Rapid Evidence Synthesis: COVID-19 Vaccine Effectiveness in Unvaccinated Moderate to Severely Immunocompromised People with a Previous Infection

Date of Literature Search: August 11, 2023
Date of Revision: Sept 14, 2023
Date of Submission: August 28, 2023

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EXECUTIVE SUMMARY

Objectives: To identify the available evidence on the benefit of one vs. two or more doses of COVID-19 vaccine in the vaccine schedule (i.e., primary series) for unvaccinated individuals at high risk of severe illness due to COVID-19 who have been previously infected with SARS-CoV-2.

Design: Rapid evidence synthesis

Methods: Two independent reviewers assessed full text of studies for eligibility and extracted data. Due to study heterogeneity, results are reported descriptively, and a formal meta-analysis was not performed. Studies that did not directly answer the question were considered for inclusion as indirect evidence within the narrative summary if they reported COVID vaccine effectiveness during the correct time frame, in a high-risk population, that included participants with hybrid immunity.

Results:
No studies directly addressing the research question and reporting clinical outcomes of interest were identified. Four studies providing indirect evidence on the clinical outcomes of interest were included. One study reporting on immunogenicity outcomes and meeting the inclusion criteria (except for providing results separately for the immunosuppressed subgroup) was included. Four additional studies providing indirect evidence on immunogenicity outcomes were also included.

Overall, both the quantity and quality of the available evidence to answer the research question is poor. Indirect evidence suggests that a minimum of two vaccine doses may provide better hybrid protection from clinical outcomes in the previously infected immunosuppressed compared to one vaccine dose. The studies reporting immunogenicity outcomes were too heterogenous to support any conclusions.

Conclusions:
Studies addressing hybrid immunity in immunocompromised patients are uncommon. No studies reporting clinical endpoints that directly address the question asked in this Rapid Evidence Synthesis were found despite an extensive search of the literature.

Primary Research Question

Among unvaccinated individuals with moderately to severely immunocompromising conditions and a prior history of SARS-CoV-2 infection, are at least two doses of any COVID-19 vaccine approved for use in Canada more effective at reducing the occurrence of SARS-CoV-2 infections, hospitalizations, or deaths, compared to one dose?

Secondary Research Questions

1. What is the incremental benefit of each additional dose?
2. What are the effects on immunogenicity, with an initial focus on seroconversion (rather than titre measures), when reported with clinical outcomes?

Rationale

The authorization of the Moderna Spikevax XBB.1.5 COVID-19 vaccine in Canada includes a shift to a "simplified" COVID-19 vaccine schedule that takes into consideration the high levels of seropositivity due to SARS-CoV-2 infection in the population. This new schedule includes offering only one dose of COVID-19 to unvaccinated individuals 5 years of age and older, and has also been implemented in the US and UK, and recommended by the European Medicines Agency. Prior to adopting the vaccine schedule for people with moderately to severely immunocompromising conditions, some of whom experience reduced responses to vaccination, the evidence must be reviewed.

This review will provide information to assess the need for a different vaccine schedule in unvaccinated special populations that are at particularly high risk of severe outcomes due to COVID-19.

PICOST Framework

	Inclusion Criteria	**Exclusion Criteria**
Population	Immunocompromised people with prior SARS-CoV-2 infection (as confirmed by PCR testing, rapid antigen test, serologic testing, or epidemiologic linkage), and who had <u>not</u> received any COVID-19 vaccine doses prior to infection. **Immunocompromised individuals**, defined as persons with HIV infection, primary immune or complement deficiency, malignancy, transplant, or on immunosuppressive therapy	Healthcare workers (subgroup of immunocompromised small and results not reported separately) Status of prior infection is unknown, including when stated as "no infection reported 90 days prior to vaccination"

	*Nursing home/retirement home residents were added after searching reviewed few studies in the subgroups defined above, and because they are considered a high-risk group for severe COVID outcomes.	
Intervention	Original or bivalent COVID-19 vaccine by dose number (identifying intervals between doses) Pfizer-BioNTech (BNT162b2; BNT), Moderna (mRNA-1273; MOD), Moderna bivalent (MOD-Bi); Novavax (NOVA)	Vaccine not currently authorized for use in Canada Follow-up period exclusively prior to the period of Omicron predominance (intervention can be given at any time) AstraZeneca (ChAdOx1) and Johnson & Johnson (AD26.COV2.S) vaccines excluded even if administered prior to Omicron period
Comparisons	**Previously infected plus** Vaccinated with one dose only Vaccinated with >1 dose	Status of prior infection is unknown, including when stated as "no infection reported 90 days prior to vaccination"
Outcomes	**Effectiveness (VE):** confirmed SARS-CoV-2 infection (PCR or serologic); asymptomatic infection, symptomatic COVID-19 disease; hospitalizations due to COVID-19; ICU admissions due to COVID-19; deaths due to COVID-19; and durability of VE (changes in VE point estimates over time), if available. **Immunogenicity:** *only as a secondary outcome detailed in literature screened for effectiveness that report on clinical measures*; including seroconversion, humoral immune responses (e.g., binding antibodies, neutralizing antibodies); Cellular immune	

	responses (e.g. B cells, CD4+ and CD8+ T-cells, and associated cytokine responses); duration of response for humoral and cellular immunity. Within the **Omicron context** (after December 1, 2021)	
Study designs	Any **comparative design**, such as interventional trials, observational (cohort, case-control), or before-after studies. **Case series** allowed for within group comparisons (e.g., followed forward with additional doses) and **with at least 100 participants** for effectiveness outcomes and safety and 10 participants for immunogenicity outcomes.	Cross-sectional studies (for clinical outcomes)

Methods

Search Sources

PHAC database supplemented by updated search to August 11, 2023, by HiRU Librarian from Medline (OVID), EMBASE, and CINAHL.

Search Strategy (HiRU): Appendix

Study Selection Criteria

English-language studies published in peer-reviewed journals or ahead-of-print prior to peer review. Comparative studies (RCTs, cohort, case-control, before-after studies) and case series (at least 100 participants for vaccine effectiveness and at least 10 for immunogenicity) reporting at least the clinical outcomes of interest. A comprehensive search for studies reporting immunogenicity outcomes only was not performed for this version. However, if studies reporting clinical outcomes also reported immunogenicity outcomes, those outcomes were also extracted.

Data Extraction

A single reviewer screened abstracts and two reviewers reviewed the full text for potentially relevant articles. Data for included studies were extracted by one reviewer and checked for accuracy by a second reviewer.

Data Synthesis

The plan was to synthesize comparative studies reporting relative risk and case series reporting rates with a random effects model. However, the included studies were too heterogeneous, and therefore the results were synthesized narratively.

Appraisal of Quality of Evidence

Risk of Bias for the studies reporting clinical outcomes was determined using an adapted version of ROBINS-I from previous Living Evidence Syntheses for COVID vaccine effectiveness.[1] Studies that did not directly answer the question were considered for inclusion as indirect evidence within the narrative summary if they reported COVID vaccine effectiveness during the correct time frame, in a high-risk population, that included participants with hybrid immunity.

Results

There were 552 studies screened, 63 selected for full text review, and 4 studies included for the primary outcome measure. The Flow Diagram of Study Selection is provided in Figure 1. The list of excluded studies will be provided in a separate file. A description of the Study Characteristics for the included studies is provided in Table 1.

Clinical Outcomes

No studies fitting all inclusion criteria and reporting the clinical outcomes of interest were identified. (Table 2) The most common reasons for exclusion were wrong population (i.e., did not include immunocompromised or didn't report results for them as a separate subgroup) or wrong comparator (i.e., did not report hybrid immunity for infection prior to first vaccine dose).

Four studies providing **indirect evidence** on the clinical outcomes of interest were included. All studies included a relevant population and timing, but none reported the relative vaccine effectiveness of previous infection+1 vaccine dose vs. previous infection+2 or more vaccine doses. The populations for these studies were as follows: nursing or retirement home population (not limited to immunocompromised)[2, 3], hemodialysis outpatients[4], and one healthcare provider population of moderately to severely immunocompromised members (which did not report hybrid immunity)[5]. All four studies included approved vaccines and were performed during the time frame for Omicron.

The reported comparisons in the indirect studies were as follows: previous infection+2 vaccine doses vs. previous infection+3 vaccine doses[4], previous infection+3 vaccine doses vs. 3 vaccine doses without previous infection[2], previous infection+4 vaccine doses vs. 4 vaccine doses without previous infection[3] and 2 vaccine doses vs. 3 vaccine doses (hybrid immunity not reported).[5]

Three of the included **indirect** studies showed **reduced risk of Omicron infection** in participants with *hybrid immunity* (previous infection and vaccination with *minimum of two doses*) compared to vaccinated participants with no previously documented infection.[2, 4-6] One study restricted to the *immunocompromised*, did not report results according to hybrid immunity, but showed **reduced risk of infection**, **hospitalization**, and **hospital death** with 3 vaccine doses vs 2 vaccine doses during the Delta to Omicron period in this high risk population.[5] Unexpectedly, one study reported increased risk of **re-infection by Omicron** in participants with *hybrid immunity* due to 4 vaccine doses plus previous Omicron infection (unclear if infection preceded vaccination).[3] Two of the included studies were assessed as moderate risk of bias[2, 5] and two were serious risk of bias.[3, 4](ROB table provided in separate file)

Evidence from the Literature: Clinical Outcomes

A recent review and meta-analysis of COVID vaccine effectiveness studies by Bobrovitz et al found that *hybrid immunity* (previous infection plus primary series vaccination) vs. *hybrid immunity* (previous infection plus partial series vaccination) had a pooled relative protection rate of **16.3%** (95% CI, 11.1 to 21.2) against **any infection** and **49.6%** (95% CI, 19.9 to 79.7) against **COVID hospitalization**.[7] Unfortunately, the results were not reported separately for immunocompromised participants even though several of the included studies enrolled this subgroup.

Carazo et al reported the results of a large test-negative study performed in Canada enrolling participants over age 60 (*27% immunocompromised*).[7] They found that protection against **hospitalization** during Omicron BA.4 or BA.5 due to *hybrid immunity* (previously infected plus two vaccine doses) was 94% (95% CI, 60 to 99) and not substantially different from *hybrid immunity* (previous infection plus three vaccine doses) 92%, (95% CI, 80 to 97).

Another study frequently cited in the literature described *hybrid* protection from recurrent infection with one dose of vaccine following a previous infection as not significantly different from two doses of vaccine following a previous infection.[8] However, it is important to note that this study did not report results separately for immunosuppressed participants, and was conducted prior to the time frame of Omicron.

Overall, both the quantity and quality of the available evidence to answer the research question is poor. Indirect evidence suggests that a *minimum* of 2 vaccine doses may provide better hybrid protection from clinical outcomes in the immunosuppressed with a prior history of SARS-CoV-2 infection compared to 1 vaccine dose.

Immunogenicity Outcomes

One study fitting all inclusion criteria, except for providing results separately for the immunosuppressed subgroup, and reporting the immunogenicity outcomes of interest was identified.[9] (Table 3) Four additional studies providing indirect evidence were also included. The populations for these studies were as follows: community nursing home population[10, 11], chronic lymphocytic leukemia patients[12], and immunocompromised patients (cirrhosis, autoimmune liver disease, allogenic hematopoietic stem cell transplant patients)[6]. All four studies included approved vaccines and were performed during the relevant time frame for Omicron.

The single study meeting most of the inclusion criteria enrolled previously infected children and adolescents (infected during Alpha, Gamma, Delta, or Lambda time frames) in Argentina (40% with chronic conditions). [9] Immunogenicity outcomes in participants with previous infection+1 vaccine dose were compared with unvaccinated previously infected participants. Similarly, participants with previous infection+2 vaccine doses were compared with unvaccinated previously infected participants. They found that Anti-S IgG levels against the Omicron variant were high after 1 or 2 doses without a significant difference between them. Similarly, neutralizing antibodies were increased compared to previously infected and unvaccinated, but not appreciably different between 1 or 2 doses in those with hybrid immunity.

The four studies providing **indirect** evidence for immunogenicity outcomes included a relevant population and timing, but none used the comparison of previous infection+1 vaccine dose vs. previous infection+2 or more vaccine doses. The comparisons in this group of studies were as follows: previous

infection+2 or 3 vaccine doses vs. 2 or 3 vaccine doses without previous infection[2, 10], previous infection+4 or 5 doses vs. 4 or 5 doses without previous infection[3, 11] and previous infection+2 or 3 doses with no comparator[6, 12]. Two out of four of the multiple dose studies failed to demonstrate a significant rise in Anti-S IgG or neutralization level with additional vaccine doses in the previously infected.[2, 11] However, serology was assessed after a variable number of doses and at different time frames, which makes comparisons across studies problematic. Overall, the data from immunogenicity studies is too heterogeneous to support any conclusions.

Figure 1. Flow Diagram of Study Selection

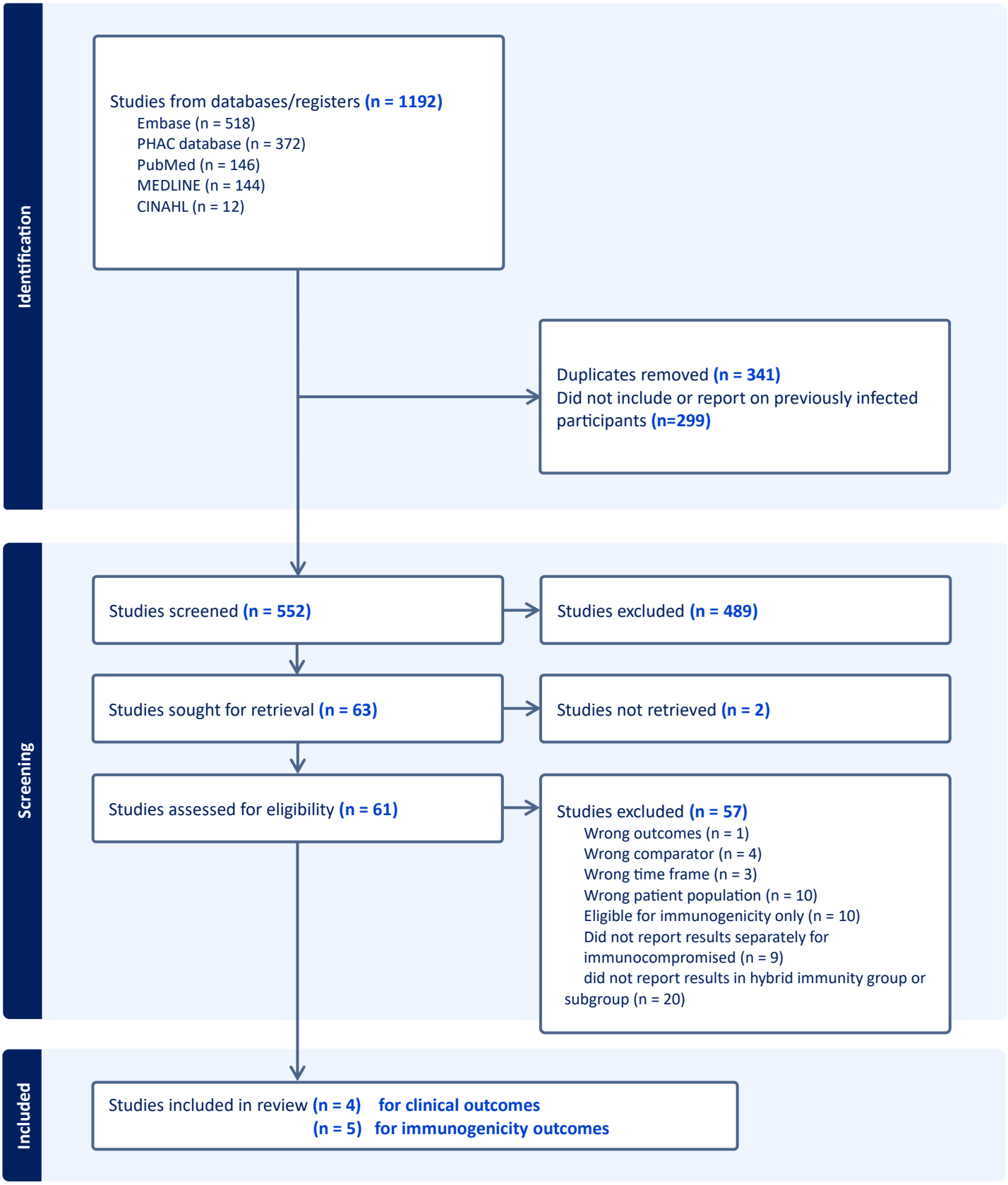

Table 1. Included Studies

Author	Study Design	Country and Population	Vaccine	Details about Infection/Vaccine	Follow-up
Clinical Outcomes					
Bruel, 2022[2]	Prospective cohort	France Nursing home residents (n=38)	BNT or MOD	Pre-vaccine infection + 2 doses mRNA vaccine (BNT or MOD) followed by booster (BNT162b2)	Enrolled: Nov 2020-April 2021 and followed to Jan 2022
Breznik, 2023[3]	Retrospective cohort	Canada Nursing and retirement residents	BNT or MOD or MOD-Bi	Infection pre-Omicron or one infection during Omicron + 4-doses	July to Sept 2022
Wing, 2023[4]	Retrospective cohort	Canada Hemodialysis outpatients	BNT or MOD	History of previous infection 2-doses vs 3-doses	Dec 2021 to Feb 2022
Ku, 2022[5]	Matched cohort	USA Kaiser Permanente members moderately or severely immunocompromised	MOD	History of previous infection (specific timing not reported) 2-doses vs 3-doses	Dec 2021 to Jan 2022
Immunogenicity Outcomes					
Al-Dury, 2023[6]	Cohort	Sweden Liver disease, Allo-HSCT	BNT or MOD	Infection after 2nd dose	Not applicable
Seery, 2022[9]	Cohort	Argentina Previously infected children including comorbidities	BNT or MOD	Pre-vaccine infection + 1 or 2 doses	Not applicable
Canaday, 2022[10]	Cohort	USA Community nursing homes	BNT or MOD	Pre-vaccine infection + primary series	Not applicable

Author	Study Design	Country and Population	Vaccine	Details about Infection/Vaccine	Follow-up
Gravenstein, 2023[11] NH residents (includes same population as for Canaday)	Cohort	USA Community nursing homes	BNT or MOD	Pre-vaccine infection + primary series+ 2 monovalent + first bivalent	Not applicable
Blixt, 2022[12]	Cohort	Sweden Previously infected CLL adults	BNT or MOD	Pre-vaccine infection + 3 doses	Not applicable

BNT: (BNT162b2), MOD: (mRNA-1273), Allo-HSCT: (Allogeneic hematopoietic stem cell transplant); NH: nursing home; CLL: chronic lymphocytic leukemia

Table 2. Results of Included Studies Reporting Clinical Outcomes

Author, Year	Vaccine	Hybrid immunity (No.)	Mean interval between infection and dose 1 (IQR)	Mean interval between dose 1 and dose 2 (IQR)	Mean interval between doses (IQR)	Non-Hybrid Immunity Comparator (No.)	Summary Measure	Adjusted/Matched
Bruel, 2022[2] NH residents	BNT or MOD	Infection/2 doses + booster (n=29)	Not reported	21 days (18-31)	236 days (184-250)	2 doses + booster/no prior infection (n=8)	Incidence **Infection** 7/30 (20%) vs 6/8 (75%) P=.0065	N/A
Breznik, 2023[3] NH and retirement home residents	BNT or MOD	Pre-Omicron [prior to Dec 2021] (n=76) or 1 Omicron infection [Dec 2021-June 2022] (n=131) /4 doses Timing of infection in relation to doses not reported	Not reported	Not reported	Time since 4th dose 154 days (130-185)	482 No infection/4 doses	HR (95% CI) **Infection** PreOmicron 1.41 (0.66 to 3.02) Prior Omicron infection [0-8 days] 2.18 (0.38 to 12.42) Prior Omicron infection [9-29 days] 47.67 (23.73 to 95.76) Prior Omicron infection [30-75 days] 1.67 (0.49 to 5.69)	

Author, Year	Vaccine	Hybrid immunity (No.)	Mean interval between infection and dose 1 (IQR)	Mean interval between dose 1 and dose 2 (IQR)	Mean interval between dose 2 and dose 3 (IQR)	Non-Hybrid Immunity Comparator (No.)	Summary Measure	Adjusted/Matched
Wing, 2023[4] Hemodialysis outpatients	BNT or MOD	Infection/2 or 3 doses (n=627) Timing of infection in relation to doses unknown	Not reported	40 days (28-63)	41 days (28-58)	2 or 3 doses/no infection (n=7830)	HR (CI) **Infection** 0.77 (0.39 to 1.54)	Age, sex, ethnicity, Public Health Unit region, Charlson Comorbidity Score, long-term care, cumulative time on dialysis, income quintile
Ku, 2022[5] Mod or severely immunocompromised	MOD	Not reported separately for hybrid 2-dose immunocompromised (n = 21,942)	Not reported	Not reported	Not reported	Not reported separately for non-hybrid 3-dose immunocompromised (n = 21,942)	Relative VE (CI) **Infection** 55% (50.8-58.9) **Hospitalization** 83% (75.4-88.3) **Hospital Death** 87.1% (30.6-97.6)	Age, sex, race/ethnicity, index date, time since second dose, # of outpt and virtual visits, preventative care, Charlson Comorbidity Score, immunocompromising sub conditions

IGR: interquartile range; BNT: (BNT162b2), MOD: (mRNA-1273), Allo-HSCT: (Allogeneic hematopoietic stem cell transplant); CLL: chronic lymphocytic leukemia

Table 3. Results of Included Studies Reporting Immunogenicity Outcomes

Author, Year (Study population)	Vaccine	Hybrid Immunity (No.)	Comparator (No.)	Specimen Collected (Median)	Assay	Test	Hybrid Result	Comparator Result
Bruel, 2022[2] NH residents	BNT or MOD	Infection/2 or 3 doses (n=29)	2 or 3 doses/ No prior infection (n=8)	56 days (28-68) after 2nd dose	Anti-S IgG median titre (range) BAU/mL	Post 2nd dose	3056 (601-17820)	456 (74-4283)
				55 days (48-64) after 3rd dose		Post 3rd dose	2485 (671-7115)	1256 (784-8832)
				56 days (28-68) after 2nd dose	Neutralizing median titre (range) ED50 Omicron	Post 2nd dose	1113 (15-57403)	15 (0-138)
				55 days (48-64) after 3rd dose		Post 3rd dose	1088 (33-34660)	188 (15-8918)
Breznik, 2023[3] NH or Retirement home residents	BNT or MOD	4 doses/early Omicron infection (n = 50)	4 doses/no Omicron infection (n = 176)	101 days (55-127)	Anti-S IgG median (IQR) AU Neutralizing Median (IQR) MNT50	After 4 doses	2.13 (1.09-2.80) 80 (40-320)	1.38 (0.55-2.75) 20 (10-80)

Author, Year (Study population)	Vaccine	Hybrid Immunity (No.)	Comparator (No.)	Specimen Collected (Median)	Assay	Test	Hybrid Result	Comparator Result
Al-Dury, 2023[6] Liver disease and Allo-HSCT	BNT or MOD	3 doses/ Infection after 2nd dose (n = 23)	3 doses/No infection (n = 55)	After 3rd dose Cirrhosis 118 days (20-157) Autoimmune liver disease 92 days (20-136) Allo-HSCT 130 days (38-212)	Anti-S IgG Median titre (CI) BAU/mL	After 3 doses	Cirrhosis 11,275 (n=10) Autoimmune liver disease 5307 (n=5) AlloHSCT 11,401 (n=8)	Cirrhosis 944 (n=28) Autoimmune liver disease 200 (n=9) AlloHSCT 1,426 (n=18)

IGR: interquartile range; BNT: (BNT162b2), MOD: (mRNA-1273), Allo-HSCT: (Allogeneic hematopoietic stem cell transplant); CLL: chronic lymphocytic leukemia

Author, Year (Study population)	Vaccine	Hybrid Immunity (No.)	Comparator (No.)	Specimen Collected (Median)	Assay	Test	Hybrid Result	Comparator Result
Seery, 2022[9] Children; 40% with chronic conditions	BNT or MOD	Infection/1 or 2 doses (n = 76)	Infection/ unvaccinated (n = 115)	23 days (17-30) after 1st dose	Anti-S IgG median titre (IQR)	Post 1 dose	5120 (680-5120) (n=13)	320 (160-1280)
				45 days (31-68) after 2nd dose		Post 2nd dose	5120 (5120-5120) (n=27)	
				23 days (17-30) after 1st dose	Neutralizing median titre (IQR) IC50	Post 1 dose	632 (108-1786) (n=13)	14 (1-32)
				45 days (31-68) after 2nd dose		Post 2nd dose	554 (304-983) (n=27)	

IGR: interquartile range; BNT: (BNT162b2), MOD: (mRNA-1273), Allo-HSCT: (Allogeneic hematopoietic stem cell transplant); CLL: chronic lymphocytic leukemia

Author, Year (Study population)	Vaccine	Hybrid Immunity (No.)	Comparator (No.)	Specimen Collected	Assay	Test	Hybrid Result	Comparator Result
Canaday, 2022[10] NH residents	BNT or MOD	Infection/3 doses (n = 36)	3 doses without infection (n = 49)	Post primary series and first booster as per Test column	Anti-Spike GMT (CI) (BAU/mL)	2 weeks post primary	957 (630,1453) (n=33)	196 (114, 337) (n=46)
						Pre boost	79.9 (40.7, 157)	15.6 (10.7, 22.6)
						Post boost	2980 (2030,4376)	1821 (1183, 2804)
					Neutralizing Omicron GMT (CI) (pNT50)	2 weeks post primary	44.9 (23.8, 84.8) (n=32)	12.5 (11.5, 13.7) (n=26)
						Pre boost	29.3 (17.7, 48.4)	12.6 (11.7, 13.6)
						Post boost	293 (162, 529)	69.5 (36.2, 134)

IGR: interquartile range; BNT: (BNT162b2), MOD: (mRNA-1273), Allo-HSCT: (Allogeneic hematopoietic stem cell transplant); CLL: chronic lymphocytic leukemia

Author, Year (Study population)	Vaccine	Hybrid Immunity (No.)	Comparator (No.)	Specimen Collected	Assay	Test	Hybrid Result	Comparator Result
Gravenstein, 2023[11] NH residents (includes same population as for Canaday)	BNT or MOD	Infection/ vaccinated multiple doses	Vaccinated without infection multiple doses	Post boosters as per Test column	Anti-S IgG GMT (CI) (BAU/mL)	Post 1st Monovalent booster (whole cohort n=452)	3500 (2301, 5324)	2228 (1397, 3552)
						Post 2nd Monovalent booster (whole cohort n=257)	2093 (1683, 2602)	968 (679, 1379)
						Post Bivalent booster (whole cohort n=321)	1390 (1180, 1637)	1216 (943, 1567)
						6 mos post Bivalent booster (whole cohort n=321)	1250 (914, 1711)	417 (196, 888)
					Neutralizing BA.5 GMT (CI) (pNT50)	Post 1st Monovalent booster	299 (174,514)	68 (43,109)
						Post 2nd Monovalent booster	1181 (840, 1660)	195 (120, 318)
						Post Bivalent booster	2075 (1518, 2835)	1136 (671, 1921)

						6 mos post Bivalent booster	424 (257, 700)	88 (28, 278)
Blixt, 2022[12] Previously infected CLL	BNT or MOD	Infection/2 or 3 doses (n = 29)	none	After Dose 2 Before and After Dose 3	Anti-S IgG U/mL (IQR)	After Dose 2 (n=29)	17,208 (2793 to >25,000)	Not applicable
						Before Dose 3 (n=27)	6825 (2532 to >25,000)	
						After Dose 3 (n=27)	24,956 (4219 to >25,000)	
					T-cell responses	Wild-type vs Omicron After Dose 3 (n=13)	Spike-specific CD4+ and CD8+ increased by similar magnitude	

IGR: interquartile range; BNT: (BNT162b2), MOD: (mRNA-1273), Allo-HSCT: (Allogeneic hematopoietic stem cell transplant); CLL: chronic lymphocytic leukemia

Appendix

Search Strategy (HiRU)

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"vaccine efficacy"[MeSH Terms] OR "vaccine efficacy"[All Fields] OR "vaccine effectiveness"[All Fields] OR ("confirmed"[All Fields]) AND ("infections"[All Fields] OR "infection"[All Fields] OR "pathogenicity"[MeSH Subheading] OR "pathogenicity"[All Fields] OR "serologic"[All Fields] OR "serological"[All Fields] OR "serologically"[All Fields]) OR "asymptomatic infections"[MeSH Terms] OR "asymptomatic infections"[All Fields] OR "asymptomatic infection"[All Fields] OR "hospitalisation"[All Fields] OR "hospitalization"[MeSH Terms] OR "hospitalised"[All Fields] OR "hospitalisations"[All Fields] OR "hospitalizations"[All Fields] OR "intensive care units"[MeSH Terms] OR (("intensive care units"[All Fields] OR "icu"[All Fields]) AND ("admission"[All Fields] OR "admissions"[All Fields])) OR "death"[MeSH Terms] OR "death"[All Fields] OR "deaths"[All Fields] OR "mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortality"[MeSH Subheading]

"immunocompromised host"[MeSH Terms] OR immunocompromised[All Fields] OR "immunosuppressed"[All Fields] OR "immunosuppression therapy"[MeSH Terms] OR "immune tolerance"[MeSH Terms] OR "immunosuppressive agents"[Pharmacological Action] OR "immunosuppressive agents"[Supplementary Concept] OR "immunosuppressive"[All Fields] OR "immunosuppressives"[All Fields] OR "autoimmune"[All Fields] OR "autoimmunity"[MeSH Terms] OR "autoimmunity"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields] OR (("solid"[All Fields]) AND ("cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "tumor"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumors"[All Fields])) OR "chemotherapies"[All Fields] OR "chemotherapy"[All Fields] OR "malignances"[All Fields] OR "malignant"[All Fields] OR "malignancy"[All Fields] OR "leukaemia"[All Fields] OR "leukemia"[MeSH Terms] OR "leukemia"[All Fields] OR hiv[MeSH Terms] OR "hiv"[TIAB] OR "rheumatic diseases"[MeSH Terms] OR "rheumatic diseases"[All Fields] OR "rheumatics"[All Fields] OR "rheumatism"[All Fields] OR "rheumatic"[All Fields] OR "rheumatisms"[All Fields] OR "arthritis, rheumatoid"[MeSH Terms] OR "rheumatoid arthritis"[All Fields] OR "multiple sclerosis"[MeSH Terms] OR "multiple sclerosis"[All Fields] OR "dialysis"[MeSH Terms] OR "dialysis"[All Fields] OR "dialyses"[All Fields] OR "haemodialysis"[All Fields] OR "renal dialysis"[MeSH Terms] OR "renal dialysis"[All Fields] OR "hemodialysis"[All Fields] OR "transplantation"[MeSH Terms] OR "transplantation"[All Fields] OR "transplantation"[MeSH Subheading] OR "transplants"[MeSH Terms] OR "transplants"[All Fields] OR "transplant"[All Fields] OR "biological products"[Supplementary Concept] OR

"biological products"[All Fields] OR "biological products"[MeSH Terms] OR "biologicals"[All Fields] OR "biological factors"[Supplementary Concept] OR "biological factors"[All Fields] OR "biological factors"[MeSH Terms] OR "biologics"[All Fields] OR "anti-interleukins"[All Fields] OR "anti-interleukin"[All Fields] OR "adrenal cortex hormones"[Supplementary Concept] OR "adrenal cortex hormones"[All Fields] OR "corticosteroid"[All Fields] OR "adrenal cortex hormones"[MeSH Terms] OR "corticosteroids"[All Fields] OR (("phosphotransferases"[Supplementary Concept] OR "phosphotransferases"[All Fields] OR "kinase"[All Fields] OR "phosphotransferases"[MeSH Terms] OR "kinases"[All Fields]) AND ("antagonists and inhibitors"[MeSH Subheading] OR "antagonists and inhibitors"[All Fields] OR "inhibitors"[All Fields] OR "inhibitor"[All Fields])) OR "calcineurin inhibitors"[Pharmacological Action] OR "calcineurin inhibitors"[Supplementary Concept] OR "calcineurin inhibitors"[All Fields] OR "calcineurin inhibitors"[MeSH Terms] OR "mtor inhibitors"[Pharmacological Action] OR "mtor inhibitors"[Supplementary Concept] OR "mtor inhibitors"[All Fields] OR "mtor inhibitor"[All Fields] OR "mtor inhibitors"[MeSH Terms] OR (("IMDH"[All Fields]) AND ("antagonists and inhibitors"[MeSH Subheading] OR "antagonists and inhibitors"[All Fields] OR "inhibitors"[All Fields] OR "inhibitor"[All Fields])) OR "antibodies monoclonal"[Supplementary Concept] OR "antibodies monoclonal"[All Fields] OR "monoclonal antibodies"[All Fields] OR "antibodies, monoclonal"[MeSH Terms] OR "immunotherapy"[MeSH Terms] OR "immunotherapy"[All Fields] OR "immunotherapies"[All Fields] OR "immunodeficience"[All Fields] OR "immunodeficiences"[All Fields] OR "immunologic deficiency syndromes"[MeSH Terms] OR "immunologic deficiency syndromes"[All Fields] OR "immunodeficiencies"[All Fields] OR "immunodeficiency"[All Fields] OR "anti-CD38"[All Fields] OR "anti-CD20"[All Fields] OR "calcineurin inhibitors"[Pharmacological Action] OR "calcineurin inhibitors"[Supplementary Concept] OR "calcineurin inhibitors"[All Fields] OR "calcineurin inhibitor"[All Fields] OR "cabin1 protein human"[Supplementary Concept] OR "cabin1 protein human"[All Fields] OR "calcineurin inhibitors"[MeSH Terms] OR "disease-modifying"[All Fields] OR "DMT"[All Fields] OR DMTs[All Fields] OR "cytotoxic"[All Fields] OR "cytotoxicities"[All Fields] OR "cytotoxicity"[All Fields] OR "cytotoxics"[All Fields] OR "cytotoxities"[All Fields] OR "cytotoxity"[All Fields]

(("COVID-19 Vaccines" OR "COVID-19 Vaccines"[MeSH Terms]) AND ("Pfizer-BioNTech"[TIAB] OR "Pfizer BioNTech"[TIAB] OR Moderna[TIAB] OR Novavax[All Fields])) OR ("BNT-162b2"[All fields] OR BNT162b2[All Fields] OR BNT[All Fields] OR mRNA-1273[All Fields] OR NVX-CoV2373[All Fields])

"omicron"[All Fields]

"COVID-19"[All Fields] OR "COVID-19"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[All Fields] OR "NCOV"[All Fields] OR "2019 NCOV"[All Fields] OR (("novel"[All Fields] OR "novel s"[All Fields] OR "novels"[All Fields]) AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields]))

Keywords used to screen for immunogenicity only studies that were likely to fit review criteria: hybrid, previously infected, pre-vaccine, prevaccination, and natural infection.

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