

The Incidence of SARS-CoV-2 Reinfection in Persons With Naturally Acquired Immunity With and Without Subsequent Receipt of a Single Dose of BNT162b2 Vaccine

A Retrospective Cohort Study

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Background: There is insufficient evidence regarding the magnitude and durability of protection conferred by a combined effect of naturally acquired immunity after SARS-CoV-2 infection and vaccine-induced immunity.

Objective: To compare the incidence rate of SARS-CoV-2 reinfection in previously infected persons to that of previously infected persons who subsequently received a single dose of BNT162b2 messenger RNA vaccine.

Design: A retrospective cohort study emulating a randomized controlled target trial through a series of nested trials.

Setting: Nationally centralized database of Maccabi Healthcare Services, Israel.

Participants: Persons with documented SARS-CoV-2 infection who did not receive subsequent SARS-CoV-2 vaccination were compared with persons with documented SARS-CoV-2 infection who received a single dose of the BNT162b2 vaccine at least 3 months after infection.

Intervention: Forty-one randomized controlled trials were emulated, in which 107 413 Maccabi Healthcare Services' members aged 16 years and older were eligible for at least 1 trial.

Measurements: SARS-CoV-2-related outcomes of infection, symptomatic disease, hospitalization, and death, between 2 March and 13 December 2021.

Results: A statistically significant decreased risk (hazard ratio, 0.18 [95% CI, 0.15 to 0.20]) for reinfection was found among persons who were previously infected and then vaccinated versus those who were previously infected but remained unvaccinated. In addition, there was a decreased risk for symptomatic disease (hazard ratio, 0.24 [CI, 0.20 to 0.29]) among previously infected and vaccinated persons compared with those who were not vaccinated after infection. No COVID-19-related mortality cases were found.

Limitation: Hybrid protection against non-Delta variants could not be inferred.

Conclusion: Persons previously infected with SARS-CoV-2 gained additional protection against reinfection and COVID-19 from a subsequent single dose of the BNT162b2 vaccine. Nonetheless, even without a subsequent vaccination, reinfection appeared relatively rare.

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Vaccination policies for SARS-CoV-2 are continuously changing in light of a rapidly growing body of research. To date, there is still no evidence-based, long-term correlate of protection (1). This lack of a correlate of protection has led to different approaches in terms of vaccine resource allocation—among others, the need to vaccinate patients who have recovered from infection.

Both short-term effectiveness of the BNT162b2 messenger RNA (mRNA) COVID-19 vaccine (Pfizer-BioNTech) (2–5) and waning of vaccine-induced immunity have been shown (6–10), although the latter has been mild against severe disease (11). Unlike the large volume of published population-based research investigating the long-term effectiveness of COVID-19 vaccines, there is a relative paucity of large studies examining long-term protection against reinfection in previously infected persons (12), although evidence suggesting long-term immunity has been published (12–14).

Part of the challenge lies in the definition of reinfection (or a “failure” of infection-induced immunity) as opposed to prolonged viral shedding (15). Although clear-cut cases exist, namely 2 separate clinical episodes with 2 distinct sequenced viruses, relying solely on such cases will likely result in an underestimation of the incidence of reinfection. Different criteria based on more widely available information have been suggested (16); for example, U.S. Centers for Disease Control and Prevention guidelines refer to 2 positive SARS-CoV-2 polymerase chain reaction (PCR) test results at least 90 days apart (17).

Even less understood are the short- and long-term effects of hybrid immunity, namely the protection conferred by a combined effect of naturally acquired immunity and vaccine-induced immunity. Although some studies have been published on hybrid immunity, they comprise small cohorts and focus on biological evidence (for example, antibodies and memory B cells) rather than on real-world data of population-based outcomes (18–23). Given

still unclear correlates of protection (24), and the global need for vaccine resource allocation, evidence of a substantial boosting effect for vaccination after recovery from COVID-19 is needed.

To this end, we compared the incidence rate of reinfection in convalescent and unvaccinated persons to that of recovered and single-dose vaccinated persons, leveraging the centralized computerized database of Maccabi Healthcare Services (MHS), Israel's second largest health maintenance organization.

METHODS

Nomenclature and Definitions

Persons with a documented SARS-CoV-2 infection, determined by a previous positive PCR test result, are defined as "previously infected," "convalescent," or "recovered" persons. Of those, persons who were subsequently vaccinated with 1 dose of the BNT162b2 vaccine are defined as "previously infected and vaccinated" or "vaccinees." Reinfection with SARS-CoV-2 (see Measured Outcomes) was defined as a positive PCR test result during the outcome period, regardless of the existence of symptoms. Persons with a documented PCR test and documented COVID-19-related symptoms were considered as having a "symptomatic infection" or "COVID-19." Of those, hospitalized patients were considered to have incurred "COVID-19-related hospitalization." Finally, the protection conferred by a previous infection is called "infection-induced immunity." In contrast, the protection conferred by the vaccine is called "vaccine-induced immunity." In this study (which examines vaccinated persons who have been previously infected), the combined immunity afforded by the vaccine and a previous infection, is called "combined immunity" or "hybrid immunity."

Data

Data Sources

Anonymized electronic medical records (EMRs) were retrieved from the MHS centralized computerized database for the study period of 1 March 2020 to 13 December 2021, a time that corresponded to the Alpha (B.1.1.7) and Delta (B.1.617.2) SARS-CoV-2 variants of concern in Israel, before the introduction of the Omicron variant (25).

Maccabi Healthcare Services is a 2.5 million-member, state-mandated, not-for-profit health fund and the second largest in Israel, covering 26% of the population and comprising a representative sample of the Israeli population. Membership in 1 of the 4 national health funds is mandatory; all citizens freely choose 1 of 4 funds, which are prohibited by law from denying membership to any resident. Maccabi Healthcare Services has maintained a centralized database of EMRs for 3 decades, with less than 1% disengagement rate among its members, allowing for a comprehensive longitudinal medical follow-up. The centralized data set includes extensive demographic data, clinical measurements, outpatient and hospital diagnoses and procedures, medications dispensed, imaging performed, and comprehensive laboratory data from a single central laboratory.

Non-COVID–Related Data

Individual-level data for the study population included patient demographic characteristics, namely age; sex; socioeconomic status; and a coded geographic statistical area, assigned by Israel's Central Bureau of Statistics, which corresponds to neighborhoods and is the smallest geostatistical unit of the Israeli census. Socioeconomic status is measured on a scale from 1 (lowest) to 10, and the index is calculated on the basis of several variables, including household income, educational qualifications, household crowding, and car ownership.

Data collected included last documented body mass index and information about chronic diseases from MHS' automated registries, including cardiovascular diseases (26), hypertension (27), diabetes (28), inflammatory bowel diseases, chronic kidney disease (29), chronic obstructive pulmonary disease, immunocompromising conditions, and cancer, from the National Cancer Registry (30).

COVID-19–Related Data

Information related to COVID-19 was captured, including dates of receipt of the first and second dose of the vaccine and results of any PCR tests for SARS-CoV-2, with all such tests recorded centrally. Records of COVID-19-related hospitalizations were retrieved as well, and ascertainment for COVID-19-related death was performed. In addition, information about COVID-19-related symptoms was extracted from EMRs, where they were recorded by the primary care physician or a certified nurse who conducted in-person or telephone visits with each person who was infected.

Measured Outcomes

We evaluated 4 SARS-CoV-2-related outcomes: documented SARS-CoV-2 infection confirmed by a reverse transcriptase PCR test, COVID-19, COVID-19-related hospitalization, and death. Outcomes were evaluated during the follow-up period of 2 March to 13 December 2021.

Study Design

In this retrospective observational study, we attempted to best emulate a "target" randomized controlled trial using MHS' database of EMRs (31–33) by leveraging data from MHS' centralized computerized database. For clarity, we first briefly describe a hypothetical randomized controlled trial, followed by the actual model fitted to our data, following the design described, among others, by Danaei and colleagues (34).

Design of a Hypothetical Randomized Clinical Trial

A hypothetical trial would include participants aged 16 years or older who have not been vaccinated and have a history of SARS-CoV-2 infection, assessed by a documented positive PCR test result in MHS' centralized database. However, this prior infection, or "previous treatment" (which could be conceptualized by an immune-activation treatment) must have occurred at least 90 days before the enrollment period (a "washout" period), assessed by no positive PCR test results in the 90-day interval. This 3-month washout period was enforced to capture reinfections (as opposed to prolonged viral shedding) by following the 90-day guideline of

the U. S. Centers for Disease Control and Prevention. The duration of the enrollment period would be set according to the pace of recruitment and needed sample size. Eligible participants would then be randomly assigned to either the treatment (vaccine) or control (no vaccine) group. The treatment will include a predefined single-dose regimen of the BNT162b2 vaccine, whereas those in the control group would receive no treatment (an open-label, comparative study design). Participants would be followed until the first occurrence of a SARS-CoV-2-related outcome, death, loss to follow-up, or end of the study period, whichever came first.

Design of This Study: Emulating the Randomized Controlled Trial

Eligibility Criteria and Washout Period. On 2 March 2021, the Israeli Ministry of Health revised its guidelines and allowed persons previously infected with SARS-CoV-2 to receive 1 dose of the BNT162b2 vaccine, after a minimum 3-month interval from their previous infection (35). Of note, the official guidelines in Israel do not recommend a second dose for convalescent patients and therefore this group was not analyzed (see further discussion in the limitation section). Therefore, we first identified all MHS members who had a positive SARS-CoV-2 PCR test result by 2 December 2020 (2 March 2021 minus 90 days) and had not been previously vaccinated, therefore meeting the eligibility exposure criteria for a vaccine (that is, hypothetically eligible to be randomly assigned and meeting the washout period criteria). In addition, these persons had to be 16 years or older by 2 March 2021.

Multiple Nested Trials Design and Defining Time Zero. Following this group of participants over a substantial period of time would pose a methodological issue with defining time zero because each day more previously infected participants would become eligible for enrollment as well as disqualify from it (that is, previously infected persons would become vaccinated). Hence, a single trial would prove challenging in applying 1 time zero that serves as both the first time of eligibility and the start of the follow-up period (36).

Therefore, we designed a series of multiple nested trials, each with a different starting week to the follow-up period (a different time zero). At each time zero, we first identified eligibility by the criteria listed earlier (having been infected and not already vaccinated). Then, we allowed a 1-week enrollment period where eligible participants could be administered 1 dose of the BNT162b2 vaccine. Next, we classified this cohort into previously infected and vaccinated or “previously infected and unvaccinated,” following it until a SARS-CoV-2 outcome (infection or COVID-19-hospitalization), death, or censoring. Censoring included the end of the follow-up period for both groups or administration of the vaccine (that is, when a previously infected and unvaccinated person was vaccinated or when a previously infected and vaccinated person received a second vaccine dose). The following week, at the next time zero, we applied the same approach; at each time zero, eligibility was assessed, treatment assigned, and the cohort was followed until censoring, as defined earlier.

Randomization and Matching. Thus far, we have yet to describe the process of dealing with the lack of randomization in our emulated trial. Although by the time the vaccine was approved for previously infected persons in Israel, all persons (regardless of age or chronic diseases) had free and readily available access to the vaccine, it is possible the vaccinees differ from unvaccinated persons in their comorbidity profile. To mitigate possible bias, we performed matching in each of the nested trials at each time zero. To reduce differences in baseline characteristics as much as possible without losing observations, we used a full matching technique (37). Therefore, the ratio between the number of vaccinated participants to control participants varies in each match. The groups were matched by demographic characteristics, namely age, sex, socioeconomic status, and the coded geographic statistical area. Matching variables also included underlying comorbidities, including obesity, cardiovascular diseases, diabetes, hypertension, chronic kidney disease, cancer, inflammatory bowel diseases, and immunosuppression conditions. Finally, we included in the matching the time of the exposure (the month of the previous infection), thereby, we matched the “immune activation” time of both groups, considering such protection conferred by previous infection may possibly wane with time—a question that was beyond the scope of our research.

Statistical Analysis

We used Cox proportional hazards models to estimate adjusted hazard ratios (HRs) with 95% CIs to examine the relationship between vaccination after a SARS-CoV-2 infection and 3 outcomes: SARS-CoV-2 infection (reinfection), symptomatic SARS-CoV-2 reinfection, and COVID-19-related hospitalizations.

Overall, we emulated 41 target trials, whereas for the analysis, we pooled participants, or person-days, across all trials (stacking the person-trial-days into a single data set), rather than applying a separate model to each trial followed by pooling of the HRs. Because participants were included in more than 1 trial, we used a robust variance estimator to adjust for repeated observations and estimate conservative 95% CI (31).

To address a potential detection bias, we did a sensitivity analysis, where we adjusted for the number of PCR tests done by each person from the beginning of the pandemic until the beginning of the follow-up period. This “PCR frequency” covariate, included as a categorical variable, serves as a proxy for SARS-CoV-2-related health-seeking behavior (6, 38).

Furthermore, to assess the potential influence of an unmeasured confounder, we did a sensitivity analysis using the E-value metric—a thorough discussion of which can be found in VanderWeele's recent article (39). The E-value is defined as the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the exposure and outcome to fully explain away a specific exposure-outcome association, conditional on the measured covariates (40). Analyses were done using R, version 4.1.0 (R Foundation).

Table 1. Number of Previously Infected, Vaccinated, and Cases in Each "Trial"

Trial Number	Calendar Week	Participants, n	Reinfection, n	Symptomatic Reinfection, n	COVID-19-Related Hospitalizations, n	Vaccinated, n	Reinfection in Vaccinated, n	Symptomatic Reinfection in Vaccinated, n	COVID-19-Related Hospitalizations in Vaccinated, n
1	2 March 2021	50 879	762	515	7	11 734	69	44	0
2	9 March 2021	40 606	740	501	7	6608	41	26	0
3	16 March 2021	36 142	726	494	8	2780	17	12	1
4	23 March 2021	36 446	736	500	7	868	1	0	0
5	30 March 2021	39 551	776	524	7	1435	5	2	0
6	6 April 2021	44 106	842	564	8	2042	7	2	0
7	13 April 2021	47 853	903	605	8	1403	7	5	0
8	20 April 2021	51 521	943	634	9	2062	8	5	1
9	27 April 2021	53 775	985	656	8	1578	6	4	0
10	4 May 2021	56 474	1022	677	8	1287	4	2	0
11	11 May 2021	58 839	1061	699	8	543	2	1	0
12	18 May 2021	60 867	1096	714	8	948	4	3	0
13	25 May 2021	61 817	1103	717	8	830	1	0	0
14	1 June 2021	62 520	1117	726	8	596	1	0	0
15	8 June 2021	63 144	1133	732	8	590	3	1	0
16	15 June 2021	63 222	1139	737	8	638	2	1	0
17	22 June 2021	62 930	1142	738	8	2417	4	0	0
18	29 June 2021	60 731	1149	742	8	3818	8	3	0
19	6 July 2021	57 075	1150	746	8	2769	12	7	0
20	13 July 2021	54 363	1133	735	8	1020	3	1	0
21	20 July 2021	53 373	1118	726	8	874	3	3	0
22	27 July 2021	52 511	1091	711	8	624	1	0	0
23	3 August 2021	51 859	1042	679	8	222	0	0	0
24	10 August 2021	51 570	954	619	8	234	1	1	0
25	17 August 2021	51 233	823	528	7	616	1	0	0
26	24 August 2021	50 575	664	428	6	1365	4	2	0
27	31 August 2021	49 250	533	346	4	1252	0	0	0
28	7 September 2021	47 778	314	202	3	533	1	1	0
29	14 September 2021	47 174	215	147	2	450	0	0	0
30	21 September 2021	46 670	146	93	1	629	1	0	0
31	28 September 2021	46 030	88	48	0	2245	0	0	0
32	5 October 2021	43 964	57	30	0	1632	0	0	0
33	12 October 2021	42 435	36	18	0	971	1	0	0
34	19 October 2021	41 685	28	13	0	610	0	0	0
35	26 October 2021	41 399	20	9	0	472	0	0	0
36	2 November 2021	41 458	17	6	0	388	0	0	0
37	9 November 2021	41 921	13	3	0	280	0	0	0
38	16 November 2021	42 967	11	2	0	243	0	0	0
39	23 November 2021	44 360	5	0	0	260	0	0	0
40	30 November 2021	46 017	0	0	0	240	0	0	0
41	7 December 2021	47 167	0	0	0	58	0	0	0
Total	-	2 044 257	26 833	17 564	212	60 164	218	126	2

This study was approved by the MHS Institutional Review Board. Because of the retrospective design of the study, informed consent was waived by the institutional review board, and all identifying details of the participants were removed before computational analysis.

Role of the Funding Source

There was no external funding for the project.

RESULTS

Overall, during the follow-up period, we emulated 41 target trials, each with a 1-week enrollment period. **Table 1** shows the number of participants and outcomes in each trial. A total of 107 413 MHS members aged 16 years and older were eligible for at least 1 trial; of them, 1374 had a positive SARS-CoV-2 PCR test result (reinfection) within the follow-up period, 874 had a symptomatic reinfection, and 10 incurred a COVID-19-related hospitalization. There was no COVID-19-related death during the study; 21 131 were

lost to follow-up (by receiving a second dose of the vaccine), and 84 901 were censored without any documented COVID-19-related outcomes. Of note, the percentage of infections occurring between March and May (that is, during the Alpha-dominant period) was 0.071% of all positive PCR test results during the entire follow-up period. Hence, this analysis largely refers to protection against the Delta variant of SARS-CoV-2.

The mean number of trials that the 107 413 eligible MHS members participated in was 19.03, and pooling the participants across all trials resulted in 2 044 257 person-trials. Of the 2 044 257 person-trials, 60 164 received the first dose, and the average duration of follow-up was 107 days, whereas 1 984 093 were not vaccinated, with a 164-day average duration of follow-up. Overall, demographic characteristics were similar between the groups, with differences in the comorbidity profile (**Table 2**).

We found a statistically significant decreased risk (HR, 0.18 [95% CI, 0.15 to 0.20]) for reinfection in persons

Table 2. Characteristics of the Study Population

Characteristic	Previously Infected and Unvaccinated (1 984 093 Person-Trials)	Previously Infected and Vaccinated (60 164 Person-Trials)
Mean age (SD), y	35.96 (17.14)	38.15 (17.02)
Male, n (%)	991 125 (50.0)	30 575 (50.8)
Mean socioeconomic status (SD)*	4.38 (2.58)	4.98 (2.78)
Comorbidities, n (%)		
Hypertension	170 128 (8.6)	7545 (12.5)
Cardiovascular diseases	80 497 (4.1)	3136 (5.2)
Diabetes mellitus	94 623 (4.8)	4030 (6.7)
Immunocompromised	24 707 (1.2)	946 (1.6)
Obesity (body mass index ≥ 30 kg/m ²)	407 835 (21.6)	13 312 (22.9)
Chronic obstructive pulmonary disease	10 980 (0.6)	519 (0.9)
Cancer	44 537 (2.2)	2065 (3.4)
Inflammatory bowel disease	14 342 (0.7)	526 (0.9)

*Scale from 1 (lowest) to 10.

previously infected who received a single vaccine dose compared with those who were previously infected but unvaccinated. In addition, there was a decreased risk for symptomatic disease (HR, 0.24 [CI, 0.20 to 0.29]) among persons who were previously infected and vaccinated (Table 3, Figures 1 and 2). Given that only 10 persons incurred COVID-19-related hospitalization, no statistical significance was reached for this outcome.

In a sensitivity analysis adjusting for the number of PCR tests a person received throughout the pandemic (the frequency of testing), the increased risk for reinfection did not change, as the test frequency score was not significant ($P = 0.099$). Similar results were found in a sensitivity analysis of symptomatic reinfection. In addition, we estimated the minimal strength that an unmeasured confounder would need to have to bias the results. The E-value for reinfection was 10.84 (9.26 for the lower bound of the CI) and 7.9 (6.42 for the lower bound of the CI) for symptomatic reinfections. Therefore, an unmeasured confounder not included in the Cox proportional hazards regression model associated with both vaccination after SARS-CoV-2 infection and with reinfection outcomes by an HR of 10.84 each could explain away the lower confidence limit, although a weaker confounder would not.

DISCUSSION

This is the largest real-world observational study comparing the protection conferred by previous SARS-CoV-2 infection combined with vaccine-induced immunity afforded by a single dose of the BNT162b2 mRNA vaccine. Our large cohort, facilitated by Israel's rapid

rollout of the mass vaccination campaign and its early decision to vaccinate convalescent persons, allowed us to investigate the risk for reinfection or an additional infection at least 90 days after the previous one over a longer period than thus far described.

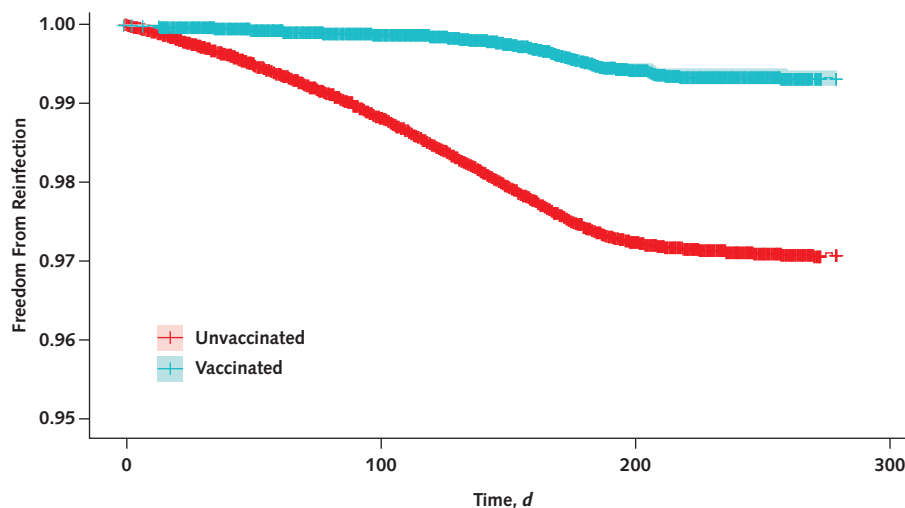
Our analysis showed that persons who were previously infected and received a single dose of the vaccine had a 82% decreased rate of breakthrough infection compared with those who were previously infected but unvaccinated. The decreased risk was significant for symptomatic disease as well. However, likely because of the small number of hospitalizations in this group (of convalescent persons, vaccinated or not), we could not determine statistical significance when comparing the risk for reinfection resulting in hospitalizations.

This finding supports previous small cohort studies pointing to evidence of a boosting effect of neutralizing antibody activity, or an anamnestic response, in previously infected persons receiving a single dose of an mRNA vaccine (18, 19, 41), as well as SARS-CoV-2-specific T-cell (42) and memory B-cell response and affinity maturation (43).

Our study has several limitations. First, because the Delta variant was the dominant strain tested in our analysis, the boosting effect of the vaccine cannot be ascertained against other strains. Second, our analysis addressed protection afforded solely by the Pfizer-BioNTech BNT162b2 vaccine, and therefore does not address other vaccines. Third, we also did not include a third group of previously infected and 2-dose vaccinated persons because this was not the official policy in Israel and including them could lead to a selection bias. However, a previous small cohort study suggested that the marginal protection afforded by another dose is not

Table 3. Hazard Ratios for SARS-CoV-2 Reinfection, Previously Infected Versus Previously Infected and Vaccinated

Variable and Category	Hazard Ratio	95% CI	P Value
Overall SARS-CoV-2 Reinfection			
Induced immunity			
Previously infected and unvaccinated	Reference	—	—
Previously infected and vaccinated	0.18	0.15-0.20	<0.001
Symptomatic Reinfection			
Previously infected and unvaccinated	Reference	—	—
Previously infected and vaccinated	0.24	0.20-0.29	<0.001

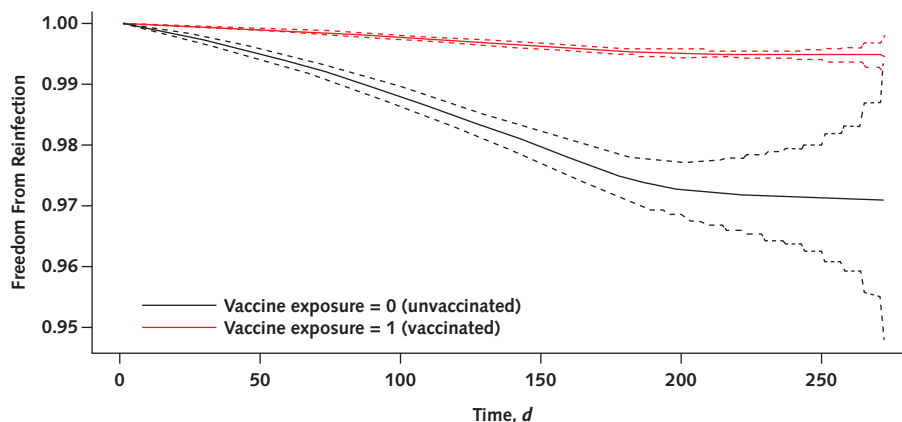
Figure 1. Standardized failure curves for SARS-CoV-2 reinfection.

consequential (18), although future studies should determine the clinical significance and duration of a second dose in previously infected persons.

In addition, because this is an observational, real-world study where PCR screening was not done by a preset protocol, we may be underestimating asymptomatic infections because these persons often do not get tested. A related concern is that the frequency of PCR testing differed between groups, meaning that 1 group manifested different health seeking behavior during the pandemic and therefore is potentially more diagnosed rather than more infected. To address that potential detection bias, we did a sensitivity analysis where the number of PCR tests undertaken throughout the pandemic serves as a proxy for COVID-19-related health seeking behavior (6, 8). This adjustment did not change the results. Moreover, because we used full matching in

each trial, including matching of geographic location at the level of neighborhoods, socioeconomic status, and chronic diseases, residual confounding by unmeasured factors is unlikely.

Nonetheless, to assess whether the association between previous infection and a following vaccination could be due to unmeasured confounding—for example, by health care seeking behavior (such as social distancing and mask wearing), we calculated the E-value for an unmeasured confounder. The E-value for the analysis suggested that only a very strong association between both convalescent patients who were subsequently vaccinated and health care seeking behavior and health care seeking behavior and reinfection would account for all of the observed association between vaccinating convalescent patients and their reduced risk for reinfection.

Figure 2. Standardized curves for SARS-CoV-2 reinfection.

This analysis showed that persons who were previously infected with SARS-CoV-2 gain additional protection from a subsequent single-dose vaccine regimen. Nonetheless, even without a subsequent vaccination, it seems that reinfection is relatively rare, at least in the first year after infection (13, 44), although the study was done before the emergence of the Omicron variant. The long-term effects of reinfection are still unknown. Therefore, policies regarding vaccination of convalescent persons of different age and risk groups will also depend on prioritization of resources in terms of global vaccination deployment.

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Reproducible Research Statement: *Study protocol and statistical code:* Specific requests for the study protocol or remote access to the code used for data analysis should be referred to KSM, Maccabi Healthcare Services Research and Innovation Center. *Data set:* According to the Israel Ministry of Health regulations, individual-level data cannot be shared openly. Specific requests for remote access to deidentified community-level data should be directed to KSM, Maccabi Healthcare Services Research and Innovation Center.

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