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Risk of COVID-19 after natural infection or vaccination

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Summary

Background While vaccines have established utility against COVID-19, phase 3 efficacy studies have generally not comprehensively evaluated protection provided by previous infection or hybrid immunity (previous infection plus vaccination). Individual patient data from US government-supported harmonized vaccine trials provide an unprecedented sample population to address this issue. We characterized the protective efficacy of previous SARS-CoV-2 infection and hybrid immunity against COVID-19 early in the pandemic over three-to six-month follow-up and compared with vaccine-associated protection.

Methods In this post-hoc cross-protocol analysis of the Moderna, AstraZeneca, Janssen, and Novavax COVID-19 vaccine clinical trials, we allocated participants into four groups based on previous-infection status at enrolment and treatment: no previous infection/placebo; previous infection/placebo; no previous infection/vaccine; and previous infection/vaccine. The main outcome was RT-PCR-confirmed COVID-19 >7–15 days (per original protocols) after final study injection. We calculated crude and adjusted efficacy measures.

Findings Previous infection/placebo participants had a 92% decreased risk of future COVID-19 compared to no previous infection/placebo participants (overall hazard ratio [HR] ratio: 0.08; 95% CI: 0.05–0.13). Among single-dose Janssen participants, hybrid immunity conferred greater protection than vaccine alone (HR: 0.03; 95% CI: 0.01–0.10). Too few infections were observed to draw statistical inferences comparing hybrid immunity to vaccine alone for other trials. Vaccination, previous infection, and hybrid immunity all provided near-complete protection against severe disease.

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Interpretation Previous infection, any hybrid immunity, and two-dose vaccination all provided substantial protection against symptomatic and severe COVID-19 through the early Delta period. Thus, as a surrogate for natural infection, vaccination remains the safest approach to protection.

Funding National Institutes of Health.

Keywords: COVID-19; Natural infection; Hybrid immunity; Vaccination

Research in context

Evidence before this study

As the percentage of individuals who have been exposed to or vaccinated against SARS-CoV-2 continues to grow, there is a need to understand whether previous infection provides comparable and/or complementary protection to vaccines against COVID-19. We searched PubMed Central from March 1, 2020 to June 1, 2022, with keywords related to SARS-CoV-2, hybrid immunity, previous infection, randomized control trial, protection, and reinfection. After identifying over one-hundred studies with these keywords, we first reviewed abstracts, then full-text articles of the most relevant manuscripts. Approximately a dozen articles evaluated efficacy or effectiveness of COVID-19 vaccines against COVID-19 infection and/or disease, and ten articles compared protection from natural infection with COVID-19, COVID-19 vaccines, and hybrid immunity. These studies generally utilized observational data from cohort studies originating from a single country/geographic location or reported secondary analysis of a randomized control trial. Additionally, the studies assessed baseline participant COVID-19 exposure using different methods, including self-reporting and antibody status, and analysed data from different pandemic periods dominated by varying circulating COVID-19 variants. Protection from vaccines and/or natural infection was demonstrated against future COVID-19 across these studies, but significantly varied in magnitude, and likely reflect the variants circulating during at-risk periods and duration of participant follow-up among other potentially confounding factors. Thus, there is still a need, and now an opportunity, to leverage more robust datasets to more decisively address these issues.

Added value of this study

Phase 3 placebo-controlled vaccine efficacy studies have not generally evaluated protection provided by previous infection or the combination of vaccination and previous infection (hybrid immunity). Individual patient data from an exceptionally diverse, international study population collated from four United States government-supported harmonized vaccine trials (Moderna, Janssen, AstraZeneca, Novavax) provide an unprecedented sample population to address this issue. Our analyses of these data identify that previous SARS-CoV-2 infection in study placebo recipients conferred a 92% reduction in the risk of COVID-19, with no severe cases in short-term follow-up. Hybrid immunity appeared generally highly protective—comparable to two-dose vaccines. For the one-dose Janssen trial, prior infection alone or in combination with vaccine provided greater protection than the single dose without prior infection.

Implications of all the available evidence

Natural infection with asymptomatic or mild disease occurring early in the pandemic produced significant protective benefit against future disease and severe COVID-19 for at least three to six months through the early Delta period. However, this protection likely varies based on the circulating variant, and natural infection without primary or booster vaccination may not sufficiently protect against all variants. Additionally previous infection comes with considerable risks of morbidity, mortality, and transmission that must be reconciled with protection against future COVID-19. Therefore, while our analysis confirms that both vaccination and previous infection protect against future disease from previously circulating variants, our data also highlight the importance of the current recommendations that adults who received single-dose Janssen receive a second dose to complete the primary series.

Introduction

Since coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization in March 2020, over 600 million cases and over 6.5 million deaths have been reported globally.[1–3] Although the rapid development of COVID-19 vaccines saved millions of lives,[4] vaccine rollout has been disproportionate on a global scale, and 33% of the world's population remains completely unvaccinated.[5,6] As more of the world's population experiences natural infection, it

is important to understand protection conferred by previous infection (PI) alone and in combination with vaccination (hybrid immunity).

Population-based studies have demonstrated that PI and vaccines provide substantial protection against future infection, and that hybrid immunity may provide superior protection compared to PI or vaccination alone.[7–10] Nevertheless, the reported differences detected between natural infection, vaccination, and hybrid immunity are small, and the studies are limited by lack of systematic case finding (ascertainment bias), accurate identification of previously infected individuals using serology, non-randomized subject selection, and incomplete information about circulating variants of concern. Furthermore, the need for vaccination in individuals with PI is controversial.[11]

Data from rigorous, prospective studies are required to characterize how PI and hybrid immunity impact durability of protection, COVID-19 disease severity, and differences in immunity among specific populations of interest (e.g., immunocompromised, elderly, etc.). These data are particularly relevant now, with a significant and growing global population of individuals with PI, and may inform future multifaceted approaches to national policies on best practices regarding vaccination of previously infected individuals. In this study, we analysed data from four phase 3 randomized placebo-controlled clinical trials (RCTs) of COVID-19 vaccines to characterize the protective efficacy of PI and to determine the impact of subsequent vaccination on clinical outcomes. While limitations such as low numbers of participants in prespecified analysis groups, limited follow-up time, and relative infrequency of outcomes restricted some analyses, consistency of study design across the U.S. government-sponsored phase 3 COVID-19 vaccine trials provided a unique opportunity to examine natural infection and hybrid immunity across multiple vaccine platforms and diverse study populations.[12]

Methods

Study population

Data for all participants from four randomized, controlled, COVID-19 vaccine clinical trials (COVE [Moderna, mRNA-1273, NCT04470427], AZD1222 [Oxford/AstraZeneca, AZD1222 (ChAdOx1 nCoV-19), NCT04516746], ENSEMBLE 1 [Janssen, Ad26.COV2.S, NCT04505722], and PREVENT-19 [Novavax, NVX-CoV2373, NCT04611802]), representing 134,935 unique individuals from Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa and the United States, were analysed.[13–16] These U.S. government-funded trials were part of Operation Warp Speed with harmonized protocols and a common Data Safety Monitoring Board.[12] All four trials identified participants with PI using baseline SARS-CoV-2 nucleocapsid (N) immunoassays (Elecsys Anti-SARS-CoV-2, Roche Diagnostics) and detected active infection at randomization using reverse-transcriptase (RT) PCR (Moderna used Eurofins Viracor, AstraZeneca used LabCorp/Roche Cobas, Janssen used University of Washington/Roche Cobas, Novavax used University of Washington/Abbott). Enrolment began at different timepoints during the pandemic, ranging from July 27, 2020 (Moderna) to December 27, 2020 (Novavax). Follow-up for this analysis concluded at the end of each blinded phase or start of blinded crossover (Moderna: March 31, 2021; Novavax: June 1, 2021; Janssen: July 17, 2021; AstraZeneca: July 30, 2021) (Fig. 1 and Supplementary Table S1).

PI was defined by positive SARS-CoV-2 nucleocapsid antibody or RT-PCR at enrolment; no previous infection (NPI) was defined as negative for both at enrolment. If both serology and RT-PCR were missing or one was negative and the other was missing, participants were excluded. Based on PI status and randomization assignment, participants were divided into four groups for this analysis: NPI/placebo; PI/placebo; NPI/vaccine; PI/vaccine. Since people with mild or asymptomatic SARS-CoV-2 seroconvert variably, we conducted sensitivity analyses whereby PI was defined solely by antibody positivity, excluding those who were RT-PCR positive but seronegative at baseline, since their future seroconversion status was technically undefined.[17–19]

The analysis was performed using existing data from trials conducted per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice guidelines, and applicable government regulations. For each trial, a central institutional review board or local ethics committee approved the protocol. All participants provided written informed consent before enrolment.

Outcome measures

As reported in initial phase 3 vaccine trials, the outcome of interest in these primary series assessments was symptomatic RT-PCR-confirmed SARS-CoV-2 infection occurring ≥14 days after the single dose for Janssen, ≥14 days after dose two for Moderna, ≥15 days after dose two for AstraZeneca, and ≥7 days after dose two for Novavax. Although definitions varied slightly across trials, solicited symptomatology overlapped significantly for both symptomatic (primary) and severe (secondary) outcomes (Supplementary Table S2).

Statistical analysis

To approximate a per-protocol analysis, we excluded enrolled participants who either did not receive all injections in the primary series per protocol or had COVID-19 diagnosed after enrolment but before the efficacy outcome follow-up period began. We did not need to explicitly exclude participants with other major protocol deviations as these were already excluded from the harmonized dataset. We calculated crude and

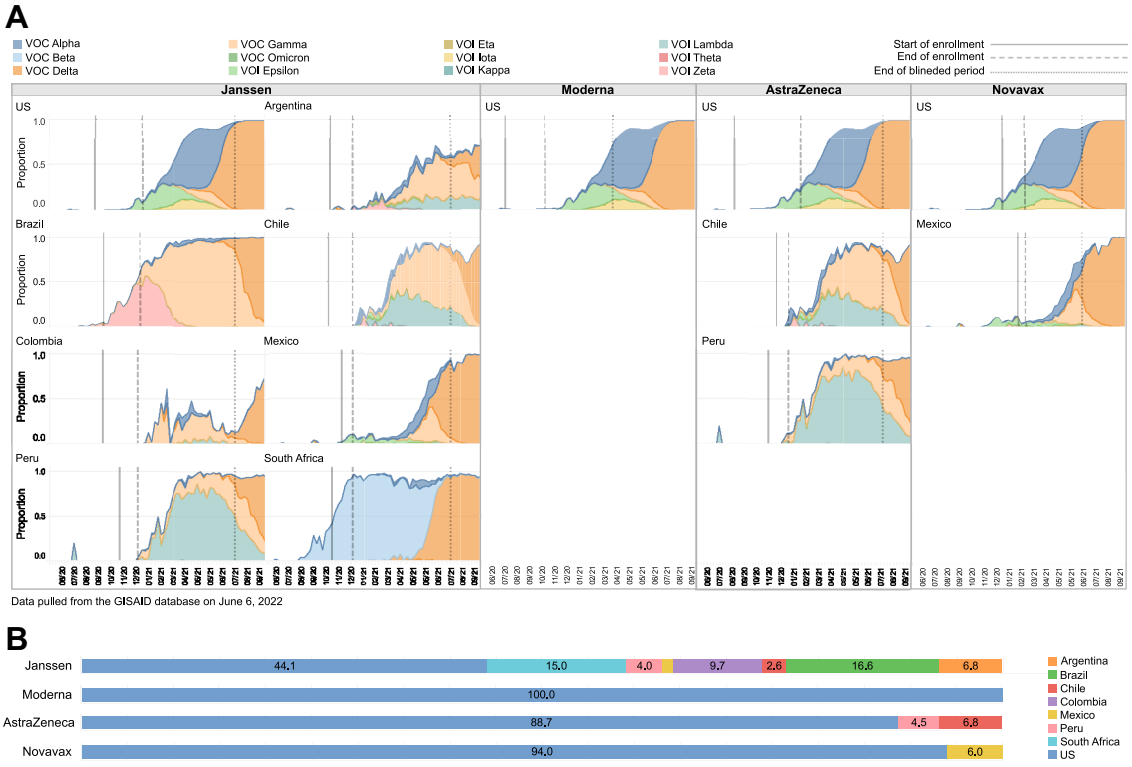


Fig. 1: **Population-level circulating SARS-CoV-2 strains during enrolment and follow-up of participants in included trials.** Proportion of SARS-CoV-2 variants of concern (VOC) and variants of interest (VOI) relative to total circulating SARS-CoV-2 by vaccine trial and geographic location over trial enrolment and follow-up period. Data obtained from GISAID (https://gisaid.org) (A). Proportion of enrolled participants from each geographic location by vaccine trial (B).

adjusted measures of efficacy for each trial. Multiple independent comparisons of interest were made: A. PI/placebo vs NPI/placebo; B. PI/vaccine vs. NPI/vaccine; C. PI/placebo vs. NPI/vaccine; D. PI/vaccine vs NPI/placebo; E. PI/vaccine vs. PI/placebo; and F. NPI/vaccine vs. NPI/placebo (primary outcome of phase 3 RCTs). For each study, crude relative risk was computed as the ratio of the proportion of cases among study participants (n/N) between the comparison groups. Hazard ratios (HR) between comparison groups of interest were estimated with a Cox proportional hazard model that used calendar time starting on September 4, 2020, and continuing through September 27, 2021.[20,21] Models were stratified by country and adjusted for age (≥65 vs. <65), sex, race, ethnicity, baseline risk of SARS-CoV-2 exposure as specified by the Occupational Safety & Health Administration (OSHA), and any baseline comorbidity, which are important COVID-19 risk factors available from the analysis dataset. Crude relative risk and HR estimates for NPI/placebo vs. PI/placebo were also computed using pooled placebo data from all studies; study and country were both stratification factors in the Cox model. Wald 95% confidence intervals of crude relative risk estimates and HR estimates based on Cox regression (as well as corresponding Wald-test p-value) were constructed assuming approximate normality of log (HR) when estimated disease prevalence is greater than zero in both comparison groups. Melded binomial confidence intervals of relative risk[22] were computed otherwise. When there were no cases in one of the two comparison groups, we obtained a Cox HR estimate, 95% CI, and p-value based on Firth's penalization method.[23]

We also report E-values for Cox HR estimate and its confidence interval as a summary measure of the evidence of a causal effect, which is the minimum strength of association that an unmeasured confounder would need to have with both exposure (on the relative risk scale) and time-to-event outcome (on the HR scale) to fully explain a specific observed exposure-outcome association, conditional on measured covariates (See Supplemental Methods).[24] Specifically, higher E-values are evidence of an association more robust with respect to unmeasured confounding, while lower E-values (closer to 1) suggest less robustness. Kaplan–Meier curves for cumulative incidence since randomization were generated for each vaccine/placebo and PI/NPI combination and for each trial separately. All statistical analyses were performed using R statistical software (version 4.0.4, R Foundation for Statistical Computing).

Variant-specific relative risks for comparison groups defined above were also computed for all studies to determine efficacy against symptomatic infection with i) the reference strain, ii) non-reference strain lineages, and iii) specific variants within Janssen, including Beta and Delta in South Africa, and Alpha, Epsilon, Gamma, Lambda, and Zeta in all countries in which each respective variant was found. In a sensitivity analysis, we also assessed relative risks for each comparison group by restricting analysis to participants enrolled both within and outside the United States.

Role of the funding source

Representatives of the funding source (NIAID) contributed to study design; collection, analysis, and interpretation of data; writing of the manuscript; and in the decision to submit the manuscript.

Results

Characteristics of the participants

Of the 134,935 participants, 131,306 (97.3%) were included in the per-protocol analysis (Janssen N = 43,598; Moderna N = 29,166; AstraZeneca N = 30,221; Novavax N = 28,321; Supplementary Fig. S1). Demographic data for each trial, including risk factors for severe COVID-19, are shown in Table 1. Median follow-up time varied by study, ranging from three to six months. In total, 52,045 (39.6%) participants belonged to the NPI/placebo group, 3367 (2.6%) to the PI/placebo group, 71,622 (54.5%) to the NPI/vaccine group, and 4272 (3.3%) to the PI/vaccine group. Among 7639 participants with PI, 92.8% were seropositive/RT-PCR negative, 0.1% were seropositive/RT-PCR missing, 5.3% were seronegative/RT-PCR positive, and 1.8% were seropositive and RT-PCR positive. By trial, PI was identified in 4456 (10.2%) participants from Janssen, 470 (1.6%) from Moderna, 865 (2.9%) from AstraZeneca, and 1848 (6.5%) from Novavax.

During Moderna and AstraZeneca trial enrolment and data collection periods, population-level circulating SARS-CoV-2 variants were similar (Fig. 1). In contrast, the Janssen and Novavax trials began later and had later data cutoffs, introducing greater variability in circulating variants by time and geographic location. Most notably, this included high circulation of the Beta (B.1.351) and early Delta (B.1.617.2) variants in South Africa, the Gamma (P.1) variant in South America.

Censoring proportions before data cutoff were estimated to be 9.7%, 5.0%, 4.5%, and 3.1% for the Novavax, AstraZeneca, Moderna, and Janssen trials, respectively.

Risk of symptomatic COVID-19

During follow-up, the cumulative incidence of symptomatic COVID-19 was 1600 (3.7%) participants in Janssen, 810 (2.8%) in Moderna, 326 (1.1%) in AstraZeneca, and 89 (0.3%) in Novavax (Fig. 2). Sequencing was available for 2099/2825 (74.3%) of those infections, of which 860 (41%) corresponded to non-ancestral strain variants (Supplementary Table S3).

Overall, participants with PI/placebo had a 92% decreased hazard of COVID-19 compared to NPI/placebo participants (overall HR: 0.08; 95% CI:0.05–0.13; Table 2 A). Although the small number of cases among the PI/placebo participants requires cautious interpretation, the hazard reduction for those with PI/placebo was similar to NPI participants receiving two doses of Moderna, AstraZeneca, or Novavax vaccines (Table 2 C). In contrast, for the Janssen trial, participants with PI/placebo had a decreased risk for COVID-19 compared to those with NPI/Janssen (HR: 0.14; 95% CI: 0.08–0.24; Table 2 C). This suggests that PI conveyed greater protection than the single dose of Janssen vaccine alone, however, participants with Janssen/hybrid immunity had lower risk of future infection compared to placebo recipients with or without PI (Table 2 B,D,E). For participants in the other three trials, the small denominators and few cases result in point estimates with wide confidence intervals, limiting statistical inferences on hybrid immunity (Table 2 B,E). However, hybrid immunity with AstraZeneca did show additional protection compared to NPI/AstraZeneca (Table 2 B). Furthermore, hybrid immunity with any of these vaccines reduced future COVID-19 risk compared to NPI/placebo (Table 2 D). Additionally, our findings corroborate published results from these trials that NPI participants who received any vaccine had a 56–93% decreased hazard of infection compared to NPI/placebo participants (Table 2 F). After excluding participants who were PCR-positive and seronegative at enrolment, results showed similar findings (Supplementary Table S4).

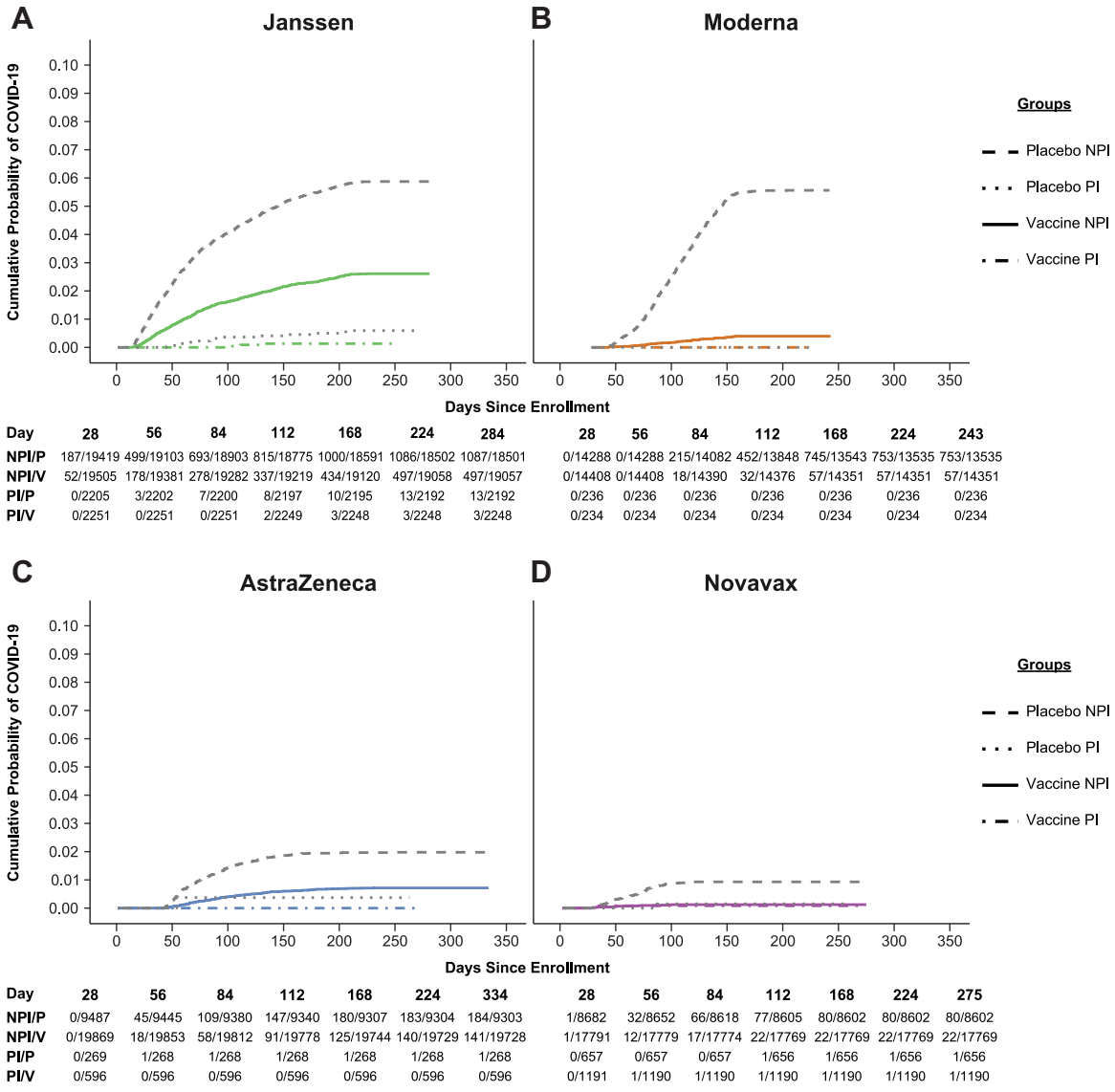
On sensitivity analysis, U.S. participants showed similar findings, with the exception of Janssen recipients (Supplementary Table S5). While hybrid immunity with Janssen vaccine still provided better efficacy against future infection compared to NPI/placebo and NPI/Janssen, hybrid immunity with Janssen did not significantly improve protection compared to PI alone (Supplementary Table S5 B,D,E). Similarly, for PI/placebo and NPI/Janssen, the point estimate for the HR was 0.19 (95% CI:0.03–1.35), suggesting enhanced protection from PI compared to single-dose Janssen, although the wide confidence intervals imply substantial uncertainty for this estimate (Supplementary Table S5 C). Findings for Janssen vaccine in non-U.S. participants was unchanged from the primary analysis (Supplementary Table S6).

On sub-analysis examining risk of specific variants in the Janssen trial, we identified similar trends in efficacy, but statistical inferences were again limited by few cases available for each comparison (Supplementary Tables S7–S15).

Characteristics	Janssen		Moderna		AstraZeneca		Novavax	
	PI[a] (N = 4456)	NPI[a] (N = 39,142)	PI (N = 470)	NPI (N = 28,696)	PI (N = 865)	NPI (N = 29,356)	PI (N = 1848)	NPI (N = 26,473)
Randomization (%)								
Placebo	2205 (49.5)	19,588 (50.0)	236 (50.2)	14,288 (49.8)	269 (31.1)	9487 (32.3)	657 (35.6)	8682 (32.8)
Vaccine	2251 (50.5)	19,554 (50.0)	234 (49.8)	14,408 (50.2)	596 (68.9)	19,869 (67.7)	1191 (64.4)	17,791 (67.2)
Median follow-up (days) (range)								
	176 (8–273)	119 (1–284)	143.5 (29–228)	146 (28–243)	125 (1–270)	96 (1–334)	93 (3–274)	92 (2–275)
Age (years) (%)								
<65	3915 (87.9)	31,152 (79.6)	418 (88.9)	21,420 (74.6)	756 (87.4)	22,643 (77.1)	1706 (92.3)	23,211 (87.7)
≥65	541 (12.1)	7990 (20.4)	52 (11.1)	7276 (25.4)	109 (12.6)	6713 (22.9)	142 (7.7)	3262 (12.3)
Comorbidity (%)								
No	2261 (50.7)	23,034 (58.8)	383 (81.5)	22,123 (77.1)	356 (41.2)	11,765 (40.1)	947 (51.2)	13,999 (52.9)
Yes	2195 (49.3)	16,108 (41.2)	87 (18.5)	6573 (22.9)	509 (58.8)	17,591 (59.9)	901 (48.8)	12,474 (47.1)
Country (%)								
Argentina	179 (4.0)	2809 (7.2)	–	–	–	–	–	–
Brazil	478 (10.7)	6745 (17.2)	–	–	–	–	–	–
Chile	63 (1.4)	1070 (2.7)	–	–	51 (5.9)	2107 (7.2)	–	–
Columbia	525 (11.8)	3701 (9.5)	–	–	–	–	–	–
Mexico	54 (1.2)	425 (1.1)	–	–	–	–	174 (9.4)	1545 (5.8)
Peru	624 (14.0)	1146 (2.9)	–	–	95 (11.0)	1311 (4.5)	–	–
South Africa	1583 (35.5)	4968 (12.7)	–	–	–	–	–	–
United States	950 (21.3)	18,278 (46.7)	470 (100.0)	28,696 (100.0)	719 (83.1)	25,938 (88.4)	1674 (90.6)	24,928 (94.2)
Ethnicity (%)								
Hispanic or latino	2114 (47.4)	17,632 (45.0)	202 (43.0)	5650 (19.7)	296 (34.2)	6529 (22.2)	602 (32.6)	5621 (21.2)
Not hispanic or latino	2219 (49.8)	20,531 (52.5)	264 (56.2)	22,782 (79.4)	556 (64.3)	22,394 (76.3)	1229 (66.5)	20,796 (78.6)
Unknown	123 (2.8)	979 (2.5)	4 (0.9)	264 (0.9)	13 (1.5)	433 (1.5)	17 (0.9)	56 (0.2)
Race (%)								
American Indian or Alaska Native[b]	880 (19.7)	3250 (8.3)	1 (0.2)	225 (0.8)	67 (7.7)	1150 (3.9)	254 (13.7)	1636 (6.2)
Asian	50 (1.1)	1368 (3.5)	10 (2.1)	1344 (4.7)	25 (2.9)	1281 (4.4)	30 (1.6)	1162 (4.4)
Black or African American	1748 (39.2)	6730 (17.2)	139 (29.6)	2763 (9.6)	187 (21.6)	2310 (7.9)	409 (22.1)	2884 (10.9)
Native Hawaiian or Other Pacific Islander	7 (0.2)	96 (0.2)	–	67 (0.2)	5 (0.6)	74 (0.3)	6 (0.3)	58 (0.2)
White	1256 (28.2)	24,336 (62.2)	294 (62.6)	22,867 (79.7)	519 (60.0)	23,367 (79.6)	1110 (60.1)	20,144 (76.1)
Multiple	329 (7.4)	2112 (5.4)	5 (1.1)	610 (2.1)	42 (4.9)	680 (2.3)	21 (1.1)	444 (1.7)
Other	186 (4.2)	1250 (3.2)	21 (4.5)	820 (2.9)	20 (2.3)	494 (1.7)	18 (1.0)	145 (0.5)
Risk of exposure per OSHA (%)								
Very high exposure risk	–	–	–	–	67 (7.7)	1783 (6.1)	–	–
High exposure risk	169 (3.8)	1092 (2.8)	183 (38.9)	10,018 (34.9)	220 (25.4)	6265 (21.3)	192 (10.4)	2515 (9.5)
Medium exposure risk	53 (1.2)	504 (1.3)	118 (25.1)	6015 (21.0)	339 (39.2)	12,329 (42.0)	733 (39.7)	8510 (32.1)
Lower exposure risk	4230 (94.9)	37,485 (95.8)	–	–	236 (27.3)	8677 (29.6)	923 (49.9)	15,448 (58.4)
Unknown	4 (0.1)	61 (0.2)	169 (36.0)	12,663 (44.1)	3 (0.3)	302 (1.0)	–	–
Sex (%)								
Female	2240 (50.3)	17,412 (44.5)	215 (45.7)	13,641 (47.5)	313 (36.2)	13,061 (44.5)	811 (43.9)	12,834 (48.5)
Male	2216 (49.7)	21,723 (55.5)	255 (54.3)	15,055 (52.5)	552 (63.8)	16,295 (55.5)	1037 (56.1)	13,639 (51.5)
Intersex	–	6 (0.0)	–	–	–	–	–	–
Unknown	–	1 (0.0)	–	–	–	–	–	–

Per-protocol cohorts are participants who received all vaccinations as planned. [a]PI (Previous infection) is defined as seropositive or PCR positive. NPI (No previous infection) is defined as seronegative and PCR negative. [b]Category is defined across all clinical sites. Indigenous people from South America were classified together with the American Indian or Alaska Native United States and Mexico demographic according to the FDA definition (American Indian or Alaska Native: A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment). In this analysis, the Moderna, AstraZeneca, Janssen, and Novavax trials included 226, 269, 226, and 1890 participants, respectively, who identified as American Indian or Alaskan Native from North America.

Table 1: **Demographic and clinical characteristics of participants included in the analysis.**



Day	28	56	84	112	168	224	284	28	56	84	112	168	224	243
NPI/P	187/19419	499/19103	693/18903	815/18775	1000/18591	1086/18502	1087/18501	0/14288	0/14288	215/14082	452/13848	745/13543	753/13535	753/13535
NPI/V	52/19505	178/19381	278/19282	337/19219	434/19120	497/19058	497/19057	0/14408	0/14408	18/14390	32/14376	57/14351	57/14351	57/14351
PI/P	0/2205	3/2202	7/2200	8/2197	10/2195	13/2192	13/2192	0/236	0/236	0/236	0/236	0/236	0/236	0/236
PI/V	0/2251	0/2251	0/2251	2/2249	3/2248	3/2248	3/2248	0/234	0/234	0/234	0/234	0/234	0/234	0/234

Day	28	56	84	112	168	224	334	28	56	84	112	168	224	275
NPI/P	0/9487	45/9445	109/9380	147/9340	180/9307	183/9304	184/9303	1/8682	32/8652	66/8618	77/8605	80/8602	80/8602	80/8602
NPI/V	0/19869	18/19853	58/19812	91/19778	125/19744	140/19729	141/19728	1/17791	12/17779	17/17774	22/17769	22/17769	22/17769	22/17769
PI/P	0/269	1/268	1/268	1/268	1/268	1/268	1/268	0/657	0/657	0/657	1/656	1/656	1/656	1/656
PI/V	0/596	0/596	0/596	0/596	0/596	0/596	0/596	0/1191	1/1190	1/1190	1/1190	1/1190	1/1190	1/1190

***Fig. 2:* Cumulative incidence of COVID-19 by trials and groups in the per-protocol cohorts.** Cumulative incidence of COVID-19 during the follow-up period in days for the Janssen trial (A), the Moderna trial (B), the AstraZeneca trial (C), and the Novavax trial (D) by SARS-CoV-2 exposure status at enrolment and vaccination status (placebo/no previous infection (NPI); placebo/previous infection (PI); vaccine/NPI; vaccine/PI).

Risk of severe COVID-19

Less than 0.1% of 71,835 vaccinated participants and none of the 7639 participants with PI or hybrid immunity developed severe COVID-19 (Table 3). In contrast, 0.6% of the 52,045 participants in the NPI/placebo group experienced severe COVID-19. COVID-19 related deaths were low overall in the analysis cohort (0.2% for Novavax, 0.1% for AstraZeneca, 0.1% for Moderna, and 0.2% for Janssen) limiting analysis of this as a separate outcome.

Discussion

The COVID-19 Prevention Network (CoVPN) was formed by the National Institutes of Allergy and Infectious Disease (NIAID) to engage a network of highly experienced, funded vaccine trial sites with established infrastructure, leadership, and access to geographically and demographically diverse populations for the conduct of COVID-19 vaccine trials using harmonized clinical protocols[12] The network studies generated a robust database to evaluate individual and combined protective efficacy of previous SARS-CoV-2 infection and four different primary vaccination regimens against COVID-19 occurring between July 2020 and July 2021. We utilized this individual-level, prospectively collected data to examine the impact of PI on protective efficacy against circulating variants in the

Vaccine trial	Placebo NPI n/N (%)	Vaccine NPI n/N (%)	Placebo PI n/N (%)	Vaccine PI n/N (%)	Crude relative risk[a] (95% CI)	Cox hazard ratio[b] (95% CI)	p-value	E-values RR, CI
A. Efficacy of previous infection								
Janssen	1087/19,588 (5.5)		13/2205 (0.6)		0.11 (0.06, 0.18)	0.07 (0.04, 0.13)	<0.001	26.8, 15.2
Moderna	753/14,288 (5.3)		0/236 (0.0)		0.00 (0.00, 0.29)	0.03 (0.00, 0.24)	<0.001	56.7, 7.9
AstraZeneca	184/9487 (1.9)		1/269 (0.4)		0.19 (0.03, 1.36)	0.12 (0.02, 0.88)	0.037	15.7, 1.5
Novavax	80/8682 (0.9)		1/657 (0.2)		0.17 (0.02, 1.19)	0.14 (0.02, 1.04)	0.055	13.3, 1.0
Total[c]	2104/52,045 (4.0)		15/3367 (0.4)		0.11 (0.07, 0.18)	0.08 (0.05, 0.13)	<0.001	25.6, 15.3
B. Efficacy of previous infection before vaccine								
Janssen		497/19,554 (2.5)		3/2251 (0.1)	0.05 (0.02, 0.16)	0.03 (0.01, 0.09)	<0.001	64.8, 20.4
Moderna		57/14,408 (0.4)		0/234 (0.0)	0.00 (0.00, 4.08)	0.60 (0.00, 4.24)	0.696	2.7, 1.0
AstraZeneca		141/19,869 (0.7)		0/596 (0.0)	0.00 (0.00, 0.88)	0.07 (0.00, 0.48)	0.001	28.3, 3.6
Novavax		22/17,791 (0.1)		1/1191 (0.1)	0.68 (0.09, 5.03)	0.66 (0.09, 4.97)	0.689	2.4, 1.0
C. Efficacy of previous infection compared to vaccine and no previous infection								
Janssen		497/19,554 (2.5)	13/2205 (0.6)		0.23 (0.13, 0.40)	0.14 (0.08, 0.24)	<0.001	13.8, 7.7
Moderna		57/14,408 (0.4)	0/236 (0.0)		0.00 (0.00, 4.05)	0.54 (0.00, 3.82)	0.633	3.1, 1.0
AstraZeneca		141/19,869 (0.7)	1/269 (0.4)		0.52 (0.07, 3.73)	0.31 (0.04, 2.26)	0.249	5.8, 1.0
Novavax		22/17,791 (0.1)	1/657 (0.2)		1.23 (0.17, 9.12)	1.16 (0.15, 8.75)	0.883	1.6, 1.0
D. Efficacy of vaccine in those with previous infection compared to those with no previous infection and placebo								
Janssen	1087/19,588 (5.5)			3/2251 (0.1)	0.02 (0.01, 0.07)	0.02 (0.01, 0.05)	<0.001	122.8, 39.1
Moderna	753/14,288 (5.3)			0/234 (0.0)	0.00 (0.00, 0.30)	0.04 (0.00, 0.26)	<0.001	51.8, 7.2
AstraZeneca	184/9487 (1.9)			0/596 (0.0)	0.00 (0.00, 0.32)	0.03 (0.00, 0.19)	<0.001	70.5, 9.9
Novavax	80/8682 (0.9)			1/1191 (0.1)	0.09 (0.01, 0.65)	0.08 (0.01, 0.59)	0.013	23.9, 2.8
E. Efficacy of vaccine in those with previous infection								
Janssen			13/2205 (0.6)	3/2251 (0.1)	0.23 (0.06, 0.79)	0.21 (0.06, 0.73)	0.014	9.2, 2.1
Moderna			0/236 (0.0)	0/234 (0.0)		–	–	–
AstraZeneca			1/269 (0.4)	0/596 (0.0)	0.00 (0.00, 17.58)	0.09 (0.00, 1.69)	0.105	21.7, 1.0
Novavax			1/657 (0.2)	1/1191 (0.1)	0.55 (0.03, 8.81)	0.56 (0.03, 10.50)	0.701	2.9, 1.0
F. Efficacy of vaccine in those with no previous infection (main trial readout)								
Janssen	1087/19,588 (5.5)	497/19,554 (2.5)			0.46 (0.41, 0.51)	0.44 (0.39, 0.49)	<0.001	4.0, 3.5
Moderna	753/14,288 (5.3)	57/14,408 (0.4)			0.08 (0.06, 0.10)	0.07 (0.05, 0.09)	<0.001	28.1, 21.4
AstraZeneca	184/9487 (1.9)	141/19,869 (0.7)			0.37 (0.29, 0.46)	0.34 (0.27, 0.42)	<0.001	5.3, 4.2
Novavax	80/8682 (0.9)	22/17,791 (0.1)			0.13 (0.08, 0.21)	0.12 (0.08, 0.20)	<0.001	15.6, 9.5

This table is based on the per-protocol population in each study. Per-protocol cohorts are participants who received all vaccinations as planned. Cases are defined as 14 days after the second vaccination, 15 days after the second vaccination, 14 days after the (single) vaccination, and 7 days after the second vaccination for the Moderna, AstraZeneca, Janssen, and Novavax studies, respectively. PI (Previous infection) is defined as seropositive or PCR positive. NPI (No previous infection) is defined as seronegative and PCR negative. [a]Crude relative risks are calculated as PIs over NPIs, vaccine recipients over placebo recipients. [b]Cox models are adjusted by age (binary), sex, race, risk of exposure, ethnicity, and comorbidity (binary). 95% CI for Cox hazard ratios cannot be calculated if no cases in either comparison group (–). [c]Cox model of pooled studies is stratified by study and country. Other Cox models are stratified by country.

Table 2: **COVID-19 case rate comparison among per-protocol subsets by protocol.**

context of clinical trials in which participants volunteered to be randomized, thus reducing bias resulting from non-random assignment to the PI and NPI groups unavoidable in other studies.[9,25,26]

Our study's key results indicate that natural infection occurring early in the pandemic produced significant protective benefit against future disease and severe COVID-19 for at least three to six months against the SARS-CoV-2 variants circulating during follow-up. Notably, this protection was observed in participants who likely had either asymptomatic or mild disease before enrolment, as known COVID-19 infection was an exclusion criterion for the Moderna, AstraZeneca, and Novavax trials. Our estimates of up to 92% protection conferred by natural infection are comparable to other studies examining reinfection risk.[9,25–31] However, this protection likely varies based on the timing of previous exposure and circulating variant. For example, Altarawneh et al. found that protection conferred by PI with non-Omicron variants was robust against reinfection with the Alpha variant (90.2%; 95% CI: 60.2%–97.6%), the Beta variant (85.7%; 95% CI: 75.8%–91.7%), and the Delta variant (92.0%; 95% CI: 87.9%–94.7%), but decreased to 56.0% (95% CI:50.6%–60.9%) for the Omicron variant.[30] Although, importantly, protection against severe COVID-19 was similar across variants.[30] Thus, natural infection without primary or booster vaccination may not sufficiently protect against all variants.[26,32,33] Our data, that mostly excluded individuals with a history of symptomatic COVID-19, also highlights that mild and/or asymptomatic disease could still provide substantial and potentially more durable (given

Vaccine trial	Placebo NPI n/N (%)	Vaccine NPI n/N (%)	Placebo PI n/N (%)	Vaccine PI n/N (%)	Crude relative risk[a] (95% CI)	Cox hazard ratio[b] (95% CI)	p-value	E-values RR, CI
A. Efficacy of previous infection								
Janssen	209/19,588 (1.1)		0/2205 (0.0)		0.00 (0.00, 0.16)	0.01 (0.00, 0.08)	<0.001	178.4, 25.7
Moderna	106/14,288 (0.7)		0/236 (0.0)		0.00 (0.00, 2.13)	0.31 (0.00, 2.13)	0.305	6.0, 1.0
AstraZeneca	10/9487 (0.1)		0/269 (0.0)		0.00 (0.00, 15.63)	1.36 (0.01, 11.29)	0.842	2.1, 1.0
Novavax	4/8682 (0.0)		0/657 (0.0)		0.00 (0.00, 19.97)	1.31 (0.01, 12.23)	0.863	1.9, 1.0
Total[c]	329/52,045 (0.6)		0/3367 (0.0)		0.00 (0.00, 0.17)	0.01 (0.00, 0.08)	<0.001	175.3, 25.3
B. Efficacy of previous infection before vaccine								
Janssen		56/19,554 (0.3)		0/2251 (0.0)	0.00 (0.00, 0.59)	−0.04 (0.00, 0.26)	<0.001	53.8, 7.1
Moderna		2/14,408 (0.0)		0/234 (0.0)	0.00 (0.00, 326.08)	−12.88 (0.09, 158.32)	0.213	25.2, 1.0
AstraZeneca		1/19,869 (0.0)		0/596 (0.0)	0.00 (0.00, 1298.03)	−6.68 (0.05, 125.13)	0.332	12.8, 1.0
Novavax		0/17,791 (0.0)		0/1191 (0.0)	–	–	–	–
C. Efficacy of previous infection compared to vaccine and no previous infection								
Janssen		56/19,554 (0.3)	0/2205 (0.0)		0.00 (0.00, 0.60)	0.04 (0.00, 0.27)	<0.001	52.0, 6.9
Moderna		2/14,408 (0.0)	0/236 (0.0)		0.00 (0.00, 323.33)	12.27 (0.09, 150.84)	0.219	24.0, 1.0
AstraZeneca		1/19,869 (0.0)	0/269 (0.0)		0.00 (0.00, 2870.24)	18.24 (0.12, 341.88)	0.177	36.0, 1.0
Novavax		0/17,791 (0.0)	0/657 (0.0)		–	–	–	–
D. Efficacy of vaccine in those with previous infection compared to those with no previous infection and placebo								
Janssen	209/19,588 (1.1)			0/2251 (0.0)	0.00 (0.00, 0.15)	0.01 (0.00, 0.07)	<0.001	183.6, 26.4
Moderna	106/14,288 (0.7)			0/234 (0.0)	0.00 (0.00, 2.15)	0.33 (0.00, 2.27)	0.339	5.5, 1.0
AstraZeneca	10/9487 (0.1)			0/596 (0.0)	0.00 (0.00, 7.08)	0.55 (0.00, 4.68)	0.658	3.0, 1.0
Novavax	4/8682 (0.0)			0/1191 (0.0)	0.00 (0.00, 11.03)	0.71 (0.01, 6.62)	0.807	2.2, 1.0
E. Efficacy of vaccine in those with previous infection								
Janssen			0/2205 (0.0)	0/2251 (0.0)	–	–	–	–
Moderna			0/236 (0.0)	0/234 (0.0)	–	–	–	–
AstraZeneca			0/269 (0.0)	0/596 (0.0)	–	–	–	–
Novavax			0/657 (0.0)	0/1191 (0.0)	–	–	–	–
F. Efficacy of vaccine in those with no previous infection (main trial readout)								
Janssen	209/19,588 (1.1)	56/19,554 (0.3)			0.27 (0.20, 0.36)	0.26 (0.19, 0.35)	<0.001	7.2, 5.2
Moderna	106/14,288 (0.7)	2/14,408 (0.0)			0.02 (0.00, 0.08)	0.02 (0.00, 0.07)	<0.001	112.5, 27.4
AstraZeneca	10/9487 (0.1)	1/19,869 (0.0)			0.05 (0.01, 0.37)	0.05 (0.01, 0.36)	0.003	42.9, 5.0
Novavax	4/8682 (0.0)	0/17,791 (0.0)			0.00 (0.00, 0.74)	0.05 (0.00, 0.45)	0.005	41.6, 3.9

This table is based on the per-protocol population in each study. Per-protocol cohorts are participants who received all vaccinations as planned. Cases are defined as 14 days after the second vaccination, 15 days after the second vaccination, 14 days after the (single) vaccination, and 7 days after the second vaccination for the Moderna, AstraZeneca, Janssen, and Novavax studies, respectively. PI (Previous infection) is defined as seropositive or PCR positive. NPI (No previous infection) is defined as seronegative and PCR negative. [a]Crude relative risks are calculated as PIs over NPIs, vaccine recipients over placebo recipients. [b]Cox models are adjusted by age (binary), sex, race, risk of exposure, ethnicity, and comorbidity (binary). 95% CI for Cox hazard ratios cannot be calculated if no cases in either comparison group (–). [c]Cox model of pooled studies is stratified by study and country. Other Cox models are stratified by country.

Table 3: **Severe COVID-19 Case Rate Comparison among Per-protocol subsets by Protocol.**

uncertainty in timing of prior exposure) compared to vaccine-induced immunity, against future infection through the early Delta wave, in agreement with other studies.[2,6,9,34–36] Additionally, we demonstrate that reinfection among those with PI resulted in no severe cases of COVID-19, which is similar to findings described by Abu-Raddad et al., and is reassuring as the number of those who have experienced primary infection increases.[37] It is, however, important to underscore that PI comes with considerable risks of morbidity, mortality, and transmission that must be reconciled with protection against future COVID-19. In addition to a case fatality rate among unvaccinated adults that ranges from 0.05% to 20.3% depending on age and comorbidities, SARS-CoV-2-related hospitalizations have fluctuated between 2 and 39 per 100,000 among adults in the United States.[38,39] Furthermore, up to half of survivors may indeterminately experience sequelae of long COVID-19 such as fatigue, shortness of breath, and concentration, memory, and mobility difficulties,[40] though this may be less common in paediatric populations.[41] Therefore, while our analysis confirms that both vaccination and PI protect against future disease from previously circulating variants, other studies comparing COVID-19 outcomes in vaccinated versus unvaccinated individuals clearly document that vaccination continues to be the safest approach.[42,43]

Although current recommendations are for adults who received the single-dose Janssen vaccine to receive a second dose to complete the primary series, our data highlight the value of these recommendations for people with NPI. This is supported by our findings that

those with Janssen hybrid immunity experienced better protection against future infection compared to those who only received the Janssen single dose or had PI. The Janssen data also provided sufficient cases to estimate the hazard ratio for hybrid immunity compared to NPI and placebo at 0.02 (0.01, 0.05), consistent with 0.03 hybrid protection predicted by Altarawneh et al.[31] and reported by Sadoff et al.[44] This makes protection from hybrid immunity with Janssen more comparable to the two-dose vaccines, which already take advantage of priming, though possibly with a shorter interval between prime and boost compared to PI Janssen recipients. Similarly, Hardt et al. found that a homologous booster dose with Janssen also increased vaccine efficacy estimates.[45] As participants in the Janssen trial were not excluded based on SARS-CoV-2 infection history,[16] participants with PI represent a more heterogeneous priming exposure ranging from asymptomatic to severe COVID-19. This heterogeneity may create differential immune protection when combined with Janssen vaccine.[34,35,46] Additionally, Janssen PI participants may have differences in the variant of their priming exposure due to the geographic diversity of the Janssen trial and differences in circulating variants at time of enrolment by country. This may account for differences in estimates identified on the sensitivity analysis restricting comparisons to U.S. and non-U.S. participants.

The high level of protection among those with PI who received the two-dose vaccines resulted in a paucity of infections detected during study follow-up that limited our analysis of hybrid immunity efficacy and may reflect sparse data bias.[47] Nevertheless, the low case counts for those with hybrid immunity and confidence intervals directionally align with enhanced protection from hybrid immunity with these two-dose vaccines compared to NPI/placebo and hybrid immunity with AstraZeneca compared to NPI/AstraZeneca. While numerous studies have identified superior protection from hybrid immunity versus vaccine alone, these primarily examined infection risk during peak circulation of the Delta (B.1.617.2) or Omicron variants.[7–9,26,48,49] However, the infections after vaccination in this study come from either before (Moderna, AstraZeneca) or early (Novavax, Janssen) in the Delta variant wave. Thus, differences in circulating variants at initial and re-exposure likely impact the degree of benefit obtained from hybrid immunity versus vaccine alone. Several studies have reported that after infection, initial protection is similar between vaccinated and unvaccinated individuals.[9,48,50] However, after six to 12 months, those with hybrid immunity experience more enduring protection, while those who are unvaccinated are more likely to experience a waning effect.[9,48,50] Thus, the limited follow-up of three to six months in this study may limit our ability to observe the full benefit of hybrid immunity over PI alone.

Our study has several other limitations. First, although our analysis includes a robust, high-quality dataset of nearly 135,000 individuals from multisite international clinical trials, interpretation is limited by the relatively few participants with PI. Many of these participants came from the Janssen trial, thus limiting inferential results for other trials and cross-vaccine comparisons. Furthermore, while inclusion/exclusion criteria and case ascertainment across studies generally aligned, some differences could bias protective efficacy estimates, including specimen collection methods, assays used, geographic locations, and circulating variants before and after study enrolment. Second, our study cannot distinguish when a PI occurred. This timing may impact future infection risk due to waning immunity or circulation of vaccine-resistant variants. However, we saw no difference in estimates when restricting analyses to seropositive participants. Additionally, we identified PI by RT-PCR or anti-N antibody assay. However, it is known that presence of anti-N antibody is more variable among those with asymptomatic or mild infection.[51] Third, the limited efficacy surveillance period and rapid changes in SARS-CoV-2 variant circulation may limit the interpretation of these results in the context of the current pandemic. Fourth, randomization was not stratified based on PI, and while our focus was on the statistically adjusted relative risks, residual confounding may bias efficacy estimates (it is also worth noting the inherent bias in hazard ratios[52]). However, E-value assessment for potential unmeasured confounding supported that unmeasured confounding was unlikely. The E-value for natural infection had a lower confidence interval of 15; thus, if an unmeasured confounder increased both risk of COVID-19 and risk of natural infection 15-fold, then significance would be lost. The largest measured factor in our study had an HR of 3.4 (American Indian or Alaska Native vs Native Hawaiian or other Pacific Islander) while all other factors had HRs of less than 1.6, well below the lower confidence interval of (1/0.13 = 7.7) for NPI/PI HR, providing reasonably strong evidence of causality.[25] Finally, this study does not incorporate COVID-19 booster vaccine strategies, including heterologous and variant boosting, which will be important considerations for future studies.

In conclusion, SARS-CoV-2 infection before study enrolment provided substantial protection against reinfection during blinded/pre-crossover follow-up of the four clinical trials. However, COVID-19 vaccines also protect and avoid the serious complications and transmission risks of SARS-CoV-2 infection. Hybrid immunity may confer additional benefit. Clinicians and health officials should encourage individuals to vaccinate against SARS-CoV-2 regardless of infection history.

Contributors

AR, MBL, TCSM, CaAR, ChAR, and RMM synthesized the analyses and wrote the initial manuscript draft. YiH, CY, PBG, HEJ, YuH, and DF designed, performed, and interpreted statistical analyses. LRB, HME,

BG, GEG, CLG, JGK, BL, IH, FS, LMD, KMN, LC, PAG, SRW, and KLK designed the study, oversaw data interpretation, and performed manuscript revisions. YiH and YuH had access to and verified the underlying data. All authors contributed to data interpretation and to the review and editing of the final manuscript. All authors had full access to all the data, read and approved the final manuscript, and accept final responsibility for the decision to submit for publication. The COVID-19 Prevention Network (CoVPN) comprises individuals who facilitated the studies that contributed data to this paper.

Data sharing statement

The data underlying these results will be shared at the discretion of the original study sponsors.

Declaration of interests

YiH, CY, TCSM, RMM, HMES, BG, GEG, PBG, JGK, LC, and DF declare no conflicts of interest. AMR declares unrelated grants or contracts from NIAID, I4kids, Society to Improve Diagnosis in Medicine, Beckwith Clinical Innovation Award, CTSI COVID-19 Pilot Award; unrelated consulting fees from Pfizer; unrelated support for attending meetings/travel from IDweek (2023); and an unrelated unpaid leadership role as the medical director of Human Milk Science Institute and Biobank. MBL declares unrelated grants or contracts from NIH VTEU paid to their institution. CaAR declares unrelated grants or contracts paid to their institution from Novavax and Moderna. ChAR declares unrelated grants or contracts paid to their institution from BioFire, Inc, GSK, Merck, Micron, MedImmune, Novavax, PaxVax, Regeneron, Pfizer, Sanofi-Pasteur, Janssen, Moderna, NIH, and CDC; unrelated royalties or licenses from Meissa Vaccines, Inc; and unrelated patent interests for "RSV Live-Attenuated Vaccine Candidates with Deleted G-Protein Mucin Domains" and "Chimeric RSV, Immunogenic, Compositions, and Methods of Use". LRB declares unrelated grants or contracts paid to their institution from NIH/Harvard Medical School and Wellcome Trust/Gates Foundation; unrelated participation on a Data Safety Monitoring Board or Advisory Board for NIAID and FDA; and unrelated involvement in HIV and SARS-CoV-2 vaccine clinical trials conducted in collaboration with the NIH, HIV Vaccine Trials Network (HVTN), Covid Vaccine Prevention Network (CoVPN), International AIDS Vaccine Initiative (IAVI), Crucell/Janssen, Moderna, Military HIV Research Program (MHRP), the Gates Foundation, and Harvard Medical School. CLG declares unrelated grants or contracts paid to their institution from NIH. HEJ declares unrelated grants or contracts paid to their institution from NIH; and unrelated participation in multiple NIH-convened DSMBs. YuH declares unrelated grants or contracts paid to their institution from WHO and unrelated participation (with payment) on a Data Safety Monitoring Board or Advisory Board for WHV. BL is an employee of Moderna, Inc. IH is an employee of AstraZeneca and declares unrelated stock options held in AstraZeneca. FS is an employee of Janssen and declares unrelated stock received as compensation for past employment with GlaxoSmithKline. LMD is an employee of Novavax, Inc. KMN declares unrelated grants or contracts from Pfizer (no salary support) and NIH. PAG declares unrelated grants or contracts from NIH and patent interests for "Human monoclonal antibodies to SARS-COV-2 and use thereof". SRW declares unrelated grants or contracts from Sanofi Pasteur, Moderna, Vir Biotechnology, Worcester HIV Vaccine, Pfizer, and Janssen Vaccines/Johnson & Johnson paid to their institution; unrelated support for attending meetings and/or travel from Sasnofi Pasteur; unrelated participation on a Data Safety Monitoring Board or Advisory Board for Janssen Vaccines/Johnson & Johnson; and that their spouse is an employee that holds stock/stock options at Regeneron Pharmaceuticals. KLK declares unrelated grants or contracts from NIAID. The CoVPN was funded by the NIH.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2023.104799.

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