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EVIDENCE BRIEF

Reinfection with SARS-CoV-2 Omicron Variant of Concern

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Key Messages

- Reinfection with an Omicron SARS-CoV-2 sub-lineage (including BA.1, BA.2, BA.4 and BA.5), following infection by any SARS-CoV-2 lineage, is more commonly reported compared to reinfection with prior variants of concern seen during the COVID-19 pandemic.
- The majority of available research indicates that reinfection with Omicron may not pose significant risk of increased acute disease severity relative to primary infections, or to reinfections with non-Omicron lineages. However, two recent preprint studies have found that multiple reinfections may be associated with increased risk of severe outcomes. As there was little evidence available related to longer-term outcomes, it remains unclear how reinfection with Omicron may impact disease severity.
- While prior infection alone provides protection against reinfection, vaccination appears to further amplify this protection. Individuals with both prior infection and vaccination (i.e., hybrid immunity) may have greater protection against reinfection with Omicron compared to vaccination or infection alone.
- Vaccine effectiveness (VE) against reinfection during the Omicron period is lower compared to VE against reinfection during periods of other VOC dominance. However, VE against hospitalization or death during Omicron reinfection remains high.
- There is mixed evidence related to risk factors for reinfection with Omicron. It is important to consider possible confounding influences between these risk factors, along with other factors such as testing processes, vaccination prioritization and health-seeking and risk behaviours across various groups. For example:
    - Time since previous infection: risk for reinfection increases as the time since previous infection increases. In other words, protection conferred from a previous infection wanes over time.
    - Age: reinfection was found be more common in younger age groups compared to older age groups across available evidence.
    - Occupational/residential factors: healthcare workers (HCW) and residents of long-term care (LTC) may be at greater risk of reinfection.
    - Gender/sex: limited available evidence suggested a possible association between being female and increased risk of reinfection.

- There is emerging evidence related to reinfection characteristics specific to Omicron sub-lineages, mainly BA.1 and BA.2, which shows reinfection with more than one Omicron sub-lineage is possible but rare, and has been observed most often in children and young adults who are unvaccinated.

- The findings of this Evidence Brief are based on studies that use various test-based and time-based definitions for reinfection (ranged from minimum 20 to 90 days after previous infection to be considered a reinfection), and included several preprint studies, which should be considered when interpreting results. High-quality research and consistent reinfection definitions are needed to better characterize and understand SARS-CoV-2 reinfections.

Issue and Research Question

In 2022, the third year of the COVID-19 pandemic, reinfection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become an increasing occurrence. Reinfection is generally made possible when immunity acquired from a previous SARS-CoV-2 infection is insufficiently protective against other emergent SARS-CoV-2 sub-lineages.[1] Emerging variants of concern (VOC), especially the Omicron VOC and several of its sub-lineages, have been associated with increased risk of immune evasion and reinfection following previous infection by other VOCs.[1-3] Future SARS-CoV-2 lineages may carry further risks of reinfection if diverging significantly from currently circulating sub-lineages.

The objective of this Evidence Brief is to explore the currently available evidence related to reinfection with the Omicron VOC and any of its sub-lineages. Outcomes of interest are the incidence and severity of reinfection, the impact of vaccination on reinfection, and risk factors for reinfection.

Methods

Between August 12 and 18, 2022, Public Health Ontario (PHO) Library services conducted searches of the indexed literature published from January 1, 2022 onwards in four databases: Medline, Embase, Scopus and National Institutes of Health (NIH) COVID-19 Portfolio (preprints). Preprints are research papers that have not undergone peer-review but are made publicly available to provide the latest data relevant to the rapidly evolving COVID-19 pandemic. Formal critical appraisal of published and preprint COVID-19 literature is out of scope for this Evidence Brief. Search strategies are available on request.

We included English language observational studies related to reinfection with the SARS-CoV-2 Omicron sub-lineages in real-world settings from any jurisdiction. In this document, unless specifically stated, evidence presented on Omicron is referring to either BA.1, BA.2, BA.4 or BA.5 sub-lineages. This Evidence Brief covers Omicron sub-lineages identified until August 18, 2022 and does not cover any additional sub-lineages that have emerged and may have different reinfection characteristics. Commentaries, editorials, and other non-study (i.e., no methods) literature were excluded. Animal studies, modelling studies, in-vitro studies, case reports, and case series were excluded. We did not limit inclusion by time-based, test-based or laboratory-confirmed definitions of reinfection in order to capture available descriptions of all study-defined reinfections.

Search Results

A total of 1,222 search results were screened for eligibility (Medline n=617; Embase n=279; Scopus n=295; preprints n=31). One systematic review and meta-analysis and 37 observational studies were included; 26 are published studies and 12 are non-peer-reviewed preprints. Results from individual studies are included in multiple sub-sections of this Evidence Brief.

Studies were conducted in many jurisdictions: Belgium, Brazil, Canada, Czech Republic, Denmark, France, Iceland, India, Ireland, Italy, Netherlands, Qatar, Serbia, South Africa, South Korea, Spain, Sweden, United Kingdom (UK) and United States (US). Study populations in the majority of studies were the general public, and other populations included healthcare workers (HCW), veterans, long-term care (LTC) residents and incarcerated adults.

All studies included data collected during or overlapping with a time period when Omicron was circulating in the jurisdiction where the study was conducted; however, not all studies stratified results by variant. It is important to consider the factor of time when interpreting these results, as time periods during the pandemic are often delineated by the current dominant VOC, or by waves. A variety of time periods between SARS-CoV-2 infections were used across studies to define time-based reinfection criteria (ranged from minimum 20 to 90 days after previous infection to be considered a reinfection). Test-based or laboratory-confirmed reinfection definitions similarly varied across studies. We did not limit inclusion based on studies' definitions of reinfection and this should be considered when interpreting results.

Outcome measures also varied widely across studies (i.e., reinfection rates [%], reinfections per month, odds ratios [OR], hazard ratios [HR], and relative risk [RR]). Statistical pooling of results was out of scope for this body of evidence, and all results are summarized descriptively. For studies examining vaccine effectiveness (VE), unless otherwise stated, evidence is primarily related to effectiveness of mRNA vaccines.

Please see Table 1 in Appendix A for additional characteristics of all included studies (i.e., study period, design, country, reinfection definition, sample size, population, and participant characteristics).

Omicron Reinfection Incidence and Disease Severity

We identified one systematic review and meta-analysis and 20 primary observational studies (four of which were preprints) that reported on rates of SARS-CoV-2 reinfection and/or severity of reinfection.[4-23] All studies included or overlapped with a time period when the Omicron VOC was dominant.

In 15 studies that compared Omicron to pre-Omicron periods, there were consistent results showing reinfections were considerably more frequently described since the emergence of Omicron.[4,6,8-10,12-15,17,18,20-22] For example, in a meta-analysis (searched to June 2022) which analyzed 91 studies (five in the Omicron period) from across Europe, Asia, US, South America and South Africa and included over 15 million total participants, pooled reinfection rates by variant were: Alpha 0.57% (95% confidence interval [CI]: 0.28, 0.94), Delta 1.25% (95% CI: 0.97, 1.55), and Omicron 3.31% (95% CI: 1.15, 6.53).[12] Nine of the 20 primary observational studies reported reinfection rates specific to the Omicron period in the general population ranging from 3.31% to 15.32%.[4,6,9-12,14,17,20] Two studies that examined HCW found Omicron reinfection rates of 28.4% and 34.4%,[16,19] and one that assessed LTC residents found an Omicron reinfection rate of 12.7%.[15]

There were various outcome measures and results across 12 primary studies regarding the severity of reinfections in time periods that included Omicron.[4-8,12,14-17,22,23] Overall, the majority of these results suggested that reinfection in the general public during the Omicron period was not associated with increased risk of acute disease severity compared to primary infections or to reinfections with non-Omicron lineages. The meta-analysis by Flacco et al. (2022a) found that reinfection disease severity did not vary according to the dominant variant (i.e., Alpha, Delta or Omicron).[12] When comparing severity of primary SARS-CoV-2 infections to reinfections, six studies found secondary infections (which occurred primarily during the Omicron period) were associated with reduced disease severity outcomes (e.g., hospitalization, pneumonia, ICU admission, mortality) compared to primary infections which occurred prior to the emergence of Omicron.[4,14-17,23] For example, in a nationwide cohort study in South Korea which assessed records from over 16 million confirmed SARS-CoV-2 cases from January 2020 to April 2022, the case fatality rates were 0.3% for all infections and 0.1% for reinfections (99% of all reinfections were detected during Omicron).[14] Similarly, Krutikov et al. (2022) found that among 2,264 LTC residents in the UK, those with a reinfection were at lower risk of hospital admission than those experiencing a first infection (adjusted HR: 0.21; 95% CI: 0.07, 0.67).[15] Chemaitelly et al. (2022a) (preprint) did not directly compare reinfections to primary infections and did not stratify by variant, but found severe reinfections were overall rare with only 0.1% cases considered severe and none deemed critical.[8] Two studies found that, among people with reinfections, older age and increased severity of first infection were associated with increased severity during reinfection.[17,22]

In contrast, Al-Aly et al. (2022) (preprint) found reinfections (not stratified by variant) in a cohort from the US Department of Veterans Affairs were overall associated with increased severe outcomes when followed up to 6 months (i.e., mortality, hospitalization, sequelae in organ systems) compared to primary SARS-CoV-2 infections, and that risk of these outcomes increased with each subsequent reinfection.[5] Another study also analyzing data from the U.S. Veterans Health Administration (preprint) reported on multiple reinfections and found greater hospitalization rates in those with three infections (26%) compared to one (19%) and two (17%) infections; however, statistical significance was not reported.[4]

Some studies reported that prior infection provided protection against severe reinfection outcomes. For example, Cerqueira-Silva et al. (2022) reported previous infection provided relatively low protection against Omicron reinfection overall in the general Brazilian public (28.9%; 95% CI: 26.9, 30.9), but did provide effective protection against severe reinfection outcomes (i.e., hospitalization or death) (85.6%; 95% CI: 82.7, 88).[7] Davies et al. (2022) (preprint) also found that prior infection provided protection against severe outcomes (i.e., hospitalization or death) during the Omicron period in South Africa (aHR: 0.13; 95% CI: 0.06, 0.27), which was not significantly different from the Delta period (aHR: 0.32; 95% CI: 0.2, 0.52).[10]

Impact of SARS-CoV-2 Vaccination on Reinfection Incidence and Severity

We identified one systematic review and meta-analysis and 12 primary observational studies (including two preprints) that reported on the impact of COVID-19 vaccination status on reinfection incidence during the time when Omicron was the dominant variant.[7,11-14,17,22,24-29]

In most studies, vaccination was shown to decrease the overall risk of reinfection during the Omicron period. For example, Sacco et al. (2022) found that the risk of reinfection for unvaccinated people in Italy was 2.9 (95% CI: 2.8, 3.0) times higher than for those who had been vaccinated with at least one dose less than 120 days prior to reinfection.[22] However, this differential was reduced when compared to individuals who had been vaccinated more than 120 days prior to reinfection (1.5 times higher; 95% CI: 1.5, 1.6), suggesting waning vaccine effectiveness (VE) against reinfection over time.

There is some evidence to suggest that immunity acquired from a prior SARS-CoV-2 infection is amplified following vaccination and individuals with this type of "hybrid immunity" may be better protected against reinfection than those with either vaccination or previous infection alone.[14,24,25,29] In a study from Quebec, Canada, Carazo et al. (2022b) (preprint) found that protection increased as more doses of mRNA vaccine were administered.[25] Vaccine effectiveness against reinfection with Omicron among those with prior infection (pre-Omicron) compared to those without any prior infection was 65% (95% CI: 63, 67) versus 20% (95% CI: 16, 24) following one dose; 68% (95% CI: 67, 70) versus 42% (95% CI: 41, 44) following two doses; and 83% (95% CI: 81, 84) versus 73% (95% CI: 72, 73) following three doses. They also found that effectiveness of prior infection against Omicron-related hospitalization was 81% (95% CI: 66-89) and increased to 86% (95% CI: 77, 99) following one dose; 94% (95% CI: 91, 96) following two doses; and 97% (95% CI: 94, 99) following three doses. It is important to note that longer-term outcomes were not studied, and further data is needed to determine the effectiveness of prior infection and vaccination against reinfection.

There is also evidence to suggest that VE against reinfection was reduced significantly during the Omicron period compared to periods where other VOCs were in circulation. A recent preprint by Nielsen et al. (2022) found that in Denmark, VE against reinfection peaked at 85% (95% CI: 37, 97) at 104 days or more after vaccination during the Alpha period, 88% (95% CI: 81, 92) 14-43 days after vaccination during the Delta period and 60% (95% CI: 58, 62) 14-43 days after vaccination during the Omicron period.[27]

Similarly, Flacco et al. (2022b) also reported slightly higher VE of two vaccine doses in the pre-Omicron period compared to the Omicron period in Italy.[13] While evidence shows a decline of VE against reinfection during the Omicron period, VE against reinfection leading to hospitalization and severe disease remained fairly high, especially following the administration of a booster dose.[12,17,28] A large study in the US by Plumb et al. (2022) reported that VE against reinfection resulting in hospitalization was highest amongst those who had received a booster (67.6%; 95% CI: 61.7, 72.8) compared to those with two doses (34.6%; 95% CI: 25.5, 42.5) or one dose (33.0%; 95% CI: 15.0, 47.2) of an mRNA vaccine.[28] They also found that VE of 1 or 2 doses was significantly lower against Omicron compared to Delta, as VE against reinfection leading to hospitalization decreased from 50–60% during the Delta period to approximately 35% during the Omicron period.

Two studies reported findings that contrasted with the majority of the results above. Shrestha et al. (2022) examined the effect of vaccines on reinfection in a cohort of employees at a health clinic in Cleveland, Ohio and found that while at least one dose provided significant protection against reinfection compared to zero doses among those previously infected (HR: 0.66; 95% CI: 0.58, 0.76), two doses compared to one was associated with higher risk of COVID-19 reinfection (HR: 1.54; 95% CI: 1.21, 1.97).[29] Likewise, Eythorsson et al. (2022) examined the rate of reinfection during an Omicron wave in Iceland and reported the overall rate of reinfection was 11.7% in those with ≤1 vaccine dose, and 10.9% in those with ≥2 vaccines doses. Results of a regression analysis found that the probability of reinfection was higher in those with ≥2 doses (n = 320) compared to those with ≤1 dose (n = 1,007) (OR: 1.42; 95% CI: 1.13, 1.78).[11] It is important to note that these findings should be interpreted with caution since the different analyses could not adjust for complex relationships among prior infection, vaccine eligibility, behaviours of individuals, household exposures, and underlying conditions; all of which can influence risk or COVID-19. Also, the timing of vaccine doses and the types of vaccines were not reported.

Risk Factors for Reinfection

One systematic review and meta-analysis and 15 primary studies (including four preprints) included results related to risk factors for reinfection.[6,9,11-14,16,17,20,24,25,29-34]

Time from Previous Infection

We identified 12 studies (including three preprints) that examined the impact of time from previous SARS-CoV-2 infection on the incidence of reinfection during the Omicron dominant period.[9,11,13,17,20,24,25,29-31,33,34] The majority (i.e., 10) of these studies indicated protection conferred by prior infection waned over time, thereby increasing the risk of Omicron reinfection as duration since previous infection increased.[11,17,20,24,25,29-31,33,34] For example, Michlmayr et al. (2022) examined reinfection rates among unvaccinated individuals in Denmark and found protection from a previous infection against reinfection during the Alpha period was 86.6% (4–6 months since primary infection); during the Delta period was 91.3% (4–6 months since primary infection); and during the Omicron period was 51% (3–5 months since primary infection) and ≤25.4% (≥6 months since primary infection).[31] Carazo et al. (2022a) (preprint) found that prior Omicron infection offered 72% protection against BA.2 reinfection amongst HCW in Canada, with an increase to 82% protection when the primary infection occurred within 30–59 days of the initial infection.[24] Carazo et al. (2022b) (preprint) also found that, without vaccination, prior non-Omicron infection reduced Omicron reinfection risk by 66% (95% CI: 57, 73) at 3–5 months post-infection, 35% (95% CI: 21, 47) at 9–11 months post-infection, and <30% thereafter.[25] Eythorsson et al. (2022) studied a period when Omicron was dominant in Iceland and found the odds of reinfection were greater at 18 months, compared to 3 months, from first infection (OR: 1.56; 95% CI: 1.18, 2.08).[11] Smid et al. (2022) found, in unvaccinated individuals with prior infection in Czech Republic, that protection against Omicron was estimated as 68% (95% CI: 68, 69) shortly after a previous infection (2–6 months) and 13% (95% CI: 11, 14) after 6 months, compared with 95% (95% CI: 94, 96) shortly after infection and 83% (95% CI: 82, 84) after 6 months for Delta.[34]

Two studies with end times of January 2022 examined the impact of time on reinfection risk but did not find statistically significant differences. These studies overlapped with a time period when Omicron was the dominant variant and reinfection rates include the predominant circulating variant (pre-Omicron and Omicron). Flacco et al (2022b) identified reinfections in 729 of 119,266 previously infected people in Italy from March 2, 2020 to January 4, 2022, for an overall rate of 6.1%, and found that at 18–22 months after primary infection, the reinfection rate did not change significantly (6.7%).[13] Cocchio et al. (2022) found protection from previous infection appeared to wane in the Delta period in Italy, with protection being lower at >12 months from first infection (76%; 95% CI: 66, 83) than at 9–12 months from first

infection (87%; 95% CI: 84, 90). However, in the Omicron period (studied up to Jan 25, 2022), there were no significant differences in reinfection rates found when analyzed by time since previous infection.[9]

Age

Across eight studies (including one preprint) that examined the impact of age on risk of reinfection, results consistently showed reinfection to be more common in younger compared to older age groups.[6,11,13,14,16,17,32,33] For example, Flacco et al. (2022b) found reinfection rates were higher in younger age groups relative to those aged ≥60 years in Italy: 30–59 years (aHR: 2.14; 95% CI: 1.62, 2.86) and 0–29 years (aHR: 2.00; 95% CI: 1.53, 2.62).[13] Eythorsson et al. (2022) reported lower odds of reinfection in all other age groups compared to the 18–29 years group, and lowest odds in the ≥75 years group in Iceland.[11] Bastard et al. (2022) found ages 18–40 were more frequently observed among reinfection cases in France, and people outside of this range (i.e., <18 years and >40 years) were less frequent among possible cases of reinfection (p<0.001).[6] Jang et al. (2022) examined characteristics associated with greater risk of reinfection in South Korea and found children (0–17 years) had greater odds of reinfection compared to the reference group of adults aged 40–49 (OR: 1.64; 95% CI: 1.59, 1.68), as did the 18–29 (OR: 1.38; 95% CI: 1.34, 1.42) and 30–39 year age groups (OR: 1.19; 95% CI: 1.16, 1.23).[14] Malhotra et al. (2022) found that reinfection hazards were 40% lower in HCW aged ≥45 years compared to HCW aged <25 years in India (adjusted HR: 0.60; 95% CI: 0.44, 0.81).[16] It is important to note that older age groups have typically been prioritized for receiving COVID-19 vaccines doses, including boosters, achieving relatively high coverage among this group which likely impacts their risk of infection and reinfection.[17] Nevejan et al. (2022) (preprint), found that early reinfections were frequently observed in young unvaccinated patients (<12 years).[32] Other factors to consider may include differing social and testing behaviours between younger and older age groups, suggesting that social behaviour of younger age groups likely resulted in an increased risk of exposure to the virus.[33]

Occupational or Residential Factors

We identified one systematic review and meta-analysis, and four primary studies that examined reinfection risk in HCW and LTC residents, groups that have greater risk of routine exposure to SARS-CoV-2 by the nature of their working/living conditions compared to the general population.[6,12,14,16,17] The meta-analysis by Flacco et al. (2022a) found the reinfection rate was higher among HCW (1.2%; 95% CI: 0.59, 1.98) compared to the general population (0.90%; 95% CI: 0.61, 1.24); however, these estimates showed largely overlapping CIs.[12] Bastard et al. (2022) found HCW in France were more frequently observed among reinfection cases (6.2%) when compared to any confirmed cases of SARS-CoV-2 (3.5%; p<0.001).[6] Medić et al. (2022) similarly found a greater proportion of HCW in the reinfection group (10.9%) relative to those without reinfection (4.37%) and the overall group of any COVID-19 infection (4.73%; p<0.001) in Serbia.[17] Malhotra et al. (2022) examined risk of reinfection between different types of HCW in India, finding that resident doctors (aHR 3.00; 95% CI: 2.14, 4.21), nursing personnel (aHR 3.00; 95% CI: 2.17, 4.14) and faculty/scientists/research staff (aHR 1.80; 95% CI: 1.23, 2.64) had greater risk compared to students, administrative and clerical staff.[16] Finally, Jang et al. (2022) found residents living in LTC had greater odds of reinfection compared to others in the general South Korean population (OR: 1.72; 95% CI: 1.64, 1.8).[14]

Gender/Sex

There was limited evidence from four studies related to gender or sex and the risk of reinfection.[6,12,13,17] One study reported the sex (i.e., female/male) of participants,[6] and the other three studies described participants' "genders" as female/male and interchanged these terms with woman/man, but did not acknowledge any other genders (e.g., transgender, non-binary or others).[12,13,17] These studies suggested a possible association between being female and increased risk of reinfection relative to being male; however, external confounders were also noted and statistical significance was not achieved in all studies. The meta-analysis by Flacco et al. (2022a) reported pooled rates of reinfection were higher among females (0.79%; 95% CI: 0.18, 1.69) relative to males (0.55%; 95% CI: 0.14, 1.16); however, these estimates showed largely overlapping CIs.[12] A primary study by Flacco et al. (2022b) reported elevated reinfection risk among females compared to males in France (aHR: 1.32; 95% CI: 1.14, 1.53), and the authors noted that testing behaviour (i.e., lower routine diagnostic testing behaviours by males) and occupational risk (e.g., females more frequently employed as HCW) may influence these results.[13] Bastard et al. (2022) also found the proportion of women was slightly, but significantly, higher among possible reinfection cases relative to all confirmed COVID-19 cases in France (55.6% and 53.4%, respectively; $p<0.001$), but the clinical significance was not explored.[6] Medic et al. (2022) similarly found reinfections were more likely to be reported by females versus males in Serbia (57.9% vs 47.05%, respectively; $p<0.001$).[17]

Transmissibility of Reinfection

Two studies assessed the transmissibility or infectiousness of Omicron reinfections to others. Tan et al. (2022) (preprint) studied reinfection transmissibility among incarcerated adults in the US with data from December 12, 2021 to May 23, 2022.[35] They found reinfection cases may have lower risk of transmitting SARS-CoV-2 to close contacts (22%; 95% CI: 18, 27) than index cases with no previous infection (30%; 95% CI: 26, 34); however, CIs overlapped. This was the case for both vaccinated and unvaccinated subjects. Qassim et al. (2022) investigated the effects of prior infection on infectiousness of Omicron reinfection with data from December 23, 2021 to February 20, 2022 in Qatar (n=156,202).[36] In people with an Omicron reinfection, the mean cycle threshold (Ct) value was 1.30 cycles higher (95% CI: 1.20, 1.39) compared with those without prior infection, indicating potentially lower infectiousness by indirect proxy of lower viral load.

Results Specific to Omicron Sub-lineages

We identified seven studies (including four preprints) that specifically investigated reinfection in relation to Omicron sub-lineages, including BA.1, BA.2, BA.4 and BA.5.[24,32,37-41] Summaries of key findings from each study are described below.

- Andeweg et al. (2022) conducted a two-part test-negative study in the Netherlands examining: 1) protection acquired from vaccination and/or previous infection with any variant against reinfection with Delta versus reinfection with Omicron sub-lineage BA.1, and 2) protection acquired from vaccination and/or previous infection with any variant against reinfection with Omicron sub-lineage BA.1 versus reinfection with sub-lineage BA.2. Data were collected from November 22, 2021 to March 31, 2022 (n = 671,763).[38]

    - Protection provided by any previous SARS-CoV-2 infection alone was much lower against Omicron BA.1 reinfection (relative reduction: 13%; 95% CI: 4, 21) compared to against Delta reinfection (relative reduction: 76%; 95% CI: 73, 70). Protection against reinfection among those with previous infection plus completion of a primary vaccine series (49%; 95% CI: 41, 55), and those with previous infection plus booster doses (68%; 95% CI: 58, 75), was greater than previous infection alone against BA.1 reinfection, but these values remained reduced compared to infection plus vaccination (92%; 95% CI: 87, 95) and infection plus booster doses (99%; 95% CI: 95, 100) against Delta reinfection.

    - In the comparison of risk for reinfection with BA.1 or BA.2 among those with previous infection alone, or with previous infection plus any vaccination status, protection from reinfection was comparable for both Omicron sub-lineages. Previous infection with any variant >7 months ago offered protection of 34% (95% CI: 31, 38) against reinfection with BA.1 and 38% (95% CI: 34, 43) against reinfection with BA.2. Similar to the findings above, a previous infection plus vaccination increased the level of protection. Protection acquired from previous infection plus a primary vaccine series against BA.1 reinfection was 69% (95% CI: 66, 72) and against BA.2 reinfection was 72% (95% CI: 68, 75). Protection provided by previous infection plus booster doses against BA.1 reinfection was 48% (95% CI: 47, 49) and against BA.2 reinfection was 40% (95% CI: 38, 43).

- Bjork et al. (2022) conducted a case-control study with data from December 2021 to March 2022 to compare VE, along with prior infection, against severe disease from the Omicron BA.1 and BA.2 sub-lineages in southern Sweden (n=593 cases; n=5,930 controls).[39] A severe COVID-19 case was defined as hospitalization for at least $\geq$24 hours from 5 days before until 14 days after a positive SARS-CoV-2 test, and requiring oxygen supply or admission to an ICU. Overall, the transition from Omicron BA.1 to BA.2 showed possible decline in protection against severe disease, but CIs were largely overlapping. Persons with 0–1 vaccine dose and no prior infection were the reference group. For people with two vaccine doses and a prior infection, protection from severe reinfection during BA.1 was 91% (95% CI: 57, 98), and during BA.2 was 53% (95% CI: 0, 82). This was similar to those with two vaccine doses and no prior infection, where protection from severe infection during BA.1 was 91% (95% CI: 79, 96), and during BA.2 was 57% (95% CI: 17, 78). For people with at least three doses and a prior infection, protection from severe reinfection during BA.1 was 100% (no CI) and during BA.2 was 88% (95% CI: 64, 96). Similar protection was observed in those with at least three doses and no prior infection.

- Chemaitelly et al. (2022c) estimated the effectiveness of BA.1 infection against reinfection with BA.2 (n = 20,994), and the effectiveness of BA.2 infection against reinfection with BA.1 (n = 110,315) in Qatar from November 1, 2021 to March 21, 2022.[40] The effectiveness of BA.1 infection against reinfection with BA.2 was 94.2% (95% CI: 89.2, 96.9). The effectiveness of BA.2 infection against reinfection with BA.1 was 80.9% (95% CI: 73.1, 86.4). Median follow-up periods ranged from 40–42 days, thereby indicating substantial (but not full) immune protection from BA.1 infection against reinfection with BA.2 and similarly from BA.2 infection against reinfection with BA.1, at least for several weeks after initial infection.

- Carazo et al. (2022a) (preprint) conducted a test-negative case control study among HCW in Quebec with data from March 27 to June 4, 2022.[24] This study compared the likelihood of BA.2 reinfection (positive test ≥30 days after primary infection) among HCW with 0–3 vaccine doses, versus infection-naïve, unvaccinated HCW. Among 37,732 BA.2 cases, 2,521 (6.7%) and 659 (1.7%) were reinfections following pre-Omicron or BA.1 primary infections, respectively. Among 73,507 controls, 7,360 (10.0%) and 12,315 (16.8%) had a pre-Omicron or BA.1 primary infection, respectively. Pre-Omicron primary infection was associated with 38% (95%CI: 19, 53) reduction in BA.2 reinfection risk, with even higher protection among those with one (56%), two (69%) or three (70%) vaccine doses. Omicron BA.1 primary infection was associated with greater protection against BA.2 reinfection (72%; 95% CI: 65, 78), and was higher in those with two doses (96%; 95% CI: 95, 96) but not significantly improved with a third dose (96%; 95% CI: 95, 97). Protection from an Omicron BA.1 primary infection plus two or three vaccine doses lasted for five months post-infection. This study suggests that individuals who received two doses of vaccine and experienced BA.1 infection were protected for a prolonged period against BA.2 reinfection.

- Nevejan et al. (2022) (preprint) conducted a cohort study in Belgium to estimate the incidence of early reinfections (<60 days from previous infection) with Omicron BA.1 after Delta infection (December 1, 2021 to February 7, 2022), and with Omicron BA.2 after BA.1 infections (January 1 to March 10, 2022).[32] From 56,381 patients tested from December 2021 to February 2022, 91 (0.16%) were found to have a second infection, and based on the timeline was presumed to be BA.1 reinfection after a Delta primary infection. From 48,929 patients tested between January to March, five (0.01%) were found to have a second infection presumed to be a BA.2 reinfection after an initial BA.1 infection. Early reinfections were most frequently observed among young, unvaccinated patients (<12 years old). In all age groups, patients with early reinfection had a lower vaccination rate compared to the corresponding age groups in the general population. Boosted patients had the lowest risk of early SARS-CoV-2 reinfection. This study illustrates that early reinfection may rarely occur within 60 days of a primary infection especially in young, unvaccinated individuals, including children.

- Stegger et al. (2022) (preprint) aimed to examine BA.1 infections followed by BA.2 reinfections using whole genome sequencing (WGS) on select samples from SARS-CoV-2 infections detected in Denmark from November 22, 2021 to February 15, 2022.[41] Data from individuals with two positive samples more than 20 and less than 60 days apart were selected for this study. From a total of 187 reinfections that were eligible for inclusion and successfully sequenced, 47 (18%) were BA.2 reinfections occurring shortly after BA.1 infections. These 47 reinfections were mostly in young (including children; median age: 15; range: 0-39), unvaccinated (89%) individuals who experienced mild disease (i.e., no hospitalization or death). Analysis of viral load found that Ct values for BA.2 (median Ct: 28.5) reinfection were higher (i.e., relatively lower viral load) when compared to the initial BA.1 infections (median Ct: 26.8; p = 0.006).

- Altarawneh et al. (2022) (preprint) conducted a test-negative case-control study that investigated the protection provided by prior SARS-CoV-2 infection against reinfection with the Omicron BA.4 or BA.5 sub-lineages in Qatar.[37] Effectiveness of a pre-Omicron infection against symptomatic BA.4 or BA.5 reinfection was 15.1% (95% CI: -47.1, 50.9) and against any BA.4 or BA.5 reinfection was 28.3% (95% CI: 11.4, 41.9%). Effectiveness of an Omicron infection against symptomatic BA.4 or BA.5 reinfection was 76.1% (95% CI: 54.9-87.3%), and against any BA.4 or BA.5 reinfection was 79.7% (95% CI: 74.3-83.9%). Sensitivity analyses accounting for vaccination status found the same results.

Discussion and Conclusions

This Evidence Brief aimed to provide an overview of the currently available evidence related to SARS-CoV-2 reinfection during the Omicron-dominant period. Based on a total of 38 studies identified from our literature search (searched to August 18, 2022), evidence consistently indicated reinfections are more frequently reported since the emergence of Omicron compared to prior variants. The majority of evidence indicates that disease severity of reinfections during the Omicron period do not appear to be increased relative to primary infections or reinfections with other variants; however, there was little evidence available related to longer-term outcomes of Omicron reinfections. VE against any Omicron reinfection may be lower compared to reinfection with previous variants, but VE against severe presentations of Omicron reinfection appears to remain high. Other than being unvaccinated, risk factors for Omicron reinfection include increased time since previous infection and younger age (including children). There is some evidence to suggest female sex, being a HCW, or being a resident of LTC may increase risk of reinfection. Emerging evidence suggests the transmissibility of Omicron reinfections may be reduced relative to primary infections.

The findings above should be interpreted along with the understanding of several limitations. Twelve of 38 included studies (32%) are non-peer-reviewed preprints. Due to the rapid rate of research production during the COVID-19 pandemic there may be additional relevant preprints or studies available since the search date for this Evidence Brief. We did not include non-English studies and we possibly missed additional articles of interest in other languages. We did not check for overlap between the included primary observational studies and the one included systematic review. As specified in the previous section, “Results Specific Omicron Sub-lineages”, few studies addressed specific Omicron sub-lineages which are currently circulating in Ontario (i.e., BA.4, BA.5). There was substantial heterogeneity across included studies in terms of: definitions and testing parameters for reinfection, time periods considered to be Omicron period in different jurisdictions (e.g., beginning in November-December 2021 or results limited to January 2022 onward); vaccines administered in different jurisdictions; reporting of participants’ vaccination status (e.g., by dose number; stating partially, fully or boosted vaccination); and outcome measures. Any statistical pooling of results was out of scope for this Evidence Brief, therefore all synthesis is descriptive only. Overall findings may change as newer high-quality peer-reviewed research becomes available.

Additional Considerations:

- The Omicron period, beyond any unique characteristics of this VOC or its sub-lineages compared to previous ones, also represents the third year of the pandemic when people are more likely to have had a primary infection, and there are generally greater opportunities for people to have exposure risks in the community as public health measures are being lifted, which may impact the risk for reinfection.

- Observational studies cannot account for all possible confounding elements, the studies included in this Evidence Brief did not consistently report participant characteristics (e.g., age, sex/gender, vaccine status), and there are a number of additional influencing factors that may intersect and impact risk factors related to reinfection. These may include testing behaviour, occupational or residential risk factors outside of healthcare or LTC (e.g., multi-residential living, safety and distancing measures in workplaces and schools), attitude towards the COVID-19 pandemic, and health seeking or risk behaviour in different demographics.

- Across included studies, there was no consistent definition for reinfection. According to the European Centre for Disease Control (ECDC),[42] SARS-CoV-2 reinfection is defined as positive PCR or rapid antigen test (RAT) sample ≥60 days after the initial positive test result, whereas the US Centers for Disease Control and Prevention (CDC)[43] and the Public Health Agency of Canada (PHAC)[44] have defined reinfection as any positive RT-PCR test ≥90 days after the initial confirmed SARS-CoV-2 positive test result. Communicable Diseases Network Australia (CDNA) has defined reinfection as positive test result (PCR or RAT) more than 28 days after release from isolation (4 weeks after recovering from COVID-19).[45]

- Testing processes, availability, equity and other factors also impact the detection of reinfections, and it is likely that the available evidence examined only a portion of a potentially larger number of reinfection cases. This may also be applicable in Ontario where accurate identification of reinfections might be limited by testing eligibility criteria, challenges in obtaining individually targeted WGS results for previous specimens, limited information on cases given case management guidelines, and the use of RATs not being reportable to public health.[46]

- Future research using longitudinal, standardized, case-control and large prospective cohort studies will be useful to characterize and understand the true prevalence of reinfections. Considerations may include longer-term outcomes for reinfection cases, the impact of reinfections on post-acute COVID-19 syndrome (i.e., “long COVID”), the incidence and severity of reinfections amongst pediatric populations, the impact of reinfections on mental health outcomes, the impact of multiple reinfections, and more information on the impact of reinfection with current and future Omicron sub-lineages.

Implications for Practice

- The number of reinfections increased during the Omicron-dominant period and given the emergence of multiple diverse Omicron sub-lineages, there is a potentially increased risk of reinfection over time. However, public health measures remain useful in limiting SARS-CoV-2 transmission.

- Measures that have been shown to limit transmission throughout the pandemic remain applicable to the prevention of reinfections: getting vaccinated, practicing respiratory etiquette, hand hygiene, staying home when sick, practicing social distancing and avoiding crowded spaces, improving ventilation and air quality in indoor spaces, using outdoor spaces where possible, and wearing a well-fitted mask indoors in close contact settings (e.g., public transit). Messaging to the general public should include education that, while presently rarely reported, reinfections can also occur less than 90 days from a previous SARS-CoV-2 infection and it remains important to stay home when sick, regardless of time since their last infection.

- The currently available evidence indicates reinfection with the Omicron VOC is not generally associated with increased acute disease severity relative to primary infections or reinfections with non-Omicron lineages. However, there is limited evidence related to the long-term impacts of multiple SARS-CoV-2 infections and further monitoring and research is needed to understand the potential health burden of multiple infections.

- While there is evidence to show some protection is provided by previous SARS-CoV-2 infection, vaccination is the safest and most effective option to enhance one's protection from SARS-CoV-2 infection or reinfection, in the absence of data on the longer term outcomes of reinfection including post-acute COVID-19 syndrome. Vaccination, especially with booster doses, remains very effective for the prevention of severe Omicron reinfections, even in those who had prior infection. Ongoing communication and education is warranted to engage the public on the benefits of COVID-19 vaccinations, and ensure vaccines are equitably accessible to all eligible populations.

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Appendix A: Study Characteristics

Table 1: Characteristics of Included Studies (n=38)[1]

Author	Country	Study Period	Study Design	Minimum Days Between Infections	Total Sample Size	Population	Female (%)	Age	Vaccine Status
Al-Aly[5] (preprint)	US	Mar 2020–Apr 2022	Cohort	NR	5,693,208	Veterans	10%	NR	0 dose: 83.17% 1 dose: 4.76% ≥2 doses: 12.07%
Altarawneh[37] (preprint)	Qatar	May 7–July 4, 2022	Test-negative	90	>33,000	General public	43.5–57.5%	Median: 29–36	NR
Andeweg[38]	Netherlands	Nov 22, 2021–Mar 31, 2022	Test-negative	30	671,763	General public	54%	Range: <11 to >60; Age 30–59 comprised 41.7%–49.3% of all participants	Unvaccinated: 39.9% Primary series: 37.7% Booster: 22.4%

[1] NR: Not Reported; Note: When characteristics were not listed for total population, data was summed from studies' tables if possible.

Author	Country	Study Period	Study Design	Minimum Days Between Infections	Total Sample Size	Population	Female (%)	Age	Vaccine Status
Bastard[6]	France	Mar 2, 2021–Feb 20, 2022	Retrospective cohort	60	18,661,139	General public	55.6%	<18: 23.6% 18–40: 51.1% 41–60: 20% 61–80: 3.8% >80: 1.4%	NR
Bjork[39]	Sweden	Dec 202–Mar 2022	Case-control	90	1,384,531	General public	BA.1 Cases: 37% BA.2 Cases: 50%	0-65+	BA.1 Cases: 0 dose: 54% 1 dose: 3% 2 doses: 18% 3 doses: 25% BA.2 Cases: 0 doses: 27% 1 dose: 4% 2 doses: 20% 3 doses: 49%

Author	Country	Study Period	Study Design	Minimum Days Between Infections	Total Sample Size	Population	Female (%)	Age	Vaccine Status
Carazo(a)[24] (preprint)	Canada	Mar 27–Jun 4, 2022	Test-negative	30	111,239	HCW	82.6%	Range: 18–59	Prior infection cases: 2 dose: 3.1% 3 dose: 3.8% Reinfection after pre-Omicron infection cases: 0 dose: 4.3% 2 dose: 32.3% 3 dose: 40.8% Reinfection after Omicron BA.1 cases: 0 dose: 19% 2 dose: 39.8% 3 dose: 36.9%

Author	Country	Study Period	Study Design	Minimum Days Between Infections	Total Sample Size	Population	Female (%)	Age	Vaccine Status
Carazo(b)[25] (preprint)	Canada	Dec 26, 2021–Mar 12, 2022	Test-negative	≥ 90	699,439	General public	61.9–70.3%	Range: 12 to ≥70	All cases: Not vaccinated, no previous infection: 7.9% Not vaccinated, previous infection: 0.4% 2 doses, no previous infection: 63.5% ≥1 dose, previous infection: 4.3%
Cerqueira-Silva[7]	Brazil	Jan 1 – Mar 22, 2022	Test-negative	90	899,050	General public	56.9%	Median: 37 Proportion: 18–64: 94% ≥65: 6%	Unvaccinated: 32.8%

Author	Country	Study Period	Study Design	Minimum Days Between Infections	Total Sample Size	Population	Female (%)	Age	Vaccine Status
Chemaitelly (a)[8] (preprint)	Qatar	1: Feb 28, 2020–Mar 6, 2022 2: Jan 5, 2021–Mar 6, 2022	Two matched (vaccinated to unvaccinated) retrospective cohorts	90	1: 188,874 2: 118,650	General public	1: 31.9% 2: 30.9%	Median (IQR) 1: 33 (26–40) 2: 33 (28–40)	Unvaccinated: 50%
Chemaitelly (b)[30] (preprint)	Qatar	Feb 28, 2020–Jun 5, 2022	Three matched (previous infection to no previous infection) retrospective cohorts	90	1: 581,276 2: 240,966 3: 814,428	General public	1: 26.8% 2: 32.9% 3: 31.1%	Median (IQR) 1: 32 (24–40) 2: 27 (9–36) 3: 30 (18–38)	Unvaccinated: 100%
Chemaitelly (c)[40]	Qatar	Nov 1, 2021–Mar 21, 2022	Two matched (BA.1/BA.2 to uninfected) retrospective cohort studies	35	1: 41,988 2: 220,630	General public	1: 48.8% 2: 41.2%	Median (IQR) 1: 33 (25–42) 2: 34 (26–43)	NR
Cocchio[9]	Italy	Nov 1, 2021–Jan 25, 2022	Retrospective cohort	90	218,698	General public	NR	NR	0 dose: 159,282 3 doses: 59,416

Author	Country	Study Period	Study Design	Minimum Days Between Infections	Total Sample Size	Population	Female (%)	Age	Vaccine Status
Davies[10] (preprint)	South Africa	Apr 19, 2020–Dec 11, 2021	Cohort	90	16,753	General public	Omicronwave: 66.2%	Omicron wave: 20–39: 64.5% 40–49: 16.5% 50–59: 11.1% 60–69: 5.2% ≥70: 2.7%	Omicron wave: Partial vaccination: 5.2% Full vaccination: 37.7%
Eythorsson[11]	Iceland	Dec 1, 2021–Feb 12, 2022	Population-based cohort	60	11,536	General population	49%	Mean: 34 SD: 19 Range: 0–102	≤1 dose: 74.5% ≥2 doses: 25.5%
Flacco(a)[12]	NA	Search up to Jun 30, 2022	Systematic review and meta-analysis	45	15,034,624 (from 91 included studies)	General public	79%	Mean age from primary studies ranged from 15–87	NR
Flacco(b)[13]	Italy	Mar 2, 2020–Jan 4, 2022	Retrospective cohort	45	119,266	General public	51%	Mean: 41.6 SD: 21.9	0 dose: 25.7% 1 dose: 30.8% ≥2 doses: 43.5%

Author	Country	Study Period	Study Design	Minimum Days Between Infections	Total Sample Size	Population	Female (%)	Age	Vaccine Status
Jang[14]	South Korea	Jan 2020–Apr 2022	Retrospective cohort	45	16,130,855	General public	53%	0–17: 23.6% 18–29: 16.6% 39–30: 14.8% 40–49: 15.4% 50–59: 12.2% 60–74: 12.7% >74: 4.6%	0 dose: 34.9% 1 dose: 2.2% 2 doses: 33.2% 3 doses: 29.4% 4 doses: 0.3%
Krutikov[15]	UK	Sep 1, 2021–Feb 2, 2022	Prospective cohort	28	2,264	LTC residents	69%	Mean: 84.5 IQR: 77.9–90	0 dose: 13.3% ≥1 dose: 86.7% Booster: 64.8%

Author	Country	Study Period	Study Design	Minimum Days Between Infections	Total Sample Size	Population	Female (%)	Age	Vaccine Status
Malhotra[16]	India	Dec 1, 2021-Feb 25, 2022	Retrospective cohort	90	11,474	HCW	34.4%	Mean: 36.2 SD: 10.7	Unvaccinated: 8.4% Partially vaccinated: 8.6% Fully vaccinated: 83.0%
Medić[17]	Serbia	Mar 6, 2020–Jan 31, 2022	Population-level observational	90	251,104	General public	53%	Mean: 45.91 SD: 18.58	Unvaccinated: 84.93% Partially vaccinated: 5.24% Fully vaccinated: 8.7% Boosted: 1.13%

Author	Country	Study Period	Study Design	Minimum Days Between Infections	Total Sample Size	Population	Female (%)	Age	Vaccine Status
Michlmayr[31]	Denmark	Feb 1, 2020–Mar 10, 2022	Nationwide cohort	90	4,234,548	General public	NR	2–17: 20.1% 18–29: 18.8% 30–64: 47.8% >65: 13.3%	Unvaccinated: 100%
Monge[26]	Spain	Jan 3, 2022-Feb 6, 2022	Matched cohort (1 dose to 2 doses)	90	778,042	General public	49.7%	Median: 44 Range: 18-64	1 dose: 50% 2 doses: 50%
Morris[18] (preprint)	US	Mar 2020–Mar 2022	Retrospective analysis	90	755	General public	NR	Median (re-infected patients): 35	0 doses: 12 Vaccinated: 32
Neilsen[27] (preprint)	Denmark	Jan 1, 2020-Jan 31, 2022	Cohort	90	245,530	General public	49%	Median: 25.4 IQR: 15.4–38.1	Fully vaccinated: 64.6%

Author	Country	Study Period	Study Design	Minimum Days Between Infections	Total Sample Size	Population	Female (%)	Age	Vaccine Status
Nevejan[32] (preprint)	Belgium	1: Dec. 1, 2021-Feb 7, 2022 2: Jan 1, 2022-March 10, 2022	Cohort	< 60	105,660	General public	NR	Range: 4–64	NR
Nunes[19]	South Africa	Nov 24–Dec 31, 2021	Cohort	NR	433	HCW	82%	Mean: 37.4–38	Unvaccinated: 16.7% Fully vaccinated: 68.7% Booster: 11.8%
Ozudogru[20]	Ireland	Apr 22, 2021-Jan 26, 2022	Retrospective	90	27,487	General public	53.5%	Mean (males): 38.9 ± 15.7 Mean (females): 36.9 ± 15.5	NR

Author	Country	Study Period	Study Design	Minimum Days Between Infections	Total Sample Size	Population	Female (%)	Age	Vaccine Status
Plumb[28]	US	Jun 2021–Feb 2022	Test-negative design	90	11,283	18+ adults	56.2%	NR	0 doses: 52.1% 1 dose (mRNA): 5.1% 2 doses (mRNA): 31.3% Booster (mRNA): 11.5%
Pulliam[21]	South Africa	Mar 4, 2020–Jan 30, 2022	Population-based cohort	90	2,942,248	General public	NR	NR	NR
Qassim[36]	Qatar	Dec 23, 2021–Feb 20, 2022	Population-based cohort	90	156,202	General public	41.2%	Median: 33 IQR: 25–42	0 doses: 28.9% 1 dose: 0.7% 2 doses: 60.1% 3 doses: 10.3%

Author	Country	Study Period	Study Design	Minimum Days Between Infections	Total Sample Size	Population	Female (%)	Age	Vaccine Status
Racine[23]	Canada	Aug 17 2020–Mar 1, 2022	Observational prospective cohort	90	569	HCW	83%	Median: 42 Range: 18–75	Unvaccinated: 100%
Rothberg[33]	US	Mar 9, 2020–Mar 1, 2022	Retrospective cohort	90	635,341	General public	54%	Mean: 47.3 SD: 24.2	Omicron infected: Unvaccinated: 37.7% Fully vaccinated: 31.8% Boosted: 27.4%
Sacco[22]	Italy	Aug 24, 2021–Mar 6, 2022	Cohort	90	8,413,857	General public	54.7%	Reinfected: 0–19: 20.6% 20–39: 32.9% 40–59: 34.5% 60–79: 8.5% ≥80: 3.5%	Reinfected: Unvaccinated: 36.1% At least 1 dose for ≤ 120 days: 32.6% At least 1 dose for > 120 days: 31.2%

Author	Country	Study Period	Study Design	Minimum Days Between Infections	Total Sample Size	Population	Female (%)	Age	Vaccine Status
Shrestha[29]	US	Nov 26, 2021–Jan 28, 2022	Retrospective cohort	90	39,766	HCW	>66%	With previous infection Reported means of sub-groups: 41–45 SD: 12–	Fully vaccinated: 34.2% Boosted: 65.8%
Šmíd[34]	Czech Republic	Dec 7, 2021-Feb 13, 2022	Population-based cohort	60	NR	General public	NR	NR	NR
Stegger[41] (preprint)	Denmark	Nov 22, 2021-Feb 15, 2022	Population-based cohort	20	1.8 million	General public	NR	Median: 15 Range: 0-39	0 dose: 89% 1 dose: 4% 2 dose: 6%
Tan[35] (preprint)	US	Dec 12, 2021–May 23, 2022	Observational	90	22,334	Incarcerated adults	3%	Mean: 39 SD: 11.2	0 dose: 22% ≥1 dose: 78%

Author	Country	Study Period	Study Design	Minimum Days Between Infections	Total Sample Size	Population	Female (%)	Age	Vaccine Status
Veterans Affairs COVID-19 Observational Collaboratory [4] (preprint)	US	Mar 1, 2020–Jan 21, 2022	Retrospective cohort	90	308,051	Veterans	NR	NR	NR

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