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(ARCHIVED) Public Health Management of COVID-19 Exposure Post Infection

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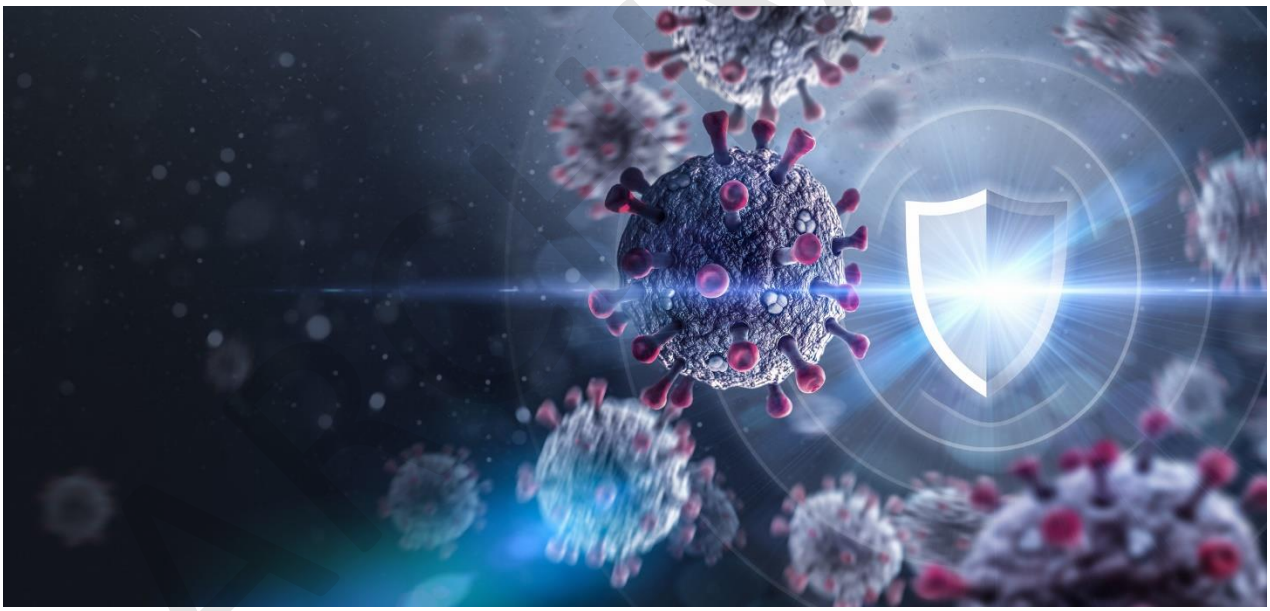

Introduction

Acceleration of spread of SARS-CoV-2 over multiple waves of the pandemic has resulted in a greater likelihood that a recovered individual may be exposed to infection again.[1] However, public health management of recovered cases with new symptoms and exposures generally remains uncertain given the limited information on immunity and risk of reinfection. Public health (PH) management is further complicated by ongoing positive viral detections (mostly non-viable) after initial infection that challenge the interpretation of new positive results after release from isolation as to whether they may represent new infection or ongoing detection.[2]

As time from the first wave of the pandemic has lengthened, evidence on the presence and duration of potential immunity has evolved to inform the possibility of reinfection risk. Additionally, there is

increasing evidence on documented cases of confirmed reinfection. Finally, some public health jurisdictions have updated their guidance for the immediate period (two to three months post infection) based on evidence of likely immunity to reinfection.[3-5]

The purpose of this document is to assess the evidence on duration of immunity (or antibody detection) and reinfection, as well as assess other jurisdictions' public health case management guidance to inform considerations for the public health management of cases in Ontario in the initial period after infection with SARS-CoV-2.

Background

In Ontario, public health case and contact management guidance[6], advises that previous positive cases are recommended to self-isolate for 14 days after a new high risk exposure to a new unrelated case. This does not apply to post-clearance exposures to related cases, such as cases within the same household or cases within an outbreak scenario. The guidance recommends that previously confirmed cases should generally not be re-tested unless clinically indicated, as ongoing positive results after clearance are not uncommon. Furthermore, it recommends that clinical discretion should be used to consider re-testing after clearance if there is a new onset of symptoms compatible with COVID-19, or potentially where there are new high-risk exposures to a known case or outbreak. Finally, all recovered cases are recommended to follow routine public health measures, such as physical distancing and masking for source control.

Methods

The Public Health Ontario Library Services conducted searches on English-language evidence related to duration of immune response and reports of reinfection. Peer-reviewed literature was searched in three electronic databases: MEDLINE, Embase, and Scopus, including systematic review articles and primary studies. Preprints were searched via the NIH COVID-19 Portfolio.

A jurisdictional scan was conducted between January 6 and January 8, 2020 of public health guidance documents on recommendations for management of cases after infection. Jurisdictions included: Australia, Canada (Alberta, British Columbia, Manitoba, Quebec, Saskatchewan), Europe, New Zealand, South Korea, United Kingdom (UK), and United States (New York). No guidance documents were found for the following jurisdictions: Canada (British Columbia, Quebec, and Saskatchewan), New York, New Zealand, and South Korea.

Results

Duration of Immune Response

The most robust evidence on duration of immune response of SARS-CoV-2 antibodies from peer-reviewed systematic reviews only contains studies with a short duration of follow-up (41 to 65 days post-symptom onset) and small numbers of participants (fewer than 50 participants) due to the limited time from the start of the pandemic.[7]

Included studies assessed immune response through a variety of methods including antinucleocapsid (anti-N) antibodies, antispike (anti-S) antibodies, cellular immunity and neutralization assays. They found very high rates of either immunoglobulin G (IgG) or neutralizing antibodies (depending on the assays used) among participants. Immune response was lower among those with asymptomatic infection, and there was less evidence for the duration of immune response for those with asymptomatic infection.

Included studies on seropositive individuals cannot assess the proportion of infected individuals that did not mount a measurable antibody immune response.

Primary studies (published and pre-print) report on the duration of the immune response among larger study populations and for longer durations of time. The following eight recent studies examined immune response at five months or longer after initial infection:

- A cohort of 121 plasma donors in New York City (NYC) with mild-moderate illness had three anti-S antibody titer measurements (median time: days 52, 82 and 148) after symptom onset. There was a slow decline over time and three individuals with initially low titers dropped to undetectable levels over time.[8]

- A cohort of 188 symptomatic adult patients (19 to 81 years old) in the United States (US) were followed with 51 providing longitudinal blood samples, and 43 with specimens 178 days or longer after symptom onset. Spike IgG, spike receptor-binding domain IgG and SARS-CoV-2 pseudo virus neutralizing antibody titers were relatively stable with modest declines in titers at 6 to 8 months post symptom onset.[9]

- In a follow-up study from Austria of patients tested in June and October, 2020, (97%, 33/34) of participants with SARS-CoV-2 spike specific IgG and immunoglobulin A (IgA) antibodies in June still had significant levels of both antibodies in October.[10]

- A study of 112 mild-moderately ill adult patients, in New Zealand were followed for up to 246 days, with 80 samples collected at four to eight months post symptom onset. At four to eight months after infection, 99% of serum specimens had spike receptor-binding domain IgG and 96% had S protein IgG. 90% of the group sampled at greater than 125 days had neutralizing antibodies above the cut-off. This suggests a strong long lasting response is attributed solely to the initial exposure since there is lack of community transmission in New Zealand.[11]

- A prospective cohort study of healthcare workers in the UK followed 349 seropositive participants for up to seven months (median follow-up time 122 days). Spike antibody assay found 99% remained positive at 200 days post symptom onset.[12]

- A study of 58 young adults (ages 21 to 40) with asymptomatic or mild infections in South Korea assessed IgG serology eight months after infection, and found 91.4% were positive for anti-N pan-immunoglobulin (pan-Ig), 25.9% for anti-N IgG, 86.2% for anti-S IgG and 69.0% were positive for anti-S1 IgG. Surrogate virus neutralization test found positive neutralization activity in 53.4% of participants.[13]

- A study of 100 adult donors six months after primary infection compared immune response of symptomatic (n=56) and asymptomatic (n=44) cases in the UK. Median T-cell responses were 50% higher in symptomatic cases.[14]

- A study of 37 asymptomatic individuals infected with SARS-CoV-2 showed weaker immune response compared to symptomatic cases. They had significantly lower IgG levels in the acute phase, were more likely to become seronegative (40% vs 12.9%) for IgG in the convalescent phase, and had lower levels of 18 pro and anti-inflammatory cytokines compared to symptomatic cases.[15]

Risk of Reinfection

Emerging evidence and reports have also assessed the risk of reinfection after initial infection. The generally accepted definition of confirmed reinfection cases is based on determining genetically distinct virus infections separated by a period of clearance.[16] Whereas, probable cases of reinfection are less well established and vary by jurisdiction and study. Due to technical challenges of obtaining initial and subsequent infection specimens in which to conduct sequencing analysis, there are very few case reports of confirmed reinfection reported.

- Mounting evidence suggests that probable reinfections may occur more frequently; however, the significance of these cases for themselves and for risk of transmission to others is unclear. There is some evidence of less severe cases with reinfection, although severe reinfections have been documented. There is also some evidence that reinfections are associated with no antibody response after first infection. Additionally, with the introduction of variants of concern, some mutations in the SARS-CoV-2 virus have been associated with cases of reinfection. The following studies below provide evidence related to the risk of reinfection after an initial infection with SARS-CoV-2: An outbreak investigation during a fishing trip with 122 individuals, included 120 with predeparture serology. Of the 120, six were serology positive, and 114 were seronegative.

  Out of the six serology positive individuals, three had neutralizing antibodies before the trip, and none of them tested positive by polymerase chain reaction (PCR), although it is unclear for how long it had been since their primary infection. This study showed that the overall rate of infection among individuals with neutralizing antibodies was zero of three compared to 103 of 117 in individuals without neutralizing antibodies.[17]

- A cohort study of healthcare workers in the UK compared risk of infection over a 31 week period. Among 11,364 anti-spike IgG seronegative participants, risk of a positive PCR test was 1.09 per 10,000 days at risk; whereas among 1265 seropositive participants, it was 0.13 per 10,000 days at risk. Three positive PCR detections occurred among seropositive participants at 160 to 199 days after initial symptom onset or seropositivity. One of the positives may have been a false positive due to low viral load and subsequent negative PCR tests two and four days later, which would lower the risk to 0.05 per 10,000 days at risk.[18]

- A study of 829 patients with confirmed infection found 87 had no detectable IgG concentration. There was one case of asymptomatic reinfection four and a half months after recovery among those with detectable IgG, whereas 25 (29%) of seronegative patients were reinfected within one to three months after their first infection.[19]

- A large multi-center prospective cohort study followed hospital staff in the UK between March and November, 2020. A total of 20, 787 individuals were included in the analysis and were linked to serology and PCR data. Between June and November, 2020, 44 potential reinfections (two probable and 42 possible) were found in the 6, 614 individuals assigned to the positive cohort (antibody positive or prior PCR positive). In comparison, 318 new positive infections and 94 antibody seroconversions were identified in the 14, 173 individuals assigned to the negative cohort (antibody negative or no prior PCR positive). The incidence density per 100 000 person days was 3.3 reinfections in the positive cohort and 22.4 in the negative cohort. The median interval between initial infection and reinfection was over 160 days.[20]

- A study analyzed data from two care homes in the UK that experienced COVID-19 outbreaks in the first wave of the pandemic in April-May 2020, followed by a second COVID-19 outbreak in both care homes in September-October 2020. The second outbreak in both care homes was due

to a genetically distinct SARS-CoV-2 strain, different from each home's respective first outbreak. Only 1.1% of the (1/88) individuals with confirmed previous exposure to SARS-CoV2 (mostly demonstrated by positive serology) became PCR positive during the second outbreak compared to 24.7% (18/73) of those who had seronegative status prior to the second outbreak across all homes.[21]

- One study reviewed 16 cases of confirmed reinfection in peer-reviewed or pre-print articles. Most (75%, 9/12) initial infections were asymptomatic/mild, and half (50%, 6/12) of the cases had a milder second episode, where comparison of first and second presentation was possible. The median (range) time from first to second infection was 66 (19 to 142) days. Ten cases reported serology results at the time of the second infection, six of which had a positive total immunoglobulin (Ig) or IgG result. None of the patients had a known immunodeficient state.[22]

Studies have also used classification criteria to assess the likelihood of reinfection in the absence of sequencing to confirm a reinfection. However, where sequencing was available to compare first and second infection, the majority showed no evidence of reinfection.

- A study of 133,266 confirmed cases found 243 (0.18%) were positive again greater or equal to 45 days after the first positive swab, and 54 (22.2%) had strong or good evidence for reinfection. Median time between infections was 64.5 days (range: 45 to 129). The majority (57.4%, 31/54) were identified asymptomatically through random testing campaigns or contact tracing. Of 23 patients with strong/good evidence for reinfection and paired viral specimens, 11 had insufficient quality of specimens, eight showed no evidence of reinfection, and four showed evidence of reinfection.[23]

Alterations in the virus (variants of concern) may also increase susceptibility of a previously infected individual to reinfection. Viral mutations may increase the risk of reinfections, and the recently described spike mutations, particularly in the receptor binding domain (RBD) in SARS-CoV-2 lineages circulating in the UK, South Africa, and Brazil, have raised concern for their potential impacts on transmissibility and escape from neutralizing antibodies.

- A case report of a confirmed reinfection case in Brazil identified an E484K spike mutation in the second infection. The 45 year old female was symptomatic in her first infection (tested positive May 26, 2020), and was treated with 40 mg prednisone for five days. She re-developed symptoms and was positive again on October 26, 2020. Serology was not collected after her first infection, and was IgG positive four weeks after her second infection.[24]

Practice examples in multiple jurisdictions

As of January 8, 2021, multiple jurisdictions including Alberta (Canada),[25] Australia,[3] Europe,[4] Manitoba (Canada),[26] UK[27] and the US[5] all acknowledge that the duration of immune response and antibody response to SARS-CoV-2 remains unknown and that further studies are needed to gain more understanding regarding immunity and reinfection. However, there is varying public health guidance as to the management of previously infected individuals with respect to quarantine after close contact with a case and testing if symptomatic after an initial infection.

Guidance for Quarantine/Isolation After Initial Infection

Australia

The Australian guidance originally published on December 23, 2020 advises that persons without significant immunocompromise do not need to quarantine if they are a close contact in the eight weeks

since their symptom onset or first positive test if asymptomatic, and that serology testing should be considered for those exposed after eight weeks or immunocompromised. Re-exposed recovered cases do not need to be furloughed from work in high-risk settings.[3]

Europe

The European Center for Disease Control (ECDC) outlines that there is evidence that shows that a person who has recovered from COVID-19 infection is at a lower risk of reinfection if they are re-exposed within three months of their initial SARS-CoV-2 infection. Unless, they work with vulnerable populations or reside in high risk settings such as prison and long term care, "individuals with a high risk exposure to COVID-19 within three months of their initial diagnosis can be reclassified as low-risk exposure contacts."[4] Low-risk exposure contacts should self-monitor daily for symptoms clinically compatible with COVID-19 for 14 days after the last exposure to a COVID-19 case, should they develop symptoms, they should self-isolate and seek medical advice.[4]

Public Health England recommends isolation for individuals who develop symptoms 90 days after their initial illness should be considered as reinfected, and should immediately isolate again and have their contacts traced.[27]

United States

The US Centers for Disease Control and Prevention (CDC) states that there is mounting evidence to suggest that individuals who have recovered from COVID-19 infection who experience another COVID-19 re-exposure within three months of their initial infection do not need to undergo repeat quarantine.[5] The CDC emphasises that all people, regardless of symptoms, with past COVID infection continue to follow all recommended PH measures to prevent SARS-CoV-2 infection (i.e., wear masks, stay 6 feet away from others whenever possible, and wash hands regularly).[28]

Canada

Manitoba, Canada, recommends that recovered asymptomatic COVID-19 cases with a new exposure, within three months of their initial infection do not need to self-isolate, but should self-monitor for symptoms of COVID-19.[26] Recovered COVID-19 asymptomatic cases with a new exposure within three months of their initial infection working in high risk settings or with vulnerable populations are not required to self-isolate but are advised to consult with their workplace occupational health and safety to ensure no additional precautions are needed. Recovered COVID-19 asymptomatic cases with a new exposure at three months or more from their initial infection should self-isolate for 14 days from their last exposure. Recovered COVID-19 cases who develop new symptoms within three months of their initial infection, with no new exposure and without the need for hospitalization, need to self-isolate until their symptoms have resolved for 24 hours, however if they work in high risk settings or with vulnerable population, they should consult with workplace occupational health and safety to ensure no additional precautions are needed.[26]

Guidance for Testing After Initial Infection

Australia

Australian guidance originally published on December 23, 2020 does not recommend retesting of recovered COVID-19 individuals who have been released from isolation if they are hospitalized for non-COVID-19 reasons. Persons who have recovered from COVID-19 who are re-exposed should self-monitor for symptoms compatible with COVID-19 for 14 days after the last contact with the confirmed case and should their symptoms return, they should immediately self-isolate and seek testing for SARS-CoV-2.[3]

Europe

The ECDC recommends that all asymptomatic low risk exposure contacts in settings with vulnerable populations or in which transmission is likely, such as health and social care settings should be tested as soon as possible after being traced. All contacts (high risk and low risk) who already have symptoms or develop new onset of symptoms should be tested as soon as possible to allow for case isolation and contact tracing.[4]

Public Health England recommends the exclusion of all immunocompetent staff, patients, and residents from routine re-testing within 90 days of SARS-CoV-2 infection or positive test unless if they develop new symptoms clinically compatible with COVID-19. If a person is retested within 90 days from their initial test or onset of symptoms and remains positive, for SARS-CoV-2, a clinically led approach should inform subsequent action taking into account factors such as COVID-19 symptoms and underlying medical conditions for example. A person who remains positive by PCR after 90 days from their initial onset of symptoms or test should be assessed for a possible new infection.[27]

United States

The CDC advises against the need for retesting individuals for asymptomatic COVID-19 infection within 90 days of their initial SARS-CoV-2 Infection or illness.[5]

Canada

The province of Alberta, Canada recommends testing of recovered COVID-19 individuals within 45 to 90 days after an initial infection if there is new symptoms clinically compatible with COVID-19. COVID-19 reverse transcription - polymerase chain reaction (RT-PCR), respiratory viral panel and other clinically warranted diagnostic tests should be done. Follow up retesting of asymptomatic individuals is not required.[25]

The province of Manitoba, Canada recommends that recovered COVID-19 cases who develop new symptoms within three months of their first infection, with no new exposure and without the need for hospitalization do not require COVID-19 testing. Recovered COVID-19 asymptomatic cases with a new exposure within three months of their initial diagnosis should self-monitor for symptoms, and should be tested if they develop symptoms compatible with COVID-19. Recovered COVID-19 cases who develop symptoms compatible with COVID-19 at three months or more after their initial infection should be tested for COVID-19. Recovered COVID-19 asymptomatic cases with a new exposure at three months or more since their initial infection should be tested if they develop symptoms.[26]

Discussion

There is evolving evidence regarding the duration of antibody response after primary infection, factors associated with populations that do not mount or sustain an antibody response, and the role of neutralizing antibodies in protection against reinfection. At this time, there is insufficient evidence regarding a correlate of protection for neutralizing antibodies, or the relative importance of other immune response mechanism, such as cellular immunity, with respect to protection against reinfection. There is also very limited epidemiological evidence regarding risk of reinfection among those with prior primary infection. Even if the risk of reinfection is low, there would still be uncertainty as to whether prior infection confers “sterilizing immunity” that prevents a pathogen from replicating or if it attenuates the pathology from a reinfection reducing its transmissibility or infectiousness.[29]

As the vast majority of patients infected with SARS-CoV-2 do not receive serological testing, at an individual level it is not likely to know whether a prior infection has provided a robust and sustained immune response. The reviewed studies have also only examined immune responses in adult populations, with no data on pediatric immune response, and no sub-population data on immune

response in the elderly, or those with other underlying conditions. Therefore, it is not possible to determine whether duration of immune response applies broadly to all individuals after infection and particularly so for those with asymptomatic infection where immune response appears less robust compared to those with symptomatic infection.

While true reinfection reports remain rare, there are several limitations with respect to the necessary laboratory testing that restrict the number of cases that may be verified relative to the number of cases that may be occurring in the population based on a broader definition of reinfection. With limited evidence on the actual risk of reinfection, it is challenging to assess the 'balance of risk' that some public health jurisdictions have referred to with respect to removing quarantine and testing requirements for patients in the two to three months after infection. As well, it is challenging to assess which sub-populations may be at increased risk of reinfection and where that 'balance of risk' would suggest a more cautious approach is required to reduce risk of transmission. Some public health jurisdictions have suggested long-term care facilities and correctional institutions as settings where there is a lower risk tolerance for the potential of missing a case of reinfection, and more stringent measures for individuals after infection would be required. Other jurisdictions have deferred decision-making on precautions for recovered individuals with new exposures to their occupational health and safety department; however, this presumes all high risk settings have capacity to provide this individual level advice.

Newly emerging evidence on the impacts of vaccination on immune response and transmission will likely further inform understanding of natural infections. However, evidence of efficacy from vaccine studies may not reflect factors that influence immune response from natural infection.

Lastly, the emerging evidence that new variants of concern and mutations in the SARS-CoV-2 may be associated with cases of reinfection[30] suggest a cautious approach to the risks of reinfection is warranted for those who have recovered from COVID-19.

Limitations and strengths

This analysis was limited to English language manuscripts and public health websites. Articles were selected based on their recency from publication and robustness of methodology.

This review did not include specific searches for evidence on the impacts of variants of concern on reinfection or immunity due to the limited available data at the time.

This review does not address issues of public health management post-vaccination.

Conclusion

- There is reasonable evidence to suggest that the majority of infected individuals that developed an immune response to their SARS-CoV-2 infection will sustain that immune response for up to eight months.
- There is some evidence to suggest that individuals that developed an immune response to their SARS-CoV-2 infection are at reduced risk of reinfection in the six months following infection, but that reinfections are still possible.
- The frequency and timing of reinfections is not known. The risk of transmission from a previously infected individual that has been re-exposed to SARS-CoV-2 is also not known.
- Changes to the recommendations for requiring quarantine after infection for new high-risk exposures would need to incorporate individual level decision-making to assess a given person's

likelihood for having developed immunity from their primary infection and the potential consequences of transmission if they were asymptomatically (or symptomatically) infected again.

- Testing in the two to three months after infection is more likely to yield ongoing detection of residual virus than a new infection. However, both asymptomatic and symptomatic reinfection cases have been documented in this timeframe.
- With the emergence of the SARS-CoV2 variants and the likelihood of increased risk of reinfection, a more conservative approach for still requiring quarantine when re-exposed after initial infection may be warranted until further evidence is available.

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- infection prevention and control
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- emergency preparedness
- health promotion, chronic disease and injury prevention
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