Saskatchewan Health Authority

University of Saskatchewan

COVID-19 Evidence Support Team
RAPID REVIEW REPORT

What is known about hybrid immunity to COVID-19?

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Full author statement available at the end of report.

Key Findings

- There is substantial immunologic and increasing epidemiologic evidence that vaccination following infection further increases protection against subsequent illness among those who have been previously infected.
- Laboratory studies indicate that hybrid immunity (i.e., immunity conferred by the combination of previous infection and vaccination) offers greater protection against COVID-19 infection.
- A single dose of the AstraZeneca COVID-19 vaccine following SARS-CoV-2 infection induced a 2 to 3-fold increase in anti-Spike and -RBD IgG levels 30 days post-vaccination.
- A study in Brazil found that hybrid immunity showed a modest increase in protection against symptomatic infection and waning over time.
- Neutralising antibody titres against SARS-CoV-2 variants over 7 months following Pfizer vaccination in SARS-CoV-2-recovered and naïve healthcare workers resulted in substantially enhanced T-cell responses, anti-spike IgG responses and neutralising antibodies effective against SARS-CoV-2 variants in recovered participants.
- Pfizer and Moderna vaccines were associated with greater IgG responses compared to Johnson & Johnson regardless of administration following infection.
- Those with vaccine-after-infection or vaccine-breakthrough-infection had a more durable anti-spike-IgG response compared to infection-alone.
- A study on healthcare workers from Oregon Health & Science University found enhanced immune responses after vaccination in COVID-19 recovered (hybrid immunity) compared with their naïve-vaccinated peers. However, the effects of post-vaccination breakthrough infections on humoral immune response remain to be determined.

Limitations

- The body of evidence for infection-induced immunity is more limited than that for vaccine-induced immunity in terms of the quality of evidence and types of studies There are insufficient data to extend the findings related to infection-induced immunity at this time to persons with very mild or asymptomatic infection or children.

Strength of Evidence

☐ Mature evidence
☒ Emerging Supportive evidence
☐ Mixed evidence
☐ Weak evidence

Quality of Evidence Assessment

1. **Adequacy of primary studies**: The degree of adequacy of primary studies is based on the emerging evidence and the accuracy of the primary findings. There is considerable correlation described in studies between the antibody response and 'hybrid immunity', interpretations of these findings should be done with caution due to the credibility and variability of laboratory findings.

2. **Methodological limitations**: There are a limited number of published studies highlighting hybrid immunity and those that do involve relatively small study populations. Various factors make it challenging to assess the effects of hybrid immunity. These include vaccine availability, degree of severity of previous infection, social economic status, individual responses to vaccinations and infection, heterogeneous vaccination regime, interactions of vaccines with other drugs and the emergence and risk of exposure to new variants. Due to the nature of the rapid review, the methodology used by various studies and the findings of the studies, these studies were not critically appraised.

3. **Relevance to review question**: The findings in this rapid review give critical information about the type of responses as seen in laboratory findings and the difference in humoral responses between different vaccines and waning immunity.

4. **Generalizability of findings**: Findings are preliminary and context specific and cannot be generalized to all contexts.

Background/Context

1. Clinical Context

The continuous emergence of the SARS-CoV-2 variants is a significant issue worldwide. It has been noted that each significant variant has created a surge in their particular country of origin and subsequently transmitted worldwide. Hybrid immunity has been regarded as the most robust immunity to fight against SARS-CoV-2 and is produced in individuals who have contracted the disease and received the COVID-19 vaccine. Further evidence is needed to make an inference on the protection this type of immunity offers against the respiratory virus. (1)

2. Purpose

To better understand the quality, duration and amount of protection against the SARS-CoV-2 variants offered by hybrid immunity

3. Review Question(s)

- What is known about hybrid immunity to COVID-19 versus vaccine or infection only mediated immunity?

Method

For each Rapid Review, the initial question is posed by a decision-maker in the health care system seeking the evidence base for a specific policy decision. According to the subject of the question, the COVID Evidence Support Team (CEST) Intake Committee allocates the question to the appropriate Working Group. Each Working Group may be comprised of a librarian, researcher, 1-2 clinicians, 1-2 subject matter experts, and a group leader. A reference interview is conducted to establish the parameters of the question to ensure it is articulated in a clear, searchable manner. The librarians assigned to the team then conduct a thorough search of the indexed literature, grey literature, news sources, or other sources as agreed upon. Some reference lists for especially pertinent articles are also reviewed. An Evidence Search Report is thereby created. See Appendix for more details on the search strategy. A Rapid Review of the identified literature is then performed by the researcher using the approach of a systematic review, but without a double review, formal assessment of quality of reported study, or meta-analysis. Importantly, the review is completed in a time-sensitive manner. Relevant evidence is summarized in both tabular and narrative form, key findings and limitations articulated, and the quality of the body of evidence evaluated using a four-point grading system that assesses the methodologies, adequacy of the included studies, the direct relevance to the question and the generalizability of the findings related to the question. The draft Rapid Review Report is reviewed and edited by the Working Group clinicians, experts, and leader. Once revisions are complete, the Rapid Review is submitted to the requesting decision-maker and placed in the COVID-19 repository and database. For certain topics with rapidly changing evidence, after a period of time an updated evidence search is performed, the review process repeated, and an updated Rapid Review released.

Summary of Evidence

As the COVID-19 pandemic is still a concern in various parts of the globe and is constantly evolving, subsequent mutations of the virus may lead to adverse outcomes and it becomes increasingly necessary for individuals to adapt their immunity through vaccinations.
It is also unclear how natural immunity interacts with immunity conferred by vaccination. Some laboratory studies have indicated that “hybrid immunity” (i.e., immunity conferred by the combination of previous infection and vaccination) offers greater broad-spectrum protection, elicits higher levels of neutralizing antibodies, and provides greater protection against infection than immunity conferred by vaccination or infection alone. (2)

Immunity is a physiological mechanism that enables the body to recognize foreign substances and neutralize, eliminate, or metabolize them without causing harm to its own tissues. The best defense comes from a combination of different sources of immunity, individuals who receive multiple types of vaccines have stronger immune responses. The best outcomes against the COVID-19 infection were seen in people who had a combination of immunity from prior infection and two vaccinations. Immunologists refer to this phenomenon as “hybrid” and “super” immunity. A growing number of

scientific communities are now questioning the extent to which the Omicron variant may provide natural immunity as a result of infection. However, it is unknown whether the symptoms are caused by the virus acting as a natural immunization or by the fact that much of the human population has been vaccinated. (3)

A large cohort study in Israel with 5.7 million participants, estimated the incidence of confirmed SARS-CoV-2 infection in the following cohorts: previously infected, unvaccinated persons; previously infected persons who had also received the Pfizer vaccine; and vaccinated persons who had not been previously infected. The study found that the number of cases of SARS-CoV-2 infection per 100,000 person-days at risk (adjusted rate) increased with the time since vaccination with Pfizer or since previous infection. Among unvaccinated persons who had recovered from infection, this rate increased from 10.5 to 30.2 among those infected 1 year ago or more. Persons that received a single dose of vaccine after previous infection, the adjusted rate was low (3.7) among those vaccinated less than 2 months ago but increased to 11.6 among those vaccinated at least 6 months ago. Among previously uninfected persons who had received two doses of vaccine, the adjusted rate increased from 21.1 to 88.9 among those who had been vaccinated at least 6 months ago. (2)

The continuous evolution of SARS-CoV-2 has generated highly mutated variants, like the Omicron sub-variants BA.1 and BA.2, able to escape natural and vaccine-induced primary immunity. The administration of a third dose of mRNA vaccines induces a secondary response with increased protection. In a longitudinal study it was found that the third dose increased the antibody neutralization potency and breadth against all SARS-CoV-2 variants of concern. It was also found that a third dose of mRNA vaccine induces an immune response similar to the hybrid immunity observed in people vaccinated after SARS-CoV-2 infection. This antibody response was characterized by a small in crease in S protein binding antibodies, a strong increase in neutralizing potency and a considerable increase in antibodies able to cross-neutralize emerging variants, including omicron BA.1 and BA.2 (4)

A prospective study measured the serum concentrations of anti-Spike and receptor-binding domain (RBD) antibodies in 52 adults who had had prior laboratory-confirmed mild/moderate COVID-19 in Blantyre, Malawi. A single dose of the AstraZeneca COVID-19 vaccine following mild/moderate SARS-CoV-2 infection induced a 2 to 3-fold increase in anti-Spike and -RBD IgG levels 30 days' post-vaccination. The anti-RBD IgG antibodies from these vaccinated individuals were broadly cross-reactive against multiple VOCs and had neutralisation potency against original D614G, beta, and delta variant. (5)

A study with 104 healthcare workers recruited from Oregon Health & Science University, directly compared the humoral immune response among individuals who received COVID-19 vaccines either before or after naturally acquired SARS-CoV-2 infection. Individuals with one (n=6) or two vaccines (n=25) doses post recovery (hybrid immunity), and fully vaccinated (n=42) with no history infection (including breakthrough infections). Individuals who previously recovered from COVID-19 have enhanced immune responses after vaccination (hybrid immunity) compared with their naïve-vaccinated peers; ELISA geometric mean titer (GMT) EC50 values for SARS-CoV-2 spike-specific antibodies were significantly elevated in both the breakthrough (2.5-fold, $P = 0.005$) and hybrid immune (3.6-fold, $P < 0.0001$) groups compared with vaccination alone, without significant difference between the breakthrough and hybrid groups. Hybrid immunity was associated with a remarkable improvement in the proportion of spike-specific antibodies that were also neutralizing. (6)

A test negative study in Brazil analyzed the impact of hybrid immunity in preventing infection and severe outcomes during the circulation of the Omicron variant. A total of 918,219 tests were included, 476,901

were cases, and 441,318 controls, and 323,704 were unvaccinated (22,935 with and 300,769 without infection prior to vaccination). Compared to those unvaccinated without infection prior to vaccination, the effectiveness of the previous infection in preventing reinfection during the Omicron period was low (28.9%), increasing with vaccination with any vaccine type (Johnson & Johnson, Pfizer, AstraZeneca or CoronaVac), especially after the booster, although this protection waned over time.
Protection against severe outcomes after a previous infection was relatively high (85.6%), increasing with vaccination (VE ranging from 88.0 to 100%). Compared to those unvaccinated with a previous infection, hybrid immunity showed a modest increase in protection against symptomatic infection, once again waning over time, and substantial protection against severe outcomes after the booster. (7)

A longitudinal study in Sweden determined the long-term impact of prior SARS-CoV-2 infection on immune responses after COVID-19 vaccination. Blood samples were collected from the COMMUNITY study, and neutralising antibody titres against SARS-CoV-2 variants over 7 months following Pfizer vaccination in 118 SARS-CoV-2-recovered and 289 SARS-CoV-2-naive healthcare workers without confirmed prior SARS-CoV-2 infection. Vaccination resulted in substantially enhanced T-cell responses, anti-spike IgG responses and neutralising antibodies effective against SARS-CoV-2 variants in SARS-CoV-2-recovered participants (GMT at 29 weeks was 514 for IgG, 95% CI 389-680 and 12 for Neutralizing Ab, 95% CI 9.6-15) as compared to SARS-CoV-2-naive participants (GMT at 29 weeks was 146 for IgG, 95% CI 113-160 and 4.7 for neutralizing Ab, 95% CI 4.5-5). These findings imply that prior SARS-CoV-2 infection should be taken into consideration when planning booster doses and design of current and future COVID-19 vaccine programmes.(8)

A retrospective study in Sweden aimed to investigate the long-term protection from a previous infection (natural immunity) and whether natural immunity plus vaccination (hybrid immunity) was associated with additional protection. The Swedish nationwide registers managed by the Public Health Agency of Sweden, the National Board of Health and Welfare, and Statistics Sweden were used to identify cohorts. Cohort 1 had 2039 106 unvaccinated individuals with natural immunity, cohort 2 had 962 318 and cohort 3 had 567 810 individuals vaccinated with one dose or two doses (two-dose hybrid immunity) of a COVID-19 vaccine (Oxford-AstraZeneca, Pfizer-BioNTech, or Moderna), respectively, after a previous infection.
During a mean follow-up of 164 days (SD 100), 34 090 individuals with natural immunity in cohort 1 were registered as having had a SARS-CoV-2 reinfection compared with 99 168 infections in non-immune individuals. During a mean follow-up of 52 days (SD 38) in cohort 2, 639 individuals with one-dose were registered with a SARS-CoV-2 reinfection, compared with 1662 individuals with natural immunity. One-dose hybrid immunity was associated with a 58% lower risk of SARS-CoV-2 reinfection (aHR 0.42 [95% CI 0.38-0.47]; p<0.001) than natural immunity up to the first 2 months, with evidence of attenuation thereafter up to 9 months (p<0.001) of follow-up.
During a mean follow-up of 66 days (SD 53) in cohort 3, 438 individuals with two-doses were registered as having had a SARS-CoV-2 reinfection, compared with 808 individuals with natural immunity. Two-dose hybrid immunity was associated with a 66% lower risk of SARS-CoV-2 reinfection (aHR 0.34 [95% CI 0.31-0.39]; p<0.001) than natural immunity, with no significant attenuation up to 9 months (p=0.07). (9)

A cohort study in Washington examined the distinguishing features of hybrid immunity to SARS-CoV-2 in comparison with vaccination alone over time and with subsequent antigen exposures in 24 naive and 30 vaccinated subjects. It was found that following vaccination, previously infected individuals generated more SARS-CoV-2 RBD-specific memory B cells and variant-neutralizing antibodies and a distinct population of IFN-gamma and IL-10-expressing memory SARS-CoV-2 spike-specific CD4(+) T cells than previously naive individuals. Although additional vaccination could increase humoral memory in

previously naive individuals, it did not show the distinct CD4(+) T cell cytokine profile observed in previously infected subjects. (10)

To estimate naturally-acquired, vaccine-induced or hybrid immunity (acquired from both vaccination and infection) against Delta- and/or Omicron symptomatic infections a test-negative case–control design was used in France. The study population consisted of 926,376 Omicron- or Delta-positive cases, 1,852,752 SARS-CoV-2-negative controls. The protection conferred by a prior infection among unvaccinated persons was 51% against symptomatic infections with the Omicron variant, while it was 89% with the Delta variant. Hybrid immunity (prior infection and at least one vaccine dose) reached 67% protection and 81% with a booster dose against symptomatic infection with the Omicron variant, and even higher levels (> 90%) were reached against Delta. (11)

A longitudinal study in Cape Town, South Africa on effect of prior infection with different SARS-CoV-2 variants on Johnson & Johnson vaccine immunogenicity in 60 HCWs who were vaccinated in a phase 3b implementation trial of single-dose Johnson & Johnson vaccine was recorded. HCWs were recruited into three groups, namely those never infected with SARS-CoV-2 (n = 20) and those with PCR-confirmed infection during the first wave (n = 20) or second wave (n = 20). The Beta variant accounted for >90% of infections in the Western Cape (South Africa) in the second wave, making it likely that this variant was responsible for infections in the latter group. Serological profiles were generated for each participant by measuring nucleocapsid and spike antibodies. It was seen that there were low titers post-vaccination in the infection-naive group (geometric mean titer GMT: 74). In both groups with prior infection, it was observed that a significant boost in neutralization after vaccination against wild-type and Beta variants was observed. For first-wave HCWs, titers were boosted 13-fold from a GMT of 210 to 2,798. Second-wave HCWs were boosted 12-fold from a GMT of 99 to 1,157. To determine cross-reactivity of neutralizing antibodies, neutralization of wild-type with Beta and Delta were compared. For antibodies induced by vaccination alone, all participants showed significantly lower titers against Beta (85% showing no neutralization, GMT: 28) and Delta (78% showing no neutralization, GMT: 29). Overall, prior infection followed by vaccination triggered high-titer neutralizing antibodies able to neutralize VOCs. However, the pattern of neutralization varied by wave, suggesting that the neutralizing antibody repertoire was shaped by the genotype of the infecting variant. (12)

A study across the U.S Military Health Systems in the United States comparing the magnitude and durability of vaccine-induced humoral immunity against humoral immune response elicited by SARS-CoV-2 infection included 2660 U.S. Military Health System beneficiaries with a history of SARS-CoV-2 infection-alone (n = 705), vaccination-alone (n = 932), vaccine-after-infection (n = 869), and vaccine-breakthrough-infection (n = 154). Peak anti-spike-IgG responses through 183 days were compared. Multivariable regression results indicated vaccine-after-infection anti-spike-IgG responses were higher than infection-alone ($p < 0.01$), regardless of prior infection severity. An increased time between infection and vaccination was associated with a greater post-vaccination IgG response ($p < 0.01$). Vaccination-alone elicited a greater IgG response, but more rapid waning of IgG ($p < 0.01$), compared to infection-alone ($p < 0.01$). BNT162b2 and mRNA-1273 vaccine-receipt was associated with greater IgG responses compared to JNJ-78436735 ($p < 0.01$), regardless of infection history. Those with vaccine-after-infection or vaccine-breakthrough-infection had a more durable anti-spike-IgG response compared to infection-alone ($p < 0.01$). Vaccine-receipt elicited higher anti-spike-IgG responses than infection-alone, although IgG levels waned faster in those vaccinated (compared to infection-alone). Vaccine-after-infection elicits a greater humoral response compared to vaccine or infection alone; and the timing, but not disease severity, of prior infection predicted these post-vaccination IgG responses. While

differences between groups were small in magnitude, these results offer insights into vaccine immunogenicity variations that may help inform vaccination timing strategies.(13)

Available evidence shows that fully vaccinated individuals and those previously infected with SARS-CoV-2 each have a low risk of subsequent infection for at least 6 months. Data are presently insufficient to determine an antibody titer threshold that indicates when an individual is protected from infection. (14)

Conclusions

Hybrid immunity can provide the strongest protection against the virus and includes components like antibodies, memory B cells, CD4+ T, and CD8+ T cells.(1) Although there appears to be varying evidence regarding the relative protection that occurs after COVID-19 infection as compared with completing vaccination without infection, there is substantial immunologic and increasing epidemiologic evidence that vaccination following infection further increases protection against subsequent illness among those who have been previously infected. (14)
There is also biological plausibility in the protection of combined infection and vaccine induced immunity.
While it seems reasonable to make correlates to current day contexts, the authors note caution should be taken in applying any immunity findings moving forward given the unknown effect any previous immunity may have on novel variants.

Table 1: Summary of Evidence

Consult the Summary of Evidence table using the following link:

- https://covid19evidencereviews.saskhealthauthority.ca/en/permalink/coviddoc496

This link provides access to the database where it is possible to view the spreadsheet for review.

Reference List

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Appendix 1: Evidence Search Details

Note: To view full search strategy details, please consult the associated Evidence Search Report.

Filters, Limits & Exclusions:	English only 2021 - Current ...
Sources Searched:	• CDC • COVID-END • ECDC • Embase • Google • Google Scholar • McMaster Plus • MEDLINE • medRxiv • NCCMT • TRIP • WHO Global Research • WHO website
Librarian(s):	Lance Fox, Clinical Librarian, Saskatchewan Health Authority Lukas Miller, Clinical Librarian, Saskatchewan Health Authority

Appendix 2: Search Strategies

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Database: Ovid MEDLINE(R) ALL <1946 to May 17, 2022>

Search Strategy:

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1 exp Adaptive Immunity/ (250907)

2 (((natural or adaptive or acquired or humoral or active or cellular) adj2 immunity) or adaptive immune response or immunologic* memory).tw,kf. (52705)

3 1 or 2 (282397)

4 Immunogenicity, Vaccine/ (3018)

5 (vaccin* adj2 (antigenic* or immunogenic*)).tw,kf. (3465)

6 4 or 5 (6156)

7 3 and 6 (1283)

8 (hybrid immune response or hybrid* immunity or hybrid antigenic response).tw,kf. (45)

9 exp COVID-19 Vaccines/im (2049)

10 (mRNA-1273 or Ad26COVS1 or BNT162 or ChAdOx1 or moderna or pfizer or "johnson and johnson" or covishield or astrazeneca or comirnaty or novavax or nuvaxovid or covovax or spikevax).tw,kf. (9104)

11 ((covid* or coronavirus or covid-19 or SARS-CoV-2 or SARS-nCoV-2 or 2019-nCoV or nCoV-2019) adj2 vaccin*).tw,kf. (16959)

12 9 or 10 or 11 (23911)

13 7 and 12 (144)

14 8 and 12 (23)

15 limit 13 to (english language and yr="2021 -Current") (135)

16 limit 14 to (english language and yr="2021 -Current") (23)

17 15 or 16 (158)

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Database: Embase <1974 to 2022 May 17>
Search Strategy:
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1 exp *adaptive immunity/ (6524)
2 (((natural or adaptive or acquired or humoral or active or cellular) adj2 immunity) or adaptive immune response or immunologic* memory).tw,kf. (67988)
3 1 or 2 (70533)
4 vaccine immunogenicity/ (5040)
5 (vaccin* adj2 (antigenic* or immunogenic*)).tw,kf. (4163)
6 4 or 5 (8580)
7 3 and 6 (576)
8 (hybrid immune response or hybrid* immunity or hybrid antigenic response).tw,kf. (56)
9 exp SARS-CoV-2 vaccine/ (16273)
10 (mRNA-1273 or Ad26COVS1 or BNT162 or ChAdOx1 or moderna or pfizer or "johnson and johnson" or covishield or astrazeneca or comirnaty or novavax or nuvaxovid or covovax or spikevax).tw,kf. (48390)
11 ((covid* or coronavirus or covid-19 or SARS-CoV-2 or SARS-nCoV-2 or 2019-nCoV or nCoV-2019) adj2 vaccin*).tw,kf. (18186)
12 9 or 10 or 11 (66812)
13 7 and 12 (70)
14 8 and 12 (37)
15 limit 13 to (english language and yr="2021 -Current") (58)
16 limit 14 to (english language and yr="2021 -Current") (37)

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Keywords Used in Other Resources

- COVID-19
- Sars-Cov-2
- Coronavirus
- Infection
- Previous
- Prior
- Post
- After
- Hybrid immunity
- Adaptive immunity
- Acquired immunity
- Adaptive immune response
- Cross-protective immunity
- Super immunity
- Vaccination
- Vaccine
- Dose
- Booster

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The authors declare they have no conflicts of interest to report.