[6], Antonia Dibernardo[7] on behalf of the Canadian Public Health Laboratory Network (CPHLN) Serology Working Group

Abstract

The landscape of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) diagnostic testing is rapidly evolving. While serology testing has limited diagnostic capacity for acute infection, its role in providing population-based information on positivity rates and informing evidence-based decision making for public health recommendations is increasing. With the global availability of vaccines, there is increasing pressure on clinical laboratories to provide antibody screening and result interpretation for vaccinated and non-vaccinated individuals. Here we present the most up-to-date data on SARS-CoV-2 antibody timelines, including the longevity of antibodies, and the production and detection of neutralizing antibodies. Additionally, we provide practical guidance for clinical microbiology laboratories to both verify commercial serology assays and choose appropriate testing algorithms for their local populations.

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Introduction

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019 resulted in a rapid global development of molecular, antigenic and serological assays for the diagnosis of acute infection and identification of past infection. While molecular testing is widely accepted as the gold standard for diagnosis of acute infection, the role of serology is limited to special clinical cases as an adjunct for diagnosis (1). The SARS-CoV-2 antibodies are not reliably detected fewer than 7–21 days post symptom onset, making their utility in diagnosis of acute infection of limited value (2–4). However, in cases such as multiple inflammatory syndrome in adults (MIS-A) or in children (MIS-C), a positive result on a serological assay can help guide clinical management in the absence of a positive molecular test result or when molecular testing is unavailable, and positive serology results have been included as part of the clinical case definition for MIS-C (5). Outside these very specific clinical scenarios, the role of serology assays is to examine population-based prevalence rates of SARS-CoV-2, and to help inform public health decisions.

To improve the utility of serology testing, an international standard is required to allow direct comparison of assays between laboratories. Population-based studies linking quantitative serology results to clinical outcomes will be needed to help determine what level of antibody may correlate with immunity to infection. Such approaches would be similar to what has been done with other viruses (e.g. rubella), where an international standard is used to calibrate assays and a quantitative serological immunoglobulin G (IgG) is used to determine immunity (more than 10 IU/ml), or

Affiliations

[1] Public Health Laboratory, Alberta Precision Laboratories, Edmonton, AB

[2] Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, AB

[3] Li Ka Shing Institute of Virology, Edmonton, AB

[4] Division of Infectious Diseases, Department of Medicine, University of Alberta, Edmonton, AB

[5] Public Health Ontario Laboratory, Toronto, ON

[6] Department of Laboratory Medicine & Pathobiology, University of Toronto, Toronto, ON

[7] National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, MB

[8] Provincial Laboratory Services, Division of Clinical Chemistry, Health PEI, Charlottetown, PE

[9] British Columbia Centre for Disease Control Public Health Laboratory, Vancouver, BC

[10] Newfoundland and Labrador Public Health Microbiology Laboratory, St. John's, NL

[11] Department of Medical Microbiology and Infectious Disease, University of Manitoba, Winnipeg, MB

[12] Cadham Provincial Laboratory, Winnipeg, MB

[13] Roy Romanow Provincial Laboratory, Regina, SK

[14] Laboratoire de santé publique du Québec, Institut national de santé publique du Québec, Sainte-Anne-de-Bellevue, QC

***Correspondence:**
carmen.charlton@albertaprecisionlabs.ca

susceptibility (less than 10 IU/ml) to infection, based on correlation with clinical outcomes (6,7). Multiple quantitative serological assays have been submitted to accreditation agencies globally, including the Food and Drug Administration (FDA), Health Canada and European Council (Conseil européen); however, to date in North America, there remains a gap in approved quantitative assays that have a correlation with immunity from infection (i.e. neutralizing antibodies). While this will not impact clinical decision making on an individual level, this remains a critical gap in the interpretation and utility of SARS-CoV-2 serology testing for serosurveillance studies.

Here we examine the current knowledge of serological testing, discuss assay limitations, describe how clinical laboratories can both validate these assays and implement appropriate algorithms for local patient populations, discuss the role for differentiating antibodies derived from natural infection versus those that are vaccine-derived and consider options for detection of neutralizing antibodies.

Seroconversion timelines

The antibody response to SARS-CoV-2 is relatively well studied; however, there is substantial variability in seroconversion timelines given the heterogeneity amongst populations studied (i.e. disease severity, age, presence of comorbidities, etc.), serologic tests used and serologic markers analyzed. In general, the overall range of seroconversion regardless of the type of antibody, is estimated to be between four and 14 days post-onset of symptoms (2,8,9). An early study evaluated seroconversion rates in 173 patients and reported median seroconversion times for total antibody (Ab), immunoglobulin M (IgM), and IgG that were 11, 12 and 14 days, respectively. However, the authors reported that fewer than 40% of patients had detectable antibodies within one week of onset of illness and this rose to 100% (total Ab), 94% (IgM) and 80% (IgG) by day 15 in the same patients (10). In contrast, another study reported the seroconversion rate of immunoglobulin A (IgA) was similar to IgM, with a median seroconversion of five days (IQR 3–6) after symptom onset compared with 14 days for IgG (11). Despite earlier detection of IgM in those studies, the time course for IgM and IgG seroconversion rates are similar for SARS-CoV-2 compared with other infectious diseases, where IgM preceded IgG by weeks. Indeed, both IgG and IgM detection signals were found to plateau six days after the first positive serology test among 285 coronavirus disease 2019 (COVID-19) patients (9). Thus, while studies agree that seroconversion occurs within 4–14 days of symptom onset and that IgG and IgM seroconversion dynamics are similar, the considerable variability leads to poor sensitivity of antibody testing for diagnosis of acute COVID-19, which has been well documented in the literature (1,2,12).

Antibody longevity

The length of time that antibody responses persists, and possibly confer protection from reinfection, is pivotal to understanding SARS-CoV-2 infection dynamics (detailed timeline for antibody detection can be seen in (9)). Using sequential serum samples from 65 patients and 31 seropositive healthcare workers, Seow *et al*. (13) showed seroconversion of IgM, IgG and IgA occurred in more than 95% of cases when sampled equal to or greater than eight days post-symptom onset. Neutralizing antibody kinetics were consistent with other acute viral infections (13), with an initial peak at 3–4 weeks (magnitude of peak dependent on disease severity) followed by declining neutralizing antibody titres. Interestingly, patients with a high peak infectivity dose maintained neutralizing antibody titres longer compared with patients with a lower peak infectivity dose (13). Neutralizing antibody decline occurred simultaneously with declines in IgG titres against SARS-CoV-2 spike (S) glycoprotein and receptor-binding domain (RBD), as well as IgM and IgA binding to S glycoprotein and RBD. In patients with mild to moderate disease, IgG antibody titres were found to be stable for up to five months, with a significant correlation between anti-spike binding titres and neutralization (14).

Additional studies using plaque reduction neutralization test (PRNT)/microneutralization assays in combination with anti-spike enzyme-linked immunosorbent assay (ELISA) procedures have further validated the findings of longitudinal neutralization antibody duration (15,16). Previously observed declines in antibody titres during the first few months after infection is expected as short-lived plasma cells are depleted; however, when these are replaced by long lived antibody secreting cells, neutralizing antibodies will persist for several months in most individuals (17).

Interestingly, longitudinal antibody longevity studies in serum and saliva showed that IgM and IgA levels rapidly declined following peak levels (18), while IgG remained relatively stable in both biofluids (up to 105 days post symptom onset). Similarly, others found that 92.3% of patients (N=427) remained IgG positive 3–6 months post symptom onset (19). While most evidence suggests that IgM and IgA antibody levels drop significantly compared with IgG isotypes, in patients with a remote history of COVID-19, they appear to play a key role in the initial neutralizing antibody response. Serum IgA was shown to contribute to virus neutralization up to one month following symptom onset (20), while IgM was shown to neutralize SARS-CoV-2 in both pseudoviral particle and wild type virus assays (21).

Lessons on antibody longevity for SARS-CoV-2 may be learned by studying other human coronaviruses; a strategy that has been reviewed extensively elsewhere (22). A recent systematic review highlighted the kinetics, protection correlations and antibody association with disease severity among human coronaviruses. In general, antibody responses to other human coronaviruses, such as SARS-CoV, Middle Eastern respiratory syndrome coronavirus (MERS-CoV) and seasonal coronaviruses, are present for one year after infection; in some cases, antibodies may persist for longer (23). Moreover, other evidence suggests that serum antibody titres remained relatively high two years

after SARS-CoV infection, and up to 55% of patients had detectable antibodies at three years post infection (24). However, no detectable anti-SARS-CoV antibodies were observed in patients six years post infection (25). Similarly, antibodies against MERS-CoV have been shown to persist for approximately three years (26), although the persistence of anti-MERS-CoV antibodies depended on disease severity, as patients with subclinical or mild disease had low or undetectable levels of antibodies two years after infection (27). In contrast, seroprevalence studies of human coronavirus (HCoV)-229E and HCoV-OC43 suggested that antibody titres wane significantly one year after infection (22). The persistence of anti-SARS-CoV-2 antibody response remains to be seen although given the association of the antibody signal and disease severity (13), it is likely that persistence of antibodies will correlate with disease severity.

Impact of disease severity and age

Given that many SARS-CoV-2 infections are subclinical or asymptomatic, it is critically import that the antibody response (including titres, seroconversion and time to seronegativity) in these patient populations be well understood. It is now widely recognized that titres of SARS-CoV-2 antibodies are positively associated with clinical severity of disease. Zhao *et al*., (10) first reported that a significantly higher titre of total antibody was independently associated with a worse clinical classification (p=0.006) at 2-weeks post illness onset. A high total antibody titre was hypothesized to be a risk factor for critical illness and that it may even be used as a surrogate marker for worse clinical prognosis. A similar observation was made in 289 COVID-19 patients clinically categorized as having mild, moderate or severe infection. Patients with a severe infection had significantly higher levels of S1-specific IgA and IgG compared with those with a mild infection (28). Moreover, S1-specific IgG was detectable after two weeks in only 20% of patients in the mild group compared with 100% of patients in the severe and moderate groups.

The impact of disease severity on seroconversion kinetics and their relationship to neutralizing properties in serum is not well understood. When compared to patients with mild symptoms, those with severe symptoms had a significantly faster time to IgG seroconversion (median 22 versus 11 days, respectively) with approximately 10% of patients with mild symptoms never seroconverting (29). Detectable IgG levels were still observed more than 75 days post symptom onset in patients who had seroconverted. Interestingly, even at 90 days post-symptom onset a small number (N=3) of patients developed total antibody levels below the limit of detection of commercial assays yet still had a detectable neutralizing response (titre range of 8–48). This observation is in direct contrast to that reported previously, where sera from 20% of discharged patients had no neutralizing properties despite sera from 100% of patients showing seroconversion (30). Furthermore, in a small study, the development of IgM in patients with severe disease was delayed (N=6; eight days) compared with mild disease (N=39; six days) (31). Jiang *et al*. (32) evaluated rates of seroconversion in non-severely ill patients with COVID-19, as well as asymptomatic patients, concluding that different IgM/IgG kinetics exist depending on the severity of the disease. Indeed, the authors reported that IgG seroconversion occurred among 94% of symptomatic and 85% of asymptomatic patients while IgM seroconversion occurred in 74% of symptomatic patients and only 31% of asymptomatic patients (p<0.001). Interestingly, the authors also reported that the median time to seroconversion (IgM or IgG) among the asymptomatic group was significantly shorter compared with the symptomatic group (median seven days from first positive polymerase chain reaction assay vs. 14 days; p<0.001).

While it is generally accepted that antibodies persist for longer periods in severe cases of COVID-19, there is considerable variation among studies even when normalized for the clinical severity. For example, IgG in mild to moderate disease appears to persist anywhere from 3–5 months (14,33). A study evaluating symptomatic and asymptomatic patients with COVID-19 associated pneumonia (apparent or subtle on radiography) found antibodies were more frequently detected among symptomatic patients (100% vs. 71%; measured at two and five months post symptom onset) (34). Furthermore, titres decreased significantly between the two time points. Another study comparing IgG and neutralizing antibody levels in asymptomatic versus symptomatic patients showed 40% of the asymptomatic patients became seronegative in the early convalescent phase (2–3 months post symptom onset) compared with only 12.9% of symptomatic patients (35). Interestingly, Choe *et al*. (36) also reported that neutralizing antibody titre correlated with severity of disease, suggesting that patients with severe disease may be more protected from reinfection compared with patients with subclinical or asymptomatic infection. It should be noted that to date, there are only a few documented cases of reinfection (37–40), which suggests that either other immune mechanisms (such as the T cell-mediated response) may contribute to protection against SARS-CoV-2 reinfection, or that, as a function of the short time that SARS-CoV-2 has been circulating and combined with implementation of public health restrictions, sufficient time has not yet passed for re-infection to be detected. Additionally, as most of these early studies examined the level of anti-nucleocapsid antibodies, association of high levels of antibody with poorer clinical outcome may be related to the production of anti-nucleocapsid rather than anti-spike antibodies.

Although there are less data on the relationship between age and the antibody response in COVID-19, recent evidence suggests there may be distinct antibody responses in children and adults. It has been shown that unlike adults, who produced robust levels of anti-S and anti-nucleocapsid (N) antibodies, children produced less anti-N and neutralizing antibodies (41).

The clinical significance of this is unknown, although it is interesting considering disease severity is positively associated with age.

The large variability in how the antibody response was measured (i.e. different assays, platforms, methods, and antigenic targets) makes it difficult to make direct comparisons between studies. Despite this limitation, it is clear that not all infected individuals will mount an antibody response and that the level of antibodies may wane over time. This has significant implications for the interpretation of antibody testing for diagnostic purposes, especially for use as a surrogate marker of immunity to SARS-CoV-2. At best, anti-SARS-CoV-2 antibodies have good positive predictive agreement for neutralizing properties; however, the negative predictive agreement is poor.

How to implement testing in the clinical laboratory

Validation of antibody tests for infectious disease often depends on studies aimed to calculate the diagnostic sensitivity and specificity (i.e. correlating assay response to true positives and true negatives). In the case of SARS-CoV-2, this is inherently difficult for several reasons. Evidence suggests that humoral response and resultant seropositivity are affected by the severity of infection (presence/absence of detectable antibody), the time since symptom onset (antibody longevity) and the antigen target (antibody isotypes and viral protein recognition). Moreover, because the sensitivity of ribonucleic acid (RNA) testing is dependent on the time of sample collection in disease and the quality of sample, discordant serology results are often difficult to interpret for most clinical laboratories that do not have access to neutralization assays. Therefore, it is recommended that clinical laboratories offer assays that have undergone extensive review by a governing body such as Health Canada or the FDA, or by published peer-reviewed performance analyses when available. The requirement is on the clinical laboratory to ensure serology assays are used as intended and meet local accreditation standards.

The complexity and scope of internal verification studies required for laboratories to offer serology testing is highly dependent on the method of choice. Many clinical laboratories will choose to offer automated chemiluminescent immunoassay methods using existing instrumentation and infrastructure that are Health Canada or FDA emergency use authorization approved. When using these validated methodologies, with provided performance characteristics, a modified method verification may be acceptable with reduced rigour of testing to ensure the assay is fit for purpose. However, modifications to a validated method, such as using a different specimen type like a dried blood spot or altering the manufacturer's cut-off, requires complete method validation prior to patient testing (considerations for verification and validation are shown in **Table 1**). In the case of a laboratory developed test, a complete method validation is required. A detailed flow diagram depicting additional possible scenarios for method validation and verification was published previously (42).

Table 1: Minimal requirements for validation and verification of qualitative assays

Item	Verification	Validation
Requirements	Assay methodology and reagents must be unchanged from the manufacturer's instructions	Assay performance and methodology must be assessed and determined in the local testing population
Purpose	Laboratory verifies that the operators using their assay platform in their laboratory environment obtain the same performance characteristics with the assay method as described in the manufacturer's validation data	Laboratory validates all performance characteristics in their laboratory and all sample types to be used
Sample number	A statistically significant number of samples (generally 50 minimum) must be used in the evaluation process to cover the full range of expected results for the intended use	A statistically significant number of samples (generally 50 positive and 50 negative run over 5–10 days) must be used, and cover the full range of expected results
Statistical analyses	A statistical correlation with existing validated methods or comparisons with known outcomes ("gold standard") are required for qualitative methods. % CV, SD and 95% CI are recommended	A statistical correlation with existing validated methods or comparisons with known outcomes ("gold standard") are required for qualitative methods. % CV, SD and 95% CI are recommended
Calculations	Confirmation of Clinical Evaluation is the minimum to be tested **Sensitivity/specificity:** Minimum of 20 samples (10 positive, 10 negative), or a recommended 100 samples: 50 samples valid for the method that are positive for SARS-CoV-2 RNA and 50 negative samples valid for the method that are negative for SARS-CoV-2 RNA OR that have been tested by a validated comparator immunoassay and were positive (N=50) or negative (N=50) for SARS-CoV-2 antibody. Apply the binary classification test ("Test outcome vs. condition") to determine both characteristics. Determine CI%.	All performance characteristics must be tested **Sensitivity/specificity:** Recommended 100 samples: 50 samples valid for the method that are positive for SARS-CoV-2 RNA and 50 negative samples valid for the method that are negative for SARS-CoV-2 RNA OR that have been tested by a validated comparator immunoassay and were positive (N=50) or negative (N=50) for SARS-CoV-2 antibody. Apply the binary classification test ("Test outcome vs. condition") to determine both characteristics. Determine CI%.

Table 1: Minimal requirements for validation and verification of qualitative assays (*continued*)

Item	Verification	Validation
Calculations (*continued*)	**Precision:** is defined as the closeness of agreement between independent test results obtained under conditions of the assay run (includes repeatability and reproducibility). Minimum of 20 samples: 10 replicates each of one positive and one negative sample; 10 RNA positive and 10 RNA negative samples. Create aliquots and freeze all aliquots necessary for testing to avoid freeze-thaw variability between repeats. If comparing to another immunoassay, a range of S/CO values within the samples would be desirable. **Repeatability:** Assay 10 replicates of the positive and negative samples in a single run. Determine the SD and % CV for the S/CO values. **Reproducibility:** Assay the 20 specimen aliquots on three different days. Determine the SD and % CV for the S/CO values for each specimen.	Diagnostic (clinical) sensitivity is defined as the percentage of individuals with the target condition (as determined by the diagnostic accuracy criteria) whose test values are positive. Diagnostic (clinical) specificity is defined by the percentage of individuals without the target condition (as determined by the diagnostic accuracy criteria) whose test values are negative. Target specificity (cross-reactivity) ensures the test is specific only for the analyte of interest. This is determined by testing other pathogens within the same family or disease group. Positive predictive value is defined as the percentage of individuals with a positive test result who have the target condition (as determined by the diagnostic accuracy criteria). Consider evaluating parameters as a function of the population prevalence. Negative predictive value is defined as the percentage of subjects with a negative test result who do not have the target condition (as determined by the diagnostic accuracy criteria). Consider evaluating parameters as a function of the population prevalence. **Precision:** Create aliquots and freeze all aliquots necessary for testing to avoid freeze-thaw variability between repeats. If comparing to another immunoassay, a range of S/CO values within the samples would be desirable. **Repeatability:** Assay 10 replicates of the positive and negative samples in a single run. Determine the SD and % CV for the S/CO values. **Reproducibility:** Assay the 20 specimen aliquots on 3 different days. Determine the SD and % CV for the S/CO values for each specimen. **Normal values:** 120 specimens should be run to establish normal range of values for local testing population.
Other considerations	When possible, laboratories should consider using multiple operators to perform verification, particularly when result interpretation is required If the assay documentation does not include a full validation report or incomplete performance characteristics as recognized by technical organizations, then a user laboratory validation is required	When possible, laboratories should consider using multiple operators to perform validation, particularly when result interpretation is required

Abbreviations: CI, confidence interval; CV, coefficient of variation; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; S/CO, signal to cut-off ratio; SD, standard deviation

Method verifications are likely to be the most common form of method evaluation performed by clinical laboratories at present. At minimum, clinical laboratories should verify manufacturer claims by assessing the diagnostic sensitivity and specificity, assay precision (reproducibility), cross-reactivity of non-SARS-CoV-2 antibodies and interfering substances (such as hemoglobin, lipids or biotin) commonly found in their patient population. A summary of the minimum suggested sample sizes for establishing diagnostic sensitivity and specificity are provided in **Table 2**. The clinical laboratory must verify the assay performance using statistical correlations and comparisons based on manufacturer claims. Careful scrutiny is required in the case of discrepant results, and arbitrator testing can be performed by external laboratories performing the same methodology. If verification specimens are sourced locally, patient history may be considered to reconcile test performance and to further characterize the testing population (outpatient, hospitalized or intensive care unit, and timing of sample collections). Furthermore, it may be prudent to interrogate the signal obtained from the assay in expected positives that may be in the equivocal range because some patient antibody titres may have waned over time, and assay cut-offs were assigned with only limited samples. A particular challenge during verification is resolving suspected false positive serologic results given the variable disease prevalence (43). Potential approaches to resolve discrepancies include testing for another assay or target antigen, reviewing the clinical history of the patient case, including time since symptom onset and contact tracing, or reviewing prior SARS-CoV-2 RNA testing results.

Table 2: Theoretical number of samples required for establishing diagnostic sensitivity and specificity estimates by error margin and confidence interval

Estimated sensitivity or specificity	Estimate with 2% error			Estimate with 5% error		
	Confidence			Confidence		
	90%	95%	99%	90%	95%	99%
90%	610	864	1,493	98	138	239
92%	466	707	1,221	75	113	195
94%	382	542	935	61	87	150
95%	372	456	788	60	73	126
96%	260	369	637	42	59	102
97%	197	279	483	32	45	77
98%	133	188	325	21	30	52
99%	67	95	164	11	15	26

Consideration of orthogonal testing algorithms for severe acute respiratory syndrome coronavirus 2 serology

In general, laboratories should strive to use serological assays with manufacturer-claimed sensitivity of greater than 95% and specificity of greater than 99.5% (1). Many of the SARS-CoV-2 specific antibody assays currently approved for use in North America meet these performance criteria when used alone (44–48). However, when testing is performed in low prevalence populations or in patients with a low pre-test probability of disease the positive predictive value or post-test odds will be unacceptably low despite excellent specificity. Therefore, laboratory professionals may adopt an orthogonal testing strategy to improve the specificity and positive predictive values of serologic test interpretation for SARS-CoV-2 (49–51). In orthogonal testing, samples that test positive or equivocal on an initial test are re-tested using a second test to confirm or refute the result (1). Orthogonal testing strategies have been recommended by public health authorities in North America in low prevalence populations (1,52), and detailed protocols are available (53). Most of the orthogonal testing approaches for SARS-CoV-2 antibodies involve two independent tests, each with unique assay design characteristics such as antigen type (54–56) or assay formats (57). However, these approaches may have practical limitations in terms of implementation because the specific epitope targeted in each manufacturers assay is unknown or not provided (58). Improvements in sensitivity can also be accomplished in orthogonal testing approaches by reducing cut-off values for commercial high-throughput automated SARS-CoV-2 assays (59); however, alteration of manufacturer recommendations requires full validation of the new cut-off values prior to clinical use.

When users are considering either a single serological testing algorithm or a two-step (orthogonal) testing algorithm, they must consider the reason for testing, the intended use of the data generated and the expected prevalence of SARS-CoV-2 in the population of interest. For example, use of serology for special clinical case testing (e.g. in MIS-C cases) or in seroepidemiological studies, requires high assay sensitivity and high negative predictive value in early infection (more than two weeks) and late convalescence, respectively. Indeed, in these scenarios reporting true cases should be the priority; although false positives are not desirable, they can be tolerated more so than false negatives. For example, in seroepidemiological studies, a sensitive assay with a good positive predictive value is critical to identify true cases to provide robust population level estimates of seropositivity. In contrast, when screening potential convalescent plasma donors, the presence of SARS-CoV-2 antibody is critical (60), and a positive predictive value more than 99% should be required. Because high negative predictive value is less important in this scenario, orthogonal testing is recommended in both low and high population prevalence levels (56). These examples illustrate the need for careful consideration of orthogonal testing strategies that are tailored to the intended use of the serological data. As a result of these different scenarios, SARS-CoV-2 antibody testing strategies will vary based on site-specific requirements.

Serological assays to determine severe acute respiratory syndrome coronavirus 2 antibody neutralization potency

To better understand and characterize SARS-CoV-2 immunity after natural infection or vaccination, functional assays such as virus neutralizing tests are required. The previous/current gold standard methodologies to detect and quantify SARS-CoV-2 neutralizing antibodies have used cell-culture-based infection assays, which block viral entry into cells *in vitro*. These live-virus assays use wild type SARS-CoV-2 virus incubated with dilutions of a patient's sera or plasma. The mixture is then added to susceptible cells to determine if the sera inhibits or neutralizes the cytopathological effect or plaque reduction is observed. PRNT provide a means to quantitate neutralization titres associated with an individual's clinical specimen. However, live virus assays require biosafety level-3 containment, are labour-intensive and due to the biologic variation associated with these assays they can be difficult to standardize (61–63).

Neutralization assays that use pseudotyped viruses, such as the vesicular stomatitis virus or lentivirus-based systems that incorporate SARS-CoV-2 spike protein, can be used in biosafety level-2 laboratories (64). An example of a basic procedure for establishing a pseudotype assay using lentivirus particles involves transfecting a "packaging" cell line, such as HEK 293T cells, with a number of plasmids to produce safe, non-replicative viral particles expressing the spike protein. Transfected plasmids include a reporter-expressing plasmid, a plasmid encoding the SARS-CoV-2 spike and a number of plasmids encoding lentiviral proteins required for assembling viral particles. The transfected cells produce the pseudotype viruses, which can then be used

to infect permissive cells expressing the SARS-CoV-2 receptor, angiotensin-converting enzyme 2 (ACE2), to measure a decrease in cytopathological effect, via the reporter signal, or by plaque reduction in the presence of patient serum.

Although pseudotype virus formats alleviate biosafety limitations, they have similar drawbacks to conventional PRNTs in that they are difficult to standardize across laboratories, and the assay characteristics may vary depending on culture conditions, virus strains and cell lines used. Furthermore, these cell-based assays require highly skilled personnel, are low throughput and have suboptimal turnaround times for clinical decision making. These drawbacks make implementation of pseudotype viral assays in the clinical laboratory impractical.

Recently, several ELISA-based surrogate neutralization assays that detect antibodies targeting the viral spike protein RBD have come to market (65–67). These more rapid assays are based on antibody-associated blockage of the interaction between the spike RBD and the ACE2 receptor. The procedure by Abe *et al.*, (67) uses immobilized ACE2 and soluble biotinylated RBD (which exhibited increased sensitivity to other reagent configurations), and provides a direct comparison with conventional ELISAs (detecting antibodies that bind RBD) in a plate format.

A number of commercial assays using a similar ELISA-based platform have also become available (e.g. GenScript cPass, Cayman SARS-CoV-2 antibody ELISA) that indirectly and semi-quantitatively measure the neutralizing capability of SARS-CoV-2 antibodies. The GenScript surrogate virus neutralization test (sVNT) kit has been compared with conventional cell-based neutralization assays (68–70) and displayed good specificity, and comparable sensitivity to virus culture-based assays, but demonstrated somewhat reduced efficacy in identifying samples with a lower level of virus neutralization potency. This observation may be explained by the specific detection of antibodies targeting the RBD in the assay, as non-RBD neutralizing antibodies are not targeted in the sVNT assays. It should also be noted that unlike functional PRNT or cell-based assays, surrogates may detect non-neutralizing antibodies in some samples. However, the advantage of both commercial and non-commercial ELISA-based sVNT assays is the ease of use and the potential for automation and standardization. Moreover, with appropriate validations, these may be incorporated into conventional virus neutralizing testing algorithms and offer an important tool to assess neutralization in clinical specimens.

Additional standardization is underway to compare cell-based neutralization assays with surrogate tests utilizing pseudotype viruses or ELISA-based competitive binding assays (71). Good correlation was observed between a modified ELISA-based surrogate assay with a conventional PRNT and spike pseudotyped viral vector-based platforms (67). Antibody titres between TCID50 neutralization tests and lentiviral/vesicular stomatitis virus pseudotype assays correlated well (71). It should be noted that although cell-based neutralization assays, such as PRNTs or micro-neutralization tests, are the reference standards for detection and quantification of neutralizing antibodies in clinical specimens, the biological nature of these test may lead to some variability in titres and sensitivity when comparing inter-laboratory results (72). The utilization of proficiency panels made up of well pedigreed control and patient sera/plasma samples facilitates standardization between laboratories.

Commercially available, high-throughput serological assays that measure the binding of antibodies to various viral antigens have been directly compared to neutralization antibody titres in patient samples using PRNT or sVNT assays (73–75). The results from these comparisons show that commercial serology assays are sensitive for the detection of total antibodies but are less robust at predicting the neutralization titre relative to conventional (e.g. PRNT) or sVNT assays. Furthermore, the reliability of commercial high-throughput platforms that are specific for spike/RBD protein antigens to infer neutralization titre equivalents may depend upon time frames for specimen collection and the specific antibody induction responses of an individual. However, more recent studies have described a strong correlation between anti-RBD antibody concentrations and spike/RBD-ACE2 inhibiting antibody titers ($r>0.86$, $p<0.001$) (76,77), with the possibility of anti-nucleocapsid antibodies (signal to cut-off greater than or equal to 5.0) serving as a surrogate for screening of high neutralizing antibody titer plasma (greater than or equal to 160) (78).

Detecting antibodies derived from vaccination versus natural infection

With the roll-out of SARS-CoV-2 vaccines, the detection and quantification of vaccine-induced antibody by current commercial assays needs to be verified in relation to the detection of natural immunity following infection. A difference in the ability to detect antibodies from both natural infection and vaccination has been seen with other viral infections, including varicella zoster virus (VZV), where commercial assays can readily detect IgG antibodies in people who have had a natural infection but many commercial assays are less robust in detecting vaccine-induced antibodies (79). Multiple studies are currently ongoing to determine what SARS-CoV-2 antibodies are detected with commercial assays, and if there are variances in detection based on the type of vaccine received by an individual. The current lack of serum from vaccinated individuals makes it challenging for a clinical laboratory to incorporate appropriate serology algorithms, particularly as both vaccine and laboratory assay targets are proprietary. Furthermore, with new vaccine candidates emerging, the variability in vaccine type and antigen may limit the ability of current commercial anti-SARS-CoV-2

serology tests to determine whether a patient has been vaccinated. Moreover, there is no evidence that the presence and titre of anti-SARS-CoV-2 antibodies can be extrapolated to immune status of vaccinated patients.

The role for differentiation of antibodies derived from natural infection versus vaccine-induced antibodies does not have importance for clinical management, and there are currently no Health Canada approved anti-SARS-CoV-2 assays specific for vaccinated populations. In the first four months following vaccination, it is likely that natural versus vaccine-induced antibodies can be differentiated using a combination of anti-nucleocapsid and anti-spike assays. In Canada, for example, where only spike-based vaccines are currently being used, a positive anti-nucleocapsid could indicate natural infection, and a negative anti-nucleocapsid but positive anti-spike could indicate vaccine-induced antibodies. However, this process is not straightforward as negative anti-nucleocapsid but positive anti-spike antibody profiles have been identified in those following natural infection (anti-spike antibodies persist longer than anti-nucleocapsid (50,80)). The landscape becomes more complicated after four months or longer because anti-nucleocapsid antibodies are expected to decline among patients who have recovered following natural infection. Therefore, current assays cannot determine whether a patient had positive anti-spike antibodies and negative anti-nucleocapsid antibodies due to a history of infection or a vaccination. From a public health perspective, it is important to understand the overall immunity of a population, and whether immunity is derived from vaccine or natural infection is academic. In jurisdictions using only spike-based vaccines, the use of spike or receptor binding domain assays should be considered as the primary targets for screening to ensure both scenarios are detected in surveillance studies. Conversely, the presence of vaccination-induced antibodies may be problematic for clinical testing; for example, in the diagnosis of MIS-C. As such, clinical serology testing is not recommended for individuals who have received the COVID-19 vaccine, especially if an assay that detects anti-N antibody is not available. Better markers of immune status are needed that are simple, reproducible and robust.

The use of serology in determination of immunity is challenging. There are currently no commercially available assays to determine immune status, which can only be evaluated using PRNT assays. In the absence of a universal standard, or a surrogate marker for immunity, the detection of antibodies in serological assays, regardless of the signal strength, cannot determine with confidence whether an individual would be susceptible or immune to a subsequent challenge with SARS-CoV-2. Therefore, the value of an "immunity passport", where individuals with detectable antibody have fewer public health restrictions, is limited and may harm public health efforts aiming to decrease the spread of infection.

Towards the end of 2020, a series of SARS-CoV-2 variants of concern have emerged within different geographic regions of the world, such as the United Kingdom, South Africa and Brazil (81). These variants include specific mutations within the spike protein (K417N, E484K, N501Y) that are shared among all independent variant lineages (82). The most pressing concern with these variants is the increased transmissibility (83) associated with them; but also troubling is the aspect of immune escape, with the potential to evade detection and thus diagnosis. These mutations have been shown to affect neutralization properties depending on whether monoclonal or polyclonal antibodies were tested (84–86). Furthermore, the P.1 variant first found circulating in Manaus, Brazil, was associated with re-infection in immunocompetent individuals (87) which presumably would make it more difficult to interpret results from serology and PRNT assays targeting wild-type virus or viral antigens.

Currently there is no recommendation for pre or post-vaccine immunity screening (88), as there is a lack of correlation between antibody detection and immunity to infection, and little work has been done to understand antibody production in immunocompromised populations. To understand what level of antibody could correlate with immunity from infection, more in-depth studies are needed, including creation of an international standard to allow comparison of antibody levels between different vaccines, assays and laboratories.

Conclusion

Implementation of SARS-CoV-2 serology in the clinical laboratory is challenging, and laboratory professionals must be aware of the limitations of these assays. There are a number of unknown factors that affect these assays, and guidelines and recommendations for their use in clinical laboratories are ever evolving. Here we present the most up-to-date testing recommendations in Canada, and provide practical guidance for laboratories to choose appropriate serological assays and employ the best testing algorithms for their local populations.

Authors' statement

CLC — Conceptualized project, original draft, review of manuscript, final editing of manuscript
JNK, VT, JVK, JG, CO, JLR, MD, TH, DRS, AL, LJ, PNL, HW, CT, LRL, MM, JDF, AD — Conceptualized project, original draft, review of manuscript
NE — Review of manuscript, coordination of drafts

All authors have approved the final version sent for publication and are accountable for all aspects of the work.

Competing interests

None.

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Simple mathematical modelling approaches to assessing the transmission risk of SARS-CoV-2 at gatherings

David Champredon[1]*, Aamir Fazil[1], Nicholas H Ogden[2]

Abstract

Background: Gatherings may contribute significantly to the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). For this reason, public health interventions have sought to constrain unrepeated or recurrent gatherings to curb the coronavirus disease 2019 (COVID-19) pandemic. Unfortunately, the range of different types of gatherings hinders specific guidance from setting limiting parameters (e.g. total size, number of cohorts, the extent of physical distancing).

Methods: We used a generic modelling framework, based on fundamental probability principles, to derive simple formulas to assess introduction and transmission risks associated with gatherings, as well as the potential efficiency of some testing strategies to mitigate these risks.

Results: Introduction risk can be broadly assessed with the population prevalence and the size of the gathering, while transmission risk at a gathering is mainly driven by the gathering size. For recurrent gatherings, the cohort structure does not have a significant impact on transmission between cohorts. Testing strategies can mitigate risk, but frequency of testing and test performance are factors in finding a balance between detection and false positives.

Conclusion: The generality of the modelling framework used here helps to disentangle the various factors affecting transmission risk at gatherings and may be useful for public health decision-making.

Affiliations

[1] Public Health Risk Sciences Division, National Microbiology Laboratory, Public Health Agency of Canada, Guelph, ON

[2] Public Health Risk Sciences Division, National Microbiology Laboratory, Public Health Agency of Canada, St.-Hyacinthe, QC and Guelph, ON

***Correspondence:**

david.champredon@canada.ca

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Introduction

Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019, data are available that confirm that gatherings can increase the risk of SARS-CoV-2 transmission at the population level and can even have the potential to act as super-spreading events (1–3). One of the measures that decision-makers have implemented to slow the progress of the coronavirus disease 2019 (COVID-19) epidemic has been to limit the number of people congregating together for both personal and professional reasons. Intuitively, the size of gatherings is directly related to the infection rate; hence, limiting their size would minimize COVID-19 transmission.

Beyond this simple statement, assessing the effectiveness of constraints on gatherings is difficult. Gatherings can take a multitude of different forms, from indoor toddler's birthday parties with local guests to weddings and conference with guests from multiple communities. These different forms reflect the diversity of values of the variables that drive disease transmission during the gathering (e.g. mixing, contact rates and patterns, gathering duration, prevalence in participants at the start of the event, etc.).

Detailed transmission models tailored to specific events have been employed to capture and evaluate the complexity of transmission risk and provide insights into the role of gatherings.

An in-depth literature review of modellings studies assessing the risk associated with gatherings showed that there was a consensus among models that limiting the size of gatherings helps to limit SARS-CoV-2 transmission (3). Unfortunately, we rarely have sufficient data to parametrize such "tailored" transmission models and, if we did, generalization of their findings would be challenging.

Here, we attempt to assess the transmission risk of SARS-CoV-2 during gatherings (both unrepeated and repeated) using relatively simple and generic modelling frameworks. We focus on the general issues of risk at gatherings that can be applied to all gatherings, risk of introduction and risk of transmission during gatherings, as well as two commonly used methods of mitigating risk: testing participants and (for repeated gatherings) cohorting. Despite being limited in providing precise guidance for a particular gathering, the results presented here may still be applicable, to a varying degree, for different kinds of gathering settings and help support high-level public health decision-making. As more detailed, quantitative information on specific aspects that are expected to affect the risk of gatherings (e.g. ventilation, density of participants, levels of vocalization) (3) becomes available, the framework developed here can be better parameterized to improve more gathering-specific risk estimates.

Unrepeated gathering

Unrepeated gatherings are those that occur only once, or infrequently with a length of time between them such that they can be considered unrepeated. Examples of such gatherings could be funerals, weddings or conferences.

Introduction risk

The first determinant of risk at gatherings is the probability that at least one infectious individual is present. A general approach would be to assume that infectious individuals are picked randomly from a general population that mixes homogenously (a conservative assumption when considering transmission risk). With these assumptions, the risk of having an infectious person in a gathering is proportional to the prevalence in the general population (here termed *prev*). The probability at least one infectious individual is present at a gathering of size N is

$$p_{intro} = 1 - (1 - prev)^N$$

This simple expression provides several outputs of value for a decision-maker. The variable p_{intro} is the probability that at least one infectious individual participates at a gathering of size N in a setting where the population prevalence is *prev*. A simple readjustment of the equation provides the largest gathering size possible for a pre-determined acceptable level of introduction risk for a given infection prevalence in the population coming to the gathering:

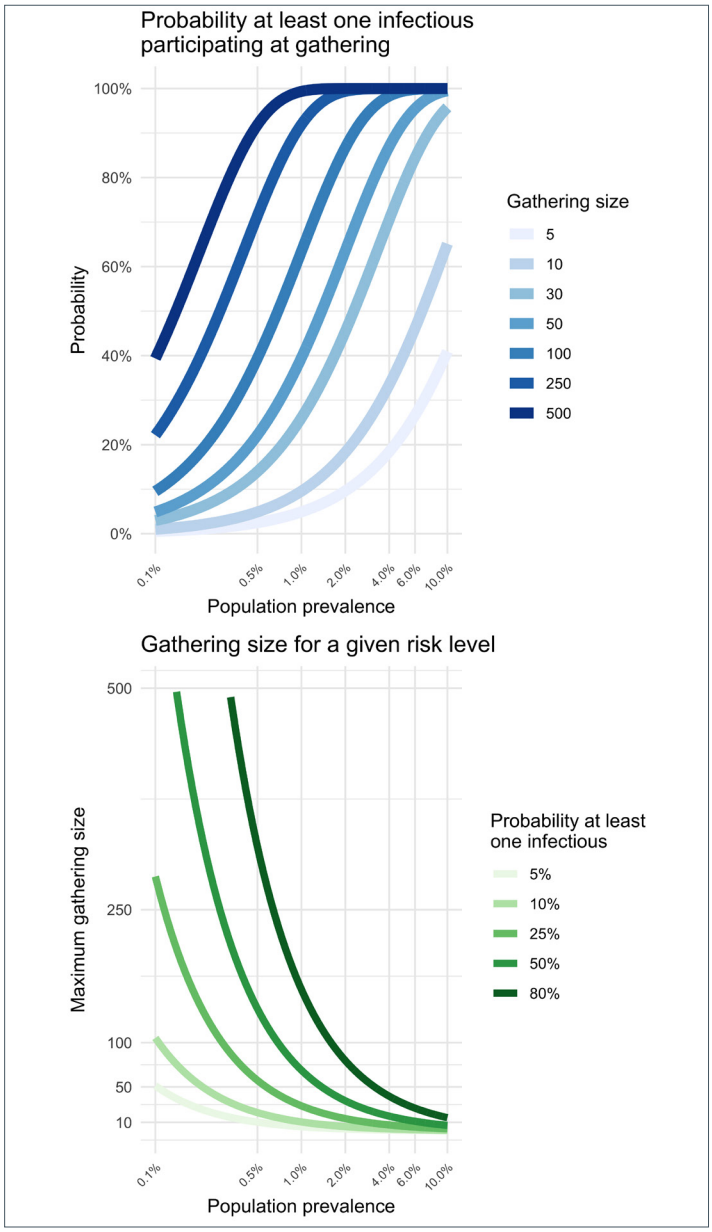
$$N = \log(1 - p_{intro}) \,/\, \log(1 - prev)$$

Another adjustment provides the level of prevalence in the population that would exceed the predetermined acceptable level of risk of introduction for a gathering of a particular size:

$$prev = 1 - (1 - p_{intro})^{1/N}$$

Note that while the three simple equations above cannot claim precision for a specific gathering, they can help understand how those three variables are related. The relationships between the gathering size, the prevalence in the community and the tolerance for the risk of introduction (p_{intro}) are illustrated in **Figure 1.**

Figure 1: Relationships between gathering size, the prevalence in the community and the tolerance for the risk of introduction



Note: The left-hand panel displays the introduction probability given a gathering size and prevalence. The right-hand panel shows the maximum gathering size for a given prevalence and risk of introduction

The assumption that the prevalence in the source population is the same as the subset attending the gathering is convenient but may not be realistic for gatherings that attract individuals from sub-populations that are either more, or less, likely to be infected.

A simple way to introduce heterogeneity is to directly change the prevalence according to the expected over or under-exposure of the participants of the gathering. The adjusted prevalence for this specific group, $prev_G$, can be simply calculated from the baseline prevalence. If we know the relative risk RR of the group compared to the whole population, and if we know the odds ratio, OR, of infection for this group, we have

$$prev_G = RR \times prev, \text{ or } prev_G = \left(1 + \frac{1-prev}{OR \times prev}\right)^{-1}$$

For example, if 1) the current prevalence of SARS-CoV-2 infections in the population coming to the gathering is $prev$ = 0.5%, 2) the gathering demographics are similar to the whole population and 3) we decide the maximum acceptable probability that an infectious individual joins this gathering is p_{intro} = 20%, then the maximum size that the gathering should be is no more than N = 44. However, if we consider a gathering where a group of participants are five times more likely than the general population to be infected ($prev_G$ = 5 × $prev$ = 2.5%), then the maximum size for this gathering should not be more than nine.

Transmission risk at the gathering

Once the probability of an infected person being present at the gathering has been determined, the second question that needs to be considered is: "What is the risk that this individual transmits the pathogen to other susceptible participants?".

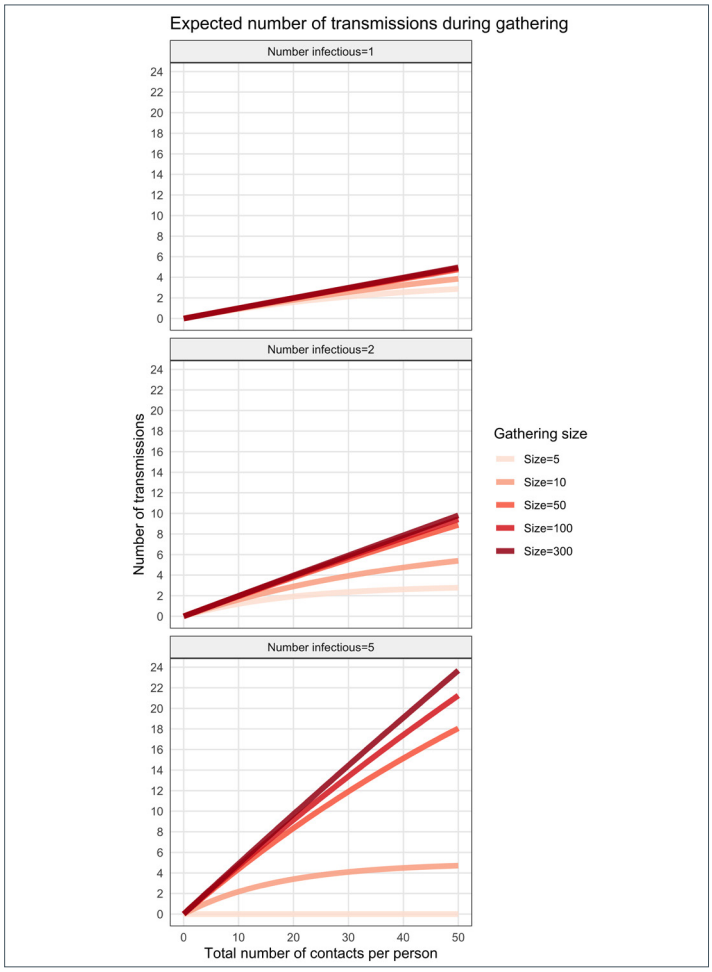
If we assume homogenous mixing during a gathering of N persons at which I infectious individuals are participating, and that that any susceptible individual will contact C different persons (infectious or not) at the gathering, then the expected minimum number of transmissions that will occur during this gathering is

$$n_{\text{transm}} = (N - I) \times \left(1 - \left(1 - \frac{I}{N-1} p_{tr}\right)^{C}\right)$$

where C is the number of contacts during the gathering with an infectious individual and p_{tr} is the probability of transmission given a contact with an infectious person (see **Appendix** for details). The variables C and p_{tr} are context-specific and should be calibrated to the best available evidence as this becomes available from epidemiological analyses and research studies. It may be useful to work with a range of estimates that will produce upper and lower bounds for n_{transm}. The formula above is simple enough to be implemented in a spreadsheet and can help disentangle the role of the gathering size and measures that help reduce the transmission probability (e.g. wearing masks) or the number of contacts (e.g. physical distancing).

Figure 2 shows n_{transm} for different values of gathering sizes and infectious individuals participating. For example, we can expect that there will be about four transmissions during a 10-person gathering where two infectious individuals are participating (Figure 2, centre panel), the contact rate is on average 30 contacts per person and the probability of transmission is p_{tr} = 10%. When only one infectious person is at a gathering (left panel), the expected number of transmissions is approximately the same for different gathering sizes. This is primarily because the probability of a susceptible person encountering an infectious person is low. The outcome was very different with five infectious people present (Figure 2, right panel). In this case, the probability that susceptible people encounter infectious people in the crowd increases and, therefore, the number of transmissions that could occur also increases.

Figure 2: Effect of gathering size and number of infected individuals on minimum number of secondary transmissions



Note: The plots were generated using a probability of transmission given contact of p_{tr} = 10%. Each panel represents a different number of infectious persons introduced in a gathering (from left to right: 1, 2 and 5) for different gathering sizes

For very large gatherings, we can reasonably assume that the number of infectious participants should be approximately equal to the population prevalence, assuming the gathering is a random sample of the population.

If C_{max} is the maximum number of contacts an infectious individual can make during the gathering, then $A=S/(C_{max}\ p_{tr})$ is the minimum number of infectious individuals needed to have a chance to infect all the S susceptible individuals at the gathering (all infectious would need to contact C_{max} times only the susceptible individuals). Rescaling A to the gathering size leads to $a = A/N$. The ratio a can act as a threshold value to assess if the extreme event where every susceptible individuals could be infected at the gathering. If $prev$ is the population prevalence, having $prev \approx a$ means it is possible that all susceptible individuals become infected. More generally, if $prev \approx f \times a$, then a fraction f of the susceptible participants is at risk of being infected during the gathering. For example, a gathering of 1,000 persons, where the maximum number of contacts for any individual is 30 and the probability that infection is transmitted when a contact takes place is 60%, has a threshold value of a = 5.5% Hence, a population prevalence above 5.5% (i.e. if we expect more than 55 infectious participants) would be worrying for this gathering, as there is a potential to infect every susceptible participant. If the population prevalence was 2.75%, then half of the susceptible participants would be at risk of being infected (f = 0.5).

The duration of the gathering also has an impact on the risk of transmission. Intuitively, the longer individuals are together, the more opportunities there are for virus-transmitting contacts to occur. The effect of time on transmissions can be modelled using survival analysis. The proportion of susceptible individuals remaining t time units after the start of the gathering (t = 0) is:

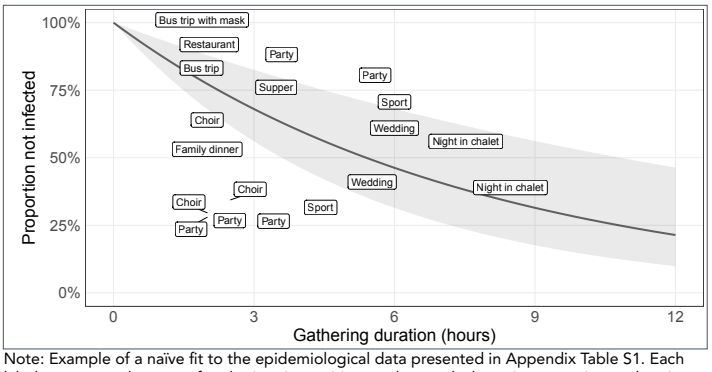
$$S(t) = e^{-\lambda t}$$

The infection hazard λ (assumed to be constant here) can be estimated from recorded infections at observed events (through contact tracing). This implicitly assumes that the time to infection is exponentially distributed. If N is the size of the gathering, T its duration and i the total number of transmissions that happened during this event, then a naive estimate of the infection hazard is

$$\hat{\lambda} = \frac{1}{T}\log\left(\frac{N}{i}\right)$$

Studies reporting on contact tracing of gathering events can provide the necessary data to calculate this estimate for a given gathering. **Figure 3** is an example of epidemiological data used to inform the survival model. Note that the information collected from such studies is likely conservative; gatherings that drew the attention of public health workers because of the large number of secondary cases are likely to be more reported than the ones where few or no transmission occurred. Figure 3 also shows a naive fit of the infection hazard during events ($\hat{\lambda}$) to the data of Appendix Table S1. Estimates of infection hazard $\hat{\lambda}$ can help support decisions regarding duration limits on gatherings.

Figure 3: Infection hazard estimated from epidemiological data from social gatherings



Note: Example of a naïve fit to the epidemiological data presented in Appendix Table S1. Each label represents the type of gathering; its position on the graph shows its approximate duration (horizontal axis) and the proportion of participants that were not infected (vertical axis). The solid black curve is the linear regression performed on the log scale (see Appendix for details) and the grey ribbon represents the 95% CI

Recurrent gatherings

The second category of gatherings are those that occur on a regular basis with the same participants. Examples of such gatherings are company employees, students and teaching staff at a school, and hospital staff.

Definitions and assumptions

Participants in recurrent gatherings frequently form cohorts (e.g. school classes, office staff) within which the individuals interact preferentially. Cohorting has also been considered as a mitigation measure for transmission at gatherings (4). Furthermore, a common intervention by public health to minimize transmission at gatherings is to reduce the contact rate between cohorts as much as possible (5).

If it is assumed there are M cohorts, G_1, G_2, ..., G_M and, for simplicity, assume that all cohorts have the same size of N individuals, then there is a total of $M \times N$ individuals that gather on a regular basis. From an epidemiological perspective, there are three main transmission pathways associated with these recurrent gatherings: introduction of infected individuals in a cohort; transmission within a cohort; and transmission between cohorts (**Figure 4**).

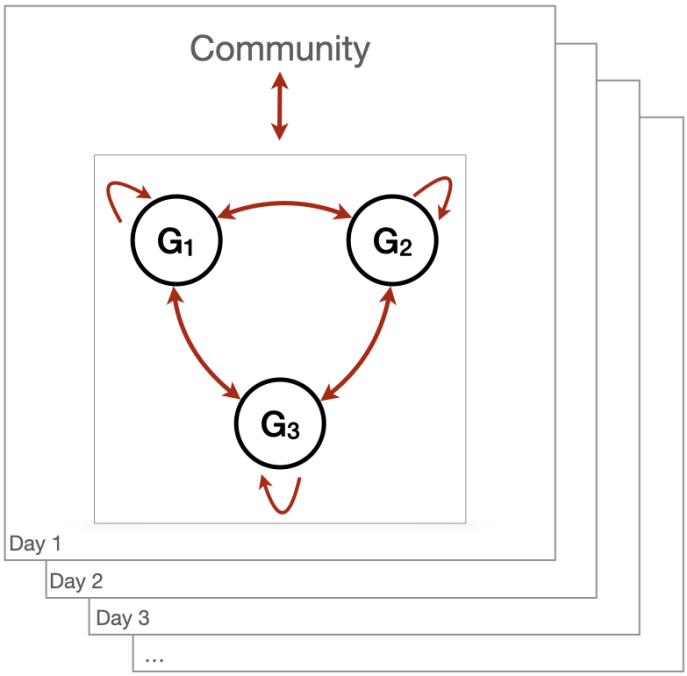
Introduction risk

For recurrent gatherings, the risk of introduction can be estimated in a similar fashion to that of non-repeated gatherings, but the frequency with which the gathering occurs (t) also needs to be considered. This then estimates the introduction risk into a recurrent gathering in a community with prevalence ($prev$), gathering size (MN), made up of M groups of size N over the course of t days.

$$p_{intro} = 1 - (1 - prev)^{tMN}$$

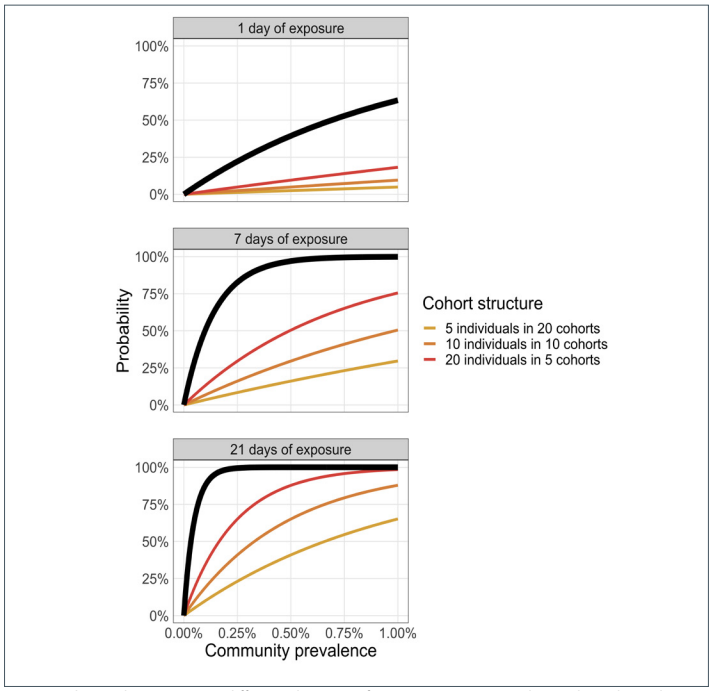
Figure 5 illustrates that for a recurrent gathering of 100 people with different cohort sizes (20 groups, each with a cohort size of five people; 10 groups with a cohort size of 10; or five groups with a cohort size of 20), cohort size does not change the risk

Figure 4: Transmission pathways associated with recurrent gatherings



Abbreviation: G, group
Note: Individuals are assigned groups with which they will preferentially interact with. Example with three groups/cohorts. Contact between groups is minimized. Individuals gather frequently to perform their duties within this organization. Individuals live within a community where the epidemic spreads. Hence, assuming that all individuals are not infected when they start their recurrent gatherings, cohorts face an introduction risk from interactions with the community they live in, then transmission within and between groups

Figure 5: Introduction risk as a function of time and cohort structure



Note: Each panel represents a different duration of exposure (1, 7 or 21 days). The coloured curves illustrate the introduction risk for each cohort structure and the thick black line shows the introduction probability at the organization level (i.e. considering all cohorts)

of introduction to the gathering as a whole. However, the risk of introduction to each individual cohort is significantly reduced by reducing the cohort size. Thus, the challenge is to develop strategies to ensure that if an infection is introduced into one of the cohorts it does not spread to the other cohorts at the gathering.

The risk of infection from the community is simply the infection prevalence in the community (assuming the gathering is representative of the population). As described above for unrepeated gatherings, if the individuals have a different prevalence, $prev_G$, than the one found in the community, the expected prevalence can be adjusted using an estimated relative risk or an odds ratio.

Transmission within a cohort

Estimating transmission within one cohort is similar to the analysis above for unrepeated gatherings, but with a larger value for the number of contacts (C) because of the recurrent nature of the gathering.

Transmission between cohorts

The probability of transmission over the duration of infectiousness between a cohort where at least one member is infectious and any other fully susceptible cohort, is p_{bw}. If the cohorts are completely isolated, $p_{bw} = 0$, then the maximum number of secondary transmissions following the introduction of an infectious person in a cohort is limited to the cohort size, N. Recall there is a total of $M \times N$ individuals (M cohorts with N individuals each), so the overall attack rate cannot be larger than $N/NM = 1/M$. For example, a company that has 20 employees separated into four cohorts, each with five individuals, will have a maximum attack rate of 1/4=25% if these cohorts are kept completely isolated.

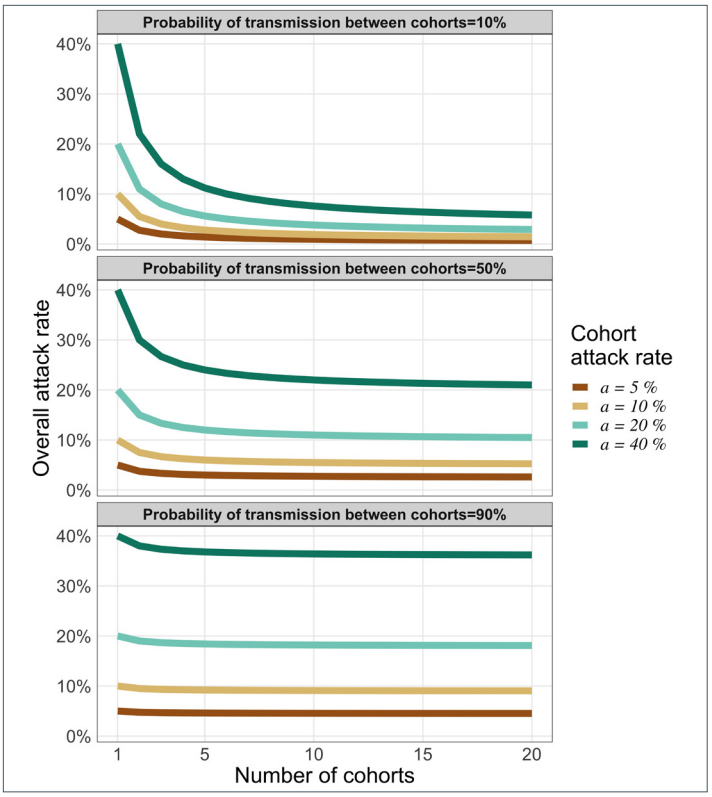
Of course, the assumption of complete isolation between cohort is rarely realistic and the probability of transmission between cohorts is greater than zero ($p_{bw} > 0$). If a is the attack rate within one single cohort ($0 \le a \le 1$ then, assuming none of the infections is detected, the expected number of infected individuals in a cohort where the initial infectious individual was introduced is aN. Taking the approach that the seeded cohort can potentially infect any other cohort at the same time (so effectively considering only two synchronous generations of infections as well as homogeneous mixing) the overall attack rate is:

$$a_{all} = a\left(\frac{1}{M} + \left(1 - \frac{1}{M}\right)p_{bw}\right)$$

When the cohorts are well isolated (p_{bw} is very small), the overall attack rate is reduced simply by the fact of splitting the organization into M cohorts and we have $a_{all} \approx a/M$: only the cohort that experiences an introduction is affected, so the overall attack rate is diluted by the number of cohorts. At the other extreme (**Figure 6**, right panel), if the cohorts are poorly isolated (p_{bw} near one) then partitioning the organization into cohorts has little effect ($a_{all} \approx a$). For low to moderate probabilities of transmission between cohorts (Figure 6, left and centre panels),

increasing the number of cohorts markedly dilutes the overall attack rate (a_{all}) when the cohort attack rate (a) is large (say, above 20%). Moreover, because of the $1/M$ terms, the dilution of the attack rate saturates as M increases (Figure 6).

Figure 6: Transmission risk between cohorts following a single introduction



Note: The vertical axis represents the overall attack rate for an organization that has separated its members in cohorts (horizontal axis). Each coloured curve represents a different cohort attack rate. Each panel illustrates how the overall attack rate (for the whole organization) varies based on three levels of isolation between cohorts (high isolation for left panel, moderate for the centre panel and low isolation for the right panel)

Mitigation using testing

Reducing the risk of infections at a gathering can be achieved by reducing the chances of contacts, by reducing the probability of transmission given a contact or both. Physical distancing, for example keeping at least two meters between participants, can reduce the probability of contact. Hand washing, surfaces sanitation and the proper use of masks have all been shown to reduce the probability of transmission.

A third strategy to limit the transmission risk is testing participants before (for unrepeated gatherings) or during (for recurrent gatherings) the gathering(s).

Pre-gathering testing

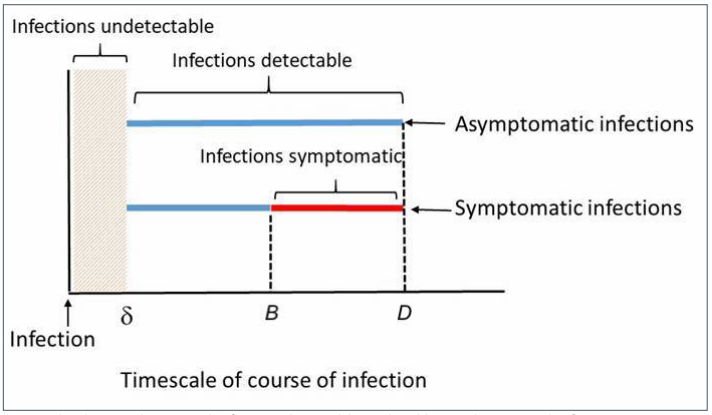
There are two types of tests currently available to diagnose a SARS-CoV-2 infection: a polymerase chain reaction (PCR)-based assay performed in well-equipped laboratories and a rapid, often point-of-care, test, which is antigen-based (e.g. the PanBio™ COVID-19 Ag Rapid Test, Abbott Point of Care Inc.). The former is considered the gold standard but usually suffers from a long turnaround time, which can make its use impractical shortly before a gathering. The latter could be deployed just before a gathering, to filter out infected participants, but it generally suffers from a poor sensitivity when used on asymptomatic individuals (6). Testing of saliva samples, which are less invasive to obtain than the nasopharyngeal swabs used currently for PCR-based assays, would increase the possibility of repeat testing (7). The application of routine repeat testing to enhance detection of transmission at gatherings and workplaces is an ongoing field of research (8).

Assuming that all the logistical hurdles associated with performing tests shortly before a gathering can be overcome, the testing of participants at a gathering could help reduce the transmission risk.

Accounting for transmission risk must take into consideration different durations when infections might be detectable. In a scenario in which viral shedding lasts for D days after the day of infection, the incubation period is B days, the minimum detectable viral concentration is reached after δ days and the asymptomatic fraction of infection in the population is α.

We assumed an infected individual would not attend a gathering once symptoms started. Thus, for symptomatic individuals, the window to identify them is $(B - \delta)$ days over a total period of B days. In contrast, for infected but asymptomatic individuals, the window to identify them is longer, $D - \delta$ days over a total of D days (see **Figure 7**). Symptomatic individuals were assumed to attend a gathering only during their pre-symptomatic infectious period.

Figure 7: Window of viral infection detectability vary between symptomatic and asymptomatic individuals



Note: Blue lines indicate viral infection detectable and red line indicates viral infection not detectable (since it was assumed that an infected individual would not attend a gathering when symptoms were present)

Hence, the probability that an infectious individual would be tested while the viral load is in the detectable window is

$$p_{detectable} = (1 - \alpha)\frac{B - \delta}{B} + \alpha\frac{D - \delta}{D}$$

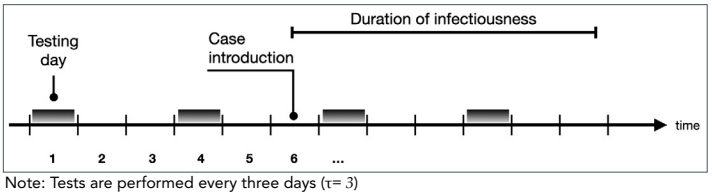
For example, taking parameters typical of a SARS-CoV-2 infection we have B = 5 days, D = 20 days (9), α = 30% and δ = 1 day we have $p_{detectable}$ = 84.5%. In other words, about one out of six infectious participants will not be within the window of viral infection detectability.

Mitigating introduction and transmission risk with testing

There are numerous ways, most of them setting-specific, to reduce the risk of introduction and onwards transmission in recurrent gatherings. In this section, we focus on mitigating the transmission risk using periodic testing.

To reduce the risk of introduction and onward transmission to other cohorts (and to the community), we can test periodically, say every τ days, all individuals in all cohorts. It is assumed that the duration of infectiousness is fixed at D days and that a test is available that can detect infection with specificity sp and sensitivity se. Note that the detection can occur at any testing point during the infectiousness period, not just at the start (**Figure 8**).

Figure 8: Periodic testing in relation to the infectious period



Note: Tests are performed every three days (τ= 3)

The probability of assessing the absence of a disease in a group using multiple rounds of testing has been extensively covered in veterinary epidemiology and is often referred to as "freedom from disease" (10). Given a sensitivity se for a test performed on n individuals every t days over T days, the probability of detecting an infection is

$$p_{detect} = 1 - (1 - prev \times se)^{nT/\tau}$$

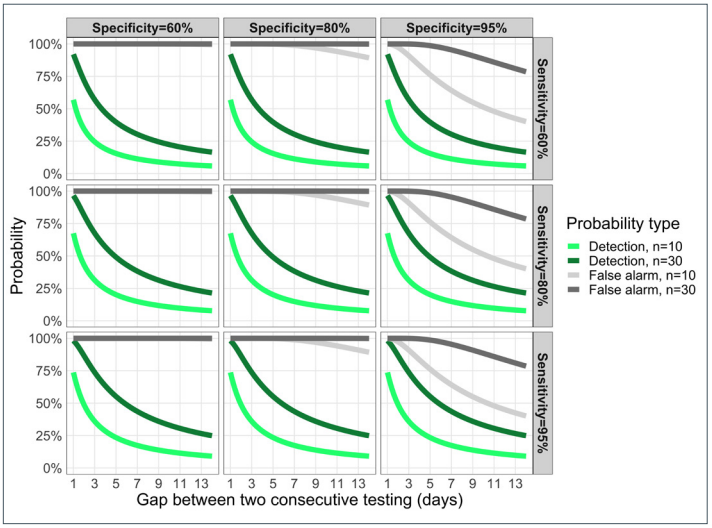
where prev is the prevalence in the group tested (11). Note that p_{detect} may overestimate the actual probability if the periodical tests are correlated with one another (for example when testing the same individuals).

To maximize the probability of detection, the tests could be done daily. This is becoming increasingly possible thanks to point-of-care antigen-based tests. However, if the test has suboptimal specificity, false positives could impose unnecessary constraints (such as closure, isolation of personnel) on the organization (school, business, hospital). The probability that, when testing n uninfected individuals, at least one test returns a false positive result during this period is (see Appendix for details).

$$p_{false\ alarm} = 1 - sp^{nT/\tau}$$

Figure 9 illustrates the balancing act between maximizing the probability of detection (p_{detect}) and minimizing the nuisance of false alarms ($p_{false\ alarm}$) when choosing the testing frequency (τ) and the sample size to test within the groups (n).

Figure 9: Trade-off between the probability of detecting an infectious case and a false positive



Note: Trade-off between the probability to detect an infectious case and the probability of a false positive as a function of the testing frequency (horizontal axis; 1 means testing every day, 7 means every week). The green curves represent the probability to detect the first individual during her/his infectious period, here set at D=14 days when testing n individuals in the organization. The grey curves represent the probability to have a false positive for n persons tested. Each panel has different values of test specificity and sensitivity (top left panel is the least accurate, bottom right panel is the most accurate)

Time from infection to discovery

Given a testing frequency and a test accuracy, what is the expected duration between the introduction of an infectious case and its detection? If we assume an individual can be infected at any time between two consecutive tests, we can show that the time from infection to discovery is bounded by the following quantity:

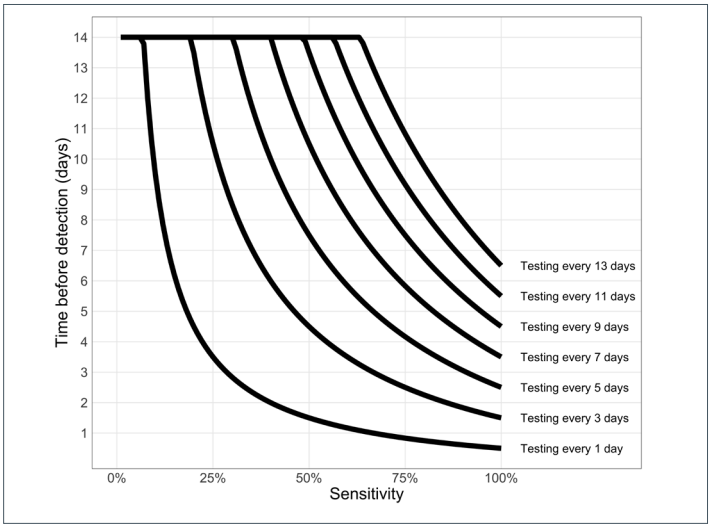
$$t_{discovery} \leq min\left(D, \tau\left(\frac{1}{se} - \frac{1}{2}\right)\right)$$

The effect of test sensitivity and test frequency on the time-to-discovery ($t_{discovery}$) is illustrated in **Figure 10**. For a high testing frequency (e.g. less than every three days) we see that the test sensitivity does not have a large impact on the speed of detection (*Personal communication, Dr. Troy Day, Queen's University, Kingston, ON*) (12).

A natural comparison unit for $t_{discovery}$ is the generation interval. The generation interval is the interval between the time when an individual is infected by an infector and the time when this infector was infected. To slow an epidemic, $t_{discovery}$ should

be much smaller than the generation interval, to prevent opportunities of secondary transmissions.

Figure 10: Testing frequency determines time from introduction of an infection to its detection



Discussion

In this study we have developed a simplistic and generic model framework to assess the risk of SARS-CoV-2 transmission at gatherings. In so doing, we have highlighted some key features of risk at gatherings, and two methods that can be used to mitigate risks.

The first determinant of risk at gatherings is the probability that at least one infectious individual is present ("introduction risk"). This risk can be broadly assessed with the population prevalence and the size of the gathering. Super-spreading events often occur during gatherings (1–3). Intuitively, limiting the size of gatherings reduces the likelihood of such super-spreading events. Several modelling studies have associated smaller gathering sizes with lower reproduction numbers (13,14).

The second determinant is the risk of onwards transmission at the gathering, which is mainly driven by the gathering size and by how many contacts were present at the gathering. Our simple modelling framework highlighted the saturating effect of the contact rate (Figure 2), that is, the transmission risk is markedly reduced only when the contact rate is sufficiently low.

For recurrent gatherings, cohorting generally reduces risk of transmission, and those gatherings with a small number of well-isolated cohorts are less risky than those with a large number of poorly isolated cohorts. How the cohorts are structured (few with many individuals versus many with few individuals) does not have a significant impact on transmission between cohorts. A smaller cohort will, however, reduce the maximum number of people that can be infected if an infection is introduced into the gathering and the cohorts are well isolated.

The probability of an infectious person arriving at the gathering is a function of the prevalence of COVID-19 within the community. Testing is a mitigation option that could be employed as the attendees arrive at the gathering; however, we demonstrated that deciding on the frequency of testing with an imperfect test may be a balancing act between the efficiency of detection and the nuisance of false positives.

The findings presented here are broadly in accordance with models that are more complex (3) as well as similar simple approaches (15). The limitations of the simple approach to quantify "gathering risk" is illustrated by Figure 3 where many factors (e.g. indoors/outdoors, age of participants) can affect the transmission risk for a given gathering type. To some extent, as knowledge increases from epidemiological investigations and prospective studies, more precise values for variables such as transmission probabilities can be used to improve the parametrization of the model. However, the high-level approach here cannot replace more in-depth and detailed modelling analysis, which can take into account the multiple factors affecting transmission risk including quantifying and representing contact patterns between age groups, effects of ventilation, masks or physical distancing.

There is still a lot of uncertainty regarding the quantitative contribution from the myriad of factors that influence transmission of SARS-CoV-2 in gatherings. As evidence accumulates, we will be in a better position to inform the variables that encompass multiple underlying factors; for example, the probability of transmission presented here should be informed by indoors/outdoors settings, distance between individuals, mask usage, etc. Listing exhaustively those factors and assessing their importance regarding the transmission risk of SARS-CoV-2 at gatherings should be the focus of future studies.

Conclusion

Introduction risk can be broadly assessed with the prevalence of COVID-19 within the population and the size of the gathering, while transmission risk at a gathering is mainly driven by the gathering size. For recurrent gatherings, the cohort structure does not have a significant impact on transmission between cohorts. Testing strategies can mitigate risk, but frequency of testing and test performance are factors in finding a balance between detection and false positives.

The simple modelling framework presented here brings clarity in the interactions between the variables at play (number of participants, contact rates, etc.) in assessing the epidemiological risk. It can be used to provide a first-step assessment of risk of a gathering, and the possibility of mitigating risk. The generality of the modelling framework used here helps to disentangle these

various factors affecting transmission risk at gatherings and may be useful for public health decision-making.

Authors' statement

DC — Conception, formal analysis, writing–original draft, writing–review and editing
AF — Conception, drafting analysis, revising of writing, critical review
NHO — Conception, revising of writing, critical review

Competing interests

None.

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Appendix

Probability of introduction in recurrent gatherings

The probability of having at least one individual from one group G_i being infected on any given day is day is

$$p_1 = 1 - (1 - prev)^N$$

For this group, the probability that no introduction occurs during t consecutive days is $(1 - p_1)^t$. The probability that at least one of the M groups has an introduction is $1 - ((1 - p_1)^t)^M$, substituting $p_{intro}(t) = 1 - (1 - prev)^{tMN}$.

Transmission risk in a gathering

Assuming homogeneous mixing at a gathering, the probability that one susceptible individual contacts an infectious one is

$$\mathbb{P}\text{ (one susceptible contats on infectious)} = \frac{I}{N-1}$$

If the susceptible individual has C contacts during the gathering, the probability that at least one of these contacts is with an infectious individual is

$$p_c = 1 - \left(1 - \frac{I}{N-1}\right)^C$$

Transmission between cohorts

The expected number of secondary infections following a single introduction is

$$\mathbb{E}(A^{\text{all}}) = aN + aN\,(M-1)p_{\text{bw}}$$

The first term (aN) represents the number of infections generated from the cohort first infected because of a single introduction. The second term represents the onward infections to the remaining $M - 1$ cohorts. To have the overall attack rate we need to normalize by the group size, hence dividing by MN gives

$$a_{\text{all}} = a\left(\frac{1}{M} + (1-\frac{1}{M})\,p_{\text{bw}}\right)$$

Nuisance probability

The probability that all tests return negative from an uninfected individual tested every τ days over T days is $\text{sp}^{T/\tau}$. Similarly, if we now consider n uninfected persons, all tested every τ days, the probability that all of these tests return negative is $\text{sp}^{T/\tau}$. Hence, the probability that at least one test returns positive (a false alarm) during this period is $1–\text{sp}^{nT/\tau}$.

Time from infection to discovery

Let L_0 be the length of time between the introduction and the next test and assume it is uniformly distributed between 0 and τ. The number of false positive tests until detection, X, is assumed to be geometrically distributed and we have $\mathbb{P}(X = k) = (1 - \text{se})^k\text{se}$, where se is the test sensitivity. The theoretical length of time before detection is then defined as

$$L = L_0 + \tau X$$

The expectation for L is simply $\mathbb{E}(L) = \tau(1 - \text{se})/\text{se}$ where the first term comes from the assumption that L_0 is uniformly distributed and the second term from the geometric distribution for X. The duration of infectiousness D is finite so the time to infection discovery L is naturally bounded by D. Applying Jensen's inequality for the concave function $f(x) = \min(x,D)$, we have:

$$\mathbb{E}(\min(L,D)) \le \min\left(D, \tau\left(\frac{1}{se} - \frac{1}{2}\right)\right)$$

Table of data source

Table S1: Observed transmissions at gatherings[a]

Event	Country	Gathering size	R_{lo}	R_{hi}	Duration (h)[b]	Source
Choir	United States	61	30	50	2.5	Tupper *et al.*, 2020
Restaurant	China	83	10	10	2	Tupper *et al.*, 2020
Party	Japan	90	5	10	4	Tupper *et al.*, 2020
Family dinner	China	7	3	3	2	Tupper *et al.*, 2020
Night in chalet	France	10	4	9	8	Tupper *et al.*, 2020
Night in chalet	France	5	1	3	8	Tupper *et al.*, 2020
Bus trip	China	39	5	5	2	Tupper *et al.*, 2020
Bus trip with mask	China	14	0	0	0.83	Tupper *et al.*, 2020
Supper	Canada	120	24	N/A	3	CTV news
Sport	Canada	72	24	N/A	6	The National Post
Sport	Canada	21	15	N/A	4	Montreal Gazette
Choir	France	27	19	N/A	2	Charlotte, 2020
Wedding	Germany	111	61	N/A	6	Gelderlander
Wedding	Australia	120	42	N/A	6	The Daily Mail

Table S1: Observed transmissions at gatherings[a] (*continued*)

Event	Country	Gathering size	R_{lo}	R_{hi}	Duration (h)[b]	Source
Party	United States	10	7	N/A	3	Ghinai et al., 2020
Party	Portugal	100	16	N/A	6	The Portugal Resident
Party	United States	25	18	N/A	2	WFAA
Party	United States	25	18	N/A	2	The Gainesville Sun
Choir	Netherlands	80	32	N/A	2	Omroepgelderland

Abbreviation: N/A, not available
[a] Low (high) estimates of transmissions is given by R_{lo} (R_{hi})
[b] Durations were estimated when not explicitly available

RAPID COMMUNICATION

Serum antibody response in COVID-19-recovered patients who retested positive

Nicole Atchessi[1], Megan Striha[1], Rojiemiahd Edjoc[1]*, Christine Abalos[1], Amanda Lien[1], Lisa Waddell[2], Imran Gabrani-Juma[1], Emily Thompson[1], Thomas Dawson[1]

Abstract

Background: Research studies comparing antibody response from coronavirus disease 2019 (COVID-19) cases that retested positive (RP) using reverse transcription polymerase chain reaction (RT-PCR) and those who did not retest positive (NRP) were used to investigate a possible relationship between antibody response and retesting status.

Methods: Seven data bases were searched. Research criteria included cohort and case-control studies, carried out worldwide and published before September 9, 2020, that compared the serum antibody levels of hospitalized COVID-19 cases that RP after discharge to those that did NRP.

Results: There is some evidence that immunoglobulin G (IgG) and immunoglobulin M (IgM) antibody levels in RP cases were lower compared with NRP cases. The hypothesis of incomplete clearance aligns with these findings. The possibility of false negative reverse transcription polymerase chain reaction (RT-PCR) test results during viral clearance is also plausible, as concentration of the viral ribonucleic acid (RNA) in nasopharyngeal and fecal swabs fluctuate below the limits of RT-PCR detection during virus clearance. The probability of reinfection was less likely to be the cause of retesting positive because of the low risk of exposure where cases observed a 14 day-quarantine after discharge.

Conclusion: More studies are needed to better explain the immune response of recovered COVID-19 cases retesting positive after discharge.

Affiliations

[1] Health Security and Operations Branch, Public Health Agency of Canada, Ottawa, ON

[2] Public Health Risk Sciences Division, National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, MB

***Correspondence:**
rojiemiahd.edjoc@canada.ca

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Keywords: COVID-19, SARS-CoV-2, RT-PCR, false-negative, reinfection, retesting

Introduction

Coronavirus disease 2019 (COVID-19) is a novel disease that results from infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). On December 31, 2019, a case of pneumonia of unknown cause was identified in Wuhan, China and reported to the World Health Organization (WHO) Country Office. The cause of the disease was later confirmed to be a novel coronavirus (2). The SARS-CoV-2 outbreak was declared a pandemic by WHO on March 11, 2020 (3). As of October 14, 2020, 75% of the 38,508,475 internationally confirmed cases of COVID-19 have recovered (4). However, there is evidence that some recovered COVID-19 cases discharged from hospital with negative COVID-19 tests later retested positive (RP) (5).

Current situation

The situation of recovered and discharged COVID-19 cases retesting positive raise concerns of potential reinfection or incomplete clearance of the virus, as well as questions related to a patient's infectiousness. Multiple hypotheses have been put forward to explain the reasons why some cases RP after discharge with negative reverse transcription polymerase chain reaction (RT-PCR) test results. The purpose of this review is to explore the current evidence regarding differences in antibody response between discharged COVID-19 cases that RP and those that did not retest positive (NRP).

Methods

Our research criteria included cohort and case-control studies carried out across the world and published before September 9, 2020, that compared the serum antibody level of hospitalized COVID-19 cases that RP after discharge to those that did not. Seven databases were searched. Search terms used included the following: reactivation; reinfection; reoccurrence; recurrent; in conjunction with hospitalization; discharge; antibody; and immunity. Articles (n=224) were screened for relevance and included studies were evaluated with the Newcastle-Ottawa Scale Risk of Bias Tool according to criteria related to the selection of the cases (score=4), the comparability of RP cases to NRP cases (score=2) and the assessment of the exposure or the outcome (score=3). A total of nine studies were found to be relevant (see **Appendix A**). A follow-up of at least four weeks was considered as adequate in cohort studies. The assessment was done by two reviewers (see **Appendix B**).

Results

We identified three prospective cohort studies (6–8), three retrospective cohort studies (9–11), two cohort studies (unclear if prospective or retrospective) (12,13) and one case-control study (14).

The sample size of the nine studies varied from 74 to 619. The prevalence of COVID-19 cases that experienced a reoccurrence of a positive PCR test after meeting discharge criteria of two consecutive negative RT-PCR tests more than 24 hours apart, varied from 7% to 21% in seven out of eight cohort studies (6–8,10–14), with the ninth study finding 58% RT (9). The average prevalence for the eight cohort studies was 16.6% (n=382/2,305 cases). Of the six studies that captured information on the time between testing negative at discharge and RP the first time post discharge, the median time across studies varied from 4.6 days to 12 days (6,8,10,11,13,14). The RP cases were significantly younger in four studies (6,8,13,14); however, no age difference was found in the five other studies (7,9–12). No association with sex was reported in any study.

Six studies reported on the positivity rate of immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies (7,8,10–13), while four specified their serum levels (8,9,12,14). There were no differences in IgG and IgM antibody positivity rates between RP and NRP cases (6–8,10–13); however, the level of IgG (9,14) and/or IgM (8,14) antibodies in the serum was lower in RP cases compared with NRP cases in three studies. No difference was observed in either IgM (9,12) or IgG level (8,12) in the other studies.

Discussion

There are several possible explanations for what a RP result following discharge such as low viral load in samples, false negative results in RT-PCR tests and re-infection. The most likely explanation is a false negative RT-PCR result due to 1) viral ribonucleic acid (RNA) concentration decreasing to levels below the limit of detection of the test during viral clearance and 2) the expected proportion of false negative results in RT-PCR tests.

According to Liu *et al.* (12), given that the presence of IgM antibodies was similar in both cases who RP and NRP, the RP RT-PCR tests in their review of 619 cases were unlikely to be due to reinfection with SARS-CoV-2 virus. The studies included in this review mainly monitored cases during the post-discharge 14-day quarantine period, which would also rule out re-infection as a likely explanation for RP results shortly after discharge.

According to Yang *et al.*, false negative RT-PCR results could also result from low virus concentrations in samples from nasopharyngeal or fecal swabs despite viruses still being present in the lower respiratory tract, leading to intermittent or fluctuating excretion of viral RNA in the upper respiratory tract (8).

Wölfel *et al.* reported that the RT-PCR for SARS-CoV-2 is an imperfect test, with a sensitivity of 89% and, thus, an expected proportion of 11% false negative results (15). Zou (11) found that performing three consecutive tests prior to discharge significantly reduced the chance of RP, which is consistent with the false-negative results hypothesis.

The findings that relate lower level of antibodies to RP suggest that cases that RP were more likely to have a weaker immune response, which aligns with the hypothesis of a viral clearance. According to Yuan (7), the lowest prevalence of subsequent positive tests experienced by cases with severe symptoms compared with those experiencing mild symptoms can be explained by a stronger immune response activated in severely ill cases that clears the virus more effectively.

One of the main concerns that arise from cases RP is the infectiousness of cases after discharge. While some authors argued that the risk of infectiousness during this period is low (8,16), others claimed the opposite and even mention the possibility of chronic infection with SARS-CoV-2 (12). This latter assumption casts doubt on the protective role of IgG antibodies and of using serology testing to establish immunity.

The findings of this review seemed to be supportive of an association between antibody response and RP after discharge. There is some evidence that IgG and IgM antibodies levels in RP cases are lower compared with NRP cases. The hypothesis of incomplete clearance also aligns with these findings.

Limitations

The current review has several limitations. Five out of nine studies had a sample size of less than 200 and all studies were restricted to China, which limits the representativeness of the review. We were unable to find research outside of China that had serology results, a comparison group and had follow-up RT-PCR testing to establish RP status. Among the included studies, the duration of follow-up after discharge and RT-PCR testing intervals varied, which could impact the results related to the timing and prevalence of RP results summarized in this study. In addition, eight out of nine studies were based on discharged cases but no information about their representativeness of hospitalized cases was provided. Further, the lack of comparison of cases with incomplete medical records or lost to follow-up to those that remained in the studies limits the assessment of potential bias estimates. This study included studies published up to September 2020 and should be interpreted accordingly, given the rapid evolution of the evidence. It could be valuable for future studies to focus on testing practices that could reduce the probability of false negative tests to ensure that hospitalized COVID-19 cases meet the required criteria before their discharge.

None of the studies examined the potential association in a multivariable analysis with antibody response to determine the adjusted associations after controlling for potential confounders.

Conclusion

The situation of COVID-19 cases subsequently RP for COVID-19 after having two negative RT-PCR test results is not uncommon. Evidence suggests a relationship between RP cases and age (6,8,13,14) and possibly between RP and disease severity. However, none of the studies examined the potential association in a multivariable analysis with antibody response to determine the adjusted associations after controlling for potential confounders. Additional evidence synthesis work with proper observational studies on the characteristics of COVID-19 cases that RP is needed to better understand who is likely to RP. Similarly, additional research and synthesis work on immune response and immunity is needed to improve our understanding of COVID-19 infection.

The evidence summarized in this report may have important implications for public health and management of recovered COVID-19 cases. There was a limited number of studies that met the inclusion criteria; however, the evidence suggests the immune response in convalescent COVID-19 cases may be associated with the incomplete viral clearance. These preliminary results can be used to inform further research or decision making on this topic.

Authors' statement

NA — Methodology, investigation, writing–original draft, review and editing
MS — Methodology, investigation, writing–original draft, review and editing
RE — Conceptualization, methodology, investigation, writing–original draft, review and editing, supervision
CA — Writing–original draft, review and editing
AL — Writing–original draft, review and editing
LW — Writing–review and editing
IGJ — Writing–review and editing
ET — Writing–review and editing
TD — Writing–review and editing

Competing interests

None to declare.

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Appendices

Appendix A: Serological characteristics of discharged hospitalized coronavirus disease 2019 cases who retested reverse transcription polymerase chain reaction-positive compared with those that did not test positive

Description of study (reference and type, location and dates of study)	Report details	Key findings and limitations
Lu *et al.*, 2020 (6) Prospective cohort study Guangdong, China Jan 23–Feb 19, 2020	• This study followed 619 discharged cases and serology was the main outcome: 288 cases had serological testing a median of 35 days post symptom onset (range=23–47 days). • Cases were followed for 66 days post discharge, and RP on day 10 on average (tested on day 7 and 14 only).	• Neutralizing antibody titers for RP and NRP cases were not significantly different 14 days post hospital discharge. • This study had the largest cohort that was followed for the longest period of time, recording a RP incidence rate of 14% (n=87/619 cases). • RP cases in this study were significantly younger than NRP cases. Sex distribution did not differ between groups. Limitations: • It was not mentioned if the discharged cases involved in the study were representative of the hospitalized cases. • Serology tests were done for only 288 out of 619 cases in the study and their selection criteria were not mentioned.
Yang *et al.*, 2020 (8) (Preprint) Prospective cohort study Shenzhen, China Feb 1–May 5, 2020	• This study followed 479 discharged cases. Serology is main outcome, with serum specimens collected on the 1st, 3rd, 7th, and 14th days post-discharge. • Cases were followed for 90 days post discharge, and retested positive on day 8 on average. An average of 46 days elapsed between disease onset and the final RP event for each patient.	• RP and NRP cases did not differ in rates of testing positive for IgG antibodies (99% and 98%, respectively). Serum levels of IgG antibodies also did not differ between groups at any point after disease onset. • RP and NRP cases did not differ in rates of testing positive for IgM antibodies (37% and 50%, respectively). Serum levels of IgM antibodies differed between groups at different points post-disease onset: At week 3, RP cases had significantly higher levels of IgM, while at weeks 6 through 8, RP cases had significantly lower IgM levels. • The incident rate of RP in this study was 19% (n=93/479 cases). In addition, 45 (9%) experience multiple RP events: two (n=32, 7%), three (n=9, 2%), or four (n=4, 1%) RP events. • RP cases in this study were significantly younger than NRP cases (34 years compared with 45 years). Sex distribution did not differ between groups. Limitations: • It was not mentioned if the discharged cases involved in the study were representative of the hospitalized cases. • From the 504 cases in the cohort, 25 were excluded because of the lack of information in their medical records.
Yuan *et al.*, 2020 (7) Prospective cohort study Shenzhen, China Before Apr 21, 2020	• This prospective cohort study followed 182 discharged cases. Serology is one of the main outcomes of this study, with 147 cases submitting for serological testing on the 7th and 14th day after discharge. • Cases were followed for 14 days. Patients were followed during the mandatory 14-day quarantine following hospital discharge and retested on day 7 and 14 of quarantine.	• RP and NRP cases did not differ in rates of testing positive for IgG antibodies (100% and 99.2%, respectively). • RP and NRP cases did not differ in rates of testing positive for IgM antibodies (71.4% for both). • The incident rate of RP in this study was 11% (20/182 cases). • RP cases were not significantly younger in this study, however, cases under 18 years of age were overrepresented in the RP group. Sex distribution did not differ between groups. Limitations: • The selection criteria of the population involved in the study was not specified. • Since the serology test was done on a voluntary basis, only a subset had serology results (14 RP cases and 133 NRP cases). No information was provided about the differences between those that did the serology test and those that did not.
Zhu *et al.*, 2020 (10) Retrospective cohort study Zhejiang, China Before Apr 2, 2020	• This retrospective cohort study followed 98 discharged cases. Serology was part of a wide range of factors examined, with testing measuring temporal changes in antibody levels. The exact timing of tests is not stated. • Cases were followed for at least 17 days following discharge, with the average time to RP being 7 days.	• In this study, 35.5% of RP cases tested positive for both IgG and IgM antibodies, compared to 8.6% of NRP cases. 58.8% of RP cases tested positive for IgG and negative for IgM antibodies, compared to 44.4% of NRP cases. Two RP and one NRP cases tested negative for both IgG and IgM antibodies. The groups were not significantly different. • The incident rate of RP was 17% (17/98 cases). • Neither age nor sex was found to differ between RP and NRP cases. Limitations: • Only convalescent patients were followed. It was not specified if they were representative of hospitalized patients.

Appendix A: Serological characteristics of discharged hospitalized coronavirus disease 2019 cases who retested reverse transcription polymerase chain reaction-positive compared with those that did not test positive (*continued*)

Description of study (reference and type, location and dates of study)	Report details	Key findings and limitations
Hu *et al.*, 2020 (9) Retrospective cohort study Chongquin, China Jan 23–Mar 3, 2020	• This study followed 221 hospitalized cases. Serology was the main outcome, with serum samples taken every 3 days post-symptom onset. • Total of 74 cases were discharged and followed for the 14-day quarantine period.	• Cases that experienced RP had post-discharge IgG levels of 8.94 on average, compared to 20.19 in NRP cases, which is significantly lower in the RP group. Levels are expressed as a ratio of the chemiluminescence signal to the cut off value (S/CO). • RP and NRP cases did not have significantly different post-discharge IgM levels (0.90 S/CO compared with 1.39 S/CO, respectively) • Reports the highest RP incidence rate of the ten studies (n=39/74, or 52.7%). No average time to retesting positive was stated. • No age/sex differences between RP and NRP cases reported. Limitations: • Only 74 cases were discharged and followed for the 14-day quarantine period. It was not specified if they were representative of hospitalized patients.
Zou *et al.*, 2020 (11) Retrospective cohort study Wuhan, China Jan 1–Mar 10, 2020	• This study followed 257 hospitalized cases. • Serology was not main outcome of the study. It is unclear how long cases were followed for or when they underwent serological testing.	• RP and NRP cases did not differ in rates of testing positive for IgG antibodies (94.4% and 85.1%, respectively). • RP and NRP cases did not differ in rates of testing positive for IgM antibodies (52.8% and 58.8%, respectively). • The incident rate of RP in this study was 20.6% (n=53/257 cases). • Neither age nor sex was found to differ between RP and NRP cases. • It is unclear how long cases were followed, but were said to retest positive an average of 4.6 days post-discharge. • The goal of this study was to compare RP rates for cases with two subsequent negative PCR tests compared to three subsequent negatives to qualify for discharge. 20.6% of cases with two negative tests experience RP, compared with only 5.4% of cases with three negative tests. Limitations: • Only a subset had serology results (36 RP cases and 114 NRP cases). Information about their difference with those that did not have the test was not mentioned.
Huang *et al.*, 2020 (13) Cohort study - unclear if prospective or retrospective Shenzhen, China Jan 11–Apr 23, 2020	• This study followed 414 hospitalized cases. Serology was part of a wide range of factors examined. 154 cases had serological testing at discharge from hospital. • Cases were followed for four weeks following discharge. They retested positive on the day 10 on average, with RT-PCR testing done every 3–5 days.	• RP and NRP cases did not differ in rates of testing positive for IgG antibodies (100% and 99.1%, respectively). • RP and NRP cases did not differ in rates of testing positive for IgM antibodies (75.0% and 48.2%, respectively). • The incident rate of RP in this study was 16.7% (n=69/414 cases). • RP cases in this study were significantly younger than NRP cases. Sex distribution did not differ between groups. Limitations: • It was not specified if the study population was representative of hospitalized patients.
Liu *et al.*, 2020 (12) Cohort study - unclear if prospective or retrospective Wuhan, China Mar 1–13, 2020	• This study followed 150 discharged cases. • Serology was main outcome measure, but neither timing of serology nor duration of follow-up was noted. Testing at different points following discharge may have affected the results.	• RP and NRP cases did not differ in rates of testing positive for IgG antibodies (100% and 90.6%, respectively). Serum levels of IgG antibodies also did not differ between groups (243 AU/mL and 185 AU/mL, respectively). • RP and NRP cases did not differ in rates of testing positive for IgM antibodies (45.5% and 47.5%, respectively). Serum levels of IgM antibodies also did not differ between groups (9.6 AU/mL and 8.9 AU/mL, respectively). • The incident rate of RP in this study was 7.3% (11/150 cases). • Neither age nor sex was found to differ between RP and NRP cases. Limitations: • Only convalescent patients were followed. It was not specified if they were representative of hospitalized patients. • The timing of the serological testing is not clear.

Appendix A: Serological characteristics of discharged hospitalized coronavirus disease 2019 cases who retested reverse transcription polymerase chain reaction-positive compared with those that did not test positive (*continued*)

Description of study (reference and type, location and dates of study)	Report details	Key findings and limitations
Chen *et al.*, 2020 (14) Case-control study Wuhan, China Feb 10–Mar 31, 2020	• This study examined the serology of 15 RP cases and 107 controls admitted to a single hospital. • Serology was part of a wide range of factors examined. Cases were followed up for 14 days. They retested positive at day 12 post-discharge on average. However, cases were only tested near the end of the 14-day quarantine.	• Cases experiencing RP had IgG levels of 78.53 AU/mL on average, compared with 147.85 AU/mL in NRP cases, which is significantly different. • Cases experiencing RP had IgM levels of 13.69 AU/mL on average, compared with 68.10 AU/mL in NRP cases, which is significantly different. • Reports the lowest RP incidence rate of the ten studies (n=2/107, or 1.9%) from the cohort in a single hospital. Fifteen cases from multiple sites were compared to 107 controls. • RP cases were found to be significantly younger than NRP cases (43 years compared with 60 years). There was no significant difference in sex of RP versus NRP cases. Limitations: • Age and sex were not matched between cases and controls. • The timing of the serological testing was not clear.

Abbreviations: COVID-19, coronavirus disease 2019; IgG, immunoglobulin G; IgM, immunoglobulin M; NRP, retested not positive; RP, retested positive; RT-PCR, reverse transcription polymerase chain reaction

Appendix B: Assessment with the Newcastle-Ottawa Scale Risk of Bias Tool of nine studies published up to September 2020, comparing immune response indicators of discharged hospitalized coronavirus disease 2019 cases who retested positive using reverse transcription polymerase chain reaction to those who did not test positive

Study	Selection (score=4)	Comparability (score=2)	Exposure/outcome (score=3)
Clinical, immunological and virological characterization of COVID-19 patients that test re-positive for SARS-CoV-2 by RT-PCR (6).	2	0	3
Recurrence of positive SARS-CoV-2 viral RNA in recovered COVID-19 patients during medical isolation observation (7).	2	0	1
Viral RNA level, serum antibody responses, and transmission risk in discharged COVID-19 patients with recurrent positive SARS-CoV-2 RNA test results: a population-based observational cohort study (8).	2	0	2
Recurrence of positive SARS-CoV-2 viral RNA in recovered COVID-19 patients during medical isolation observation (7).	2	0	1
Clinical features of COVID-19 convalescent patients with re-positive nucleic acid detection (10).	3	0	2
The production of antibodies for SARS-CoV-2 and its clinical implication (9).	3	0	1
The issue of recurrently positive patients who recovered from COVID-19 according to the current discharge criteria: investigation of patients from multiple medical institutions in Wuhan, China (11).	3	0	1
Recurrence of SARS-CoV-2 Positivity of Infected and Recovered Patients: A Single Center COVID-19 Experience and Potential Implications (13).	4	0	2
Recurrent positive SARS-CoV-2 - immune certificate may not be valid (12).	3	0	2
Clinical Characteristics of Recurrent-positive Coronavirus Disease 2019 after Curative Discharge: a retrospective analysis of 15 cases in Wuhan China (14).	3	0	3

Abbreviations: COVID-19, coronavirus disease 2019; RNA, ribonucleic acid; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Rapid disappearance of influenza following the implementation of COVID-19 mitigation measures in Hamilton, Ontario

Kevin Zhang[1]*, Avika Misra[2], Patrick J Kim[3], Seyed M Moghadas[4], Joanne M Langley[5], Marek Smieja[3,6]

Abstract

Background: Public health measures, such as physical distancing and closure of schools and non-essential services, were rapidly implemented in Canada to interrupt the spread of the coronavirus disease 2019 (COVID-19). We sought to investigate the impact of mitigation measures during the spring wave of COVID-19 on the incidence of other laboratory-confirmed respiratory viruses in Hamilton, Ontario.

Methods: All nasopharyngeal swab specimens (n=57,503) submitted for routine respiratory virus testing at a regional laboratory serving all acute-care hospitals in Hamilton between January 2010 and June 2020 were reviewed. Testing for influenza A and B, respiratory syncytial virus, human metapneumovirus, parainfluenza I–III, adenovirus, and rhinovirus/enterovirus was done routinely using a laboratory-developed polymerase chain reaction multiplex respiratory viral panel. A Bayesian linear regression model was used to determine the trend of positivity rates of all influenza samples for the first 26 weeks of each year from 2010 to 2019. The mean positivity rate of Bayesian inference was compared with the weekly reported positivity rate of influenza samples in 2020.

Results: The positivity rate of influenza in 2020 diminished sharply following the population-wide implementation of COVID-19 interventions. Weeks 12–26 reported 0% positivity for influenza, with the exception of 0.1% reported in week 13.

Conclusion: Public health measures implemented during the COVID-19 pandemic were associated with a reduced incidence of other respiratory viruses and should be considered to mitigate severe seasonal influenza and other respiratory virus pandemics.

Affiliations

[1] Faculty of Medicine, University of Toronto, Toronto, ON

[2] Faculty of Medicine, University of Ottawa, Ottawa, ON

[3] Department of Medicine, McMaster University, Hamilton, ON

[4] Agent-Based Modelling Laboratory, York University, Toronto, ON

[5] Canadian Center for Vaccinology, Dalhousie University, IWK Health Centre and Nova Scotia Health Authority, Halifax, NS

[6] St. Joseph's Healthcare Hamilton, Hamilton, ON

***Correspondence:**
kevink.zhang@mail.utoronto.ca

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Keywords: COVID-19, influenza, testing, public health interventions, Canada

Introduction

The coronavirus disease 2019 (COVID-19) has led to devastating global morbidity and mortality (1). Restrictive public health measures have helped to mitigate COVID-19 transmission (2,3), but have led to widespread disruptions to the economy (4,5), trade (6), and education (7). Following the declaration of COVID-19 as a pandemic on March 11, 2020 by the World Health Organization (8), the province of Ontario, Canada announced the closure of all schools and non-essential workplaces (9,10). Months later, public health measures, such as physical distancing and mask-wearing, continue to be in place to reduce the toll associated with the COVID-19 pandemic (11).

Public health measures have reduced the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Ontario (3). In some jurisdictions, these measures have also been associated with a lower incidence of other respiratory virus infections (12,13). We performed a time-series analysis, using a hierarchical regression model, to determine the timelines and positivity rates of influenza A and B viruses from 2010 to 2019 in an urban center in Ontario, and compare them to those of 2020 prior to and following the implementation of COVID-19 interventions in response to initial outbreaks.

Methods

Sampling and testing

We reviewed all nasopharyngeal swab specimens (n=57,503) submitted for routine respiratory virus testing at a regional laboratory serving all acute-care hospitals in Hamilton, Ontario between January 2010 and June 2020.

Testing was done using a *TaqMan* real-time reverse transcription polymerase chain reaction multiplex respiratory viral panel, developed by the Hamilton Regional Laboratory Medicine Program, for influenza A and B, respiratory syncytial virus, human metapneumovirus, parainfluenza I–III, adenovirus, and rhinovirus/enterovirus. On March 16, 2020, parainfluenza II was replaced by the SARS-CoV-2 virus. Sample ribonucleic acid (RNA) extraction and amplification were primarily performed on the bioMérieux NucliSENS easyMag and QIAGEN Rotor-Gene Q, respectively, from 2010–2019 and primarily performed on the BD MAX System from July 2019–2020. Clinical results were validated by experienced staff and recorded in a laboratory information system, following standard operating procedures.

Data

A respiratory virus database with all test results and demographic information is updated weekly and has been in place since 2010. A 10-year datacut with basic demographic information (age, sex, postal code, date, facility, accession number) and test results was exported from the laboratory database on June 29, 2020. The database included only samples sent for multiplex testing. Laboratory test results were filtered by postal code to exclude samples from persons living outside of Hamilton.

Ethics approval

The study was approved by the Hamilton Integrated Research Ethics Board (Project: 07-2923). The study was categorized as minimal risk, defined as no potential for negative impact on the health and safety of the participant, and waiver of individual consent for participation was obtained.

Statistical analysis

We used a Bayesian linear regression model with uninformative prior distributions to determine the trend of positivity rates of all influenza A and B samples for the first 26 weeks of each year from 2010–2019 (**Appendix: Table A1**). We then compared the mean positivity rate of Bayesian inference with the weekly reported positivity rate of influenza samples in 2020 (**Appendix: Table A2**).

The hierarchical regression model has the form

$$y \sim \text{Normal}(\mu, \sigma)$$
$$\mu = \beta^T \mathbf{x}$$
$$\beta = \text{Normal}(0, 100)$$
$$\sigma^2 = \text{InverseGamma}(2.5, 25)$$

where *y* represents the positivity rate over the first 26 weeks (variable *x*) of each year from 2010–2019. All parameters were sampled using Markov Chain Monte Carlo (MCMC) simulations in three independent chains. Each chain consisted of 10,000 iterations, with a burn-in period of 1,000 iterations and a thinning factor of five. To assess convergence, we inspected the trace plots and applied the Gelman-Rubin convergence test by computing the potential scale reduction factors (PSRF). All PSRF values were computed to be less than 1.1 (and remained close to 1), indicating the convergence of the model parameters to their posterior distributions. We used the posterior distributions of the parameters ($\beta 1$, $\beta 2$, σ) from our Bayesian analysis to derive mean estimates and credible intervals (**Appendix: Table A3**) by employing the method of Highest Posterior Density (14).

Results

A description of individuals included in our study is provided in **Table 1**. A total of 48,459 patients were tested for respiratory viruses in Hamilton, Ontario in 2010–2019, of which 49.3% (n=23,898) were male and 30.6% (n=14,818) were children under 18 years. The bimodal age distribution had a median age of adults of 72.4 years (IQR: 59.4–83.5) and 1.5 years among children (IQR: 0.4–4.4). A median of 4,626 (IQR: 3,376–5,936) samples were tested each year, with a mean influenza positivity rate of 9.6% (SD: 2.9%). Mean percent positivity was also

Table 1: Demographics, sample size, and positivity rate of laboratory-confirmed respiratory viruses in Hamilton, Ontario in 2010–2019 (n=48,459) and 2020 (n=9,044)

Description	2010–2019		2020	
Age in years	**Median**	**IQR**	**Median**	**IQR**
Adults	72.4	59.4–83.5	63.0	46.1–77.2
Children	1.5	0.4–4.4	1.9	0.5–6.0
Demographics	**Number**	**%**	**Number**	**%**
Male	23,898	49.3%	4,073	45.0%
Adults	33,641	69.4%	7,983	88.3%
Children	14,818	30.6%	1,061	11.7%
Respiratory virus samples	**Median**	**IQR**	**Number**	
Samples per year	4,626	3,376–5,936	9,044	
Positivity rate	**Mean**	**SD**	**Mean**	
Influenza	9.6%	2.9%	2.5%	
Respiratory syncytial virus	6.9%	1.5%	0.9%	
Metapneumovirus	2.8%	0.4%	0.4%	
Parainfluenza	3.2%	0.6%	0.1%	
Adenovirus	1.0%	0.6%	0.2%	
Rhinovirus/enterovirus	8.0%	5.5%	0.9%	

Abbreviations: IQR, interquartile range; SD, standard deviation

calculated for respiratory syncytial virus (6.9%, SD: 1.5%), metapneumovirus (2.8%, SD: 0.4%), parainfluenza (3.2%, SD: 0.6%), adenovirus (1.0%, SD: 0.6%), and rhinovirus/enterovirus (8.0%, SD: 5.5%). A total of 9,044 patients were tested for respiratory viruses in 2020, of which 2.5% were positive for influenza. The percent positivity of other respiratory viruses ranged from 0.1% (parainfluenza) to 0.9% (respiratory syncytial virus and rhinovirus/enterovirus).

Figure 1 shows the positivity rates of influenza A and B in the database for the different age groups.

Figure 1: Positivity rates of influenza A and B in 2010–2020 for different age groups in Hamilton, Ontario

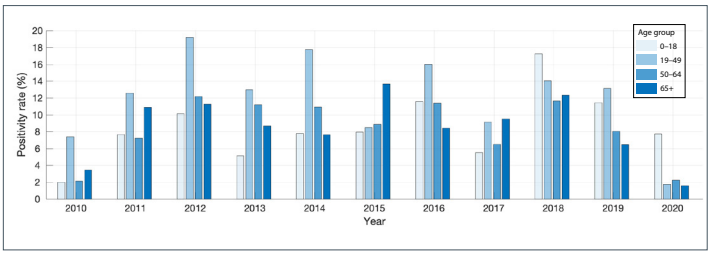
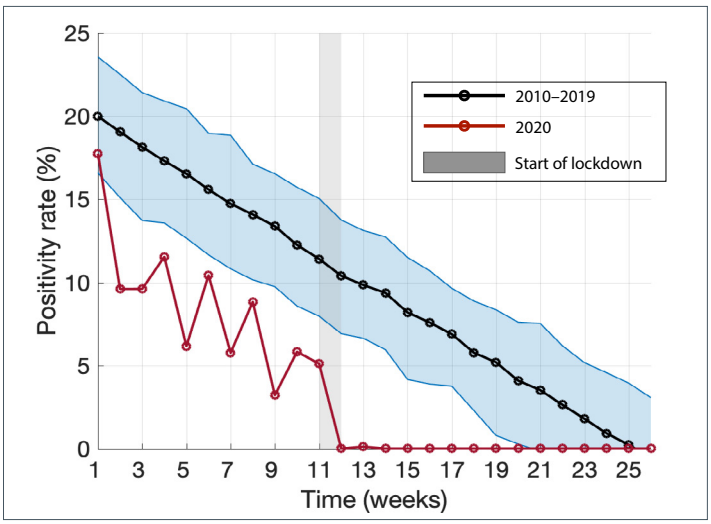


Figure 2 illustrates the mean positivity rate derived from posterior distributions of parameters in the Bayesian linear regression model using positivity rates reported for 2010–2019 (black curve). The positivity rate of influenza in 2020 (red curve) was highest at 17.7% in week 1, and dropped below the 95% credible interval for the preceding 10 years after the first week, with an ensuing declining trend (Figure 2; Appendix: Table A2). Following the implementation of COVID-19 interventions during week 12 (from March 12, 2020; grey bar in Figure 2), the positivity rate of influenza diminished sharply and remained at 0% for weeks 12–26, with the exception of 0.1% reported in week 13.

Figure 2: Bayesian inference for the mean positivity rate and its 95% credible interval of influenza A and B for the first 26 weeks in 2010–2019



Note: The red curve shows the positivity rate of influenza A and B for 2020, with the shaded grey bar indicating the start of COVID-19 lockdown

Discussion

Public health measures have been used to interrupt the spread of influenza during pandemics, with variable levels of success. For example, school closures and physical distancing during the 2009 H1N1 pandemic in Mexico resulted in a 27%–29% reduction in influenza transmission during the spring wave (15). During the 1957–1958 influenza pandemic, school closures contributed to reducing the attack rate by over 90% (16). Similarly, following the implementation of COVID-19 mitigation measures, the influenza positivity rate was suppressed in the United States (US) (12,13). Our results suggest that COVID-19 public health measures may have contributed to a substantial disruption of the spread of influenza in Hamilton.

The 2020 influenza season was observed to be relatively mild in Hamilton, as compared with previous seasons (Appendix: Table A1, A2). However, the lower positivity rate observed in our analysis (Figure 2), may be attributed to several factors including voluntary precautions taken by individuals as a result of initial news reporting of the spread of COVID-19 in China and internationally, normal seasonal variation, or changes in sampling behaviour and diagnostic testing. For the 2010–2019 winter influenza season, the median influenza positivity rate reached 0% by week 23. In 2020, however, after the implementation of COVID-19 mitigation measures, percent positivity for influenza dropped precipitously—to 0% in week 12. The US Centers for Disease Control and Prevention reported similar findings through their weekly influenza surveillance system, in which the percent positivity for influenza decreased from 7.5% in week 12 to 1.0% in week 14. This abrupt change, without another explanation, suggests that COVID-19 mitigation measures may have reduced the spread of laboratory-confirmed influenza in the US (12,13). Moreover, the positivity rates for respiratory syncytial virus, metapneumovirus, parainfluenza, adenovirus, and rhinovirus/enterovirus were reported to be 0% by week 14 of 2020 (Appendix: Table A2), suggesting that public health measures could have also suppressed the transmission of other respiratory viruses.

Understanding the effect of COVID-19 interventions on other communicable diseases requires further study. A number of explicators may be considered to describe the rapid interruption in transmission chains of influenza compared with COVID-19 due to the pressure exerted by public health measures. First, there is relatively strong cross-immunity for influenza virus strains during seasonal epidemics, in addition to population immunity conferred by vaccination (17,18). In contrast, the population was naive to SARS-CoV-2, and still remains largely susceptible in the absence of vaccination. Furthermore, there are major differences in the epidemiological characteristics between influenza and COVID-19 that influence the outcomes of interventions (19). For example, the transmissibility of influenza has been estimated to be in the range 1.2–1.8 (20), which is lower than the initial estimates of greater than two for COVID-19 in most

settings (21,22). The average incubation period of 5.2 days for COVID-19 (21) is significantly longer than the same period for influenza A, which is estimated to be 1.4 days (23). Moreover, the pre-symptomatic period is longer and more infectious in COVID-19 than in influenza (24,25). Future studies will need to account for these factors when evaluating the effect of interventions against emerging infectious diseases.

The findings of our study should be interpreted in the context of study limitations. First, respiratory samples were not collected systematically, but rather they were obtained as part of routine clinical care. As such, the samples may not fully represent the prevalence of respiratory viruses in the region. It is also possible that clinicians may not have strictly followed hospital infection control policy and failed to sample patients who otherwise would have been eligible. Furthermore, sampling behaviour may have changed during the early stage of COVID-19 spread in Canada. However, these factors are unlikely to change our conclusions due to the near-elimination of the absolute number of laboratory-confirmed respiratory virus cases, despite the large increase in testing which accompanied concern for COVID-19 in the community.

Conclusion

Our findings suggest that efforts to control the COVID-19 pandemic may have had additional benefits in suppressing the transmission of other respiratory viruses in Hamilton, Ontario. Mitigation strategies, such as physical distancing, mask-wearing, and school closures, could play an important role in combating future seasonal respiratory viruses and emerging infectious diseases with pandemic potential.

Authors' statement

KZ, AM, PJK, SMM, and MS contributed to the conception and design of the work
KZ, SMM, JML, and MS contributed to the acquisition of data, analysis, and interpretation of results

All authors drafted, read, and approved the final manuscript.

The content and view expressed in this article are those of the authors and do not necessarily reflect those of the Government of Canada.

Competing interests

Dr. J Langley reports that Dalhousie University has received payment for the conduct of vaccine studies from Sanofi, Glaxo-SmithKline, Merck, Janssen, VBI and Pfizer. Dr. Langley holds the Canadian Institutes of Health ResearchGlaxo-SmithKline Chair in Pediatric Vaccinology. No other competing interests were declared.

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Appendices: Tables

Table A1: Percent positivity of laboratory-confirmed influenza in Hamilton, Ontario in weeks 1–26 of 2010–2019

Week	Mean	Median	Quartile 1	Quartile 3	Standard deviation
1	18.5	21.1	11.0	26.2	10.3
2	16.0	15.6	3.6	29.8	11.2
3	17.4	21.0	5.4	26.1	10.0
4	16.5	12.2	5.8	26.6	11.9
5	16.8	17.3	8.8	24.9	10.3
6	17.5	16.7	12.7	23.8	9.2
7	15.2	16.0	7.4	21.5	8.8
8	15.9	15.2	6.8	23.8	9.3
9	14.6	13.9	8.2	20.7	9.1
10	14.8	14.2	5.8	20.0	10.1
11	12.7	11.2	3.9	21.6	8.5
12	10.2	10.9	5.1	16.0	6.2
13	11.4	10.9	5.6	18.4	6.8
14	11.5	9.8	3.6	20.3	8.4
15	8.5	7.6	4.1	11.7	5.8
16	7.4	5.4	2.5	13.1	5.9
17	7.3	5.8	2.2	11.9	5.6
18	5.5	6.3	2.2	7.1	3.4
19	3.2	2.0	0.9	5.8	3.2
20	3.3	1.6	0.7	6.3	3.3
21	1.9	0.7	0.0	2.4	3.0
22	1.4	0.7	0.0	3.0	1.5
23	1.2	0.0	0.0	2.1	1.9
24	0.8	0.0	0.0	1.9	1.1
25	0.3	0.0	0.0	0.3	0.6
26	0.0	0.0	0.0	0.0	0.0

Table A2: Percent positivity of laboratory-confirmed influenza, respiratory syncytial virus, metapneumovirus, parainfluenza, adenovirus, and rhinovirus/enterovirus in Hamilton, Ontario in weeks 1–26 of 2020

Week	Influenza percent positivity	Respiratory syncytial virus percent positivity	Metapneumovirus percent positivity	Parainfluenza percent positivity	Adenovirus percent positivity	Rhinovirus/ enterovirus percent positivity
1	17.7	5.9	0.5	0.0	0.5	2.2
2	9.6	5.6	0.8	0.4	0.8	1.6
3	9.6	1.8	0.9	0.4	0.4	3.9
4	11.5	5.8	0.8	0.0	0.4	1.2
5	6.2	4.5	0.7	0.0	0.3	2.4
6	10.4	2.3	1.2	0.4	0.8	1.5
7	5.8	1.9	1.0	0.0	1.0	1.4

Table A2: Percent positivity of laboratory-confirmed influenza, respiratory syncytial virus, metapneumovirus, parainfluenza, adenovirus, and rhinovirus/enterovirus in Hamilton, Ontario in weeks 1–26 of 2020 (*continued*)

Week	Influenza percent positivity	Respiratory syncytial virus percent positivity	Metapneumovirus percent positivity	Parainfluenza percent positivity	Adenovirus percent positivity	Rhinovirus/ enterovirus percent positivity
8	8.8	2.4	2.4	0.0	0.0	2.4
9	3.2	0.5	0.5	0.0	0.5	0.0
10	5.8	1.5	1.9	1.0	1.0	4.4
11	5.1	0.6	2.4	0.4	0.4	6.1
12	0.0	0.0	0.5	0.2	0.0	0.2
13	0.1	0.0	0.1	0.1	0.0	0.2
14	0.0	0.0	0.0	0.0	0.0	0.0
15	0.0	0.0	0.0	0.0	0.0	0.0
16	0.0	0.0	0.0	0.0	0.0	0.0
17	0.0	0.0	0.0	0.0	0.0	0.0
18	0.0	0.0	0.0	0.0	0.0	0.0
19	0.0	0.0	0.0	0.0	0.0	0.0
20	0.0	0.0	0.0	0.0	0.0	0.0
21	0.0	0.0	0.0	0.0	0.0	0.0
22	0.0	0.0	0.0	0.0	0.0	0.0
23	0.0	0.0	0.0	0.0	0.0	0.0
24	0.0	0.0	0.0	0.0	0.0	0.0
25	0.0	0.0	0.0	0.0	0.0	0.0
26	0.0	0.0	0.0	0.0	0.0	0.0

Table A3: Estimated model parameters from Bayesian inference

Parameter	Mean	95%	Credible interval
$\beta 1$	13.494	-0.891	21.695
$\beta 2$	0.114	-0.888	1.985
σ	4.005	1.932	5.102

Suboptimal prenatal screening of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections in a Montréal birthing and tertiary care centre: A retrospective cohort study

Victoria Ivensky[1], Romain Mandel[1,2], Annie-Claude Boulay[1], Christian Lavallée[1,3,4], Janie Benoît[5], Annie-Claude Labbé[1,3,4]*

Abstract

Background: The Canadian Paediatric Society no longer recommends the use of universal ocular prophylaxis with erythromycin ointment to prevent ophthalmia neonatorum. Screening for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in all pregnant women is considered the most effective way of preventing vertical transmission and ophthalmia neonatorum.

Objective: The aims of this study were to assess prenatal screening rates of *C. trachomatis* and *N. gonorrhoeae* and to compare sociodemographic factors between those screened and those not screened.

Methods: The list of all women who delivered at a tertiary care hospital in Montréal, Québec, between April 2015 and March 2016, was cross-referenced with the list of samples tested for *C. trachomatis* and *N. gonorrhoeae*. Maternal medical records were reviewed for demographic, prenatal and diagnostic information.

Results: Of 2,688 mothers, 2,245 women were screened at least once, but only 2,206 women had at least one valid *C. trachomatis* and *N. gonorrhoeae* result the day of delivery (82.1%; 95% CI: 80.6%–83.5%). Infection was detected in 46/2,206 (2.1%) screened women: 42 had *C. trachomatis* infection, two had *N. gonorrhoeae* infection and two were co-infected. *C. trachomatis* infection was more frequent in women younger than 25 years (9.8%; 95% CI: 6.7%–13.8%) than in older women (0.8%; 95% CI: 0.4%–1.3%; $p<0.001$). Each increase in parity decreased the probability of being tested (adjusted odds ratio=0.89; 95% CI: 0.80%–0.97%; $p=0.01$). Of those with an initial negative test result, 35/267 (13.1%; 95% CI: 9.3%–17.8%) of women younger than 25 years and 122/1,863 (6.6%; 95% CI: 5.5%–7.8%; $p<0.001$) of women aged 25 years and older were retested. Subsequent infection was detected in 4/35 (11%) women, all younger than 25.

Conclusion: Suboptimal screening rates for *C. trachomatis* and *N. gonorrhoeae* suggest that current universal ocular prophylaxis cannot be discontinued. Repeating universal screening should be considered, especially among those younger than 25 years.

Affiliations

[1] Faculty of Medicine, Université de Montréal, Montréal, QC

[2] Department of Paediatrics, Hôpital Maisonneuve-Rosemont, CIUSSS de l'Est-de-l'île-de-Montréal, Montréal, QC

[3] Department of Microbiology, Infectious Diseases and Immunology, Université de Montréal, Montréal, QC

[4] Division of Infectious Diseases and Medical Microbiology, Hôpital Maisonneuve-Rosemont, CIUSSS de l'Est-de-l'île-de-Montréal, Montréal, QC

[5] Department of Obstetrics and Gynecology, Hôpital Maisonneuve-Rosemont, CIUSSS de l'Est-de-l'île-de-Montréal, Montréal, QC

***Correspondence:**
ac.labbe@umontreal.ca

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Keywords: chlamydia, gonorrhea, screening, pregnancy, prenatal, Montréal

Introduction

Chlamydia trachomatis and *Neisseria gonorrhoeae* are the two most common bacterial sexually transmitted infections (STIs) and a major public health concern (1,2). When an infected pregnant woman is left untreated, vertical transmission can occur at the time of delivery. This may result in ophthalmia neonatorum and cause permanent corneal damage (3,4).

The American Academy of Pediatrics and the Québec Ministry of Health and Social Services recommend the use of universal ocular prophylaxis with erythromycin ointment 0.5% at birth for neonatal gonococcal ophthalmia (5–8). However, *N. gonorrhoeae* strains isolated in Canada have shown increasing resistance to erythromycin in the past few years, with 31% (n=1,642) of the 5,290 isolates tested in 2017 showing resistance. It is unclear whether neonatal gonococcal ophthalmia can be overcome with high local antibiotic levels during prophylaxis (9,10).

With the efficacy of erythromycin ointment in doubt, the Canadian Paediatric Society (CPS) and equivalent organizations in several high-income countries no longer recommend its universal use (10–12). Instead, for primary prevention of neonatal infections, CPS advocates prenatal screening and treatment of infected women. As 77% of *C. trachomatis* and 45% of *N. gonorrhoeae* infections are asymptomatic, routine screening is critical for diagnosing and treating those infected (13).

In order to prevent neonatal gonococcal ophthalmia, the Public Health Agency of Canada (PHAC) and CPS recommend that all pregnant women be screened for *C. trachomatis* and *N. gonorrhoeae* infections during the first trimester. Those at risk of acquiring infection later in pregnancy should be retested each trimester (PHAC) or in the third trimester (CPS), with treatment, test of cure and follow-up ensured in the event of a positive test result (6,10,14).

Although Manitoba and Ontario recently assessed the prevalence of *C. trachomatis* and *N. gonorrhoeae* infections and screening rates during pregnancy, these rates remain unknown in Québec, a province where 23% of all births in Canada were recorded in 2016 (15–17). In light of an eventual abrogation of universal ocular prophylaxis, the aim of this study was to:

- Determine sociodemographic characteristics of pregnant women in a tertiary care hospital in Montréal
- Assess prenatal screening rates
- Determine prevalence of *C. trachomatis* and *N. gonorrhoeae* infection in pregnant women
- Compare sociodemographic factors between those screened at least once for *C. trachomatis* and *N. gonorrhoeae* and those who were not screened

Methods

In this cohort study, we performed a retrospective review of the medical records of all women who gave birth to newborns of at least 19 weeks' gestation (live and stillbirths) at Hôpital Maisonneuve-Rosemont, a tertiary care hospital in Montréal, between April 1, 2015 and March 31, 2016.

The medical records included the clinical data during pregnancy of each woman who had given birth (age at delivery and cigarette, drug and alcohol use); obstetric history (gravidity, parity, abortus and date of last menstrual period); pregnancy follow-up (specialty of the health practitioner, date of first prenatal visit); and delivery (gestational age and type of delivery). Date of the last menstrual period was calculated according to date of delivery and gestational age at delivery, which takes into consideration the prenatal ultrasound results.

We obtained the list of all women who delivered during the study period from the hospital medical records department and the list of HIV and *C. trachomatis* and *N. gonorrhoeae* tests performed at the hospital laboratory during that period and nine months prior. Using STATA version 14.2 (StataCorp LP, College Station, Texas, United States), we cross-referenced the two lists, based on the health insurance number of each woman, retaining only the tests performed during pregnancy. In cases where no *C. trachomatis* and *N. gonorrhoeae* test was performed at the hospital's laboratory, the chart was reviewed for tests performed in other laboratories in Québec. We also searched for mentions of screening test completion in the pregnancy follow-up chart notes.

We considered the women adequately screened if they had at least one valid *C. trachomatis* and *N. gonorrhoeae* result (positive or negative) during pregnancy follow-up, before the day of delivery. If a test had been ordered, but no result was available (specimen rejected by the laboratory, invalid result, etc.) and no additional sample was collected at follow-up, the woman was not considered screened during pregnancy. If we found no documentation of prenatal care and no screening tests for HIV or *C. trachomatis* and *N. gonorrhoeae* at least one week before delivery, the woman was considered to have had no pregnancy follow-up. This also applies to women who were only followed outside of Canada or in other provinces until one week before delivery.

We used the Pearson Chi-square test to analyze categorical data (with statistical significance set at $p \leq 0.05$). Each variable associated with screening at $p \leq 0.20$ in the univariable analysis was considered for the multivariable logistic regression model, which was constructed using a forward design, retaining only age and variables that increased the model fit.

This study was approved by the Ethics Committee of the Centre intégré universitaire de santé et de services sociaux (CIUSSS) de l'Est-de-l'île-de-Montréal.

Results

Sociodemographic characteristics of the study population

The study included 2,688 pregnant women aged 15–50 years (median age=31.7; interquartile range=7.4). **Table 1** shows the sociodemographic distribution of the study population.

Table 1: Characteristics of the study population

Maternal characteristics	%	n
Age at delivery (N=2,688)		
15–19 years	2.0	55
20–24 years	10.9	292
25–29 years	25.8	694
30–34 years	35.3	949
35–39 years	20.5	551
40+ years	5.5	147
Gravidity (N=2,678)		
1	30.6	820
2	30.7	822
3	19.0	510
4+	19.6	526
Parity (N=2,678)		
0	46.5	1,246
1	32.7	876
2	14.4	386
3	4.3	116
4+	2.0	54
Maternal habits		
Smoking (N=2,575)	10.7	276
Alcohol (N=2,569)	2.3	60
Drugs (N=2,571)	2.5	65
≥1 habit (N=2,688)	12.1	324

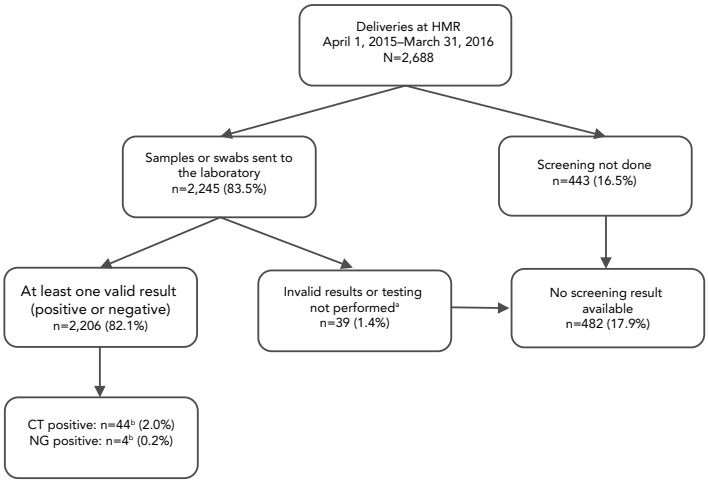
At least one prenatal clinical visit was documented in the medical chart of 2,661/2,688 (99%) women: 1,571 (58%) were followed by an obstetrician–gynecologist (OBGYN); 1,062 (40%) by a general practitioner (GP) and 3 (0.1%) by the organization Doctors of the World. We could not find information about health practitioners for 25 (0.1%) women; of these, seven were followed in another country.

Of the 2,633 (98%) women who were followed either by a GP or an OBGYN during pregnancy, 2,312 (87.8%) had their first prenatal visit in the first trimester (1–14 gestational weeks), 280 (10.6%) in the second trimester (15–28 weeks) and 41 (1.6%) in the third trimester (29–42 weeks).

Screening for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections in pregnancy

No screening test was ordered during pregnancy follow-up for 443/2,688 (16.5%) of the women (**Figure 1**). Of the 74 women whose first sample was rejected by the laboratory or gave an invalid *C. trachomatis* and *N. gonorrhoeae* result, 35 (47.3%) were retested and obtained a valid result. Final screening rate was estimated at 82.1% (2,206/2,688; 95% confidence interval [CI]: 80.6%–83.5%).

Figure 1: Proportion of women screened for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections during pregnancy, before the day of delivery



Abbreviations: CT, *Chlamydia trachomatis*; HMR, Hôpital Maisonneuve-Rosemont; NG, *Neisseria gonorrhoeae*
[a] The samples/swabs were sent to the laboratory, but there was no corresponding positive or negative CT/NG result (i.e. the sample rejected/not tested because of inadequate identification or invalid result obtained)
[b] Two cases were co-infected with CT and NG

Of the 482 women who were inadequately screened during pregnancy follow-up, 22 (4.6%) were screened at the time of delivery.

Prevalence of infection in pregnancy

Infection was detected in 46/2,206 (2.1%) screened women: 42 had *C. trachomatis* infection, two had *N. gonorrhoeae* infection and two were infected with both. Prevalence of *C. trachomatis* was estimated at 2.0% (95% CI: 1.5%–2.7%) and of *N. gonorrhoeae* at 0.2% (95% CI: 0.005%–0.5%). Women younger than 25 years were more likely to have *C. trachomatis* infection (29/296; 9.8%; 95% CI: 6.7%–13.8%) than those aged 25 years and older (15/1,910; 0.8%; 95% CI: 0.4%–1.3%; $p<0.001$). Prevalence of *N. gonorrhoeae* infection was also significantly higher in younger women (1.0% vs 0.05%; $p<0.001$).

Of the 2,130 women with an initial negative test result for *C. trachomatis* and *N. gonorrhoeae*, 157 (7.4%) were retested: 35/267 of women younger than 25 years (13.1%; 95% CI: 9.3%–17.8%) and 122/1,863 of women aged 25 years and older (6.6%; 95% CI: 5.5%–7.8%; $p<0.001$). A subsequent infection for *N. gonorrhoeae* was detected in one woman (age 23 years) and for *C. trachomatis* in three women (ages 19, 24 and 24 years). In other words, 11.4% (4/35; 95% CI: 3.2%–26.7%) of women aged 15–24 years with an initial negative test result tested positive at their second screening.

Sociodemographic factors associated with screening

Screening rates for *C. trachomatis* and *N. gonorrhoeae* were slightly higher in women younger than 25 years (296/347; 85.3%; 95% CI: 81.1%–88.9%) than among older women (1,910/2,341; 81.6%; 95% CI: 80.0%–83.1%; *p*=0.09). Globally, as shown in **Figure 2**, the association between maternal age and prenatal screening was statistically significant (*p*=0.04), but the difference across age groups was marginal (**Table 2** and **Table 3**).

Figure 2: *Chlamydia trachomatis* and *Neisseria gonorrhoeae* screening rates, by maternal age

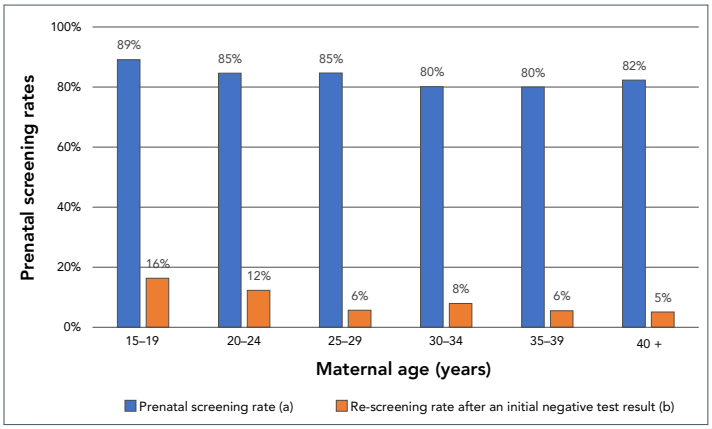


Table 2: Sociodemographic characteristics of screened and non-screened pregnant women

Description		Screened[a] (n=2,206)		Not screened (n=482)	
		Median	SD	Median	SD
Age		31.5	5.4	32.4	5.1
Maternal characteristics		n	%	n	%
Smoking	Yes (n=276)	234	11	42	9.4
	No (n=2,299)	1,896	89	403	90.6
Alcohol	Yes (n=60)	50	2.3	10	2.3
	No (n=2,509)	2,076	97.7	433	97.7
Drugs	Yes (n=65)	60	2.8	5	1.2
	No (n=2,504)	2,068	97.2	438	98.8
≥1 habit	Yes (n=324)	274	12.4	50	10.4
	No (n=2,364)	1,932	87.6	432	89.6
First prenatal visit	First trimester (n=2,329)	1,932	87.6	397	87.3
	Second trimester (n=288)	239	10.8	46	10.1
	Third trimester (n=47)	35	1.6	12	2.6
Medical specialty	OBGYN (n=1,571)	1,308	59.4	263	61.0
	GP (n=1,062)	894	40.6	168	39.0

Abbreviations: OBGYN, obstetrician–gynecologist; GP, general practitioner
[a] At least one valid *C. trachomatis* and *N. gonorrhoeae* result obtained during pregnancy follow-up, before the day of delivery

Table 3: Odds ratios of prenatal screening for chlamydial and gonococcal infections in relation to maternal sociodemographic characteristics (n=2,688)

Maternal characteristics	Odds ratio	95% CI	*p* value	Adjusted odds ratio[a]	95% CI	*p* value
Age (continuous)	0.97	(0.96–0.99)	0.006	0.99	(0.97–1.01)	0.17
Smoking	1.18	(0.84–1.67)	0.30	N/A	N/A	N/A
Alcohol	1.04	(0.52–2.07)	0.90	N/A	N/A	N/A
Drugs	2.54	(1.01–6.37)	0.04	2.35	(0.93–5.94)	0.09
≥1 habit	1.23	(0.89–1.69)	0.20	N/A	N/A	N/A
Prenatal visit in first trimester	0.92	(0.71–1.18)	0.50	N/A	N/A	N/A
OBGYN follow-up[b]	1.07	(0.87–1.32)	0.50	N/A	N/A	N/A
Gravidity (per additional pregnancy)	0.92	(0.87–0.98)	0.01	N/A	N/A	N/A
Parity (per additional delivery)	0.83	(0.75–0.90)	<0.001	0.89	(0.80–0.97)	0.01

Abbreviations: CI, confidence interval; OBGYN, obstetrician–gynecologist; N/A, not applicable
[a] Each variable associated with screening with a p value ≤0.20 in the univariable analysis was considered for the multivariable model. This multivariable model was constructed using a forward design, retaining only age and variables that increased the model fit
[b] In comparison to general practitioner follow-up

Screening rates were also higher at low parity and gravidity and in women who used drugs. After multivariate analysis, parity was the only factor associated with higher prenatal screening rate: each additional pregnancy decreased the odds of being tested for *C. trachomatis* and *N. gonorrhoeae* (adjusted odds ratio [aOR]=0.89; 95% CI: 0.80%–0.97%; *p*=0.01) (Table 3).

Prenatal screening rates were identical for GPs (894/1,062; 84.2%; 95% CI: 81.8%–86.3%) and OBGYNs (1,308/1,571; 83.3%; 95% CI: 83.1%–85.1%).

Discussion

In our study, the median age of the pregnant women was 32 years. The majority of women had their first prenatal visit in the first trimester (88%) and were followed by an OBGYN (58%) or GP (40%). Prenatal screening rate was 82% and prevalence of infection was estimated at 2.0% for *C. trachomatis* and 0.2% for *N. gonorrhoeae*. Low parity was the sole sociodemographic factor associated with higher screening rates.

Our findings are similar to those of previous studies. Vainder *et al.* investigated records for 1,220 pregnancies over a 6-month period in 2015–2016 (16). Of these, 1,034 (85%) pregnant women in a tertiary care hospital in Toronto were screened at least once during pregnancy. Poliquin *et al.* found that 78% (45,601/58,488) of live births in Manitoba in 2011–2014 were associated with at least one prenatal test for *C. trachomatis* and *N. gonorrhoeae* (17).

In a tertiary care hospital in Bordeaux, France, over 6-month period in 2011, Peuchant *et al*. estimated prevalence of *C. trachomatis* at 2.5% and *N. gonorrhoeae* at 0% in 1,004 pregnant women (18). At 7.9%, prevalence of *C. trachomatis* was reported to be higher in women aged 18–24 years, a finding similar to ours (9.4%). The maternal age distribution at delivery and the proportion of women who smoked during pregnancy in our study population are comparable to the rates found in the total population of pregnant women in Canada (19,20).

Strengths and limitations

Some medical charts had incomplete information on maternal habits, pregnancy follow-up and obstetric or past medical history, eliciting a potential risk of selection bias.

Maternal age younger than 25 years and substance use (alcohol and drugs) were the sole STI risk factors available in the study; maternal STI risk behaviours are rarely specified in medical charts (14). Yet, some clinicians could have used a risk factor–based approach to decide which women to screen, rather than testing all pregnant women. We therefore could not thoroughly evaluate what led clinicians to screen some women rather than others.

Finally, the study was conducted in a single hospital and accounted for about 3% (2,688/86,000) of all births in Québec in 2016 (15). A multicentric study would increase generalizability to the province of Québec.

In terms of the strengths of our study, in addition to laboratory software extraction, we reviewed medical charts to capture screening tests analyzed in other laboratories. We also took into account rejected or invalid screening tests as well as subsequent retesting to obtain a valid result.

This is the first Canadian study to evaluate screening and prevalence of infection in pregnancy after an initial negative test result, helping to provide a more accurate portrait of prenatal screening. High prevalence of *C. trachomatis* infection in women aged 15–24 years in our study highlights the importance of screening this high-risk age group. High prevalence was also found at their second screening (11.4%), after an initial testing negative, further confirming that a first negative result does not guarantee absence of infection throughout the entire pregnancy (21).

Suboptimal screening rates suggest that universal ocular prophylaxis cannot currently be discontinued. If we extrapolate our findings to the province of Québec, with 86,000 annual deliveries in 2016, around 15,000 neonates could be born to women who had not been adequately screened during pregnancy (15). Assuming that the prevalence of infection is similar in the whole province, that the prevalence is similar in women who are screened and those who are not and that there is no spontaneous clearance of infection, our finding of a *C. trachomatis* infection rate of 2.0% and a *N. gonorrhoeae* infection rate of 0.2% in pregnant women would mean that 300 *C. trachomatis* and 30 *N. gonorrhoeae* infections would be missed each year. With a 30% and 40% rate of vertical transmission to the eye for *C. trachomatis* and *N. gonorrhoeae*, respectively, each year 102 neonates would be expected to have *C. trachomatis* and *N. gonorrhoeae* ophthalmia (22).

Apart from the increased risk for serious systemic complications, abrogation of universal ocular prophylaxis would also increase the risk of neonates developing ophthalmia neonatorum, which can lead to permanent visual impairment (3,4,23,24). The newborns of 15,000 unscreened women in Québec would therefore have to be closely monitored for infection every year.

Changes in screening practices could prevent such outcomes. Increasing the use of self-administered swabs could contribute to increased screening, particularly by those who are not comfortable with clinician sampling and those who are asymptomatic (25).

In order to confirm absence of infection later in pregnancy, a second universal *C. trachomatis* and *N. gonorrhoeae* screening of all women should be considered in the third trimester. In addition to identifying women who become infected later in pregnancy, an examination of a prenatal syphilis screening program in Alberta found that this strategy reduced the number of women who are not screened for disease during pregnancy (26).

Although screening at entry into prenatal care and at another time point during pregnancy (such as the third trimester) would be the costliest strategy, doing so would provide the greatest health benefits. This screening strategy would be cost-effective if the willingness-to-pay threshold was under $11,468 per quality-adjusted life-year (QALY) (27).

Conclusion

Suboptimal screening rates for *C. trachomatis* and *N. gonorrhoeae* in pregnant women raise concerns about discontinuation of ocular prophylaxis for ophthalmia neonatorum. Ocular prophylaxis will continue to be necessary to prevent ophthalmia neonatorum as long as universal screening cannot be guaranteed. Clinicians need to be more aware of the importance of universal screening in pregnant women and further encouraged to document test results in medical charts.

Authors' statement

ACL — Conceptualization, methodology, funding acquisition, formal analysis, visualization, statistical analysis, project administration, supervision, writing–review & editing
ACB — Investigation, writing–review & editing
CL— Software, investigation, formal analysis, writing–review & editing

JB — Conceptualization, writing–review & editing
RM — Conceptualization, methodology, formal analysis, visualization, supervision, writing–review & editing
VI — Conceptualization, investigation, data curation, formal analysis, data interpretation, statistical analysis, funding acquisition, investigation, writing–original draft, visualization

Competing interests

ACL is a member of the National Advisory Committee on STBBI (CCN-ITSS) of the Public Health Agency of Canada, as well as of the Committee on STBBI (CITSS) of the Institut national de santé publique du Québec. The opinions expressed in this article are those of the author and do not necessarily reflect those of these committees.

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Part of our results were presented at the STI & HIV 2019 World Congress - Joint meeting of the 23rd International Society for STD Research (ISSTDR) & 20th International Union against Sexually Transmitted Infections (IUSTI) in Vancouver (BC), on July 16, 2019: Screening rates and follow-up of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections during pregnancy. The abstract was published in Sex Transm Infect 2019; 95(Suppl 1):A219.

We also presented our results at the following meetings:

- The AMMI Canada – CACMID Annual Conference in Ottawa on April 4, 2019: Prenatal Screening of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* Infections: Sufficiently Reliable to Abrogate Topical Ocular Prophylaxis to Newborns?
- Santé publique 2018, ACSP, Montréal (QC), May 31, 2018. Dépistage prénatal des infections à *Chlamydia trachomatis* (CT) et *Neisseria gonorrhoeae* (NG) : peut-on s'y fier pour cesser la prophylaxie oculaire aux nouveau-nés?

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COVID-19 outbreak in a personal service setting in Kingston, Ontario, 2020

Anthony Li[1,2], Stéphanie Parent[1,2], Azim Kasmani[1,3], T Hugh Guan[1,3], Kieran Moore[1,3]*

Abstract

Background: During the coronavirus disease 2019 (COVID-19) pandemic, Ontario created a three-phase reopening framework for the economy. Outbreaks were expected at each phase. One week after Phase Two of reopening in the provincial public health administration region of Kingston, Frontenac, Lennox and Addington (KFL&A), a positive case was reported after three weeks of zero new COVID-19 cases. The objective of this report is to describe this COVID-19 outbreak, linked to a personal service setting (PSS), and the public health response to contain the outbreak.

Methods: The outbreak investigation included all COVID-19 cases in KFL&A between June 20, 2020 and July 3, 2020. Public health inspectors and nurses were rapidly deployed to inspect the PSS. A multimodal approach to high-volume testing involved fixed assessment centres, drive-through testing capacity and targeted testing at the outbreak site. Testing was conducted through a real-time polymerase chain reaction assay at the local Public Health Ontario laboratory.

Results: Thirty-seven cases were associated with the outbreak: 38% through direct PSS exposure; 32% through household contact; and 30% through social and workplace contact. A superspreading event contributed to 38% of total cases. The majority of cases were in the low to mid-quintiles when analyzed for material deprivation. Testing rates increased four-fold compared to the prior baseline weeks in response to media attention and public health messaging, resulting in a low percent positivity.

Conclusion: The interplay of aggressive accessible testing, quick lab turnaround time, contact tracing within 24 hours of positive laboratory results as per provincial standards, frequent public communication, rapid inspections, mandatory self-isolation and face coverings were measures successful in halting the outbreak. Inspections or self-audits should be required at all PSSs prior to reopening and outbreak management must work with PSSs to reduce the possibility of superspreading events.

Affiliations

[1] Kingston, Frontenac, Lennox & Addington (KFL&A) Public Health, Kingston, ON

[2] School of Medicine, Queen's University, Kingston, ON

[3] Public Health and Preventive Medicine Residency Program, Queen's University, Kingston, ON

***Correspondence:**

kieran.moore@kflaph.ca

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Keywords: COVID-19, SARS-CoV-2, outbreak, personal service setting, public health, infection prevention and control, case and contact management, superspreading event

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped ribonucleic acid (RNA) beta-coronavirus that causes coronavirus disease (COVID-19), with common symptoms including fever, cough, shortness of breath and fatigue (1,2). Severe COVID-19 presentations may require intensive care unit admission and may potentially result in death (3). The SARS-CoV-2 is most commonly transmitted through close contact via liquid droplets released by infected individuals and was classed with other novel coronaviruses as a reportable communicable disease in Ontario on January 22, 2020 (4,5).

While the COVID-19 pandemic has caused 100,000 positive cases and nearly 9,000 deaths in Canada as of July 2020, the Kingston, Frontenac, Lennox and Addington (KFL&A) region has had a very low community incidence of COVID-19 (6). Although KFL&A has a population of 209,023 with 20% of individuals aged

over 65 years, there have been zero attributed deaths, only one case in a long-term care home and 63 total cases prior to this outbreak (7).

The Ontario government provided a three-phase reopening plan for the economy (8). The KFL&A region was allowed to move from Phase One to Phase Two on June 12, 2020, which permitted personal service settings (PSSs) such as nail salons, barbershops and tattoo parlours to reopen. Although PSSs were provided with guidance and best practices, inspections were not required prior to reopening. After a three-week period of zero new COVID-19 cases in KFL&A, a positive case was detected on June 20, 2020 in a hospital staff member, a week after Phase Two of reopening. Two more positive cases were reported three days later, neither of which had any connection to the hospital. Through repeated case interviews and social network analyses, case investigators identified a nail salon as the common source. KFL&A Public Health sent an inspector and nurse team to investigate infection prevention and control practices (IPAC) and to test workers. Six workers tested positive for COVID-19 and an outbreak was declared on June 25, 2020.

This outbreak demonstrates how PSSs can contribute to disease transmission. Inspections or self-audits with a report back mechanism should be required at all PSSs prior to reopening and should be considered as potential sources of infection during case and contact investigations. A collaborative regional response between the community, local public health agency, laboratory and hospitals running the assessment centres allowed for rapid outbreak management. The objective of this report is to describe the investigation that led to the discovery of the outbreak source and the interventions to contain the outbreak.

Methods

Detection of the outbreak

The index case for this outbreak, reported on June 20, 2020, was a hospital staff member. Initial investigations did not uncover a source among occupational or household contacts. On June 23, two additional positive cases were identified. None of the three reported each other as contacts nor identified any shared contacts. Upon repeated interviews by case investigators, a common link was discovered: all three cases had visited the same nail salon the week of June 14. KFL&A Public Health rapidly deployed a public health inspector and nurse team on site to investigate the PSS, test all workers and review IPAC practices. A worker tested positive for COVID-19 within 48 hours, with a total of six workers ultimately testing positive; providing strong evidence that this setting was the outbreak source. On June 25, KFL&A Public Health officially declared an outbreak to the public and ordered the nail salon to close until further notice.

Case investigation

Cases were determined by a positive real-time polymerase chain reaction (PCR) assay, according to the provincial ministry definition (9). The internal case definition used by KFL&A Public Health for this outbreak was a client or a close contact of a positive client of the nail salon. The risk of transmission was hypothesized to have started at the official opening date of the PSS on June 12, 2020. Individuals who tested positive for COVID-19 were contacted within 24 hours of their result by KFL&A Public Health staff following provincial guidelines (10). The case and contact management investigation included onset date, symptoms, exposure history including travel or positive contacts, risk factors and any close contacts (with level of exposure risk). All cases were actively monitored for a 14-day period following guidance from the Ontario Ministry of Health (11). The estimated average cost per case was $400 and required seven staff hours, while the average cost per contact was $160 and required three staff hours.

Laboratory investigation

The Public Health Ontario Laboratory (PHOL) Kingston site conducted real-time PCR testing on specimens and reported cases following the case definition of COVID-19 set by the Ministry of Health. A confirmed case is outlined as "a person with laboratory confirmation of COVID-19 infection using a validated assay, consisting of positive nucleic acid amplification test on at least one specific genome target" (9). The PHOL used the envelope (E) gene assay as the genome target for its laboratory-developed test. The COVID-19 testing turnaround time was 24–48 hours.

Data analysis

Microsoft™ Excel 2016 software was used to create the epidemic curve and descriptive analyses while a social network analysis was conducted using the SocNetV 2.5 tool. Spatial analysis was done with geographical information systems to construct a choropleth map to identify census tracts of high incidence.

Crude attack rates for subsequent generations were calculated using number of confirmed cases per generation and number of susceptible persons (12). Susceptible persons were defined as high-risk contacts, with contacts being counted only once if shared between cases. Swabbing data from the assessment centres and case data from PHOL were used to calculate percent positivity.

The material deprivation score measures the inability of individuals to access basic material needs such as educational attainment or quality housing (13). Deprivation indices were determined for each case to construct an overall material deprivation profile as a proxy for socio-economic status. The material deprivation profile was grouped into quintiles, with higher quintile scores indicating a higher level of deprivation.

Interventions

The client contact list provided by the nail salon was incomplete, preventing effective contact management from occurring. As such, on June 25, 2020, KFL&A Public Health released a public announcement urging any clients of this PSS between June 12

and June 24 to get tested for COVID-19 and self-isolate for 14 days from the date of their last visit. A number of businesses voluntarily closed as a precautionary measure, having employees who had attended the PSS and tested positive.

In addition to the initial nail salon, four employees at two other nail salons eventually tested positive for COVID-19 through contact with staff at the first salon. The KFL&A Public Health issued a media release requesting that all clients who frequented these two PSSs self-isolate and be tested. Both salons were closed until further notice. Over 500 customers visited the initial nail salon associated with the outbreak between June 12 and June 20, all of whom were requested to self-isolate and get tested. An additional 180 close contacts of the positive cases were also requested to self-isolate and obtain testing.

To minimize the risks of additional outbreaks in public settings, the Medical Officer of Health of KFL&A issued an order on June 27, 2020 under Section 22 of the *Ontario Health Protection and Promotion Act* prohibiting individuals from entering and remaining inside indoor commercial establishments if not wearing a face covering and also ensuring the availability of alcohol-based hand rubs at all entrances and exits. Furthermore, on June 30, KFL&A Public Health mandated self-isolation and quarantine for COVID-19 cases or close contacts of a positive case. An advisory was also released requiring all PSSs to complete a checklist developed to ensure PSS compliance with IPAC regulations (14).

Results

There were 37 cases of COVID-19 associated with the outbreak between June 20 and July 3 (**Figure 1**). The majority of cases (65%) were female, and the average age was 38.6 years old, with a range of 11 months to 69 years old. The cases had various occupations, including in healthcare, education, construction, restaurant, retail and corrections. Of the 37 cases, 14 (38%) were from direct exposure through the PSS, 12 (32%) were household contacts with another case, and the remaining 11 (30%) were social and workplace contacts with a case (**Figure 2**). One PSS client alone infected six people at a social gathering and two coworkers.

Once KFL&A Public Health identified the nail salon as the common link between the initial three cases, a public health inspector and nurse team were rapidly deployed on site to investigate. Considerable deficiencies in IPAC practices were noted. Staff were observed having inadequate hand hygiene, washing only for several seconds and without the use of soap. Staff were not screened for COVID-19 symptoms and showed up to work with symptoms. Improper wearing of face masks was also observed by both clients and staff, including hanging under the chin, exposing the nose, or being removed when using a phone. Workstations and equipment were not cleaned prior

Figure 1: Epidemic curve for the COVID-19 outbreak in a Kingston, Frontenac, Lennox & Addington personal service setting outbreak, 2020 (n=37)

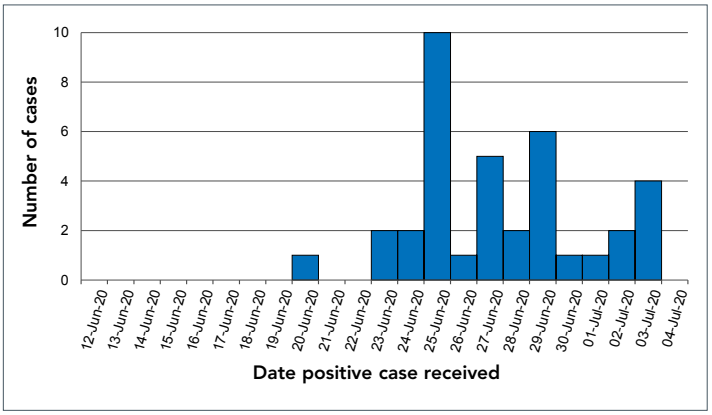
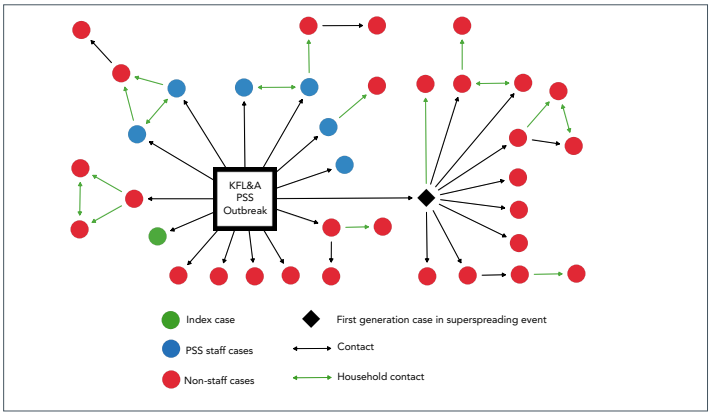


Figure 2: Social network analysis for COVID-19 cases in the Kingston, Frontenac, Lennox & Addington personal service setting outbreak, 2020



Abbreviations: KFL&A, Kingston, Frontenac, Lennox & Addington; PSS, personal service setting

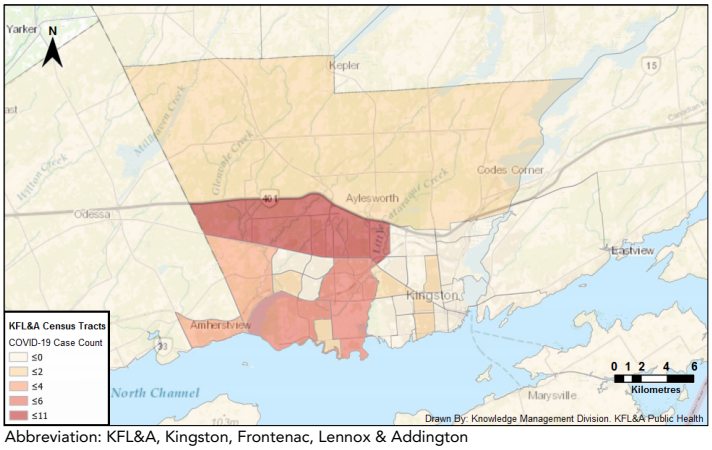
to disinfecting, and high-touch surfaces were only cleaned and disinfected once a day. Furthermore, handwritten records of client names and phone numbers were often incomplete and/or illegible. Six workers eventually tested positive for COVID-19.

Seven (19%) of the 37 cases were asymptomatic at the time of diagnosis. Three of the seven asymptomatic cases never went on to develop symptoms of COVID-19. One case of transmission of COVID-19 was identified from a true asymptomatic case. Only one case associated with the outbreak was hospitalized. This individual had comorbidities, requiring an eight-day admission to hospital and five-day stay in the intensive care unit. No deaths were associated with this outbreak.

Choropleth map profiling indicated higher case counts closer to the outbreak source and relatively even spatial distribution across census tracts (**Figure 3**). The material deprivation profile of cases indicated that 54% of cases were in the low to mid-quintiles of material deprivation, associated with areas of higher socio-economic status, whereas 38% of cases were in the

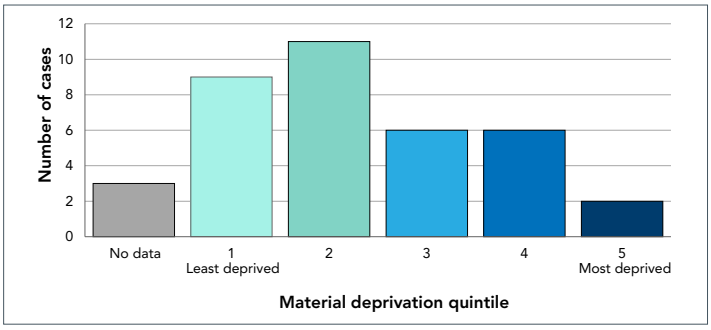
top quintiles of material deprivation, associated with areas of lower socio-economic status (**Figure 4**). No data was available for the remaining 8% of cases.

Figure 3: Choropleth map for COVID-19 cases associated with the Kingston, Frontenac, Lennox & Addington personal service setting outbreak, 2020



Abbreviation: KFL&A, Kingston, Frontenac, Lennox & Addington

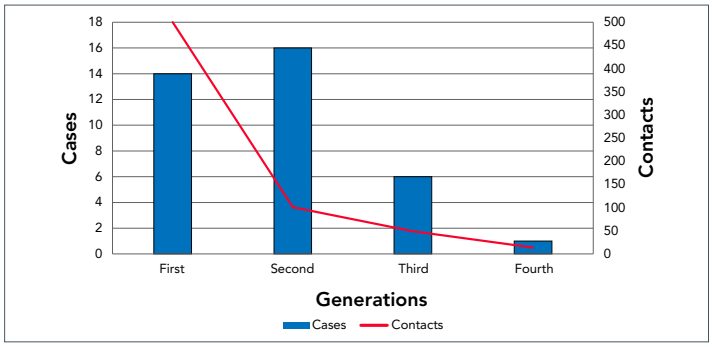
Figure 4: Material deprivation profile of cases associated with the Kingston, Frontenac, Lennox & Addington personal service setting outbreak, 2020



Four generations of transmission were identified (**Figure 5**). There were 14 cases in the first generation, with an estimated 500 patrons and staff who were potentially exposed to COVID-19. Due to incomplete client records, an estimate was needed and was calculated using the likely number of clients serviced daily based on salon capacity during the 13 days it was open. As such, the attack rate for the first generation was 2.8%. The second generation of 16 cases and 101 contacts had an attack rate of 15.8%. The third generation of six cases and 49 contacts had an attack rate of 12.2%. The fourth generation of one case and 14 contacts had an attack rate of 7.4%. Crude estimated total costs for the case and contact management of this outbreak investigation were approximately $41,040 and 751 staff hours.

The KFL&A Public Health had a multimodal approach to swabbing, including fixed assessment centres, drive-through testing capacity and targeted testing at the outbreak site.

Figure 5: COVID-19 cases and contacts per generation in the Kingston, Frontenac, Lennox & Addington personal service setting outbreak, 2020



Testing rates between June 20 and July 5 were high in response to media attention and messaging from KFL&A Public Health and there was approximately a four-fold increase in testing during the outbreak compared to the prior baseline weeks (**Figure 6**). In addition, the cumulative number of tests completed in the KFL&A region from the start of this outbreak surpassed 10,000 by July 7. Percent positivity remained low and reached a peak of 0.61% on June 29 (**Figure 7**).

Figure 6: Number of patients swabbed by day in assessment centres

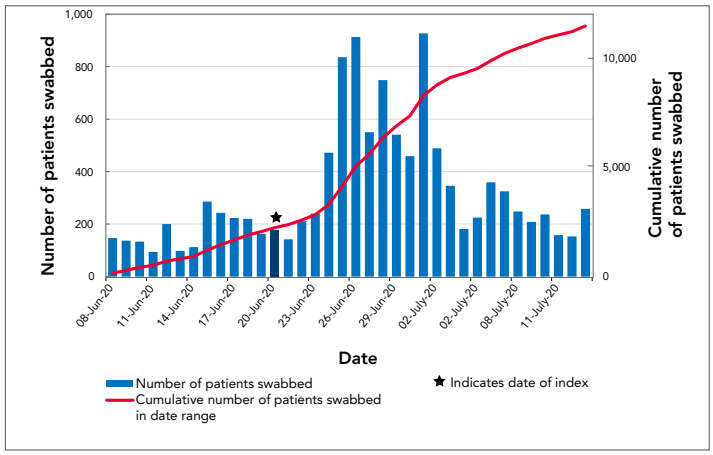
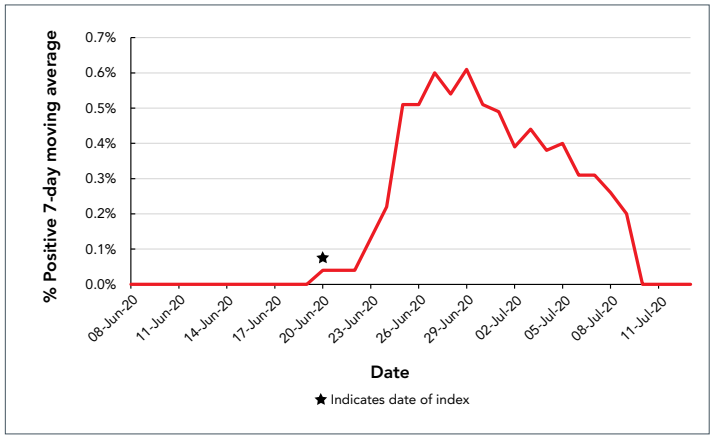


Figure 7: Percent positivity 7-day moving average of COVID-19 tests



Discussion

Prior to this PSS outbreak, KFL&A had one of the lowest case rates in Ontario with 29.1 cumulative cases per 100,000 population (15). After three weeks of zero new COVID-19 cases in KFL&A, the detection of an outbreak one week after Phase Two of reopening indicated deficiencies in adherence to government recommendations and best practices.

Transmission of disease is facilitated in a PSS due to difficulties in maintaining physical distancing while receiving a service. Staff can come into close contact with dozens of clients each day, and any reuse of inadequately sterilized equipment exacerbates the situation. The transmission of mycobacteria, hepatitis B virus and hepatitis C virus has been well documented in PSSs (16–19). A combination of factors contributed to this PSS outbreak. Insufficient hand hygiene, improper face mask usage and staff working while symptomatic allowed for the transmission of COVID-19. Handwashing for only several seconds without soap usage and face mask wearing that exposed the mouth or nose indicated poor IPAC practices, in addition to the deficiencies in cleaning of workstations and equipment. The effectiveness of good adherence to IPAC has been seen in a PSS in Missouri, United States where two infectious (COVID-19) symptomatic hair stylists did not transmit to any of their 139 exposed clients, as all staff and clients wore face masks properly and followed robust hand hygiene practices (20). An inspection of adherence to best IPAC practices prior to reopening are essential to preventing future outbreaks. A self-audit of IPAC practices with a report back mechanism to public health could be another approach.

The 37 cases of COVID-19 linked to the nail salon required an aggressive local public health response to contain the spread of the virus, including early outbreak source identification, broad community awareness, high-volume testing initiatives and identification of subsequent cases. This permitted rapid contact tracing within the 24-hour provincial guidelines and allowed for isolation of cases and contacts to contain the outbreak. The effectiveness could be seen by the decrease in attack rates after the second generation, indicating that cases and contacts were isolating and preventing further transmission (Figure 5).

Seven (19%) cases were asymptomatic at the time of diagnosis, and three (8%) remained asymptomatic. This falls within the lower end of the 18%–57% range of asymptomatic rates previously reported in the literature (21–24). These cases were found due to high-volume swabbing and testing rates, resulting in a low percent positivity throughout the outbreak. Early detection of asymptomatic cases allowed for timely isolation preventing further transmission (25). Individuals who are asymptomatic are difficult to trace, less likely to self-isolate, and more likely to engage in social behaviours (26). Our outbreak provides support that initially asymptomatic cases often develop symptoms and become pre-symptomatic cases. More evidence is required for a better understanding of the prevalence and role of true asymptomatic transmission compared to pre-symptomatic transmission in COVID-19.

Secondary transmission to people who did not attend the nail salon occurred mainly through household contact. In total, 12 (32%) cases were household contacts with another case in the outbreak. Previous reports have shown household secondary attack rates for COVID-19 of 11.2%–35% (27–31). This type of transmission was expected, having been described with SARS-CoV, Middle East respiratory syndrome (MERS) and influenza (32–34). People living in the same household generally practice activities that facilitate infection via droplets, such as intimacy and sharing food and drinks. Although it may be challenging to interrupt transmission of SARS-CoV-2 between household contacts, management of this outbreak showed that limiting spread outside of the household was made easier by identifying cases early in the course of illness and isolating them along with close contacts.

Superspreading events occur when a case spreads disease far more widely than others. They have been seen worldwide including at a choir in the United States, a nightclub in South Korea and a blessing ceremony in China (35–37). A superspreading event was noted in this PSS outbreak: one client was responsible for 14 (38%) cases, none of whom attended the nail salon. Of these, two were workplace contacts while six attended a social event with the first-generation case, subsequently transmitting the virus to their own contacts. Contact tracing for this cluster was very challenging: a number of contacts were not identified during the intake interview of the initial case; however, individuals later testing positive subsequently identified having close contact with the initial case. Superspreading events have played a large role in COVID-19 transmission, with a recent modelling study proposing that an effective way to control the epidemic was limiting random contacts outside of workplace and household environments (35). This supports the provincial guidelines at the outbreak onset of maintaining a social circle of up to 10 people (38). The client in the KFL&A superspreading event had a social circle much larger than 10, highlighting the importance of maintaining small social circles to avoid superspreading events.

The mass quarantine of hundreds of individuals had widespread social, health and economic consequences. The day after the outbreak was announced, hundreds of people lined outside the assessment centre; some waiting for hours to be tested. Businesses closed due to the necessity of quarantining workers, and the community was hesitant to access businesses that remained open. In Ontario, regions with the lowest socio-economic status have carried the largest burden of COVID-19 (39); however, the majority of cases associated to this outbreak were located in geographical areas associated with higher socio-economic status. It is possible that the greater

impact on individuals of higher socio-economic status was due to their increased likelihood of being able to purchase aesthetic services. The choropleth map indicated no major associations beyond proximity to the outbreak source.

Limitations

There are several limitations to this report. Data on symptoms and close contacts was self-reported and vulnerable to social desirability and recall bias. With media coverage and stigma surrounding social activities, respondents may have provided reports that were deemed more socially acceptable; a common trend in case and contact management (40–42). Some of the data may be incomplete due to resource and data management system limitations. The assessment centres, PHOL, local public health agency and hospitals use different electronic information systems, which are not integrated. In addition, the sudden large increase in cases and contacts partially overwhelmed the assessment centres leading to potential data quality issues. Also, it is not possible to determine a causal relationship between any single initiative and its effect on controlling the outbreak as all initiatives likely worked in conjunction to limit the outbreak. Furthermore, inferences based on geographical indicators may be flawed and not apply at the individual level leading to the ecological fallacy. Finally, data was only collected on cases and contacts within the KFL&A jurisdiction, with extra-jurisdictional individuals being referred to their respective local public health agency. As such, they may not be captured, resulting in under-reporting. Despite these limitations, this report adds to the literature by reviewing a COVID-19 PSS outbreak and describing the subsequent initiatives that led to its interruption in a medium-sized local public health agency in Ontario.

Conclusion

Overall, KFL&A Public Health, PHOL and the hospitals running the assessment centres were able to contain and manage a COVID-19 outbreak in a PSS with continuous public communications, rapid inspections, aggressive testing, public health orders, short testing turnaround times and thorough case and contact management occurring within 24 hours of positive laboratory results. The KFL&A community also played a crucial role in protecting one another by getting tested and adhering to KFL&A Public Health's orders to self-isolate and wear face coverings in indoor public spaces. These actions can inform decision-making by other jurisdictions that may be dealing with similar future outbreaks. A collective collaborative approach is needed in an outbreak, as all members of the community must work together to limit the spread of disease.

Authors' statement

AL and SP — Writing–original draft
AL — Data visualization, analysis and interpretation
AK and THG — Epidemiologic and environmental investigations and response and provided feedback
KM — Oversaw the epidemiologic and environmental investigations, provided feedback, supervised the work
All authors contributed to the conceptualization of the manuscript.

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Competing interests

None.

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An outbreak of hepatitis C virus attributed to the use of multi-dose vials at a colonoscopy clinic, Waterloo Region, Ontario

Arianne Folkema[1]*, Hsiu-Li Wang[1,2], Kristy Wright[1], M Mustafa Hirji[2,3], Anton Andonov[4], Kathryn Bromley[1], Chad Ludwig[1], Amy MacArthur[1]

Abstract

Background: Hepatitis C virus (HCV) transmission has been epidemiologically linked to healthcare settings, particularly out-of-hospital settings such as endoscopy clinics and hemodialysis clinics. These have been largely attributed to lapses in infection prevention and control practices (IPAC).

Objective: To describe the public health response to an outbreak of HCV that was detected among patients of a colonoscopy clinic in Ontario, and to highlight the risks of using multi-dose vials and the need for improved IPAC practices in out-of-hospital settings.

Methods: Screening for HCV was conducted on patients and staff who attended or worked at the clinic within the same timeframe as the index case's procedure. Blood samples from positive cases underwent viral sequencing. Inspections of the clinic assessed IPAC practices, and a chart review was done to identify plausible mechanisms for transmission.

Outcome: A total of 38% of patients who underwent procedures at the clinic on the same day as the index case tested positive for HCV. Genetic sequencing showed a high degree of similarity in the HCV genetic sequence among the samples positive for HCV. Chart review and clinic inspection identified use of multi-dose vials of anesthesia medication across multiple patients as the plausible mechanism for transmission.

Conclusion: Healthcare workers, especially those in out-of-hospital procedural/surgical premises, should be vigilant in following IPAC best practices, including those related to the use of multi-dose vials, to prevent the transmission of bloodborne infections in healthcare settings.

Affiliations

[1] Region of Waterloo Public Health and Emergency Services, Waterloo, ON

[2] Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON

[3] Niagara Region Public Health & Emergency Services, Thorold, ON

[4] National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, MB

***Correspondence:**
afolkema@regionofwaterloo.ca

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Keywords: HCV, infection prevention and control practices, IPAC, contamination, outbreak, out-of-hospital healthcare settings

Introduction

About 246,000 Canadians were living with chronic hepatitis C virus (HCV) infection in 2011 (1).

HCV is a bloodborne virus, and the most common modes of infection are through using drug paraphernalia contaminated with infected blood, receiving body services (e.g. tattooing) that use unsanitary tools or work practices, or sharing personal care items (2).

HCV outbreaks have been epidemiologically linked to healthcare settings in Canada and elsewhere, particularly out-of-hospital surgical/procedural settings such as endoscopy clinics and hemodialysis clinics (3–16). Transmission in these settings has been attributed to syringe reuse; contamination of medication vials used on multiple patients; storage and preparation of medication, intravenous solution and injections in a contaminated environment; and other infection prevention

and control (IPAC) lapses that resulted in the contamination of injectable medications or flush solution used for multiple patients (3–16).

The purpose of this report is to:

- Describe the public health response to this outbreak of HCV in a colonoscopy clinic
- Highlight the risk of using multi-dose vials
- Show the need for continued improvement in IPAC practices in out-of-hospital settings

Background

As mandated through the *Health Protection and Promotion Act*, HCV is a reportable disease and Ontario public health departments must investigate all new diagnoses of HCV that occur within their jurisdiction (17,18).

Region of Waterloo Public Health and Emergency Services (hereafter referred to as Public Health), in southern Ontario, coordinates the public health activities for its urban and rural population of approximately 550,000. As part of its reportable disease investigation, Public Health follows up with all HCV cases to identify possible sources of infection and to take measures to prevent further spread (18).

Methods

Detection of the outbreak

In October 2014, during a routine follow-up with an individual who had been recently diagnosed with HCV and who had previously tested negative for HCV through repeat blood donation screening, Public Health identified that this individual's only risk factor was a procedure at a colonoscopy clinic on December 24, 2013. All other HCV cases reported within the jurisdiction since January 1, 2010 (the year the clinic opened) were subsequently reviewed to determine if other cases had identified colonoscopy as a risk factor.

The review identified a second individual who had been reported to Public Health earlier in 2014 and who had also undergone a procedure on the same day at the same clinic. Although this person had been born in an endemic country, they had no other obvious risk factors. Given that the two cases shared a common risk factor and were linked by time and place, an outbreak was suspected and further investigation was conducted. Blood samples from the two identified HCV cases were obtained and sent to the National Microbiology Laboratory of the Public Health Agency of Canada in Winnipeg for genotyping and sequencing.

Investigation

Public Health used the Centers for Disease Control and Prevention (CDC) *Viral hepatitis: Healthcare Investigation Guide* and documentation from a previous health care–associated investigation as guidance for a systematic approach to the investigation and public health response to this outbreak (19,20).

Patient lists for December 23 and 24, 2013 were obtained from the colonoscopy clinic and the provincial reportable diseases database was searched to determine whether any other cases of HCV reported in the province had undergone procedures at the clinic since its inception on October 14, 2010. Patient screening was not conducted for the two-day interval before and after December 23 and 24, 2013 because the clinic was closed on December 21 and 22 (a Saturday and a Sunday), and December 25 and 26 (statutory holidays).

As per the Public Health Ontario Laboratory Protocol for HCV testing, patients were first screened for HCV antibodies using an anti-hepatitis C antibody assay; those with anti-hepatitis C antibodies then had HCV antibody supplemental testing performed for confirmation (21). Any patients with positive results on the confirmatory testing then had new samples submitted for molecular testing for HCV ribonucleic acid RNA and genotyping.

Public Health conducted a search on the College of Physicians and Surgeons of Ontario's (CPSO) website to confirm that all physicians working at the clinic on December 23 and 24, 2013 held valid professional licences and to determine if any previous IPAC violations had been reported.

Public Health staff contacted all patients who underwent procedures at the clinic on December 23 and 24, 2013 and recommended HCV screening. Daytime and early evening screening clinics were offered locally. For patients who resided outside of the health department's jurisdiction, Public Health facilitated follow-up with physicians in their areas. Blood samples were submitted to the National Microbiology Laboratory in Winnipeg for HCV testing and positive samples underwent genetic sequencing.

A case was defined as an individual with a laboratory-confirmed HCV infection (both HCV antibody and RNA testing) that had undergone any procedure performed at the clinic on December 23 or 24 that could be associated with disease transmission (colonoscopy, esophagogastroduodenoscopy/gastroscopy, glucose monitoring and intravenous medication administration).

Between November 17, 2014 and April 21, 2015, Public Health conducted multiple inspections of the clinic to assess and follow-up on IPAC practices. The inspection was guided by a comprehensive assessment tool based on the Ontario Provincial Infectious Diseases Advisory Committee's (PIDAC) *Infection Prevention and Control for Clinical Office Practice* document (22). Inspections were supplemented by lengthy interviews with staff to understand their processes and IPAC practices. The final inspection was conducted jointly with the CPSO, which has

regulatory oversight over community colonoscopy clinics (public health departments in Ontario only investigate out-of-hospital premises in response to suspected infection control lapses) (23).

The inspections involved observation of high-risk procedures including the preparation and storage of medications; use of multi-dose vials; endoscope reprocessing practices; cleaning and disinfection of surfaces and equipment; use of materials and equipment such as medical gels, intravenous saline flushes and glucometers; as well as a review of the clinic's IPAC policies and procedures. Several colonoscopy procedures were observed directly to assess the IPAC practices, including anesthesia administration.

An extensive review of all the charts of patients who visited the clinic for procedures on December 23 and 24, 2013 was also conducted to identify patterns that might indicate potential routes of transmission. The chart review included review of the time of the visit; procedure room used; endoscope serial number; glucometer use; anesthetic (propofol) dose received; other medications received; and the attending surgeon, anesthesiologist and nursing staff.

Results

In total, 40 individuals underwent procedures at the clinic on December 23 and 24, 2013. Public Health was successful in screening 39 out of the 40 patients and 11 out of 13 staff (**Table 1**); one patient and two staff could not be contacted. Of the 26 patients who attended and nine staff who worked at the clinic on December 23, all screened negative for HCV. Of the patients who attended the clinic on December 24, 5 out of 13 (38%) tested positive for HCV (**Table 2**).

Table 1: HCV screening results for staff and patients who attended colonoscopy clinic on December 23 and 24, 2013

Clinic date	Total	HCV positive	HCV negative	Not screened[a]
Patients				
2013-12-23	27	0	26	1
2013-12-24	13	5	8	0
Staff				
2013-12-23 only	8	0	6	2
2013-12-24 only	2	0	2	0
Both 2013-12-23 and 2013-12-24	3	0	3	0
Total	53	5	45	3

Abbreviation: HCV, hepatitis C virus
[a] Not screened because patients/staff were unable to be contacted or were lost to follow-up

Table 2: Description of HCV-positive patients

Characteristics		Number of cases
Sex	Male	4
	Female	1
Age group, years	0–19	0
	20–49	1
	50–69	3
	70+	1
Risk factors[a]	Born in endemic country	1
	Previous medical/surgical procedure (>20 years prior)	2
	Procedure at colonoscopy clinic on Dec. 24, 2020	5

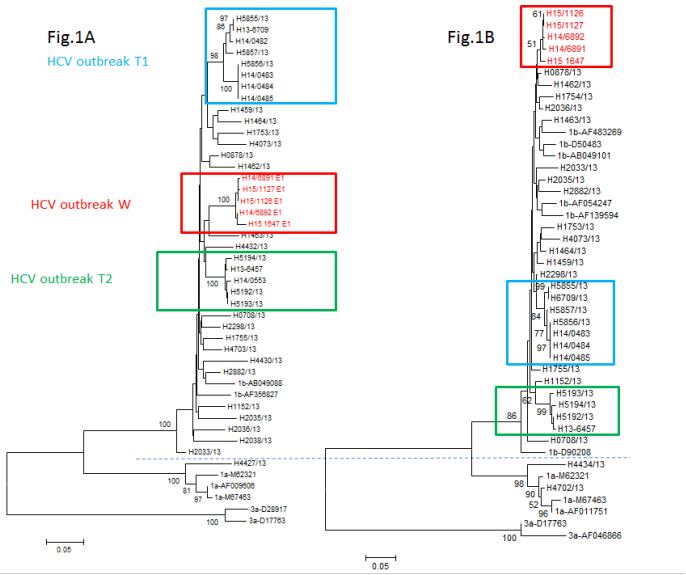
Abbreviation: HCV, hepatitis C virus
[a] An individual could have more than one risk factor reported

None of the staff who worked on December 24 tested positive. The review of all known HCV cases in Ontario since the clinic's inception in October 2010 did not identify any additional cases of HCV linked to this clinic. The search on the CPSO website indicated that all physicians working at the clinic at the time of the outbreak held valid licences.

Phylogenetic analysis conducted by the National Microbiology Laboratory based on partial sequences from the HCV core (C), envelope (E1) and non-structural (NS5B) genes clearly indicated that the HCV strains from the five outbreak patients were genetically closely related (**Figure 1**), consistent with a cluster of transmission. All five cases clustered in a monophyletic group based on the E1 gene sequences. A more detailed analysis based on next-generation sequencing (NGS) revealed that the HCV quasispecies population of all five patients clearly clustered together on a single branch with a 99% probability (**Figure 2**). The average genetic distance within the five cases involved in the outbreak quasispecies was 0.036 while the genetic distance between this group and similar outbreaks as well as unrelated Ontario cases and GenBank HCV strains was significantly higher ($p<0.001$).

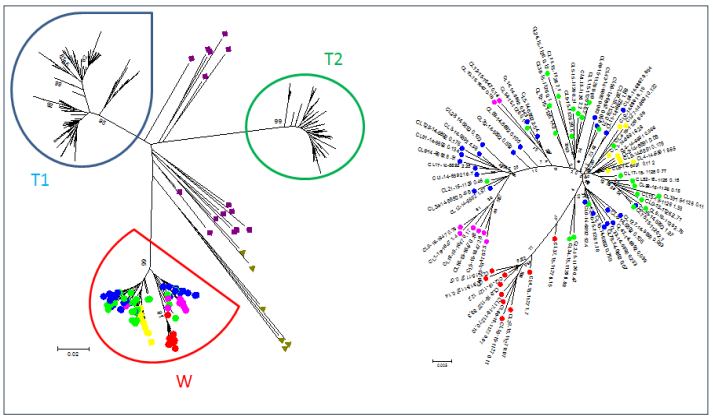
The inspections of the clinic and interviews with staff identified no concerns or deficiencies with respect to the use, cleaning or reprocessing of endoscopes. Glucose monitoring was not performed on all five HCV patients, ruling out the use of a shared glucometer as a potential source of infection. Of the 13 patients who received an intravenous saline flush, only five were HCV positive, which decreased the likelihood that the bag of intravenous saline used for the entire day was a potential source of infection.

Figure 1: Phylogenetic analysis of Sanger population-based sequencing of HCV E1/NS5B subgenomic regions from five patients in an outbreak investigation[a]



Abbreviation: HCV, hepatitis C virus
[a] Neighbour-joining tree was created by using Kimura's two-parameter model in MEGA software version 6. Outbreak sequences from this outbreak (W) and two other similar outbreaks in endoscopy clinics from Toronto (T1 and T2) are in red, green and blue boxes, respectively. Epidemiologically unrelated HCV sequences from the province of Ontario collected in the same year (2013) as well as some randomly selected sequences from GenBank are in black. The dendrogram in Fig. 1A is based on E1 region and that in Fig. 1B is based on the NS5B region. Note that phylogenetic analysis based on NS5B region did not have the same strong bootstrap support as that observed for E1 region. In comparison the bootstrap measures for the two other similar outbreaks T1 and T2 remained robust for both the E1 and NS5b although dropped somewhat from 98 to 84 for T1

Figure 2: Phylogenetic analysis of HCV HVR-1 quasispecies in samples of five patients involved in a transmission event in this outbreak (outbreak W)[a]



Abbreviation: HCV, hepatitis C virus
[a] Sequences of HCV genotype 1b quasispecies population derived from three different outbreaks (T1, T2 and W), sequences of unrelated HCV strains from Ontario and GenBank (green triangles) and randomly selected HCV strains from GenBank (purple squares) are shown on the left side of the figure. Bootstrap values are shown at the bottom of the nodes. Sequences of the five cases from outbreak W are colour-coded and magnified on the right corner of the figure. Each colour dot (node) represents a single HCV variant. Quasispecies of patient #6 (transmission source) green; patient #7 red; patient #8 pink; patient #10 blue; patient #13 yellow.
Note that consensus sequences from the unrelated HCV strains from Ontario and GenBank, as well as the quasispecies from two other HCV outbreaks T1 and T2 occupy entirely different sequence space

The chart review of patients attending the clinic on December 24 showed that only one procedure room was used. All patients who attended the clinic that day had the same surgeon, anesthesiologist and nurses during their procedures. The first 11 patients had the same pre-procedure nurse, while the last two patients had a different pre-procedure nurse. The procedures for the five patients who tested positive for HCV used different endoscopes.

All HCV patients were administered the anesthetic drug, propofol, using multi-dose medication vials across multiple patients, and this was the only plausible mechanism of HCV transmission identified. Based on the amount of propofol administered to each patient according to their medical charts, a patient medication map was developed to present the hypothesized distribution of contaminated 100 mL vials of propofol alongside the distribution of HCV cases at the clinic on December 24, 2013 (**Table 3**). Since all patients who had a procedure performed also had propofol administered during their procedure, a pattern was identified in the occurrence of HCV positivity and the use of propofol.

As shown in Table 3, it is hypothesized that all 100 mL of the first vial of propofol (Vial #1) was used up on the first five patients, none of whom tested positive for HCV. Then, propofol Vial #2 was contaminated with the blood of patient #6 who had a pre-existing undiagnosed HCV infection. This same vial was then used for patients #7, #8 and #10. Finally, the remaining 15 mL of propofol in Vial #2 was mixed with 5 mL of propofol from a third vial to make 20 mL of propofol for patient #11, thereby contaminating Vial #3 but diluting the amount of contamination. This dilution could explain why only one of the three patients who received propofol from Vial #3 tested positive for HCV.

Given that the actual propofol vial used for each patient was not identified in the patient charts, this interpretation was hypothesized based on the type of vials used by the clinics, the doses administered to the patients as recorded in their charts and finding out from the inspections and interviews that multi-dose vials were being used across multiple patients.

Table 3: Colonoscopy patient medication map for December 24, 2013

Patient number	Procedure start time	Procedure type	HCV lab result	Medication administered	Total dose administered (mg)[a]	Total volume administered (mL)[b]	Hypothesized vial #	Hypothesized use of propofol vials (100 mL per vial)
1	08:54	Colonoscopy	Negative	Propofol	250	25	Vial #1	All 100 mL of the first vial of propofol (Vial #1) was used on the first five patients.
2	09:16	Colonoscopy	Negative	Propofol	150	15		
3	09:54	Endoscopy	Negative	Propofol	200	20		
4	10:08	Colonoscopy	Negative	Propofol	200	20		
5	10:42	Colonoscopy	Negative	Propofol	200	20		
6	11:10	Endoscopy/ colonoscopy	Positive	Propofol	250	25	Vial #2	The second vial of propofol (Vial #2) was contaminated with the blood of Patient #6 with HCV and was then used on Patients #7, #8 and #10.
7	11:54	Colonoscopy	Positive	Propofol	200	20		
8	12:25	Colonoscopy	Positive	Propofol	200	20		
9	N/A	IV start only	Negative	None	None	None		
10	13:40	Colonoscopy	Positive	Propofol	200	20		
11	14:10	Colonoscopy	Negative	Propofol	200	20	Vial #3	The last 15 mL of Vial #2 was mixed with 5 mL of propofol from a third vial (Vial #3) to make 20 mL of propofol for Patient #11, thereby contaminating Vial #3, but diluting the amount of contamination. This dilution could explain why only one of the three patients who received propofol from Vial #3 tested positive for HCV.
12	14:35	Endoscopy/ colonoscopy	Negative	Propofol	250	25		
13	15:11	Colonoscopy	Positive	Propofol	200	20		

Abbreviations: HCV, hepatitis C virus; IV, intravenous; N/A, not applicable
[a] Dose obtained from patient charts
[b] Volume administered was deduced from the dose administered and the concentration of the 100 mL vials of propofol used at the clinic

Disscussion

The findings from the outbreak investigation support the hypothesis of HCV transmission from a previously undiagnosed HCV patient to four uninfected persons. Laboratory results demonstrated that all five cases of HCV had genetically related viruses, indicating a high likelihood of transmission from a common source. The investigation identified an association between the administration of propofol from multi-dose vials and the patients who tested positive for HCV.

Contamination of multi-dose vials has been associated with other instances of transmission of bloodborne infections in colonoscopy clinics, among other places (4,8,12,24,25). There is a risk of bloodborne pathogen transmission when devices (e.g. blood glucose monitors) and medications (e.g. multi-dose vials, saline bags) are shared among patients, even in the absence of visible blood on objects (6,25–28).

Out-of-hospital settings may be more vulnerable to infection control lapses than hospitals because specific IPAC resources and

oversight have been less robust in this practice setting (29,30). Out-of-hospital settings typically do not have on-site infection control specialists, guidance on policies and procedures tailored to their practice setting, requirements to audit staff practices, nor in many jurisdictions, a clear procedure to report and investigate infection control lapses (29).

In addition, non-hospital settings may have physically smaller procedure rooms; this may provide more opportunities for body fluids from patients to contaminate nearby surfaces, supplies and equipment (23,31). In 2014, Canadian hospital operating rooms were a minimum of 400 square feet; in comparison, non-hospital procedure rooms do not have a set minimum size and only require that the space allow for the physician and assisting staff to move around the procedure table with access to the patient without contamination (23,31).

At the time of the outbreak, out-of-hospital premises were inspected only once every five years, which resulted in out-of-date practices, declined adherence to standards of practice over time and/or failure to recognize critical errors in practice for long periods (23,32,33).

It is not routine practice to screen clients for bloodborne pathogens prior to invasive medical procedures, and IPAC procedures have been put in place to prevent transmission of bloodborne pathogens. However, researchers estimate that 44% of Canadians with HCV infection remain undiagnosed due to the asymptomatic nature and slow progression of infection (34). Further, for a sub-group of people born between 1945 and 1975 ("baby boomers"), up to 70% of people who have the virus are unaware of their infection status (34). In its updated guidelines, the Canadian Association for the Study of the Liver has emphasized that healthcare providers should offer HCV testing to people at risk for infection, including baby boomers (35). These updated guidelines for screening could help raise awareness of HCV-positive status prior to medical procedures and contribute to the prevention of bloodborne pathogens in all settings.

Outbreak response challenges

The approaches of Public Health and the regulatory bodies were not necessarily consistent and had to be aligned. Further, knowledge of infection control and prevention best practices varied among healthcare practitioner groups. The IPAC investigation also needed to be conducted while allowing the clinic to continue operating and providing procedures for clients during the investigation.

Finally, at the time of the outbreak, although cases were identified through patient screening, not all cases were eligible for treatment. Fortunately, changes have since been made to the Ontario Drug Benefit to cover the cost of medication for all HCV patients.

Conclusion

This outbreak investigation resulted in increased local and provincial awareness of medication injection safety (23). On April 30, 2015, Public Health Ontario published updated guidance on the use of multi-dose vials. The CPSO adopted the Public Health Ontario best practices guidance as the standard for IPAC in out-of-hospital premises (22). The updated guidelines refer to the overwhelming preference for single-use medication vials and state that multi-dose vials should be restricted to single patients. The guidelines also state that patient safety should be prioritized over cost when choosing between multi-dose and single-use mediation vials.

Since this outbreak in 2013, other outbreaks related to IPAC lapses in out-of-hospital premises have occurred in Canada (15,16). Public health investigations of IPAC complaints are also on the rise in Ontario, including in settings where regulated health professionals work (36). Given continued pressures on delivery of health care in Canada and around the world, the number of procedures that occur in out-of-hospital premises could increase, leading to an increased risk of outbreaks if IPAC practices are suboptimal. Careful consideration of IPAC resources, supports and regulations is needed as such an expansion of out-of-hospital premises occurs.

Authors' statement

AF — Writing–original draft, writing–review & editing
HW — Supervision of outbreak management and public health response, writing–review & editing
KW — Supervision of outbreak management and public health response, writing–review & editing
MH — Investigation, writing–review & editing
AA — Viral sequencing and interpretation, writing–review & editing
KB — Writing–review & editing
CL — Investigation, writing–review & editing
AM — Writing–review & editing

Competing interests

None.

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The National Collaborating Centre for Healthy Public Policy in times of COVID-19: Building skills to "Build Back Better"

Olivier Bellefleur[1]*, Marianne Jacques[1]

Abstract

This article, the second in a series on the six National Collaborating Centres for Public Health, focuses on the National Collaborating Centre for Healthy Public Policy (NCCHPP), a centre of expertise, and knowledge synthesis and sharing that supports public health actors in Canada in their efforts to develop and promote healthy public policy.

The article briefly describes the NCCHPP's mandate and programming, noting some of the resources that are particularly relevant in the current coronavirus disease 2019 (COVID-19) context. It then discusses how the NCCHPP's programming has been adapted to meet the changing needs of public health actors throughout the pandemic. These needs have been strongly tied to decisions aimed at containing the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and mitigating its immediate impacts in various societal sectors since the beginning of the crisis. Needs have also gradually emerged related to how public health is expected to help inform the development of public policies that will allow us to "build back better" societies as we recover from the pandemic. The article concludes by discussing the orientation of the NCCHPP's future work as we emerge from the COVID-19 crisis.

Affiliation

[1] National Collaborating Centre for Healthy Public Policy, Institut national de santé publique du Québec, Montréal, QC

***Correspondence:**
olivier.bellefleur@inspq.qc.ca

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Introduction

The National Collaborating Centre for Healthy Public Policy (NCCHPP) is part of a network of six National Collaborating Centres for Public Health (NCCs) established in 2005 by the federal government as part of an effort to renew and strengthen Canada's public health infrastructure in the wake of the epidemic caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-1) (1). The NCCs are funded by the Public Health Agency of Canada (PHAC) and their goal is to support the timely use of scientific and other knowledge-based evidence to inform public health practice, programs and policy in Canada. More specifically, the NCCs' mandate is to develop, synthesize and share knowledge, identify research gaps and the knowledge needs of public health actors, and foster the development of networks among public health professionals, researchers and policy makers across Canada. Each of the NCCs specializes in a specific area of public health and is hosted by a Canadian university or governmental organization (2).

This article is the second in a series of articles describing each of the NCCs and their contribution to the response to the coronavirus disease 2019 (COVID-19). It focuses on the NCCHPP, a centre specializing in healthy public policy hosted by the Institut national de santé publique du Québec (INSPQ) in Montréal. The article begins with a brief presentation of the NCCHPP's mandate and programming, describing some of the resources that are particularly relevant to the current COVID-19 context, and then focuses on adjustments that have been made to maintain the Centre's relevance in the context of the pandemic.

A Centre devoted to healthy public policy

The NCCHPP is a centre of expertise whose mandate is to support public health actors in Canada in their efforts to develop and promote healthy public policy. These policies shape the

"circumstances in which people are born, grow up, live, work and age" (3). In other words, they are levers for acting on the social, cultural, ecological and economic determinants of health (4). Thus, even when these policies fall under the responsibility of non-health government sectors, they have the potential to significantly impact population health and health inequalities (5,6). Such policies may include, for example, housing, education, transport, environmental and income policies. It is therefore not surprising that building healthy public policy was identified as one of the pillars of health promotion by the World Health Organization (WHO) in the Ottawa Charter (7).

An updated program

In 2019, PHAC renewed funding for the NCCs for an eight-year period, reaffirming the added value the NCCs bring to Canada's public health infrastructure. The NCCHPP's new programming is organized around three axes, whose overarching goal is to support the development of the individual skills and organizational capacity required to act to promote healthy public policy.

The first axis of the NCCHPP's programming is devoted to the development of resources and knowledge-sharing activities aimed at facilitating policy analysis, improving understanding of public policy processes, and assisting actors in more effectively sharing knowledge within these processes. These resources and activities seek to strengthen public policy competencies, which are recognized as essential within public health (8,9); given that policies are indispensable levers for acting upstream and in a structuring manner to benefit population health and reduce health inequalities. The NCCHPP's resources include two online courses, one on a framework for analyzing public policies (10) and the other on public health ethics (11). These courses have been taken by nearly 3,000 and 2,000 participants respectively since their launch and are included in the curricula of several Canadian universities. The NCCHPP's resources related to this axis also include various documents focused, in particular, on working with municipalities (12), policy approaches to reducing health inequalities (13), policy agenda setting (14), and public policy competencies for public health (8).

As part of the second axis of its programming, the NCCHPP develops and shares resources related to intersectoral approaches to integrating a public health perspective into the policies, programs and projects of other government sectors such that they address health determinants and health inequalities. The NCCHPP focuses mainly on two approaches promoted by the WHO: Health in All Policies (HiAP) and Health Impact Assessment (HIA) (15,16). These two approaches have been put forward in recent years as a way to act upstream on health, wellbeing and health equity in Canada (17–19) and calls to take action to further their implementation have multiplied since the beginning of the pandemic (20,21). To support their implementation, the NCCHPP has developed, among other things, an online training course on HIA (22), which has been taken by nearly 3,000 participants since its launch, as well as various documents on HIA and HiAP (23–26). The NCCHPP's expertise in the area of HiAP has also enabled it to assume the mandate of secretariat for the Global Network for Health in All Policies, a network affiliated with the WHO. It allows the Centre to remain in close contact with international actors in the field of HiAP and to facilitate networking and knowledge sharing with Canadian actors.

Finally, the NCCHPP uses the approaches, methods and tools developed in its first two program axes to address emerging or priority public health issues in the third axis of its programming. This axis of the NCCHPP's program involves working on population mental health and wellness, climate issues and, for the past year or so, COVID-19. For several years, the NCCHPP has been working with its partners to clarify the roles of public health actors in promoting population mental health and wellness, to identify the needs associated with these roles, and to respond to these needs. Activities have included hosting a pan-Canadian forum (27), developing an inventory of mental health strategies in Canada (28), and producing a framework for supporting action in population mental health (29) that has been used in several jurisdictions, including Ontario, to support the implementation of the Mental Health Promotion Public Health Standards. More recently, the NCCHPP has also begun work on policy approaches to reducing the health risks associated with climate change, in particular by exploring the potential of the ecological economics model (30) and by identifying tools and methods for integrating health into climate change adaptation or mitigation policies and strategies (31).

The National Collaborating Centre for Healthy Public Policy in times of COVID-19

Since the beginning of the pandemic, public health actors have been heavily involved in government-wide efforts to contain the spread of the SARS-CoV-2 virus and to mitigate its immediate impacts on different sectors of society. As the pandemic has evolved, efforts to mitigate its medium and long-term effects on population health and wellbeing have expanded. Some public health actors are also being called upon to contribute to efforts to "build back better" societies, notably through action on healthy public policy (20). Anticipating this development, the NCCHPP quickly adapted its programming to meet certain pressing needs, but above all to prepare appropriate resources to help mitigate the medium and long-term effects of the pandemic and to "build back better" societies.

As early as March 2020, the NCCHPP developed and made available online a directory of selected resources to facilitate the integration of an ethical dimension in decisions related to COVID-19 (32). The directory, which is updated regularly,

provides a brief summary of each resource and groups them into categories (frameworks, equity, Indigenous health, communication, etc.) for easy retrieval. It has been referenced by multiple actors, including the Québec Population Health Research Network, the First Nations Health Consortium in Alberta, and Manitoba Shared Care.

The NCCHPP has also coordinated the development of an initiative involving all six NCCs, in partnership with the Canadian Institutes of Health Research (CIHR). Through this initiative, the NCCs are leveraging their knowledge translation expertise, their networks and their dissemination channels to support efforts to mobilize and disseminate new knowledge arising from CIHR-funded research projects related to COVID-19. To date, this initiative has provided support to 23 research teams across Canada.

Responding to the earliest calls for action to "build back better" societies, the NCCHPP began a series of documents on "wellbeing budgets," which could offer a promising pathway for governments intent on achieving an economic recovery focused on improving the wellbeing of citizens. This is an approach to integrating wellbeing indicators into government budgeting processes. While interest in this approach existed in Canada prior to the pandemic (as evidenced, for example, by the federal Minister of Middle Class Prosperity and Associate Minister of Finance mandate letter (33)), this interest has only deepened during the pandemic (34,35).

Finally, the NCCHPP, together with the Global Network for Health in All Policies and WHO, has undertaken to document the potential of the HiAP approach to contribute to gradually transform the intersectoral collaboration observed since the beginning of the pandemic. One of the anticipated challenges will be to redirect this collaboration toward longer-term objectives related to the promotion of health, wellbeing and equity (20,21). To this end, the NCCHPP worked with its Canadian and international partners to deliver a series of webinars focused on the HiAP approach in times of COVID-19 (36). These activities attracted just over 300 participants and garnered very positive evaluations, particularly as a means of knowledge acquisition and for their relevance to public health practice. In the same vein, the NCCHPP has also begun work on establishing a Canadian network for HiAP in partnership with the PHAC.

Conclusion

The NCCHPP is a centre of expertise that works to build public health skills and capacity for intersectoral action on healthy public policy by offering a range of resources and activities. With the advent of COVID-19, the NCCHPP quickly adapted its programming not only to meet some of the pressing needs of public health actors, but above all to develop resources to support longer-term public health action on the determinants of health affected by the pandemic and on the widening of health inequalities in Canada.

Future work will build on the initiatives outlined in this article. However, given the likelihood of forthcoming pressures to balance budgets at all levels of government, work will also be done to examine the opportunities and challenges that these pressures present for intersectoral collaboration that benefits health and health equity. In short, the NCCHPP will continue to work with all of its partners to support public health actors who wish to act on public policy to mitigate the medium and long-term impacts of the pandemic, to "build back better" societies, and to strengthen our resilience in the face of future crises.

Authors' statement

OB — Conceptualization, drafting of original text, review and revision
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Ethics check-up of public health immunization programs in Canada

Noni E MacDonald[1]*, Shawn Harmon[1,2], Janice E Graham[1,3]

Abstract

The World Health Organization (WHO) recognizes immunization as one of the most successful and effective public health interventions for saving lives. In developing a roadmap for prioritizing use of the coronavirus disease 2019 (COVID-19) vaccines in the context of limited supply, WHO highlighted the importance of a values (ethical principles) framework. Immunization does need to be subject to independent ethical scrutiny of vaccine research data, manufacturing practices, the legal and ethical assurance of informed consent, and also social justice issues with respect to program equity, including right to access. An ethics review of Australia's immunization program was reported in 2012. This CANVax (Canadian Vaccination Evidence Resource and Exchange Centre) Brief offers an ethics review of immunization in Canada using the criteria utilized for Australia.

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Affiliations

[1] Department of Pediatrics, Dalhousie University, IWK Health Centre, Halifax, NS

[2] Policy Analyst, Health Law Institute, Schulich School of Law, Dalhousie University, Halifax, NS

[3] Technoscience and Regulation Research Unit, Faculty of Medicine, Dalhousie University, Halifax, NS

***Correspondence:**
noni.macdonald@dal.ca

Introduction

The World Health Organization (WHO) recognizes immunization as one of the most successful and effective public health interventions for saving lives (1). The effects of immunization reach far beyond the health and well-being of individuals and communities by improving social determinants of health that affect work productivity, equity, institutional stability, economic development and innovation (see **Figure 1**). The coronavirus disease 2019 (COVID-19) pandemic has focused global attention on the importance of public health interventions and immunization to restore health and well-being of individuals and communities. In developing a roadmap for prioritizing use of COVID vaccines in the context of limited supply (2), WHO highlighted the importance of a values framework (3). This values framework draws from ethical principles focusing on human well-being, equal respect, global equity, national equity, reciprocity and legitimacy. These principles, while important for COVID-19 vaccines, apply to all immunization programs. Immunization needs to be subject to independent ethical scrutiny of vaccine research data and manufacturing practices, the legal and ethical assurance of informed consent, and social justice issues, including right to access.

In this Brief, we offer an "ethics check-up" of Canada's public health immunization programs and suggest some areas for further improvements.

Figure 1: Immunization and the Sustainable Development Goals

Adapted from GAVI – the Vaccine Alliance (https://www.gavi.org/about/ghd/sdg/)

The check-up criteria used

Immunization programs merit scrutiny for ethical practice not only by practitioners delivering the vaccines to patients but also to ensure ethical principles are followed over the whole program as the communities and populations targeted for immunization vary by age, disease burden, vulnerability and marginalization.

The risks and benefits of immunization might vary in communities seen as vulnerable (e.g. infants, children, pregnant women, immunocompromised and older adults).

Attention to ethical issues has mainly focused on national risk/benefit for policy recommendations and on trust through the lens of vaccine hesitancy/acceptance, while the ethical issues that arise at the front line (benefits, risks, effectiveness, equity and justice, autonomy, reciprocity and trust) have received less attention. Country-wide ethics assessment of immunization programs is a relatively nascent area.

Isaacs (4) developed seven ethical principles to inform assessments of public health immunization programs in Australia. These apply across the program from policy to frontline practices:

- Benefits
- Risks
- Effectiveness
- Equity and justice
- Autonomy
- Reciprocity
- Trust

This CANVax (Canadian Vaccination Evidence Resource and Exchange Centre) Brief applies Isaac's Australia ethics criteria (4) to Canada and draws attention to several concerns.

Applying the criteria

At the policy level, the National Advisory Committee on Immunization (NACI) and each of the provinces and territories make decisions on who is and who is not eligible for vaccines using an evidence-based framework. NACI is working to incorporate ethics, equity, feasibility and acceptability into their national recommendations (5). Assessment of the outcomes of the application of these ethical principles will only be known over time.

As noted, NACI provides evidence-based recommendations that take into account population burden and risks of disease, including the safety and expected benefits of the vaccine in different populations in Canada. The provinces and territories then make their public health policy decisions about including and paying for vaccine(s) in their immunization programs, for whom it will be made available, how the program will be delivered and whether catch-up programs will be introduced. (This does not include COVID-19 vaccines, for which the federal government is paying.)

Not all vaccines recommended by NACI are equally accessible across the country. Provincial differences in implementation can foster provider and public confusion, raising national equity and social justice concerns to do with access. For example, introduction of conjugated pneumococcal vaccine and varicella vaccine varied across the country, despite that both vaccine-preventable diseases (VPDs) are prominent everywhere (6). The disparity in timing of vaccine introduction continues, with Alberta introducing a school-based human papillomavirus (HPV) vaccine program for girls in 2008 and Nunavut only doing this in 2010. Not all provinces and territories offer HPV vaccine catch-up programs for boys, and Nova Scotia's approval of routine rotavirus vaccine in their infant program only came in 2019, years after other provinces (7). Thus, access to NACI-recommended vaccines varies depending on where one lives in Canada, underscoring equity and social justice issues.

Risk, benefits and effectiveness

Both the benefits of immunization, i.e. prevalence of VPD, and risks of immunization, i.e. adverse events following immunization (AEFI) are tracked in Canada through surveillance systems. Canada has both passive and active AEFI (8) and VPD reporting, with VPD reporting from laboratories now more automated than in the past. VPD and AEFI summary findings are regularly reviewed and discussed within the provinces or territories where they are reported as well as nationally at NACI and the Public Health Agency of Canada (PHAC). There are many examples where the introduction of a new vaccine across Canada has led to a marked decrease in the VPD, e.g. invasive *Haemophilus influenzae* type b (9) and pneumococcal-related diseases (10), providing data on vaccine effectiveness in Canadian populations. IMPACT (Immunization Monitoring Program ACTive), Canada's paediatric hospital–based national active surveillance network, which looks for vaccine failures, serious AEFI (i.e. hospitalization) and selected VPD and infectious diseases, has provided much valuable data on the effects of pediatric vaccines over the past two decades. Similar data for the effects of adult vaccines are not routinely collected. The Serious Outcomes Surveillance (SOS) Network collects data on adults admitted to hospital with influenza or pneumonia, but it does not track serious AEFI (11). Neither of these systems collect immunization uptake data for the specific region served by the reporting site, meaning that the effectiveness of the different vaccines locally can only be estimated. The CANImmunize app tailored for COVID-19 vaccines addresses some of these deficits but is not used fully across the country (12).

Vaccine failures are less well tracked. VPD-microbe reporting by microbiology laboratories is increasingly active across the country as they become automated. However, the detected VPD cases may lack information on whether this is a vaccine failure. The need to detect COVID-19 vaccine failures—due to the failure of the vaccine itself and due to program errors such as mishandling of vaccine storage and missed populations/subgroups—in order to establish effectiveness in different age groups and settings has pushed all the provinces and territories to collect immunization data for these vaccines so that vaccine-receipt failures as well as immunization failures can be more readily detected. However, not all regions have quality immunization registries for all vaccines. Overall, the principles of risk and effectiveness could be more broadly and better addressed across all age groups.

Autonomy and informed consent

With respect to autonomy, school-based immunization programs raise unresolved consent and assent issues. While such programs are routinely offered across Canada, the age varies, from Grade 4 (approximately 10–11 years old) to Grade 9 (approximately 15–16 years old). Typically, parents sign a consent form for the vaccines to be administered, but if there is no consent and the student wants to be immunized, or if the consent and the student's stated decision are at odds, public health practitioners may be unclear about how to proceed and jurisdictional practices differ (13). In the case of positive parental consent with a student refusal, the vaccination is unlikely to proceed. But for the student who expresses a desire to be vaccinated in the face of parental refusal, there is more ambiguity. This uncertainty is confounded by variation across Canada at which age "capacity" is assumed, and the differences in approaches to "mature minors" (14). In Ontario, for example, there is no specific age at which a minor's capacity is assumed; children are assessed on their capacity to give consent, and this is informed less by their age and more by their understanding, which the healthcare provider must assess (15). Furthermore, some healthcare workers will not disregard the parental veto on immunization even if the minor appears to have capacity. A national standard of practice has not yet been established, which may impinge on adolescents' rights and undermine ethical consent standards.

Another uncertainty associated with informed consent involves vaccine information meeting user needs. In Canada, each province and territory develops their own patient/parent information packages. While these may draw on NACI information and advice, they often differ, leaving uncertainty as to whether the same vaccine is being described (16). For those seeking to make an informed decision, this can be confusing, if not off-putting, especially when proponents of no vaccination ("antivaxxers") state that the provided information is inadequate. Improving collaboration on developing materials that provide information about vaccines could make this area less confusing and contentious for those seeking information and may improve coverage in populations where new data confirm safety and effectiveness.

Reciprocity

Canada has a mixed picture of reciprocity for public health immunization programs. Hospital care costs associated with rare serious AEFI are covered by the publicly funded healthcare system. Any long-term disabilities caused by an AEFI may be supported, in part, by disability benefits offered through ministries of community and social services in the provinces and territories. However, these benefits usually do not cover lifelong loss of income due to inability to work. But vaccine causality is not always easy to assess. For example, causality assessment of narcolepsy incidents in Finland and Sweden after administration of the H1N1 vaccine is confounded by the known increased risk of narcolepsy with H1N1 infection, with the virus already circulating in the community when the immunization programs began (17). Disentangling the effect of natural infection concurrent with immunization is not simple. The onset of narcolepsy in childhood has a profound effect on education attainment, capacity for work and many social, family and personal outcomes. There are strong ethical arguments that such serious AEFIs, when due to immunization, should be compensated, especially if vaccines are mandatory (18). In Canada, only Québec has a vaccine injury compensation program, in place since 1987 (19). In December 2020, Canada announced that PHAC is implementing a no-fault vaccine injury support program for all vaccines approved by Health Canada (20), but details are pending as of April 2021. This is a complex undertaking: there are seven characteristics essential to ensure fair, transparent and efficient operation of a vaccine injury compensation program (21).

Trust, social justice and equity

Issues of trust may arise for public immunization programs in a number of different areas. A cluster of AEFIs may undermine trust in the program and in the vaccine if their causality is not addressed quickly and satisfactorily. This occurred in Japan and in Denmark with human papilloma vaccine (22,23). It is unclear if all the provinces and territories or PHAC have serious AEFI rapid science review procedures and communication templates in place, or if the coordination between the government levels across the country is good. Of note, the last reported biannual update on the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) is for the period January to June 2019 (24). While the COVID-19 pandemic may have delayed further updates, it is disturbing that no new summary report has become available for AEFIs in the past 18 months.

Providing mixed messages on AEFIs, whether vaccine related or a coincidence, can rapidly undermine public trust (25). The media attention when Norway noted deaths in frail elderly people following COVID-19 vaccination illustrates how trust may be easily undermined (26).

Trust concerns also arise when different vaccines are available for the same disease but some are funded and other ones are not (e.g. different influenza vaccines targeting seniors) (27). This also raises ethical issues about cost-effectiveness assessment, social justice and the valuation of equity. Canada's contribution to COVAX, the global sharing of COVID-19 vaccines, followed by Canada's plan to receive vaccines from COVAX, unlike many other high-income countries, has raised concerns about Canada's commitment to global vaccine equity (28). Again, communication is key. We need discussions about public values and priorities that include voices from diverse communities. Moreover, evidence that these voices are valued and taken into consideration must be shown, or trust will be undermined.

Ethical considerations for healthcare practitioners who provide vaccination

Public health nurses and physicians and their office staff represent the front line interacting with patients and caregivers in vaccination situations. The Canadian Medical Association Code of Ethics and Professionalism (29) and the Canadian Nurses Association Code of Ethics for registered nurses (30) articulate the ethical and professional commitments and responsibilities of the medical and nursing professions. The codes provide standards of ethical practice to guide physicians and nurses in fulfilling their obligation to provide the highest standard of care and to foster patient and public trust in the medical professions.

The Codes are not exhaustive; they are intended to provide standards of ethical practice that can be interpreted and applied in particular situations. How these could be applied to vaccination situations, especially for COVID-19 vaccines in these times of vaccine constraints, has not been well articulated.

Conclusion

Overall, this high-level ethics check-up of Canadian public health immunization programs suggests that Canada is generally on the right track, although there is room for improvement. Canada has "pass marks" in relation to principles such as benefits, risk and effectiveness. There are gaps and uncertainties to do with other principles, however (i.e. equity, justice, autonomy, reciprocity, trust). These speak to a need for greater attention to matters affecting other principles, including solidarity and transparency. The COVID-19 vaccine constraint context has further exacerbated some of these concerns.

Universal solutions are not easy given Canada's size and health system structure; regional differences in prevalence and burden of VPD result in different decisions. Provincial and territorial priorities in health care also result in variation in implementation. Having acknowledged this, readily justifiable steps that can improve collective coherence across immunization settings in Canada can be put into place in the short term; fragmentation and duplication are problematic. For example, providing a simple ethics self-assessment questionnaire for provinces and territories might identify both common and region-specific challenges and stimulate development of effective shared tools and responses. In addition, jointly developed best practices for issues such as consent and assent in school-based immunization programs would have country-wide benefits. Finally, a comprehensive review of serious AEFIs and the development of a template for AEFI crisis communication are undeniably valuable and within existing capacities. COVID-19 vaccine mass rollouts have added the pressure on this. Leadership is needed to tackle these challenges so that the results of the next ethics check-up—which might consider solidarity and transparency—might be improved.

Authors' statement

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Protective immunity post-COVID-19 infection

Source: Emerging Science Group of the Public Health Agency of Canada. Emerging Evidence on COVID-19: Rapid Review on Protective Immunity. Full report available from: phac.evidence-donnees.probantes.aspc@canada.ca

Background: Understanding the extent and limits of protective immunity has important implications for the COVID-19 pandemic. An evidence review was conducted to address whether antibodies to SARS-CoV-2 confer immunity against reinfection; to determine if protective immunity lasts more than six months; and to identify if past infection with the original wild-type SARS-CoV-2 protects against the current variants of concern (VOC).

Method: Three separate searches relevant to reinfection, immunity, and VOC and immunity were conducted in 20 databases to identify relevant reviews and primary research in the form of peer-reviewed publications or pre-prints. Evidence published before February 11, 2021 was included.

Results: There were 49 studies identified, including 15 cohort studies on risk of reinfection, 21 studies on antibody kinetics and other immunity markers >6 months post initial infection, 10 studies on immunity and the new VOCs and three systematic reviews. In the appendix, 21 case reports of confirmed reinfection were summarized.

Documented cases of confirmed reinfection of COVID-19, based on genomic data, are rare. In most cohort studies, reinfection was based on serology, documented proof of a non-infected phase between infections and polymerase chain reaction (PCR) evidence of reinfection.

- Cohort studies on reinfection that targeted the general population or healthcare workers indicate a low risk of reinfection (0%–3.4%) compared to the COVID-19 in the susceptible population (1.3%–27.7%). Data on time to reinfection was highly variable, with a median of 52–172 days across studies and a range of 13–250 days.
- Older age, duration of symptoms, and number of symptoms were correlated with higher IgG antibody levels after primary infection. Higher and prolonged serum IgG antibody levels were correlated with a lower risk of reinfection.

Protective immunity lasts at least six months:

- Immunity following an infection arises from both B-cell and T-cell responses. Memory B-cell and T-cell activity was elevated and expanded beyond six months post infection in eight studies, which may be better measures of long term protective immunity than circulating antibodies. CD4+ T-cell activity continued to be detected in 92% of individuals between 6–8 months following infection.
- Twenty studies reported on circulating antibodies, eleven of which reported >86% of people remained positive for SARS-CoV-2 specific neutralizing antibodies (NAbs) ≥6 months after infection and levels were higher among people who had been hospitalized for COVID-19 compared to those who had been mildly symptomatic.

There is preliminary evidence that the extent of cross-protection of the original wild-type SARS-CoV-2 for VOC depends on the variant. In vitro evidence shows consistent neutralization of B.1.1.7 and reduced neutralization of B.1.351 by convalescent or vaccinated sera to wild-type SARS-CoV-2. Further research on how other immune responses (e.g. T-cell and B-cell) are affected by variants is a knowledge gap.

Conclusion: Reinfection with SARS-CoV-2 virus is rare but can occur. Despite a lot of variability in both antibody and T-cell response, protective immunity appears to last at least six months. Research and surveillance monitoring on reinfection and post vaccine infections coupled with sequencing data are needed to study the extent of cross protection between the original wild-type virus and VOC.

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Public Health Agency of Canada
130 Colonnade Road
Address Locator 6503B
Ottawa, Ontario K1A 0K9
phac.ccdr-rmtc.aspc@canada.ca

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