

COVID-19 Scientific Advisory Group Evidence Summary and Recommendations

Immunization after COVID-19 Infection

November 23, 2021

16 December 2021

The data in this review is from before the emergence of the Omicron Variant of Concern, which has been associated with a reduction of both post-infection immune protection and vaccine immune protection. The findings of this review do not apply in an Omicron dominant setting and will be updated once data is available.

Additionally, in this review, "post infection immunity" refers only to formal laboratory documented infection, not clinically suspected COVID-19.

This document summarizes the Public Health Agency of Canada report on protective immunity (August 13, 2021), the National Collaborating Centre for Methods and Tools report on vaccine effectiveness in previously infected individuals (October 15, 2021), and other select references, and develops key messages and recommendations grounded in the Alberta healthcare context.



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Summary for Members of the Public

16 December 2021

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Additionally, in this review, "post infection immunity" refers only to formal laboratory documented infection, not clinically suspected COVID-19.

Background

- COVID-19 vaccines are safe and effective for preventing COVID-19 symptoms and severe outcomes from the disease.
- Over 300 000 Albertans have recovered from a documented COVID-19 infection. There is evidence that previous infection provides some immunity to COVID-19, but it is unclear how long protection lasts after either infection or vaccination.
- The goal of the COVID-19 immunization program in Alberta is to reduce both COVID-19 infections and severe outcomes from the disease. As a substantial number of Albertans having recovered from COVID-19, it is important to understand how best to vaccinate this population.
- Some jurisdictions suggest a single dose of COVID-19 vaccine following infection, while others recommend the complete two-dose series. There are different recommendations for when to give COVID-19 vaccine after COVID-19 infection as well, ranging from right after recovery to more than 6 months after infection.
- This review summarizes evidence on the effectiveness of one rather than two doses of COVID-19 vaccine following documented COVID-19 infection, and evidence around the timing of COVID-19 vaccination post-infection to provide guidance to public health officials.

Key Findings

- There are not many real world reports of the effectiveness of one dose after infection yet. A preprint study from Israel found that one dose of vaccine following infection provided better protection compared to no doses after infection, and compares well to two doses in people who hadn't been infected. Other smaller studies also suggest that one dose of vaccine following infection offers similar protection to two doses in uninfected people but the studies didn't include large numbers of people and they weren't followed for long.
- Many studies of the immune response to infection and vaccination were reviewed and all show that single dose of COVID-19 vaccine boosts post infection antibodies to a level comparable to two doses of vaccine in uninfected people. However, it is not yet fully known how well lab studies of immune response translate into real world effectiveness.

- People with advanced age, compromised immune systems and chronic medical conditions may be more likely to have a low antibody response after either infection or vaccination, there is not much known about the response to one vaccine dose after COVID-19 infection in these high risk groups.
- Only two small studies looked at how long to wait to vaccinate after infection, including gaps from 2-10 months between infection to vaccination. These suggest a longer duration may be better in terms of immune response (there was no data looking at vaccination earlier, within 2 months after infection). Experience from immune responses to first (prime) and second (boost) dose vaccines suggest an interval of 8-12 weeks may result in a better immune response, and one of the two studies that we reviewed supports this.
- People who have been infected may have slightly higher rates of non-severe side effects after a first dose of vaccine (reactogenicity) but there were no reports of increased severe adverse events (including myocarditis) after vaccination of previously infected people found. Worldwide there have been many previously infected people (who may not have been tested positive) vaccinated without noticeable problems.

Recommendations and Guidance for consideration:

- In people with prior documented COVID-19 infection who do not have risk factors for a poor antibody response (such as advanced age, specific medical conditions and immunocompromise, etc.), a single dose of COVID-19 vaccine can be considered an acceptable equivalent to a two-dose initial series in uninfected individuals.
- Booster doses may be required after any initial series (post infection single vaccine dose, or two vaccine doses in those without prior infection) based on evidence of decreasing immune protection in specific groups of people at risk, or on decreased vaccine effectiveness across a population, related to changes in circulating virus strains or time from initial vaccination.
- There is not enough evidence to recommend a specific optimal interval between infection and vaccination. Practical guidance, based on current antibody studies, vaccine effectiveness data and limited reinfection, supports vaccination a minimum of 8 weeks after COVID-19 infection for patients that will be able to attend for a later vaccination, rather than immediately offering vaccination upon recovery from the initial COVID-19 symptoms. Reinfection risk seems to start increasing from 6 months after infection, so vaccination from 2-6 months after infection may be preferred. For people infected 6-9 months ago, some studies suggest a single dose of vaccine would still be expected to boost their response and limited data suggest a good response up to 12 months post infection.
- Knowledge in this area is growing and this review will need to be updated.

Authorship and Committee Members

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This document summarizes the Public Health Agency of Canada report on protective immunity (August 13, 2021) and the National Collaborating Centre for Methods and Tools report on vaccine effectiveness in previously infected individuals (October 15, 2021), and develops key messages and recommendations grounded in the Alberta healthcare system context.

Topic: Immunization after COVID-19 infection

- 1. Does post-infective immunity AND one dose of a COVID-19 vaccine provide comparable/equivalent protection to two doses of a COVID-19 vaccine?**
- 2. Is there any evidence to suggest an optimal time interval between recovery from active infection and immunization?**

Context

- Three COVID-19 vaccines (Spikevax/mRNA-1273/Moderna), Comirnaty/BNT162b2/Pfizer), and Vaxzevria/ChAdOx1-S/AstraZeneca) have been fully approved for use by Health Canada as a two-dose series. Billions of doses of COVID-19 vaccine have been given around the world and have proven safe and effective at reducing both COVID-19 infections and the severe outcomes associated with COVID-19.
- At the time of this review, over 300 000 Albertans have recovered from documented COVID-19 infection, with over 3000 having died.
- Immunity to COVID-19 following infection appears to be relatively robust, reducing reinfection risk by over 80% through at least 6 months, with reinfection rates of under 1% in most studies (Sheehan et al., 2021). However, there may be a higher risk of reinfection with particular SARS-CoV-2 variants, including Delta, based on antibody studies (Cromer et al., 2021).
- Some countries, such as [France](#), [Switzerland](#), [Italy](#), and [Germany](#) consider immunocompetent people who have recovered from documented COVID-19 infections fully immunized if they receive a single dose of COVID-19 vaccine, whereas others, such as most of [Canada](#) and the [United States](#), currently recommend two doses for this population (Quebec currently recommends a single dose following infection).
- The [European Union Digital COVID Certificate](#) allows travel for people with a [single mRNA vaccine dose](#) and a positive test within the previous 6 months.
- In the UK people with a positive PCR test can obtain an [NHS COVID pass](#) up until 180 days after infection.
- Recommendations for the timing of administration of the COVID-19 vaccine following infection varies; for example, Italy recommends the vaccine be given within 6 months of recovery from COVID-19 infection, Germany recommends vaccination after at least 6 months have elapsed since recovery, and the UK suggests 1 month minimum. Currently, in Alberta, COVID-19 vaccination is recommended at any time after recovery from COVID-19 infection; however, vaccination is delayed in recipients of antiviral monoclonal antibodies (REGEN-COV or sotrovimab).

- Given this significant proportion of Albertans with documented past COVID-19 infection, understanding the risk of reinfection prior to vaccination, whether a second vaccine dose is beneficial and required, and the optimal timing of post infection vaccination is crucial.
- The relative incidence of vaccine reactogenicity (side effects) and vaccine related adverse events between first and second doses, and in previously infected or uninfected people has not been well described.
- This review is intended to support public health decisions related to Alberta's vaccine schedule. Given the short timeline for this request, this report is predominantly a synthesis of the evidence contained in two Canadian rapid reviews on closely related topics, along with a pragmatic search of the literature for additional evidence that directly informed the specific questions.

Key Messages for Alberta

Does post-infective immunity AND one dose of a COVID-19 vaccine provide comparable/equivalent protection to two doses of a COVID-19 vaccine?

- Available evidence comes from two main types of research: observational studies in cohorts where prior infection was documented, and laboratory studies of immune responses after infection and/or vaccination. Overall, observational data suggests that the immunity from documented COVID-19 infection followed by a single dose of COVID-19 vaccine appears to provide protection from both COVID-19 infection and severe disease which is similar to two doses of vaccine in previously uninfected people, and is better than post infection immunity without vaccination.
- The evidence is limited by relatively small numbers of participants, methodologic issues, or comparisons that do not directly address our question/our population in Alberta, given the extended second dose interval employed here.
- Immunologic studies report a variety of antibody and cellular immunity outcomes, but we do not currently have validated “cut off” values of immunologic parameters that correlate with protection from infection, though studies are ongoing. However, within-study comparisons consistently show that show post-infection status (laboratory documented) with one vaccine dose compares very favourably to a two dose series in people without documented infection across all measured immunologic responses. In real world effectiveness assessment, one preprint observational matched cohort study (Gazit et al., 2021) showed that in previously infected individuals, a single dose of mRNA vaccine increased protection against Delta reinfection compared to remaining unvaccinated post infection and to 2 doses in people without previous documented infection.
- However, some people have risk factors for a less protective antibody response after COVID-19 infection or vaccination, based on population based post infection antibody studies as well as observed groups at higher risk groups of breakthrough infection after vaccination, including advanced age, certain medical conditions and significant immunocompromise. These groups would be recommended for a two dose initial series.

- In total the current evidence suggests that in people who do not have these risk factors, post-infection status AND one dose of a COVID-19 vaccine likely provides comparable protection to two doses of a COVID-19 vaccine.
- These data are evolving and will need to be followed.

Is there any evidence to suggest an optimal dose interval from recovery to immunization?

- There is insufficient evidence to recommend an optimal dose interval from recovery to immunization. The infection-dose 1 intervals reported in reviewed studies span 2 months to 10 months, with no data found on shorter intervals.
- Theoretic considerations include the observation that more than 7 weeks between dose 1 and dose 2 of COVID-19 mRNA vaccines is associated with higher vaccine effectiveness (Skowronski et al., 2021) consistent with prime-boost data from other vaccines as well, with intervals of 11 weeks or longer resulting in higher Astra Zeneca vaccine efficacy (Voysey et al., 2021).
- If one considers documented COVID-19 infection the “priming” exposure, delaying vaccination for at least 8 weeks could be preferred for COVID-19 patients who do not have excess risk for loss to follow up for vaccination. This consideration is most relevant in the absence of circulating variants to which post infection immunity has been shown to be limited.
- Currently, Delta reinfection of previously infected individuals appears to be unlikely within the first 6 months after infection, so deferring vaccination until 8-12 weeks post infection, and optimally administering it within 6 months appears a reasonable strategy to minimize reinfection risk and maximize effectiveness. It is noted that regardless of the interval, previously infected participants appear to develop robust immune responses following vaccination in studies that report vaccination at 2-10 months after infection.
- Data on adverse events after vaccination of previously infected persons is inconsistently reported but is in general consistent with adverse events in uninfected persons. There is some suggestion that people who have been infected may have slightly higher rates of side effects after initial immunization (reactogenicity) but there are no reports of increased severe adverse events, and worldwide there have been many previously infected people (both documented and undocumented) vaccinated without noticeable problems.
- No data on the incidence of myocarditis in previously infected people after one or two doses of COVID-19 vaccination was found. Overall, the risk of myocarditis is higher in COVID-19 infection than post vaccination, and as with other causes of myocarditis, the highest risk is seen in younger males. There is a higher risk associated with dose 2 of vaccine, and there is no reported data yet in younger children although the risk in 5-12 year olds is not expected to be elevated as this group usually does not have a higher risk of post infection or immune mediated myocarditis.

Research Gaps

- Only a single preprint study directly addressed the real-world effectiveness of a single dose of COVID-19 vaccine following COVID-19 infection.
- Studies addressing the **long-term** immunogenicity of a single dose of COVID-19 vaccine following COVID-19 infection were not identified, due to pandemic timelines.
- Few studies examined the effect of the time interval between infection and immunization on immunogenicity and vaccine side effects, and those that did had small numbers and nonstandard intervals in the assessments.
- No studies examined the impact of the interval between recovery from COVID-19 infection and immunization on real world vaccine effectiveness.
- Studies examining effectiveness of two doses of COVID-19 vaccine (in previously uninfected and survivors) predominantly used the dose interval initially used in the clinical trials, which does not apply to Canada in which much of the population received a vaccine series with an extended dose interval.
- The strategy of a primary series consisting of one dose of vaccine following previous documented COVID-19 infection, though supported in many jurisdictions, is based primarily on immunologic data. Further population based studies of the effectiveness and durability of one dose of vaccine following past infection would be useful.
- A significant number of the publications reviewed, comprising both immunogenicity and efficacy studies are preprints lacking peer review. The contents of these studies may change after peer review

Limitations of this review

- This report is predominantly a synthesis of the evidence contained in two relevant Canadian rapid reviews. The specific questions addressed in this topic are somewhat distinct from those asked in the reviews so not all references pertained to our topic, so a pragmatic search of the literature for additional evidence was also conducted.
- The additional studies were identified through a topic-based search strategies including grey literature and forward snowballing approaches rather than a systematic librarian search, and the rapid turnaround time of this report introduced time constraints.
- Observational effectiveness studies can be powerful with the ability to include large numbers of participants but can have between group differences that bias results in unpredictable ways.

Committee Discussion

There was general agreement that the available clinical data and the consistency of the immunologic data, as well as experience in other jurisdictions, presently support accepting a single dose of vaccine after infection as a complete initial series, with documented infection as the “prime” and vaccination as a “boost”. It was recognized that messaging needs to include the evidence that vaccination after infection confers additional protective benefit against reinfection based on both immunologic data and clinical data.

Uncertainty around the longevity of the immune response after complete vaccination, after infection plus 1 or doses, and after infection alone was acknowledged so a commitment to following evolving data was highlighted, particularly in high risk populations or with emergence of VOCs to which vaccines may be less effective.

There was discussion of the practice of giving a vaccine dose soon after recovery while people are still engaged in care and it was agreed that for individuals who have a higher risk of loss to followup, the theoretical immunologic benefits of delating the boost for 2-3 months could be outweighed by the risk of not being able to vaccinate, so discretionary guidance was provided.

Recommendations for Consideration in Alberta

Recommendation 1: In the absence of risk factors for a poor antibody response (eg. advanced age, medical conditions and immunocompromised) a single dose of COVID-19 mRNA vaccine in people with prior documented COVID-19 infection may be accepted as offering comparable protection against reinfection to a two dose series in previously non-infected individuals.

Rationale: In people with previous lab documented COVID-19 infection, substantial immunologic evidence shows a strong first dose response, with more limited but consistent clinical data showing a similar (if not higher) benefit of single dose vaccination in this group in a Delta dominant setting over the timelines reported, compared with a two-dose series in uninfected individuals.

Recommendation 2. Booster dose planning (for additional dose(s) among those who received an initial 2 dose series or equivalent) should be based on:

- 1) regular assessment of clinical outcomes (including infection, hospitalization, and death) in all immunized patients (including those who may have a poor antibody response) in Alberta and other jurisdictions
- 2) Periodic assessment of primary scientific literature review (updating this report)
- 3) Review of interim vaccine effectiveness reports from jurisdictions in which one dose has been recommended for the previously infected, including Quebec, France, and Germany.

Rationale: the clinical data is evolving and there is a possibility of increasing reinfection risk related to changes in circulating Variants of Concern or waning immunity in specific patient groups. Booster strategies can be considered if immunologic or epidemiologic data suggests possible increasing risk.

Recommendation 3. Analysis of data on reinfection in Alberta (individuals testing SARS-CoV-2 RT-PCR positive > 3 months apart) including the proportion with 1 or 2 dose immunization, with assessment of demographics, and outcomes is suggested as a baseline for future follow-up analysis.

Practical Considerations

Timing of immunization post infection:

- There is not enough evidence to recommend a specific optimal interval between infection and vaccination, but current antibody studies, vaccine effectiveness data

and limited reinfection data supports vaccination a minimum of 8 weeks after COVID-19 infection for most patients, unless there is substantial risk of loss to follow-up, in which case administration after recovery from the acute infection may be considered.

- There is insufficient evidence to inform a maximum acceptable delay in a boost vaccination dose. Reinfection risk appears to start increasing from 6 months after infection, so vaccination between 2-6 months after infection may be preferred. For unvaccinated people infected 6-9 months ago, immunologic studies suggest a single dose of vaccine appears to result in an effective measured immune response. with more limited data suggesting a potentially good response up to 12 months post infection
- However, immunologic considerations that support a greater than 6 month duration between infection and vaccination need to be weighed against the current community-based risk of COVID-19, and the risk setting of the individual patient.
Documentation of prior COVID-19 infection: Laboratory documentation of previous COVID-19 infection (ie positive RT-PCR or approved rapid antigen test) is required. Although many infections have not been documented with PCR testing, previous symptom history is not sufficiently accurate in identification of past infection. Validated serologic testing for prior infection may be a future consideration upon availability of provincial laboratory validated testing to identify prior infection.
- **Additional Dose eligibility:** The group of people currently eligible for an additional vaccine dose on the basis of identified greater risks of insufficient immunity (related to medical or immunocompromised status) applies to those with post-infection immunity (eligible people should receive a third dose if non-infected, and a second dose if they have had previous documented infection).

Summary of Evidence

Approach:

- This was designed as an umbrella review of two large national rapid reviews addressing similar, though distinct, questions from our own. The goal was to review the text of these reviews, along with their sources, to generate answers to our review questions. Additional resources were also identified by targeted searches.
- The first, from the Public Health Agency of Canada (PHAC), focuses on the long-term immune response following either infection or vaccination. Their two questions are: “Do antibodies to SARS-CoV-2 confer immunity against reinfection or breakthrough infection with SARS-CoV-2”, and “is there long-term protective immunity greater than 6 months post-infection or after full vaccination?” (*Emerging Evidence on COVID-19 Rapid Review on Protective Immunity, Update 2, 2021*)
- The second rapid review, from the National Collaborating Centre for Methods and Tools (NCCMT), evaluated the [effectiveness, immunogenicity, and safety of COVID-19 vaccines in people with a prior COVID-19 infection](#) (*Rapid Review Update 1: What Is the Ongoing Effectiveness, Immunogenicity, and Safety of*

COVID-19 Vaccines in Persons Who Have Had a Prior, Confirmed COVID-19 Infection, 2021).

- Both reviews incorporated multiple relevant real world effectiveness studies along with studies of the immune response following infection and/or vaccination. These were reviewed individually through the lens of our questions.
- Additional evidence: Additional studies that were not in the above reviews were identified by a pragmatic search of the literature and were reviewed separately. This includes effectiveness studies, notably including a preprint comparing post-infection immunity to both full series vaccination in uninfected people and to post-infection immunity followed by one dose of vaccine. Many immune response studies were found with this pragmatic search and were included to strengthen the conclusions of this review.

Does post-infective immunity AND one dose of a COVID-19 vaccine provide comparable/equivalent protection to two doses of a COVID-19 vaccine?

Background: Immunologic studies, which most commonly use antibody levels, and effectiveness studies, which assess the reduction in observed infections, are both considered throughout this review. Immunologic studies allow timely comparisons but ultimately must be correlated with effectiveness data. For a variety of pathogens, neutralizing antibody is typically seen as one of the best correlates of effective immunity. A standardized immune correlate of protection against COVID-19 (antibody level cut off to be considered immune) is not available but studies showing high neutralizing or binding antibody titres are relevant, given evolving literature that show an association between antibody levels in vaccine studies to observed efficacy (Earle et al., 2021). Furthermore, in an Israeli healthcare worker cohort study, breakthrough infections were correlated with lower neutralizing antibody levels (Bergwerk et al., 2021). One such analysis suggested that protection against severe disease is maintained even with 6.5X lower antibody levels, suggesting reinfections will generally be milder (Khoury et al., 2021). However, immune responses vary by age, medical conditions, vaccine type, and responses after infection vary by disease severity with considerable individual variation (Milne et al., 2021). A variety of studies have shown antibody persistence lasting 8-12 months in patients with severe disease, with more variability in those with mild infection (potentially in a range of 5-6 months) and possibly more rapid loss of antibody in asymptomatic infection over 2-3 months based on limited data. As asymptomatic or mild infection is generally more likely to be undocumented, these data further support relying on documentation of infection. In this review few studies evaluated cell mediated immune memory; these may outlast antibody responses after infection or vaccination. Community based studies in Qatar (Abu-Raddad, Chemaitelly, Coyle, et al., 2021) and Denmark (Hansen et al., 2021) do not show increased risk of reinfection after COVID-19 infection over 7 months.

Evidence from PHAC Rapid Review on Protective Immunity **Real World Effectiveness**

No studies identified in this review directly assessed the real-world effectiveness of one dose of COVID-19 vaccine in people previously infected with COVID-19, either in

comparison to full vaccination in uninfected individuals or on its own as it predated the additional references we identified. One study included a group predominantly composed of previously infected individuals who received one dose of vaccine, and sporadic infections after one dose of vaccination following infection are reported in various cohorts, but without appropriate comparator groups.

One observational study of healthcare workers in the United Kingdom (Lumley et al., 2021) included the following groups: “Vaccinated twice, previously seronegative,” and “Vaccinated, previously seropositive.” The “Vaccinated, previously seropositive” group was predominantly single dose vaccinated, although full details were not available. Data from this study was reported until February 28th, 2021, during Alpha variant predominance. Participants received either Comirnaty or Vaxzevria. During this study, no symptomatic infections and two asymptomatic infections were identified among 940 members of the “Vaccinated twice, previously seronegative” group, and one symptomatic infection and no asymptomatic infections were reported among 974 members of the “Vaccinated, previously seropositive” group. Both seropositive and 1 or 2 dose vaccinated groups were highly protected compared to the “unvaccinated, seronegative group.” With data collection ending on February 28th, 2021, long term immunity following vaccination could not be evaluated.

The SIREN cohort, which prospectively follows 44546 HCW in the United Kingdom with PCR testing every two weeks for members of this cohort, identified 51 reinfections out of 9813 (~0.1%) previous infections between April and July 2021 (Public Health England, 2021). 44 infections occurred while the Delta VOC was prominent in the UK. 95% of members of this cohort had been vaccinated, and 45(88%) of the infections occurred at least 21 days following the first vaccine dose. This report did not provide information on post-vaccine breakthrough infections, making any comparison between post-infection and post-vaccine immunity impossible, but supports a high level of overall immunity to the delta VOC following infection with a possible trend to increased effectiveness following additional vaccination. Another study, done in India when the Delta variant was predominant, identified only 2 infections in healthcare workers with both a previous infection and a single dose of the Vaxzevria vaccine (Kale et al., 2021); though comparisons with other groups is difficult. Another study examined reinfection and breakthrough infections in a cohort of 3395 COVID-19 recovered individuals in Italy. Two reinfections were identified in 2723 (0.1%) of previously infected individuals (7 and 12 months after infection), at an estimated risk of 1.1 per 1000 person-years (Massimo et al., 2021).

Immune Response Studies

This review identified many studies measuring the humoral immune response following administration of a single dose of COVID-19 vaccine to previously infected individuals, most of which resulted in a robust immune response.

One French cohort examined antibody response and infection risk in health care workers (Gallais et al., 2021). Though there were not enough participants to calculate efficacy of the one dose post-infection, anti S IgG measurements of one dose following infection (including Comirnaty, Spikevax, and Vaxzevria) had a similar humoral response as two dose vaccination with high post vaccination titres persisting for at least

100 days post-vaccine at the time of report. In an Italian cohort, 54 healthcare workers received one or two doses of Comirnaty, Spikevax, or Vaxzevria following infection; all had increased neutralizing antibody levels with vaccination, and there was no association between neutralizing antibody levels and number of doses of vaccine in this population(Massimo et al., 2021).

Three additional studies examined the humoral immune response to vaccination and included measurements after a single dose following infection(Cagigi et al., 2021; Sarkar et al., 2021; Shields et al., 2021). These studies measured quantitative IgG to either spike protein or to the receptor binding domain and showed rapid, effective boosting of the IgG response after previously infected individuals received a single dose. One of these studies included a second dose (Cagigi et al., 2021) and showed that the second dose did not increase IgG and IgA to spike protein and that vaccination resulted in a durable antibody response up until 6 months post vaccination.

A cohort study of 300 healthcare workers in Spain assessed antibody concentrations following remote moderate-severe infection, and showed high seropositivity in vaccinated and unvaccinated HCW, with sustained seropositivity in 76.8% overall along with persistent neutralizing antibody titers throughout the cohort(Varona et al., 2021).

Evidence from NCCMT Rapid Review on COVID-19 Vaccination in previously infected individuals

Real World Effectiveness

In this synthesis, three studies were identified that compared either a 2 dose series with or without previous infection, or compared full vaccination to previous infection without vaccination. A comparison of nursing home residents fully vaccinated with Comirnaty showed additional protection of previous infection to 2 dose vaccination alone in Delta variant outbreaks which both occurred in July-August 2021. In this cohort, 1/44 (0.1%) previously infected/vaccinated residents and 55/96 (57%) previously uninfected/vaccinated tested positive. The severity of these infections was not reported(Blain et al., 2021).

A large national retrospective matched cohort study in Qatar, in which either the Comirnaty or Spikevax vaccines were administered at a 3-4 week interval, revealed that previous infection was associated with numerically greater effectiveness of Comirnaty vaccine and no significant difference in Spikevax effectiveness Abu-Raddadet al., 2021). The incidence of infection overall low, at 0.06% in vaccinated/infected and 0.08% in vaccinated/uninfected. At the time, the alpha and beta variants were predominant. Though this study is relatively robust given that it included a national cohort, its weakness is that the outcome was defined only by SARS-COV2 test positivity, and did not allow for an examination of either symptomatic or severe disease.

One preprint study from the Cleveland Clinic examined a cohort of approximately 50,000 healthcare workers, comparing immunized/infected, non-immunized/infected, immunized/uninfected, and unimmunized/uninfected groups(Shrestha et al., 2021). All immunized individuals received two doses of mRNA vaccine, and comparisons were pre-delta when a variety of variants were circulating. Over 5 months, they found no infections in any previously infected individuals regardless of vaccination status, with 15 breakthrough infections (0.5%) in the 28,555 person immunized uninfected cohort

(Shrestha et al., 2021). Another study, a preprint prospective cohort analysis in employees enrolled in the Kaiser Permanente Health System, included a comparison between previously infected, unvaccinated and previously infected, Moderna vaccinated individuals, at a time when a variety of variants were present in California (Bruxvoort et al., 2021). Previously infected individuals had low infection rates overall, with vaccination possibly providing an additional 33.6% efficacy in patients with past lab diagnosed infection and 8.2% efficacy in patients with past asymptomatic COVID-19 infection. These differences were not statistically significant, due to a similar number of infections in both comparison groups.

Unfortunately, as these studies looked at previously infected individuals with two doses of vaccine or with no vaccine, it is difficult to draw conclusions about the effectiveness of a single dose of vaccine after infection, although benefit from vaccination was shown.

Immune Response Studies

In the NCCMT review 13 studies, examining the immune response in 12 cohorts, were reported (*Rapid Review Update 1: What Is the Ongoing Effectiveness, Immunogenicity, and Safety of COVID-19 Vaccines in Persons Who Have Had a Prior, Confirmed COVID-19 Infection*, 2021). These studies compared the humoral immune responses following vaccination with and without prior infection, with 9 studies reporting humoral responses after dose 1. In all these studies, the antibody response (variably examined as the anti-spike, anti-receptor binding domain or the neutralizing antibody response) was higher following the first dose of vaccine in previously infected individuals than it was following two doses of vaccine in unimmunized individuals. Furthermore, in these studies, administration of the second dose of vaccine had little effect on the humoral immune response in previously infected individuals.

Given that all the immune response studies included in this review administered the two-dose series to all participants, the long-term immune response from one dose of vaccine following previous infection could not be evaluated. However the one dose titres exceeded post infection titers, suggesting that the durability of the one dose response may be similar or better to that seen after infection.

This NCCMT review sought to compare the immune response to full dose vaccination in previously infected individuals to previously uninfected individuals. These 13 immunologic studies compared fully vaccinated, previously infected individuals to fully vaccinated, previously uninfected individuals. All 13 studies, with a duration of follow up lasting up to six months, demonstrated a higher peak humoral immune response with a slower decline following full vaccination in previously infected individuals.

Additional Evidence from Targeted Searches

Effectiveness Studies

One study not included in these reviews is a preprint Israeli analysis of organizational electronic health records for 2.5 million individuals, where vaccinated individuals received Pfizer vaccines at a 3 week interval (Gazit et al., 2021). It involved a series of matched cohort analyses, with matching of age, gender, and comorbidities, with the following comparisons: 1) immunized/uninfected versus unimmunized/infected matched by date of previous infection of vaccination, 2) Same comparison not matched by date

of previous infection or vaccination, 3) Comparison of unimmunized/infected and single dose administered 3+ months after infection. This study compared PCR positive test results, symptomatic infections, and hospitalizations taking place between June 1, 2021, and August 14, 2021, when the delta variant predominated in Israel. In the first comparison, 238/16215 (1.5%) of vaccinated versus 19/16215 (0.1%) of previously infected had a subsequent positive PCR test, with a 13-fold higher risk of positive PCR test, a 27-fold higher risk of a symptomatic infection, and 8 admissions in the vaccinated group compared with one in the previously infected group. The most relevant cohort to our question compared previously infected individuals with and without a single vaccine dose, showing 20/14029 (0.15%) vaccinated versus 37/14029 (0.26%) unvaccinated with positive RT-PCR tests, along with a trend towards decreased symptomatic infection in single dose vaccinated group.

This study has several strengths, in that it is a large-scale study whose groups are well matched with respect to age comorbidities. Several limitations make the results of this study difficult to generalize, particularly between the vaccinated uninfected group and the previously infected group. The matching process generated a younger than average adult cohort at 36, and in addition cohort enrollees had to be fully vaccinated by February 28th so these young, vaccinated people may have been prioritized due to higher risk of developing infection, for reasons not necessarily captured by comorbidity matching (such as working in health care). Test seeking may have differed between vaccinated and unvaccinated groups. Finally, the initial schedule was a 3-week interval, which was seldom used in Canada. Overall, although the infection rate in previously infected individuals was very low, one dose of vaccine seems to provide additional protection (0.11% absolute difference, 42% reduction) to post infection immunity.

Data from the SIREN cohort in the UK (Hall et al., 2021) also looked at the real-world efficacy of one or two doses of the Pfizer vaccine in 23,324 health care workers, including both previously infected and uninfected individuals. The study reports infections between December 7, 2020, and February 8, 2021, during an alpha variant wave and a vaccination rollout. PCR testing was performed every two weeks; the overall number of documented infections was very small across all fully vaccinated and previously infected groups (977 infections in unvaccinated cohort and 71 in the partially or fully vaccinated cohort with infection incidence rates per 10,000 person days lowest in seropositive with previous infection group with no vaccine, one dose, two doses respectively at 3, 2, 2, and significantly higher in the previously uninfected groups with incidence rates per 10,000 with no vaccine, one dose, two doses respectively at 20,11,5. This is a large surveillance cohort with 1057 confirmed positive PCR tests during the follow up period. Limitations include a lack of long-term data, with a cut of date of analysis during the vaccination rollout, and an outcome measure of PCR positivity, which is less clinically meaningful than symptomatic infection. However, despite the limitations of this study, one dose of Pfizer vaccine post infection appeared to confer similar protection to 2 doses in an uninfected group.

Other studies did not directly review the single vaccine dose post infection strategy but evaluated both vaccine induced and post-infection immunity in a variety of ways. One case control study included all Kentucky residents infected with laboratory confirmed COVID-19 between March and December 2020, comparing the rate of infection

between vaccinated and unvaccinated individuals (Cavanaugh et al., 2021), and found that unvaccinated individuals were 2.34 times more likely to develop reinfection (defined by PCR or antigen positivity between May 1 – June 30, 2021) than vaccinated individuals. Another study, comparing patients hospitalized with COVID-19 like illness in nine US states, found that the adjusted odds ratio that unvaccinated previously infected people had a positive PCR for COVID-19 compared to vaccinated uninfected people was 5.49, indicating vaccines provide superior protection against severe outcomes compared to previous infection (Cavanaugh et al., 2021). Limitations to this study include the study population, which does not directly compare the general previously infected vs vaccinated populations, possibly bias by only including hospitalized patients with a COVID-19 test within the 14 days prior to hospitalization, and the magnitude of the effect that the multivariate adjustment had on the outcome measure (adjusting the odds ratio from 1.7 to 5.49).

Furthermore, a large, national, cohort study compared infection rates in previously infected and uninfected two dose mRNA vaccinated individuals in Qatar from December 21, 2020 to September 19, 2021 (Abu-Raddad, Chemaitelly, Ayoub, Yassine, Benslimane, al Khatib, et al., 2021); this study is an updated version of the preprint reviewed by the NCCMT by the same first author. This study found statistically significant increased protection from previous infection in individuals who received either Comirnaty or Spikevax, though low infection rates were reported in all groups (Abu-Raddad., 2021). For Comirnaty recipients, infection incidence rate was 1.00 per 10000 person weeks in previously infected individuals compared with 5.40 in previously uninfected individuals. For Spikevax recipients, infection incidence rates were 0.83 per 10000 person weeks in previously infected individuals, compared with 1.83 in previously uninfected individuals (Abu-Raddad et al., 2021).

Limited data exists on post-infection immunity and vaccine immunity in children under 12. The phase 3 trial for the Pfizer/biontech vaccine in children 5-11 (Non-FDA, 2021), had 3 infections in the vaccinated group (1517 members), and 16 in the unvaccinated group (751 members), showing vaccine efficacy of 90.7%. No previously infected patient in either group developed COVID-19 infection (198 members across both groups); however, the small number of infections in vaccinated children and the small numbers of previously infected children make it difficult to effectively compare immunity between the two groups.

Immune Response Studies

An additional 35 studies were found that, in part, examined the immune response following one dose of vaccination in previously infected individuals. Of these, 33 examined humoral immunity to the SARS-CoV2 spike protein or to the receptor binding domain (Angyal et al., 2021; Anichini et al., 2021; Appelman et al., 2021; Buonfrate et al., 2021; Casado et al., 2021; Chan et al., 2021; Ciccone et al., 2021; Demonbreun et al., 2021; Ebinger et al., 2021; Eyre et al., 2021; Forgacs et al., 2021; Fraley et al., 2021; Glück et al., 2021; Hirotsu et al., 2021; Jahrsdörfer et al., 2021; Kontopoulou et al., 2021; Krammer et al., 2021; Lozano-Ojalvo et al., 2021; Mazzoni et al., 2021; Michos et al., 2021; Racine-Brzostek et al., 2021; Ramos et al., 2021; Reynolds et al., 2021; Salvaggio et al., 2021; Samanovic et al., 2021; Sasikala et al., 2021; Stamatatos

et al., 2021; Tejedor Vaquero et al., 2021; Tré-Hardy et al., 2021; Trougakos et al., 2021; Tut et al., 2021; Velasco et al., 2021), 9 examined neutralization titres (Appelman et al., 2021; Demonbreun et al., 2021; Favresse et al., 2021; Forgacs et al., 2021; Jahrsdörfer et al., 2021; Racine-Brzostek et al., 2021; Reynolds et al., 2021; Saadat et al., 2021; Samanovic et al., 2021), and 8 examined anti SARS CoV 2 T cell mediated immunity. 31 studies used the Pfizer vaccine (Angyal et al., 2021; Anichini et al., 2021; Appelman et al., 2021; Blazhevskaja et al., 2021; Buonfrate et al., 2021; Casado et al., 2021; Ciccone et al., 2021; Demonbreun et al., 2021; Ebinger et al., 2021; Eyre et al., 2021; Favresse et al., 2021; Forgacs et al., 2021; Fraley et al., 2021; Glück et al., 2021; Hirotsu et al., 2021; Jahrsdörfer et al., 2021; Kontopoulou et al., 2021; Krammer et al., 2021; Lozano-Ojalvo et al., 2021; Mazzoni et al., 2021; Michos et al., 2021; Racine-Brzostek et al., 2021; Ramos et al., 2021; Reynolds et al., 2021; Saadat et al., 2021; Salvaggio et al., 2021; Samanovic et al., 2021; Stamatatos et al., 2021; Trougakos et al., 2021; Tut et al., 2021; Velasco et al., 2021), 10 studies used the Moderna vaccine (Chan et al., 2021; Ciccone et al., 2021; Demonbreun et al., 2021; Forgacs et al., 2021; Glück et al., 2021; Krammer et al., 2021; Saadat et al., 2021; Stamatatos et al., 2021; Tejedor Vaquero et al., 2021; Tré-Hardy et al., 2021), 4 studies used the Oxford/AstraZeneca vaccine (Eyre et al., 2021; Glück et al., 2021; Sasikala et al., 2021; Tut et al., 2021) (some studies used multiple vaccines).

All of these studies showed a rapid, robust anti-spike antibody response following one dose of COVID-19 vaccine in previously infected individuals, which was statistically equivalent to the response to two doses of COVID-19 vaccine. In previously uninfected patients, two doses of vaccine were required for a similar immune response. In studies in which a second dose of vaccine was administered to previously infected individuals, antibody levels were high and not further boosted compared to one dose.

Individual studies listed here included small numbers of patients, and are heterogeneous in terms of antibody assays, populations assessed, type of immune response measured, and vaccines used. Furthermore, many of the studies reference are preprints that have not completed formal peer review. However, taken together, they demonstrate that, under a wide variety of parameters, a single dose of vaccine following infection provides a robust immune response. Given the recency of the COVID-19 pandemic and availability of vaccination, none of these studies were able to evaluate the immune response over a longer duration of time after a single dose of vaccine in previously infected individuals.

T cell responses: One study evaluated T cell and antibody responses, showing that the T cell response in COVID-19 recovered individuals is boosted by the first dose but the second dose did not increase the spike specific T cell response further, overall concluding that a second dose is not required (Lozano-Ojalvo et al., 2021).

Another study included partially immunized and fully immunized previously infected individuals. T cell and antibody responses were compared in 237 immunized - uninfected, partially immunized - infected and immunized/infected health care workers, showing equivalence of antibody and T cell responses in 2 dose immunized and 1 dose immunized/infected (Angyal et al., 2021). This study also showed effective

neutralization of Delta VOC after 1 dose in previously infected individuals but only after two doses in uninfected individuals (Angyal et al., 2021)

Population based antibody response data: A large UK cohort study showed that in individuals with lab confirmed previous infection (documented by RT-PCR positivity or anti spike antibody positivity) prior to vaccination, a single dose of either Astra Zeneca or Pfizer vaccine increased antibody levels in all age ranges, with >95% seropositive by 28 days after vaccination regardless of age, similar to the 2 dose uninfected group. In those receiving single dose Pfizer (post infection), only 5.1% had a lower antibody response. In this study antibody titres after AstraZeneca dose one were not as high but remained constant, and those to Pfizer were higher but waned. Risk factors for not becoming seropositive after documented infection included higher Ct values (inferring lower viral loads) at initial RT-PCR testing, mild or asymptomatic infection, older age (over 60 years with the lowest antibody responses those >80 years), or not working in patient facing healthcare. After single dose vaccination of previously infected intermediate aged people, antibody levels were significantly higher with a single dose following natural infection than with two BNT162b2 doses, whereas two doses achieved similar antibody levels to one dose following natural infection at younger and older ages. People with long term health conditions were less likely to seroconvert (aOR 0.64) after vaccination as well. Health conditions more common in low responders overall included taking immunosuppressants (aOR 3.91), rheumatoid arthritis (aOR 2.50) chronic liver disease (2.34 cancer (1.62), taking corticosteroids (1.59), type 2 diabetes (1.44), obesity (BMI \geq 30 kg per m², 1.25) and asthma (1.25).

Mild illness and antibody response: Multiple other smaller studies have shown that patients with more severe illness had higher antibody responses than those with mild/asymptomatic illness (Favresse et al., 2021; Lau et al., 2021). These studies indicate that the immune response to COVID-19 infection is not homogenous, and indicate that undocumented infection, which is more likely to be mild or asymptomatic, may not offer reliable immunity to COVID-19 infection without additional vaccination.

Effective post infection boosting regardless of seropositivity: One study compared those with a confirmed previous COVID-19 infection by PCR test who were seropositive to post infection seronegative individuals, and found that the seropositive group had a similar dose 1 response to the seronegative group (Demonbreun et al., 2021). Another study stratified by mild and severe infections and found that initial vaccination effectively boosted a lower antibody response after mild infection (Favresse et al., 2021).

This indicates that vaccination may effectively boost immunity in those with previous documented infection, with or without documented seroconversion following infection.

Synthesis of the Information Relating to Question 1

The effectiveness of one versus two doses of COVID19 vaccine in previously infected people has not been directly compared. A large body of immunologic studies suggest that a single dose of COVID-19 vaccine following infection results in robust immunologic responses which compare favorably to immunity from 2 doses in uninfected individuals

The recent preprint study by Gazit et al is relevant, suggesting that prior infection plus a single dose of vaccine given at least 3 months after infection is highly protective in a

Delta dominant setting, and is superior to prior infection without immunization, but does not directly compare 1 and 2 dose vaccination in previously infected cohorts. Other studies confirm a low rate of infections in the population that received one dose of vaccine following previous infection.

Overall, both laboratory studies and cohort studies support a high probability of substantial protection from post infection immunity boosted by one dose of vaccine but there is no direct data that compare one vs. two doses of vaccine in previously infected people. Furthermore, there is immunologic data that suggests that post-infection immunity is heterogenous and may not be generated as reliably following asymptomatic or pauci-symptomatic infections as after more severe COVID-19 infection.

Is there any evidence to suggest an optimal dose interval from recovery to immunization?

Evidence from PHAC Rapid Review on Protective Immunity

None of the studies on vaccine effectiveness directly examined the relationship between timing of immunization after recovery from COVID-19 and vaccination effectiveness.

This review was focused on long term immunity from either infection or vaccine immunity; consequently, studies included had long intervals between infection and vaccination. (Gallais et al., 2021) had an interval up to 200 days, though the reporting of the exact duration between infection and vaccination is unclear. A study that included immune indices after single dose mRNA study (Wang et al., 2021) reported an interval from infection to vaccination between 272 – 373 days. A further study (Cagigi et al., 2021) reported an interval between 270-407 days, and Moderna /Spikevax was given. In all cases, a robust immune response was generated following vaccination. Vaccine side effects and adverse events were not reported in either study. Based on the studies included in this review a delay from infection to vaccination is not expected to impair the immune response to vaccination.

Evidence from NCCMT Rapid Review on COVID-19 Vaccination in previously infected individuals

None of the studies directly addressed this question. Three studies provided some data on the interval between COVID-19 infection and immunization. One study, comparing breakthrough infections in uninfected and previously infected vaccinated nursing home residents, included two cohorts of residents(Blain et al., 2021); 36 who were infected approximately 3 months prior to vaccination, and 6 who were infected 7-9 months prior. The only infection in the previous infection plus vaccination cohort was in a resident infected 7-9 months prior to immunization.

Two studies found robust antibody responses after first dose vaccination occurring from 3.5 to 10 months after infection. Another study immunized participants who were infected at least 7 months prior to vaccination. Another assessed response in patients immunized at a median interval from onset of COVID-19 of 262 days, with an interquartile range of 101.5-275 days. Immune responses were robust in all cases.

Additional Evidence found by targeted searches

Duration of time between infection and vaccination:

A large cohort study of mRNA vaccinated people in Qatar compared breakthrough infections in people with an infection vaccination interval of less than six months to those with an interval greater than 6 months, during a time in which the delta variant predominated in Qatar (Abu-Raddad et al., 2021). In individuals who received the Comirnaty vaccine, infection incidence was 0.85 per 10000 person-weeks in those with an infection to vaccination interval of greater than 6 months, compared to a rate of 1.41 in those with an interval of less than 6 months. For recipients of Spikevax, infection incidence was 0.40 per 10000 person weeks in those with an infection vaccination interval of greater than 6 months, compared to an incidence of 1.00 in those with an infection vaccination interval of less than 6 months. Findings in both of the above comparisons reached statistical significance. This study suggests an interval of greater than 6 months could provide enhanced protection against infection, though we note that the incidence rate was low in all comparator groups (Abu-Raddad et al., 2021).

In addition, two small detailed immunologic studies directly assessing antibody response that reported on the duration between infection and vaccination. In the first study, 18 health care workers who had a short (<6 month) infection to vaccine interval (IQR 2-3 months, median 2 months) were compared to 19 health care workers who had a long (>6 month) infection to vaccination interval (IQR 9-10 months median 9 months) using the Comirnaty vaccine with doses administered 21 days apart (Appelman et al., 2021). Both recently and earlier infected participants showed comparable humoral immune responses after a single mRNA vaccination, while exceeding those of previously uninfected persons after two vaccinations with 2.5 fold ($p = 0.003$) and 3.4 fold ($p < 0.001$) for binding antibody levels, and 6.4 and 7.2 fold for neutralisation titres, respectively (both $p < 0.001$). The second vaccine dose yielded no further substantial improvement of the humoral response in the previously infected participants (0.97 fold, $p = 0.92$), while it was associated with a 4 fold increase in antibody binding levels and 18 fold increase in neutralisation titres in previously uninfected participants (both $p < 0.001$). This paper therefore supports likely effectiveness of single dose vaccination in a range of 2-10 months after infection.

A paper by Anchini et al. also reported significantly higher neutralizing titers in previously infected individuals after the first dose compared to the uninfected individuals who had received two doses (Anichini et al., 2021). In this study ($n=60$), there was a trend to higher neutralizing titres if the duration from infection to immunization was longer, with immunization at 3+ months, 2-3 months, and < 2 months showing mean titres of 694 (95% CI, 565 to 823), 559 (95% CI, 389 to 730), 437 (95% CI, 231 to 643) respectively. This was not statistically significant.

Therefore, multiple immunologic studies suggest that vaccine boosting with a single dose between 2-10 months after documented infection results in a strong immune response in laboratory studies. However, the small number of participants in each of these studies make conclusions preliminary, and neither study evaluated effectiveness outcomes.

Other considerations in prime-boost timing:

Indirect considerations of duration include the immune response to vaccination, as the second dose of vaccine is thought to boost the immune response in a similar way to

vaccination post-infection. Indeed, in British Columbia and Quebec, vaccine effectiveness was enhanced by an interval of at least 7 weeks between doses (Skowronski et al., 2021). In the Astra Zeneca vaccine trials, intervals of 11 weeks or longer resulted in a higher Astra Zeneca vaccine efficacy (Voysey et al., 2021). Furthermore, when an extended dose interval of Comirnaty (6-14 weeks) was compared with a shorter interval (3-4 weeks), the extended interval resulted in significantly higher neutralizing antibody titres and T cell responses (Payne et al., 2021). Modelling studies also support a potentially better response with boosting longer after the primary response (Garg et al., 2021). For most vaccines, second doses are offered months after the initial vaccine (NACI, 2020), with the first dose providing priming/short term protection, and a delay given to promote a long lasting, effective immune response.

Adverse effects and side effects (reactogenicity) of vaccination after infection:

There is some evidence that previous infection is associated with increased reactogenicity side effects, most pronounced following administration of the first dose of vaccine (d'Arminio Monforte et al., 2021; Krammer et al., 2021; Menni et al., 2021; Raw et al., 2021; Tré-Hardy et al., 2021). The largest data set is from a self reporting system in the UK, which compiled side effects recorded via the COVID symptoms study app in 627 383 individuals; they found that systemic side effects were more common in the previously infected with both the first and second doses of Comirnaty, along with the first dose of Vaxzevria (Menni et al., 2021). Local side effects were also reportedly more severe in those with previous infection following all vaccines, though the difference was not as large between the groups (Menni et al., 2021). However, in all cases, serious adverse events were not increased in previously infected individuals compared with non previously infected individuals receiving 1st or second dose vaccination.

There has not been a signal of serious adverse effects among previously infected persons receiving vaccination and at this point in the pandemic, millions of people with known or unknown previous infections have received COVID-19 vaccines. Few studies have explicitly stratified serious vaccine adverse effects, such as myocarditis, by previous infection. One study in nursing home residents suggested that SARS-CoV-2 infection, regardless of whether it was symptomatic or asymptomatic, did not increase the risk of adverse events following COVID-19 vaccination. This group evaluated serious adverse events in approximately 20,000 American nursing home residents in the time period after vaccination and described an increased rate of post vaccination events in those with no previous infection compared to previously infected vaccinees (including MI, Bell's palsy, seizures, strokes, and VTE) (Bardenheier et al., 2021), which may suggest differences in the populations (COVID-19 infection survivors may have been less frail than the general nursing home population.). However, the numbers were small (no more than 1-3 for any individual adverse event), and represent conditions that are not uncommon in a nursing home population. In addition the adverse events in this study cannot be convincingly linked to vaccination.

No data on the incidence of myocarditis in previously infected people after one or two doses of COVID-19 vaccination was found. Overall, the risk of myocarditis is higher in COVID-19 infection than post vaccination (Boehmer et al., 2021; Le Vu et al., 2021), and as with other causes of myocarditis, the highest risk is seen in younger males (12-29

years of age; Gargano et al., 2021), with a higher risk associated with dose 2 of vaccine. No myocarditis events were reported in vaccine efficacy trials in 5-12 year old children, and the risk in 5-12 year old is not expected to be elevated as this group usually does not have the higher risk of myocarditis seen in youth and younger adults (Russell Woodworth, 2021).

Synthesis of the Information Relating to Question 2

One limitation, in addition to the paucity of data addressing this question, is that many of the studies analyzed were preprints, and may be modified following the peer review process. There is heterogeneity in reported infection - vaccine intervals, ranging from 2-10 months, with no studies looking at shorter intervals. Furthermore, all studies report small numbers of participants, including the two studies that directly compared different infection to vaccination intervals. All of the relevant immunologic studies suggest possibly stronger immune responses with a longer duration from infection to vaccination, with a robust immune response to vaccination after infection demonstrated across all studies. Therefore extant evidence suggests that the immune response will likely be robust in immunization after infection across all of the intervals (2 months to 10 months) reported. Using a two dose vaccine series as a prime boost model, vaccine effectiveness may be optimized by 8-12 week interval between vaccine doses; it is plausible that a similar interval between infection and vaccination may optimize the prime-boost of infection plus vaccination as well.

Most of the gathered studies did not comment on any differences in adverse events after immunization in previously infected people. No studies were identified that compared adverse events based on the infection - vaccine interval, nor were there any that suggested one interval might be more harmful than another. There is poorer quality evidence that the previously infected people have an increased risk of minor post-vaccine side effects; however, the overall safety profile of these vaccines remains very reassuring across populations that undoubtedly include significant numbers of previously infected individuals.

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