Immunity after SARS-CoV-2 infection

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Definitions

- **Infection-induced immunity** is defined as the immune protection in an unvaccinated individual after one or more SARS-CoV-2 infections. Also called “natural immunity”.
- **Vaccine-induced immunity** is defined as the immune protection in an individual who has not been previously infected with SARS-CoV-2 but has completed a primary series (currently one or two doses of a COVID-19 vaccine depending on the product) of any COVID-19 vaccine, or has also received a booster vaccination.
- **Hybrid immunity** is defined as the immune protection in individuals who have had one or more doses of a COVID-19 vaccine and experienced at least one SARS-CoV-2 infection before or after the vaccination.

https://www.who.int/news/item/01-06-2022-interim-statement-on-hybrid-immunity-and-increasing-population-seroprevalence-rates

Measuring immunity

- Exposure to SARS-CoV-2 through infection or vaccination triggers the production of antibodies that can be readily measured in the blood (referred to as ‘seroconversion’).
- Inferring the level of population-level protection against infection and/or severe outcomes from seroprevalence estimates is challenging.
- Both infection- and vaccine-induced immunity confer high protection against severe disease, with hybrid immunity being superior,

Global Seroprevalence

According to the most recent estimates by the WHO UNITY Studies Collaborator Group shared with SAGE, the percentage of seropositive individuals increased in all regions during 2021, globally rising from 16% in February to 67% by October 2021.

In most low- and middle-income countries, the rise in seroprevalence in this period has been driven by an increase in infections rather than vaccination, given the very low vaccination rates through the end of 2021.

Global epidemiology of SARS-CoV-2 infection: a systematic review and meta-analysis of standardized population-based seroprevalence studies, Jan 2020-Dec 2021. 2021.12.14.21267791 (2022)

Immunity after infection

- Protective immunity against infection and mild disease has been observed to persist for 10-12 months post-infection for pre-Omicron VOC.
- SARS-CoV-2 infection has also been found to induce durable cell-mediated immunity for at least 6-8 months.
- Infection-induced immunity confers significantly less protection against Omicron than against non-Omicron VOC six or more months after a previous infection.
- Infection-induced protective immunity against disease and severe outcomes wanes faster against VOCs, especially against Omicron.

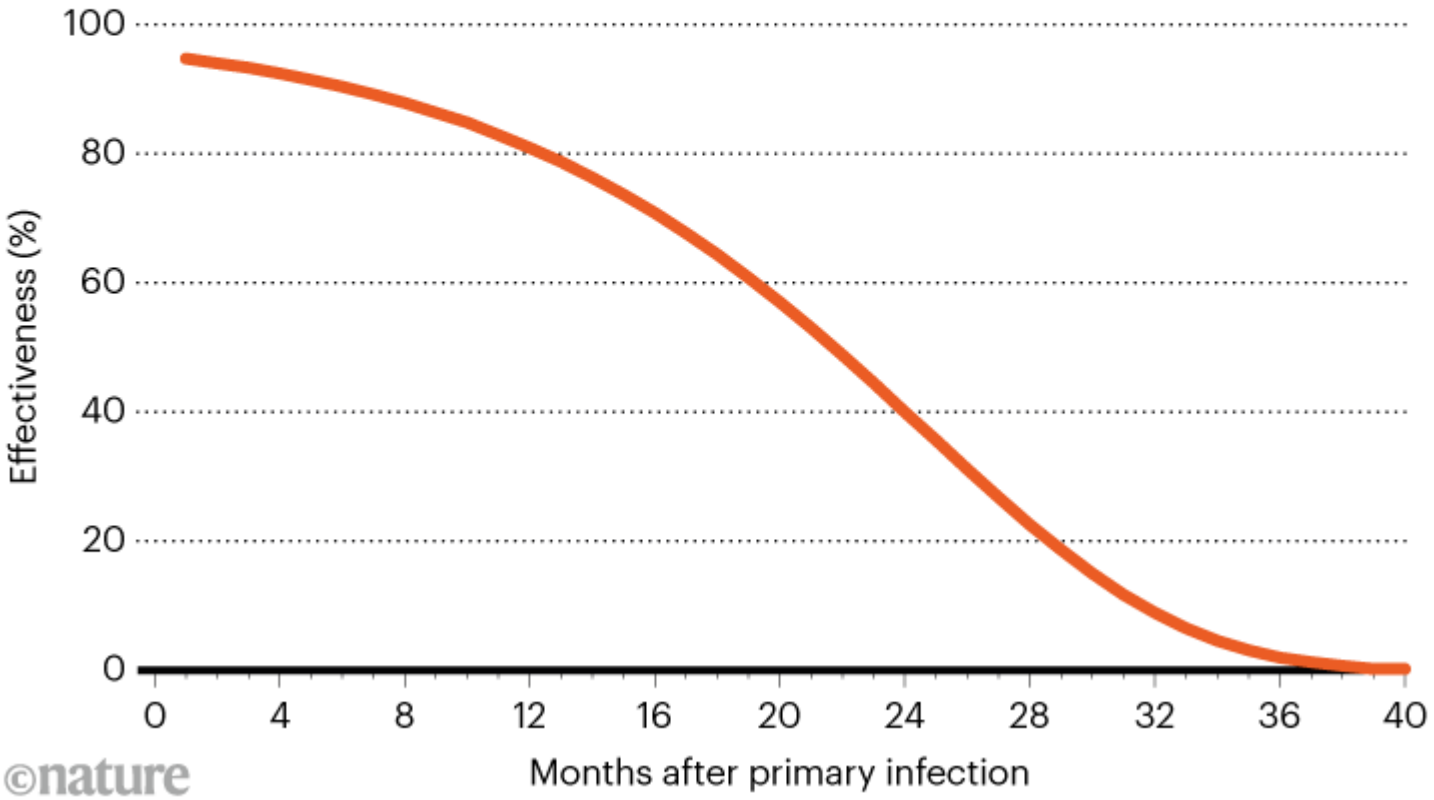
Protection against infection and disease from primary infection

- A study from Qatar suggests that effectiveness of pre-Omicron primary infection against pre-Omicron reinfection was 85.5% (95% CI: 84.8 – 86.2%).
- Protection waned over time and was < 10% by the 32nd month after infection.
- Effectiveness of pre-Omicron primary infection against Omicron reinfection was 38.1% (95% CI: 36.3 – 39.8%) and declined over time to < 10% by month 15.
- Effectiveness of primary infection against severe, critical or fatal COVID-19 reinfection was 97.3% (95% CI: 94.9 – 98.6%) irrespective of the variant of primary infection or reinfection.

https://www.medrxiv.org/content/10.1101/2022.07.06.22277306v1.full.pdf

IMMUNITY FADES AWAY

Seven months after infection with a pre-Omicron variant of SARS-CoV-2, natural immunity prevents reinfection by another pre-Omicron variant with an effectiveness of more than 90% — but this falls to less than 10% after another 25 months, modelling says.



https://www.nature.com/articles/d41586-022-01914-6#ref-CR2

Biological, epidemiological, and clinical evidence that previous COVID-19 infection reduces the risk of reinfection (a review of studies through Sept 28, 2021)

Biological studies

- Dan et al (2021):[1] about 95% of participants tested retained immune memory at about 6 months after having COVID-19; more than 90% of participants had $CD4^+$ T-cell memory at 1 month and 6–8 months after having COVID-19
- Wang et al (2021):[2] participants with a previous SARS-CoV-2 infection with an ancestral variant produce antibodies that cross-neutralise emerging variants of concern with high potency

Lancet Inf Dis Nov 8, 2001

Biological, epidemiological, and clinical evidence that previous COVID-19 infection reduces the risk of reinfection (a review of studies through Sept 28, 2021)

Epidemiological studies

- Hansen et al (2021):[3] in a population-level observational study, people who had had COVID-19 previously were around 80·5% protected against reinfection
- Pilz et al (2021):[4] in a retrospective observational study using national Austrian SARS-CoV-2 infection data, people who had had COVID-19 previously were around 91% protected against reinfection
- Sheehan et al (2021):[5] in a retrospective cohort study in the USA, people who had had COVID-19 previously were 81·8% protected against reinfection
- Shrestha et al (2021):[6] in a retrospective cohort study in the USA, people who had had COVID-19 previously were 100% protected against reinfection
- Gazit et al (2021):[7] in a retrospective observational study in Israel, SARS-CoV-2-naive vaccinees had a 13·06-times increased risk for breakthrough infection with the delta (B.1.617.2) variant compared with those who had had COVID-19 previously; evidence of waning natural immunity was also shown
- Kojima et al (2021):[8] in a retrospective observational cohort of laboratory staff routinely screened for SARS-CoV-2, people who had had COVID-19 previously were 100% protected against reinfection

Lancet Inf Dis Nov 8, 2001

Biological, epidemiological, and clinical evidence that previous COVID-19 infection reduces the risk of reinfection (a review of studies through Sept 28, 2021)

Clinical studies

- Hall et al (2021):[9] in a large, multicentre, prospective cohort study, having had COVID-19 previously was associated with an 84% decreased risk of infection
- Letizia et al (2021):[10] in a prospective cohort of US Marines, seropositive young adults were 82% protected against reinfection

Lancet Inf Dis Nov 8, 2001

Evidence Brief on Protective Immunity Post Infection with Omicron

- Omicron infection boosted correlates of immunity against all previous variants for those that had prior immunity (vaccination and/or infection), whereas those with no immunity prior to Omicron infection had limited cross protection against other variants.
- Short-term reinfections (20-60 days after initial Omicron infection) post Omicron infection can occur, however, the risk is low against reinfection with the homologous strain (i.e., BA.1 to BA.1 reinfection, >95%).
- There is slightly less robust protection for a heterologous Omicron strain (i.e., BA.1 to BA.2 reinfection >85%), but still higher compared to people not infected with Omicron.
- Protective immunity of a prior Omicron infection (BA.1 or BA.2) against BA.4/BA.5 reinfection is robust but slightly lower (76%) than for BA.1/BA.2 reinfections (>86%) for those with two doses-and three doses (94% vs. 96%).

https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/canadas-reponse/summaries-recent-evidence/protective-immunity-post-infection-omicron.html

Immunity after vaccination

- Vaccine-induced immunity following a primary vaccine series is modest against infection due to Omicron in the months after vaccination, and wanes significantly over time.
- Vaccine-induced immunity against Omicron-related mild symptomatic disease, asymptomatic infection, and viral shedding is also modest and short-lived even following a booster dose.
- Vaccines provide higher levels of protection than SARS-CoV-2 infection against severe disease outcomes, with modest waning in the 6 months following completion of primary vaccine series.
- Vaccine-induced protection against symptomatic disease, including severe disease, is enhanced by booster doses.

Immunity after infection + vaccination (hybrid immunity)

- Hybrid immunity against infection and mild symptomatic disease is similar, or modestly better than that by infection-induced or vaccine-induced immunity alone.
- Hybrid immunity offers superior protection against severe outcomes due to COVID-19 compared to infection-induced or vaccine-induced immunity alone.
- The duration of protection provided by hybrid immunity has not yet been determined, particularly that induced by Omicron infections.

PNAS RESEARCH ARTICLE | MEDICAL SCIENCES OPEN ACCESS

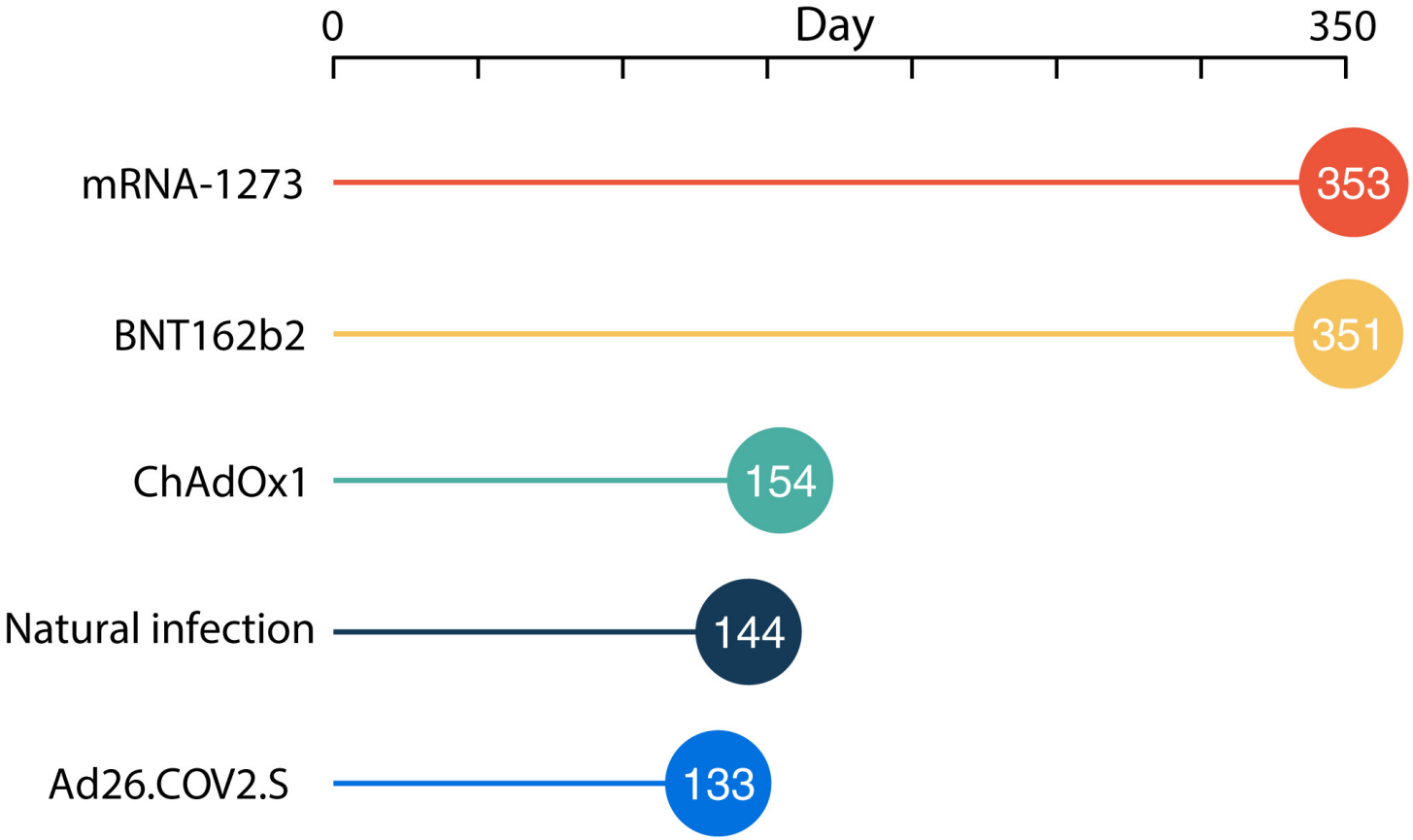
The durability of natural infection and vaccine-induced immunity against future infection by SARS-CoV-2

Jeffrey P. Townsend[a,b,c,d,1], Hayley B. Hassler[a], Pratha Sah[e,f], Alison P. Galvani[b,e,f], and Alex Dornburg[g]

Edited by David Hillis, The University of Texas at Austin, Austin, TX; received March 11, 2022; accepted May 31, 2022

Peak antibody levels elicited by messenger RNA (mRNA) vaccines exceeded that of natural infection and are expected to typically yield more durable protection against breakthrough infections (median 29.6 months) than natural infection (median 21.5 months).

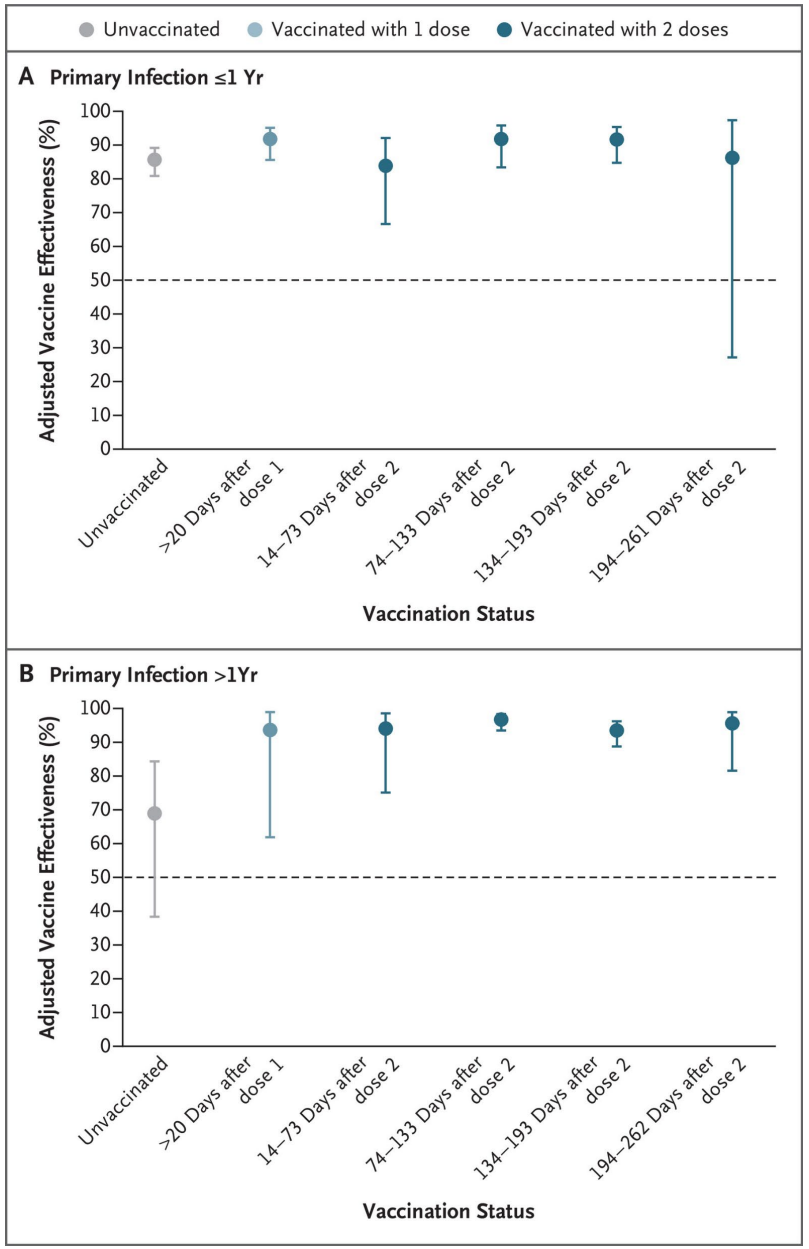
Viral vector vaccines exhibit similar peak anti-S IgG antibody responses to that from natural infection and are projected to yield lower, shorter-term protection against breakthrough infection (median 20.5 to 22.4 months).



Hybrid immunity protection

- Effectiveness of previous infection alone against symptomatic BA.2 infection was 46.1% (95% CI: 39.5 to 51.9).
- Effectiveness of vaccination with two doses of BNT162b2 and no previous infection was negligible.
- Effectiveness of three doses of BNT162b2 and no previous infection was 52.2% (95% CI: 48.1 to 55.9).
- Effectiveness of previous infection and two doses of BNT162b2 was 55.1% (95% CI: 50.9 to 58.9).
- Effectiveness of previous infection and three doses of BNT162b2 was 77.3% (95% CI: 72.4 to 81.4).
- Previous infection alone, BNT162b2 vaccination alone, and hybrid immunity all showed strong effectiveness (>70%) against severe, critical, or fatal Covid-19 due to BA.2 infection.
- Similar results were observed in analyses of effectiveness against BA.1 infection and of vaccination with mRNA-1273.

NEJM 2022; 387: 21 – 34.



Protection against Reinfection with SARS-CoV-2 up to 18 Months after the Primary Infection.

- Two doses of BNT162b2 vaccine were associated with high short-term protection against SARS-CoV-2 infection.
- Protection waned considerably after 6 months.
- Infection-acquired immunity boosted with vaccination remained high more than 1 year after infection.

NEJM 2022; 386: 1207 – 1220.

Conclusions

- Current evidence suggests that most individuals develop strong protective immune responses following infection with SARS-CoV-2.
- Vaccination against COVID-19 as well as immunity after infection reduces the risk of severe morbidity and curtails the burden on health systems by protecting against hospitalization and death.
- Both natural immunity and vaccine-induced immunity wane over time.
- Hybrid immunity confers improved protection compared to infection-induced immunity alone.
- Integrating infection and vaccination-induced immunity into vaccination strategies and/or schedules may provide gains through simplified and/or more effective immunization schedules in countries or communities that have already experienced high levels of community transmission.