Is there protective immunity after an Omicron infection?

Source: Emerging Science Group of the Public Health Agency of Canada. Evidence Brief on Protective Immunity Post Infection with Omicron. July 26, 2022. Full report available from: ocsoevidence-bcscdonneesprobantes@phac-aspc.gc.ca

Background: Although the literature is well-established on protection and waning of immunity following infection with previous SARS-CoV-2 strains and COVID-19 vaccination, little is known about protective immunity following Omicron infection. Assessment of this must also consider key Omicron sublineages (BA.1, BA.2, BA.4 and BA.5), as each sublineage has a unique complement of mutations. A review of existing evidence was conducted to answer a series of questions. When there is a history of Omicron infection with one strain what is the risk of reinfection with the **same** Omicron strain or reinfection with a **different** Omicron strain? How does the risk of reinfection vary by the history of vaccination and/or infection prior to the first Omicron infection? What are the trends in *in vitro* immunogenicity studies, measuring neutralizing antibodies and T and B cell activity, after an Omicron infection?

Methods: Targeted keyword searching was conducted within twenty databases to identify all relevant studies on COVID-19. The database was then filtered for articles on Omicron prior to use of the following search terms to identify potentially relevant citations: reinfect*, recurrent, re-positive, longitudinal, immun*, neutraliz* and neutralis*. The search netted 1,721 citations up to July 26, 2022. Real-world data on reinfections post Omicron infection and immunogenicity studies on Omicron more than 14 days post diagnosis were included. Animal studies and immunogenicity measurements fewer than 14 days after diagnosis with COVID-19 were excluded. Data were extracted from relevant studies into evidence tables to address each of the questions and then summarized. For this article, only the observational studies were referenced.

Results: Twenty-three studies were identified, including six observational studies and 17 *in vitro* studies.

- The six observational studies included three test negative case-control studies and three retrospective cohort studies. Of those, none was peer-reviewed: five were pre-prints and one was a Letter to the Editor.
- The 17 *in vitro* studies examined immune responses 0.5–3 months after an Omicron infection, which corresponds to the peak immune response time.

Previous infection with one Omicron strain was associated with significant protection against reinfection with other Omicron strains, but this varied by how different the strains were from each other and by vaccine status.

- In all studies, prior infection with the BA.1 Omicron strain offered more than 95% protection against reinfection with another BA.1 Omicron strain and more than 85% protection against reinfection with a BA.2 Omicron strain (1–6).
- Prior infection with a BA.1 or BA.2 Omicron infection offered 76% protection against a BA.4/BA.5 reinfection (5).

Protective immunity from reinfection is greater when there is a history of COVID-19 vaccination rather than a history of a previous infection prior to the initial Omicron infection.

- Immunity from vaccination prior to the first Omicron infection reduced the risk of Omicron reinfection by 96% (6).
- Immunity from previous infection prior to the first Omicron infection reduced the risk of Omicron reinfection by 72% (2–4).
- One Canadian study found the risk of reinfection with Omicron BA.2 following a BA.1 infection was the same for those who had two or three mRNA COVID-19 vaccinations (4); however, there were a disproportionate number of reinfections among individuals who were unvaccinated (3,4), of which a disproportionate number were younger than 20 years old (2).

Trends in immunogenicity studies

Studies on immune markers, such as neutralizing antibodies and T and B cell activity, do not directly equate with protection but they do indicate the immune system is primed to respond to a pathogen. Immunogenicity studies were consistent with observational studies.

- Infection with Omicron BA.1 neutralized subsequent BA.1 infections most efficiently, followed by BA.2, BA.2.13 and BA.2.12.1.
- Omicron BA.4 and/or BA.5 were most resistant to neutralization by both BA.1 and BA.2 convalescent sera (i.e. samples from people recovered from COVID-19).
- Convalescent sera from people who were infected with the Omicron strain and who were also vaccinated had higher neutralizing antibody responses against Omicron sublineages compared to convalescent sera from people who were infected with the Omicron strain and who were unvaccinated.
- The level of B cell responses significantly increased when there was a history of two or three-dose vaccination as well as an Omicron infection, compared to those with two or three-dose vaccination who had not been infected with the Omicron strain.

Conclusion: After an initial Omicron infection, the level of protective immunity against an Omicron reinfection varied from 72%–96%, depending on how closely related the two Omicron strains were and the previous vaccination history. Observational evidence was limited by the small number of studies, the lack of peer review, short follow-up times and the risk of bias inherent to retrospective studies. The findings from *in vitro* immunogenicity studies findings were consistent with the observational studies; however, they were limited in that they were short-term and could only provide indirect evidence of protection. Peer-reviewed prospective studies and longer-term immunogenicity studies are needed.

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