Robert H. Tyler, Esq., CA Bar No. 179572
rtyler@faith-freedom.com
Nada Higuera, State Bar No. 299819
nhiguera@faith-freedom.com
Mariah Gondeiro, State Bar No. 323683
mgondeiro@faith-freedom.com
ADVOCATES FOR FAITH & FREEDOM
25026 Las Brisas Road
Murrieta, California 92562
Telephone: (951) 600-2733
Facsimile: (951) 600-4996

Attorneys for **Plaintiffs**

UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

SAN JOSE DIVISION

UNIFYSCC, an unincorporated California association on behalf of employees in Santa Clara County; **TOM DAVIS,** an individual; and **MARIA RAMIREZ,** an individual;

Plaintiffs,

vs.

SARA H. CODY, in her official capacity as the Santa Clara County Public Health Officer; **JAMES WILLIAMS,** in his official capacity as the County Counsel of Santa Clara County; **JEFFREY SMITH,** in his official capacity as the County Executive of Santa Clara County; and **SANTA CLARA COUNTY**;

Defendants.

Case No. 5:22-cv-01019-SVK

[Honorable Beth L. Freeman]

DECLARATION OF DR. JAYANTA BHATTACHARYA IN SUPPORT OF PLAINTIFFS' MOTION FOR TEMPORARY RESTRAINING ORDER AND ORDER TO SHOW CAUSE

Date: June 23, 2022
Time: 9:00 a.m.
Courtroom: 3

I, Dr. Jayanta Bhattacharya, declare as follows:

1. I am a resident of Los Altos, California. I am 52 years old and am otherwise competent to render this declaration. I submit this declaration in support of Plaintiffs' Motion for Temporary Restraining Order and Order to Show Cause. I have personal knowledge of the matters set forth below and could and would testify competently to them if called upon to do so.

EXPERIENCE & CREDENTIALS

2. I am a former Professor of Medicine and current Professor of Health Policy at Stanford University School of Medicine and a research associate at the National Bureau of Economic Research. I am also Director of Stanford's Center for Demography and Economics of Health and Aging. I hold an M.D. and Ph.D. from Stanford University. I have published 155 scholarly articles in peer-reviewed journals in the fields of medicine, economics, health policy, epidemiology, statistics, law, and public health, among others. My research has been cited in the peer-reviewed scientific literature more than 12,400 times.

3. I have dedicated my professional career to the analysis of health policy, including infectious disease epidemiology and policy, and the safety and efficacy of medical interventions. I have studied extensively and commented publicly on the necessity and safety of vaccine requirements for those who have contracted and recovered from COVID-19 (individuals who have "natural immunity"). I am intimately familiar with the emergent scientific and medical literature on this topic and pertinent government policy responses to the issue both in the United States and abroad.

4. My assessment of vaccine immunity is based on studies related to the efficacy and safety of the one vaccine to receive full approval from the Food and Drug Administration (FDA) and the two vaccines for which the FDA has granted Emergency Use Authorization (EUA) for use in the United States. These include two mRNA-technology vaccines (manufactured by Pfizer-BioNTech and Moderna) and an adenovirus-vector vaccine technology (manufactured by Johnson & Johnson). Of those, the Pfizer vaccine, also known as Comirnaty, has full FDA approval.

5. I have not and will not receive any financial or other compensation to prepare this Declaration or to testify in this case. Nor have I received compensation for preparing declarations or reports or for testifying in any other case related to the COVID-19 pandemic or any personal or research funding from any pharmaceutical company. My participation here has been motivated solely by my commitment to public health, just as my involvement in other cases has been.

6. I have been asked to provide my opinion on several matters related to the Occupational Safety and Health Administration's recently enacted regulation, COVID-19 Vaccination and Testing: Emergency Temporary Standard.

- Whether, based on the current medical and scientific knowledge, immunity after COVID recovery (sometimes referred to as natural immunity) is categorically inferior to vaccine immunity to prevent reinfection and transmission of the SARS-CoV-2 virus;
- Whether, based on the existing medical and scientific understanding of SARS-CoV-2 transmission and recovery, there is any categorical distinction between natural immunity and vaccine immunity;
- Whether there is scientific evidence to support OSHA's determination that immunity provided by COVID recovery should not be considered as a reason to be excused from OSHA's vaccine mandate.

7. I can summarize my opinions briefly. The scientific evidence strongly indicates that the recovery from COVID disease provides strong and lasting protection against severe disease if reinfected, at least as good and likely better than the protection offered by the COVID vaccines. While the COVID vaccines are effective at protecting vaccinated individuals against severe disease, they provide only short-lasting and limited protection versus infection and disease transmission. Requiring vaccines for COVID recovered patients thus provides only a limited benefit while exposing them to the risks associated with the vaccination. Therefore, OSHA's emergency rule incorrectly does not provide an exclusion for naturally immune workers from its vaccination, masking, and testing requirements.

OPINIONS

I. COVID-19 Infection Fatality Risk

8. SARS-CoV-2, the virus that causes COVID-19 infection, entered human circulation some time in 2019 in China. The virus itself is a member of the coronavirus family of viruses, several of which cause typically mild respiratory symptoms upon infection. The SARS-CoV-2 virus, by contrast, induces a wide range of clinical responses upon infection. These presentations range from entirely asymptomatic infection to mild upper respiratory disease with unusual symptoms like loss of sense of taste and smell, hypoxia, or a deadly viral pneumonia that is the primary cause of death due to SARS-CoV-2 infection.

9. The mortality danger from COVID-19 infection varies substantially by age and a few chronic disease indicators. For most of the population, including the vast majority of children and young adults, COVID-19 infection poses less of a mortality risk than seasonal influenza. By contrast, for older people – especially those with severe comorbid chronic conditions – COVID-19 infection poses a high risk of mortality, on the order of a 5% infection fatality rate.

10. The best evidence on the infection fatality rate from SARS-CoV-12 infection (that is, the fraction of infected people who die due to the infection) comes from seroprevalence studies. The definition of seroprevalence of COVID-19 is the fraction of people in a population who have specific antibodies against SARS-CoV-2 in their bloodstream. A seroprevalence study measures the fraction of a population who have antibodies that are produced specifically by people infected by the SARS-CoV-2 virus. The presence of specific antibodies in blood provides excellent evidence that an individual was previously infected.

11. Seroprevalence studies provide better evidence on the total number of people who have been infected than do case reports or positive reverse transcriptase-polymerase chain reaction (RT-PCR) test counts. PCR tests are the most common type of test used to check whether a person currently has the virus or viral fragments in their body (typically in the nasopharynx). The PCR test should not be used to count the total number of people who have been infected to date in a population. Case reports and PCR test counts both miss infected people who are not identified by the public health authorities or who do not volunteer for RT-PCR testing. That is, they miss people who were infected but recovered from the condition without coming to the attention of public health authorities. Because they ignore unreported infections, fatality rate estimates based on case reports or positive test counts are substantially biased toward reporting a higher fatality rate.

12. According to a meta-analysis by Dr. John Ioannidis of every seroprevalence study conducted to date of publication with a supporting scientific paper (74 estimates from 61 studies and 51 different localities worldwide), the median infection survival rate—the inverse of the infection fatality rate—from COVID-19 infection is 99.77%. For COVID-19 patients under 70, the meta-analysis finds an infection survival rate of 99.95%. A separate meta-analysis by other scientists independent of Dr. Ioannidis' group reaches qualitatively similar conclusions.

13. A study of the seroprevalence of COVID-19 in Geneva, Switzerland (published in *The Lancet*) provides a detailed age breakdown of the infection survival rate in a preprint companion paper 99.9984% for patients 5 to 9 years old; 99.99968% for patients 10 to 19 years old; 99.991% for patients 20 to 49 years old; 99.86% for patients 50 to 64 years old; and 94.6% for patients above 65.

14. I estimated the age-specific infection fatality rates from the Santa Clara County seroprevalence study data (for which I am the senior investigator). The infection survival rate is 100% among people between 0 and 19 years (there were no deaths in Santa Clara in that age range up to that date); 99.987% for people between 20 and 39 years; 99.84% for people between 40 and 69 years; and 98.7% for people above 70 years.

15. Those numbers are consistent with what the US CDC has reported. A US CDC report found between 6 and 24 times more SARS-CoV-2 infections than cases reported between March and May 2020. Correspondingly, the CDC's estimate of the infection fatality rate for people ages 0-19 years is 0.003%, meaning infected children have a 99.997% survivability rate. For people ages 20-49 years, it was 0.02%, meaning that young adults have a 99.98% survivability rate. For people age 50-69 years, it was 0.5%, meaning this age group has a 99.5% survivability rate. Finally, for people ages 70+ years, it was 5.4%, meaning seniors have a 94.6% survivability rate. There is thus no substantial qualitative disagreement about the infection fatality rate reported by the CDC and other sources in the scientific literature. This should come as no surprise since they all rely on seroprevalence studies to estimate infection fatality rates.

16. It is helpful to provide some context for how large the mortality risk is posed by COVID infection relative to the risk posed by other infectious diseases. The case fatality rate for SARS-CoV-2 is ~2% (though that number has decreased with the availability of vaccines and effective treatments). By contrast, the case fatality rate for SARS is over five times higher than that, and for MERS, it is 16 times higher than that.

17. Perhaps the most important implication of these estimates is that they identify two distinct populations of people who face a very different risk from COVID infection. One segment – the elderly and others with severe chronic disease – faces a higher risk of mortality if infected (especially if unvaccinated). A second segment – typically non-elderly people – face a very low risk

of mortality if infected and instead face much greater harm from lockdowns, school closures, and other non-pharmaceutical interventions than from COVID infection itself. The right strategy, then, is focused protection of the vulnerable population by prioritizing them for vaccination while lifting lockdowns and other restrictions on activities for the rest since they cause harm without corresponding benefit for the non-vulnerable. The Great Barrington Declaration, of which I am a primary co-author, describes an alternate policy of focused protection. This policy would lead to fewer COVID-related deaths and fewer non-COVID-related deaths than universal lockdowns or a strategy that lets the virus rip through the population. My co-authors of this Declaration include Prof. Martin Kulldorff of Harvard University and Prof. Sunetra Gupta of Oxford University. Over 15,000 epidemiologists and public health professionals and 50,000 medical professionals have co-signed the Declaration.

18. The infection fatality rate estimates presented in this section are drawn from data before widespread vaccination in the U.S. and elsewhere. The COVID-19 vaccines approved for use in the U.S. are very effective in substantially reducing the infection fatality rate. According to the US Centers for Disease Control, the mRNA vaccines were 94% effective against COVID-19 hospitalization for patients 65 and older. So, the infection fatality rates that I provide above are overestimated by at least one order of magnitude. Fully vaccinated, non-elderly professors in classrooms face a vanishingly small risk of mortality even if the SARS-CoV-2 virus infects them.

II. Natural Immunity Provides Durable Protection Against Reinfection and Against Severe Outcomes If Reinfected; COVID-19 Vaccines Provide Limited Protection Against Infection but Durable Protection Against Severe Outcomes if Infected.

19. Both vaccine-mediated immunity and natural immunity after recovery from COVID infection provide extensive protection against severe disease from subsequent SARS-CoV-2 infection. There is no reason to presume that vaccine immunity provides a higher level of protection than natural immunity. Since vaccines arrived one year after the disease, there is stronger evidence for long-lasting immunity from natural infection than from the vaccines.

20. Both types of immunity are based on the same basic immunological mechanism - stimulating the immune system to generate an antibody response. In clinical trials, the efficacy of

those vaccines was initially tested by comparing the antibody levels in the blood of vaccinated individuals to those who had natural immunity. Later Phase III studies of the vaccines established 94%+ clinical efficacy of the mRNA vaccines against severe COVID illness. A Phase III trial showed 85% efficacy for the Johnson & Johnson adenovirus-based vaccine against severe disease.

21. Immunologists have identified many immunological mechanisms of immune protection after recovery from infections. Studies have demonstrated prolonged immunity with respect to memory T and B cells, bone marrow plasma cells, spike-specific neutralizing antibodies, and IgG+ memory B cells following naturally acquired immunity.

22. Multiple extensive, peer-reviewed studies comparing natural and vaccine immunity have now been published. These studies overwhelmingly conclude that natural immunity provides equivalent or greater protection against severe infection than immunity generated by mRNA vaccines (Pfizer and Moderna).

23. Specifically, studies confirm the efficacy of natural immunity against reinfection of COVID-19 and show that the vast majority of reinfections are less severe than first-time infections. For example, an Israeli study of approximately 6.4 million individuals demonstrated that natural immunity provided equivalent if not better protection than vaccine immunity in preventing COVID-19 infection, morbidity, and mortality. A true and correct copy of this study is attached hereto as **Exhibit A** and can be found here: https://www.medrxiv.org/content/10.1101/2021.04.20.21255670v1. Of the 187,549 unvaccinated persons with natural immunity in the study, only 894 (0.48%) were reinfected; 38 (0.02%) were hospitalized, 16 (0.008%) were hospitalized with severe disease, and only one died, an individual over 80 years of age. Another study, analyzing data from Italy found that only 0.31% of COVID-recovered patients experienced a reinfection within a year after the initial infection.

24. Variants do not escape the immunity provided by prior infection with the pre-variant virus or vaccination. This is true of the delta variant as well. In a study of a large population of patients in Israel, *vaccinated* people who had not been previously infected were 13 times higher odds of experiencing a breakthrough infection with the Delta variant than patients who had recovered from COVID but were never vaccinated. A true and correct copy of this study is attached hereto as **Exhibit B** and found here: https://www.medrxiv.org/content/10.1101/2021.08.24.21262415v1. They had 27

times higher odds of experiencing subsequent symptomatic COVID disease and 7 times higher odds of hospitalization. The design of this Israeli study was particularly strong – it tracked large cohorts of people over time from the time of vaccination or initial infection, and thus carefully distinguished the effect of time since initial exposure or vaccination in estimating its effect estimates. This is important because both vaccine-mediated and infection-mediated protection against subsequent infection diminish with time.

25. In summary, the overwhelming conclusion of the pertinent scientific literature is that natural immunity is at least as effective against subsequent reinfection as even the most effective vaccines.

26. Furthermore, based on such evidence, many scientists have concluded that natural protection against severe disease after COVID recovery is likely to be long-lasting. A survey article published on June 30, 2021, in the *British Medical Journal* concluded, "[t]here is reason to think that immunity could last for several months or a couple of years, at least, given what we know about other viruses and what we have seen so far in terms of antibodies in patients with COVID-19 and in people who have been vaccinated."

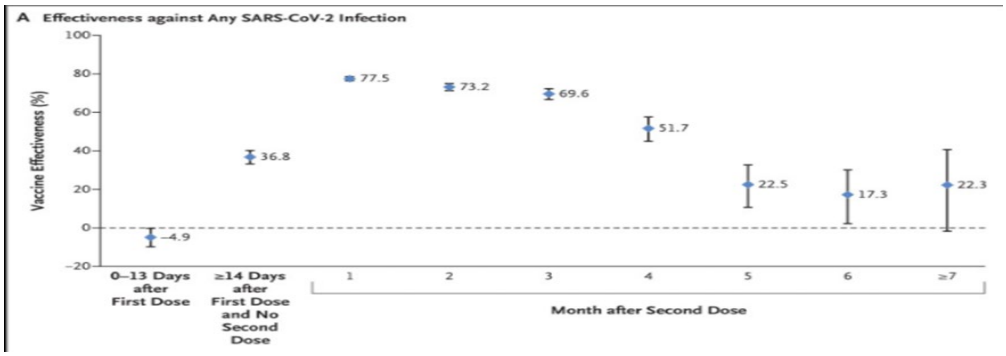
27. These findings of highly durable natural immunity should not be surprising, as they hold for SARS-CoV-1 (the virus that causes SARS) and other respiratory viruses. According to a paper published in *Nature* in August 2020, 23 patients who had recovered from SARS-CoV-1 still possess CD4 and CD8 T cells 17 years after infection during the 2003 epidemic. A *Nature* paper from 2008 found that 32 people born in 1915 or earlier still retained some level of immunity against the 1918 flu strain—some 90 years later.

28. In contrast to the concrete findings regarding the robust durability of natural immunity, it is yet unclear in the scientific literature how long-lasting vaccine-induced immunity will be. Notably, the researchers argue that they can best surmise the predicted durability of vaccine immunity by looking at the expected durability of natural immunity.

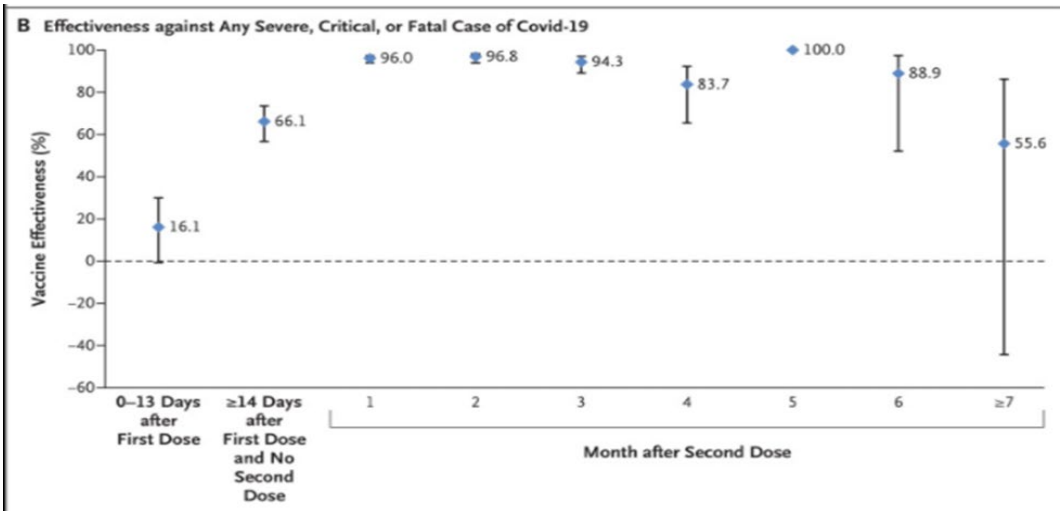
29. A study from Qatar by Chemaitelly and colleagues (recently published in the New England Journal of Medicine), which tracked 927,321 individuals for six months after vaccination concluded that the Pfizer vaccine's "induced protection against infection appears to wane rapidly after

its peak right after the second dose, but it persists at a robust level against hospitalization and death for at least six months following the second dose." A true and correct copy of this study is attached hereto as **Exhibit C** and can be found here: https://www.nature.com/articles/s41591-021-01583-4

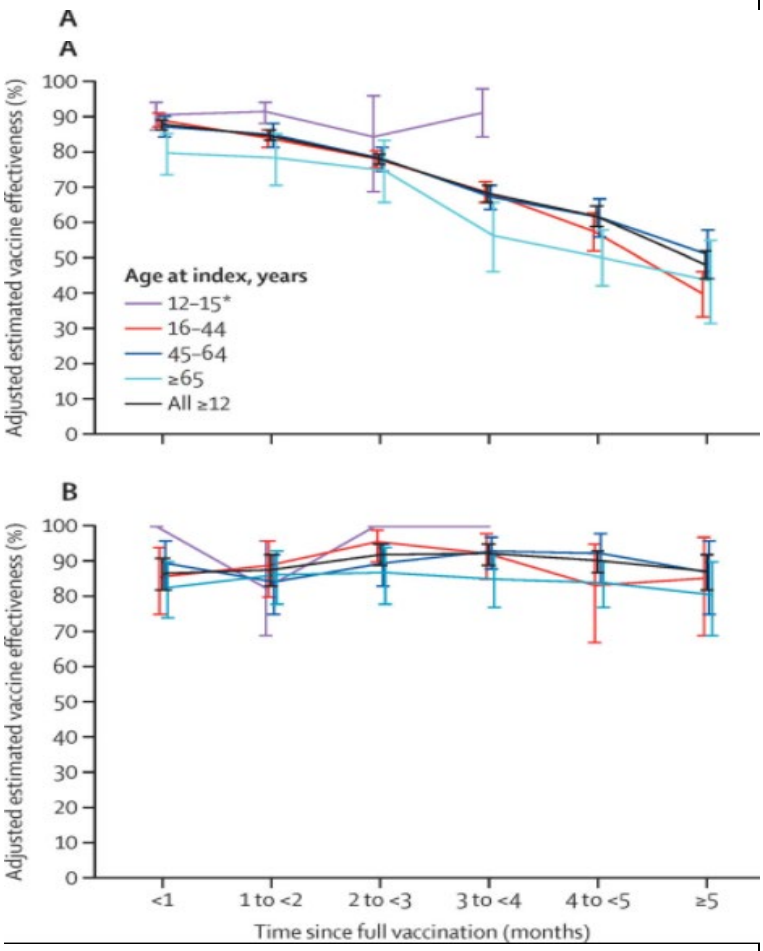
30. The key figures from the Qatari study are reproduced immediately below. Panel A shows that vaccine mediated protection against infection peaks at 77.5% one month after the second dose, and then declines to 22.5%, five months after the second dose. According to this result, vaccines effectively protect against infection (and therefore disease spread) for a short period of time after the second dose of the mRNA vaccines.



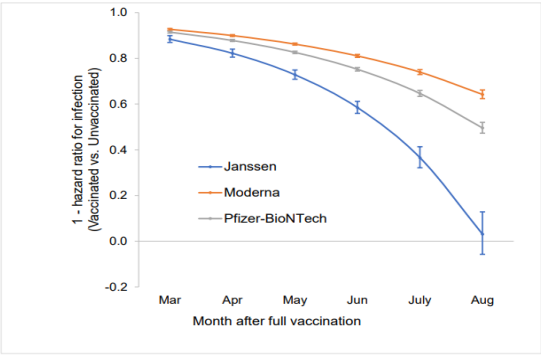
31. On the other hand, Panel B shows that protection versus severe disease is long lasting after vaccination – even though the person will no longer be fully protected against infection and, presumably, disease spread. At 6 months after the second dose, the vaccine remains 88.9% efficacious versus severe disease. While it appears to dip at 7 months to 55.6% efficacy, the confidence interval is so wide that it is consistent with no decrease whatsoever even after 7 months.



32. The Qatari study is no outlier. A large study in California tracked the infection rates for nearly 5 million patients vaccinated with two doses of the Pfizer mRNA vaccine. The study tracked both SARS-CoV-2 infections as well as COVID-19-related hospitalizations. The figure immediately below plots the trend in vaccine efficacy over time for different age groups in the population cohort. **Panel A** on the right plots effectiveness versus SARS-CoV-2 *infections*. A true and correct copy of the study is attached hereto as **Exhibit D** and can be found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8489881/ Though the drop in effectiveness is not as steep as in the Qatari study, there is nevertheless a sharp drop. While in the first month, vaccine effectiveness is near 90% for all age-groups, by month 5, it drops to nearly 50% for all the groups. By contrast, **Panel B** plots vaccine efficacy versus *hospitalizations*. It remains high with no decline over time – near 90% throughout the period. The vaccine provides durable private protection versus severe disease, but declining protection versus infection (and hence transmission).



33. Another recent study tracked 620,000 vaccinated U.S. veterans to measure



breakthrough infections for the three vaccines in common use in the U.S. Like the other studies, the authors of the study found a sharp decline in vaccine effectiveness versus infection. Five months after vaccination, the effectiveness of the J&J vaccine dropped from ~90% to less than 10%; the Pfizer vaccine dropped from ~90% to ~50%; and the Moderna dropped from ~90% to ~65%. The figure on this page tracks the decline in effectiveness of the vaccines against infection over time documented in this study. This study corroborates yet another study that documented declining vaccine efficacy in the first three months after vaccination against disease transmission in the era of the Delta variant.

34. Yet another study conducted in Wisconsin confirmed that vaccinated individuals can shed infectious SARS-CoV-2 viral particles. The authors analyzed nasopharyngeal samples to check whether patients showed evidence of infectious viral particles. They found that vaccinated individuals were at least as likely as unvaccinated individuals to be shedding live virus. They concluded: Combined with other studies these data indicate that vaccinated and unvaccinated individuals infected with the Delta variant might transmit infection. Importantly, we show that infectious SARS-CoV-2 is frequently found even in vaccinated persons.

35. A recent study in the U.K. during its wave of delta COVID cases compared the likelihood of a vaccinated individual passing on the disease to someone within their same household relative to unvaccinated patients. A true and correct copy of this study is attached hereto as **Exhibit E** and can be found here: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00648-4/fulltext This study tracked these groups of patients over time to the point they tested positive for COVID. At that point, study investigators measured levels of the SARS-CoV-2 virus in the patients, and observed whether the patients passed on the disease to other household members. The authors find that while vaccination does reduce the fraction of time that a patient passes the disease on to household members from 38% [95% confidence interval: 24-53] to 25% [95% confidence interval: 18-33], there was no statistically significant difference (p=0.17). They conclude: Vaccination reduces the risk of delta variant infection and accelerates viral clearance. Nonetheless, fully vaccinated individuals with breakthrough infections have peak viral load similar to unvaccinated cases and can efficiently transmit infection in household settings, including to fully vaccinated contacts.

36. The CDC recognizes the importance of natural immunity in its updated science brief analyzing the difference in immunity from infection-induced and vaccine-induced immunity. The CDC noted that "confirmed SARS-CoV-2 infection decreased risk of subsequent infection by 80–93% for at least 6–9 months," with some studies showing "slightly higher protective effects (89-93%)." It also noted that "researchers have predicted that the immune response following infection would continue to provide at least 50% protection against reinfection for 1–2 years following initial infection with SARS-CoV-2 or vaccination. This would be similar to what is observed with seasonal coronaviruses."

37. The CDC science brief does claim that vaccine-induced immunity is stronger than immunity from natural infection. This study the CDC relies on to support this claim is not determinative for several reasons. First, its result is contrary to the weight of other evidence, as set forth above. Second, the study compared hospitalization of those infected—and had natural immunity - 90-225 days after their infection while against those who had completed their RNA vaccine regime 45-213 days before reinfection. Because immunity—regardless of how gained—wanes over time, the failure to adequately compare like periods means that the study's conclusions are biased in favor of vaccine-induced immunity. Indeed, the study admits this weakness. Third, the study design itself does not permit it to address the critical question of interest – whether COVID-recovery without vaccination or vaccination without COVID-recovery provides stronger protection against COVID-related hospitalization. The study analyzes only patients who are already in the hospital. To obtain an accurate answer to the question of interest, it would need to include and analyze patients before entering the hospital. As it is, the study implicitly and incorrectly assumes that the set of hospitalized patients with COVID-like symptoms is representative of the population at large, which is untrue.

38. In summary, the evidence to date strongly suggests that while vaccines - like natural immunity - protect against severe disease, they, unlike natural immunity, provide only short-lasting protection against subsequent infection and disease spread. In short, there is no medical or scientific reason to believe that vaccine immunity will prove longer-lasting immunity than natural immunity, much less more durable immunity.

III. The CDC's Recommendation for Vaccination of Recovered COVID Patients Applies with Equal Force to Those Who Have Been Previously Vaccinated, Whose Protection Against Infection Wanes Within a Few Months After Vaccination.

39. The CDC, in the Frequently Asked Questions (FAQ) section of its website encouraging vaccination, provides the following advice to previously recovered patients:

> Yes, you should be vaccinated regardless of whether you already had COVID-19. That's because experts do not yet know how long you are protected from getting sick again after recovering from COVID-19. Even if you have already recovered from COVID-19, it is possible - although rare - that you could be infected with the virus that causes COVID-19 again. Studies have shown that vaccination provides a strong boost in protection in people who have recovered from COVID-19. Learn more about why getting vaccinated is a safer way to build protection than getting infected.

40. The text of this advice by the CDC does not address any of the scientific evidence included here about the lack of necessity for recovered COVID patients to be vaccinated. While it is true that I do not know how long natural immunity after recovery lasts, the immunological evidence to date suggests that protection against disease will last for years. Uncertainty over the longevity of immunity after recovery is a specious reason for not exempting COVID-recovered patients from vaccination mandates, since the same can be said about vaccine mediated immunity. I do not know how long it will last either, and there is no reason to believe it provides longer lasting or more complete immunity than recovery from COVID.

41. Similarly, just as reinfections are possible though rare after COVID recovery, breakthrough infections are possible after vaccination, as the CDC's team investigating vaccine breakthrough infections itself recognizes. On the same CDC FAQ webpage, I cite above, the CDC writes about vaccine-mediated immunity, "We don't know how long protection lasts for those who are vaccinated."

42. The CDC's main concern in this FAQ seems to be to help people understand that it is safer to attain immunity against SARS-CoV-2 infection via vaccination rather than via infection. This is a point not in dispute. Rather, the question is whether someone who *already* has been infected and recovered will benefit on net from the additional protection provided by vaccination. On this point, the CDC's statement in the FAQ is irrelevant. Here again, the possibility of reinfection does not alter the conclusion that, especially for those who have already recovered from COVID, accommodations can be allowed without threatening public safety.

IV. Conclusion

43. Based on the scientific evidence to date, those who have recovered from a SARS-CoV-2 infection possess immunity as robust and durable (or more) as that acquiredthrough vaccination. The existing clinical literature overwhelmingly indicates that the protection afforded to the individual and community from natural immunity is as effective and durable as the efficacy levels of the most effective vaccines to date.

44. Based on my analysis of the existing medical and scientific literature, any policy regarding vaccination that does not recognize natural immunity is irrational, arbitrary, and counterproductive to community health. This is certainly true of Santa Clara County's vaccination policies. The individuals placed in high risk are more likely to have contracted COVID-19 in the past and therefore have immune protection. It is counterproductive to public health to strip these employees of their employment when the public relies greatly on their services. For instance, COVID-19 and lockdown policies have created a mental health crisis, and social workers and counselors are more important now than ever before. Placing nurses and doctors on unpaid leave is counterproductive and dangerous for public health.

45. Indeed, now that every American adult, teenager, and child five and above has free access to the vaccines, the case for a vaccine mandate is weaker than it once was. Since the successful vaccination campaign already protects the vulnerable population, the unvaccinated—especially recovered COVID patients—pose a vanishingly small threat to the vaccinated. They are protected by an effective vaccine that dramatically reduces the likelihood of hospitalization or death after

infections to near zero. At the same time, natural immunity provides benefits that are at least as strong and may well be stronger than those from vaccines.

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct. Executed March 3, 2022.

Dr. Jayanta Bhattacharya

EXHIBIT “A”

Protection of previous SARS-CoV-2 infection is similar to that of BNT162b2 vaccine protection: A three-month nationwide experience from Israel

Yair Goldberg[1]*, Micha Mandel[2], Yonatan Woodbridge[3], Ronen Fluss[3], Ilya Novikov[3], Rami Yaari[3], Arnona Ziv[3], Laurence Freedman[3], Amit Huppert[3,4]

[1]Technion - Israel Institute of Technology, Israel

[2]The Hebrew University of Jerusalem, Israel

[3]The Gertner Institute for Epidemiology & Health Policy Research, Sheba Medical Center, Israel

[4]Tel Aviv University, Israel

Contributed equally

*corresponding author

email: yairgo@technion.ac.il

Abstract

Worldwide shortage of vaccination against SARS-CoV-2 infection while the pandemic is still uncontrolled leads many states to the dilemma whether or not to vaccinate previously infected persons. Understanding the level of protection of previous infection compared to that of vaccination is critical for policy making. We analyze an updated individual-level database of the entire population of Israel to assess the protection efficacy of both prior infection and vaccination in preventing subsequent SARS-CoV-2 infection, hospitalization with COVID-19, severe disease, and death due to COVID-19. Vaccination was highly effective with overall estimated efficacy for documented infection of 92·8% (CI:[92·6, 93·0]); hospitalization 94·2% (CI:[93·6, 94·7]); severe illness 94·4% (CI:[93·6, 95·0]); and death 93·7% (CI:[92·5, 94·7]). Similarly, the overall estimated level of protection from prior SARS-CoV-2 infection for documented infection is 94·8% (CI:[94·4, 95·1]); hospitalization 94·1% (CI:[91·9, 95·7]); and severe illness 96·4% (CI:[92·5, 98·3]). Our results question the need to vaccinate previously-infected individuals.

Keywords: vaccine efficacy, COVID-19, SARS-CoV-2, previous infection, protection from reinfection

Introduction

Israel is currently in the later stages of a vaccination campaign to reduce both SARS-CoV-2 infection and the number of COVID-19 cases. Israel is administering the BNT162b2 vaccine, developed by BioNTech in cooperation with Pfizer,[1] for which an Emergency Use Authorization (EUA) was issued by the Food and Drug Administration (FDA).[2] The vaccine is administered in two doses, with a 21-day interval between doses. Israel launched its COVID-19 vaccination program on December 20, 2020. The vaccine became available, free of charge, to different risk groups in stages: first to those older than 60 years old, nursing home residents, healthcare workers, and patients with severe comorbidities, and then gradually to younger age groups. As of February 6, 2021, the vaccine was made available to all individuals aged 16 or older not previously infected by SARS-CoV-2. As of March 20, 2021, 77% of the eligible population is vaccinated. Due to the high caseload and the local detection of viral mutants such as B.1.1.7, Israel went into a third nationwide lockdown during the vaccination campaign. A light lockdown began on December 24, 2020, and was tightened on January 5, 2021. Restrictions were eased in stages starting February 7, 2021. The dynamics of the epidemic as well as the vaccination campaign appear in Figure 1.

SARS-CoV-2 testing in Israel is carried out according to the following policy: individuals may request testing due to either symptoms or contact with an individual who tested positive. These PCR tests are given free of charge. Individuals who have come into contact with an individual who tested positive are required to self-quarantine for 14 days. This quarantine period may be shortened to 10 days if the individual is tested twice during the first 10 days, and both test results are negative. Individuals who have received both vaccine doses, and had the second dose seven days or more before a contact with a positive individual, and do not have symptoms, are not required to self-quarantine, and thus have

less motivation to get tested. In addition to voluntary testing, Israel conducts routine testing of all nursing-home workers.

Recent results based on aggregated data[3–5] and individual level data[6–10] have shown that the vaccine substantially reduces the number of severe COVID-19 cases. Two studies also indicate that the viral load of vaccinated individuals is significantly reduced.[11,12] These encouraging initial results are based on a short follow-up of vaccinated individuals. Results on previous COVID-19 infection[13–16] suggest protection against reinfection compared to uninfected unvaccinated individuals.

In this study, we estimate the efficacy of the vaccine in the reduction of documented SARS-CoV-2 infection and severe COVID-19 disease. We focus on four cohorts: unvaccinated individuals; vaccinated individuals followed from first dose to a week after the second dose; vaccinated individuals followed from a week after the second dose onwards, and the Recovered Cohort of unvaccinated individuals previously infected with SARS-CoV-2. For more details, see the Methods section. All efficacies, of vaccine or previous infection, are compared to the unvaccinated cohort.

The prospective observational analysis that we present faced several challenges. The first challenge was self-selection of treatment, which implies differences in potential risk factors between vaccinated and non-vaccinated individuals. These include age, sex, socio-demographic level,[17] level of infection in the immediate environment, and possibly other behavioral variables that could affect level of exposure to the virus. The second challenge was detection bias: willingness to undergo vaccination can be associated with trust in the healthcare system, which may also imply a tendency to comply with testing regulations. On the other hand, vaccinated individuals may feel more protected and may ignore mild symptoms indicative of the disease, and have less motivation to get tested as they are not required to self-quarantine after a contact with a positive individual. The third challenge was the variation in infection risk throughout the vaccination campaign, mainly due to varying lockdown levels, relative prevalence of viral mutants, and local outbreaks. Lastly, the status of individuals (i.e., unvaccinated, partially vaccinated, or fully vaccinated) was

dynamic: with time, individuals move from one cohort to another, and between risk groups. In the Methods Section we explain how we designed the analysis to address these challenges.

Methods

Data

The database included two main tables. The first table was of all 1373 municipalities in Israel, with data on the number of residents, the daily count of PCR tests, and the daily positive results. This table was constructed based on data from the Israel Ministry of Health and the Israel Central Bureau of Statistics.

The second table was an individual-level table on persons aged 16 and above collected by the Israeli Ministry of Health based on data received routinely from all HMOs and hospitals and linked using the person's identity number. This table contained basic demographic data and information on dates of first and second vaccinations, if received, and dates and results of all PCR tests performed from March 1, 2020, up to March 20, 2021. For individuals with a positive PCR test, the table contained information on symptoms, as well as the maximum severity status throughout the course of the disease (hospitalization, severe disease, death). The definition of hospitalization, severe disease, and death due to COVID-19 is based on international recommendations.[18] Specifically, hospitalization is defined as being admitted due to COVID-19. Disease is considered severe when a patient has >30 breaths per minute, oxygen saturation on room air <94%, or ratio of arterial 148 partial pressure of oxygen to fraction of inspired oxygen <300mm mercury. Data on symptoms were also available but we found them less reliable and thus did not include symptomatic COVID-19 as an outcome.

Thus, the table contained an entry for every adult (age $\geq$ 16) in Israel who had at least one PCR test or had received at least the first dose of the vaccine (with a total of 5,682,928 entries). Adults with no PCR test and no vaccination (668,975) were added to the table using data from the Israel Central Bureau of Statistics. Thus, this second table included

6,351,903 entries with basic demographic data of the total adult population in Israel, as well as their PCR tests and vaccination dates. Individuals under age 16 are not eligible for vaccination and were excluded from this study. A summary of the data appears in Table 1.

To account for environmental risk, we calculated a municipality daily risk index by the number of cases newly confirmed in the past seven days per 10,000 residents. We used a 7-day moving average since the number of PCR tests typically drops at weekends. The index was categorized into four risk levels (up to one , one to four, four to ten, and more than ten daily cases per 10,000) to yield the municipality daily risk category, and was used as a covariate in the risk model.

Behavioral differences among people may result in different levels of exposure to infection and compliance with PCR testing guidelines. We partially accounted for this by counting the number of PCR-test clusters that an individual underwent from March 1, 2020, to December 20, 2020 (i.e., prior to the vaccination program). Here, a PCR-test cluster comprised all consecutive test performed within 10 days of each other. We then defined three individualized background risk levels: no PCR tests, one cluster, and two or more clusters, and this covariate was also included in the risk model. For previously-infected individuals, we set the level to one cluster and checked sensitivity to this value. Note that the time interval for defining this variable (up to December 20, 2020) did not overlap with the follow-up period.

In addition to estimating vaccine efficacy, we estimated the protection of prior SARS-CoV-2 infection against a recurrent infection. Thus, we also included in the dataset individuals who had recovered from COVID-19. Recovery from SARS-CoV-2 infection is not well-defined, and individuals may continue to show traces of the virus weeks and sometimes even months after the infection.[14] We defined as a recurrent infection only cases occurring three months or more after the first diagnosis. We also considered only individuals for whom the first infection was diagnosed between June 1 and September 30, 2020, as the PCR results before June 1 are considered less reliable. Hence, individuals infected before

June 1, 2020 or between October 1, 2020 and December 20, 2020 were excluded from the analysis.

Statistical Modeling

To estimate the efficacy of the Pfizer BNT162b2 vaccine in reducing documented SARS-CoV-2 infection and other COVID-19 events, we considered four dynamic sub-populations or cohorts:

- Cohort 0: Unvaccinated and not previously infected with SARS-CoV-2;
- Cohort 1: Vaccinated and followed from the day of first vaccination to 6 days after the second dose;
- Cohort 2: Vaccinated and followed from a week after the second dose onwards;
- Recovered: Unvaccinated and previously diagnosed with SARS-CoV-2 between June 1 and September 30, 2020.

On any given calendar day, each individual included in the analysis belongs to a single cohort, but cohort membership is dynamic. Moreover, individuals may not only move between cohorts over time (for example, from cohort 0 to cohort 1 after first vaccination, or from cohort 1 to cohort 2 at 7 days after the second vaccination), but also exit from the follow-up (for example, on infection with SARS-CoV-2 or death). The outcomes hospitalization, severe disease, and death, were attributed to the date on which COVID-19 was documented.

We modeled the daily risk of each individual from December 20, 2020 to March 20, 2021, as a function of calendar time, the cohort to which the individual currently belonged, and the individual's current risk factors, which included fixed covariates: age group (16-39, 40-49, 50-59, 60-69, 70-79, and 80+), sex, and background risk level (0,1, and 2+ past PCR tests), and the time-dependent variable: municipality risk level(low, medium, medium-high,

and high). We refer to each combination of possible covariate values (age group, sex, background risk level, and municipality risk level) as the risk profile.

Our analysis model falls within the framework of multi-state survival models, where each cohort represents a separate state;[19] see Figure S1. Similar to the study of mRNA-1273, the vaccine developed by Moderna,[20] we defined the efficacy of the vaccine in terms of hazard ratios, where the main interest is in comparing the hazard of a non-vaccinated individual (Cohort 0) to that of an individual who had completed the recommended protocol (Cohort 2). Hazard ratios between cohorts and for each adjusting covariate were estimated via a generalized linear model with a Poisson distribution and logarithmic link function, and an offset for each risk profile.[21]

Our model assumes that for a given cohort and risk profile, the hazard was constant and did not depend on the time from the second dose (Cohort 2). Obviously, the hazard of individuals who have never received the first dose (Cohort 0) cannot depend on the time of the first dose, but we also assumed that the time elapsed from the second vaccination did not affect the hazard in Cohort 2. In other words, we assumed that the protection level did not change with time after the "completion" of the vaccination protocol. While protection by vaccination is expected to decrease in the long run, our assumption is reasonable given the time frame of only three months after first vaccination, where waning immunity is not expected to play a role. We split Cohort 1 into two sub-cohorts: Cohort 1A from the first dose to two weeks after the first dose, and Cohort 1B from 15 days after the first dose to six days after the second dose. Following Skowronski and De Serres,[22] we considered, as a crude approximation, a constant hazard for each of these two sub-cohorts for every risk profile. To estimate the level of protection among the Recovered Cohort, we made a similar assumption, that the time elapsed from SARS-CoV-2 infection did not affect the hazard ratio.

The formal definition of vaccine efficacy adopted was as follows. Consider any particular risk profile. Let h_i denote the hazard of an individual in one of the vaccinated cohorts 1A, 1B, 2, or Recovered, and let h_0 be the hazard of an individual having the identical risk

profile in the unvaccinated group. Efficacy of the vaccine in that cohort for that risk profile is defined as $1 - h_i/h_0$. Note that the calendar time affects the hazards of the different cohorts only via the time-dependence of the municipality risk level. From the model assumptions, the ratio h_i/h_0 is the same for each risk profile, so the estimate of vaccine efficacy may be combined over all the risk profiles. For more details about the model, see Appendix. We analyzed efficacy separately for each of the following outcomes: documented infection, hospitalization, severe disease, and death.

Results

The data are based on follow-up of the four cohorts from December 20, 2020 up to March 20, 2021, with over 573 million person-days of follow-up. The lengths of follow-up for the fully vaccinated and the recovered cohorts appear in Figures S2 and S3, respectively. During this time 4,606,247 PCR tests were performed (8,040 per million person-days), and 306,712 individuals tested positive (5·4 infections per 10,000 person-days). Of those testing positive, 14,019 (4·6%) required hospitalization, 8,463 (2·8%) were defined as severe cases, and 2,727 (0·9%) died. Table 2 presents these numbers by cohort and age group. The numbers of PCR tests performed per million person-days appear in Table 3. There is a decrease in the rate of PCR testing in both Cohort 2 and the Recovered Cohort compared to the other cohorts. This is likely since fully vaccinated or recovered individuals (Cohorts 2 & Recovered) are more protected against SARS-CoV-2 infection. Additionally, people in Israel need to self-quarantine for 14 days after contacting SARS-CoV-2 infected persons, which can be shortened to ten days if they present two negative PCR tests. This is not required for fully vaccinated and recovered persons unless they develop symptoms.

We first investigated the dynamics of the vaccination program, disease outcomes, PCR testing, and municipality risk as a function of calendar time. Figures S4 and S5 present the proportion of vaccinated over time among different age and municipality risk groups, respectively. As can be seen from Figure S4, the Israeli vaccination policy was initially to immunize the older population, and as time progressed, younger age groups. Figure S5 shows the association between environmental risk and vaccination. Figure S6 shows the

rates over time of the different age groups among those tested, infected, hospitalized, having severe disease, and dying. Table 4 shows, by age group, the estimated vaccine efficacy for the main outcomes for Cohort 2 (fully vaccinated) adjusted for sex, municipality risk, and past PCR. Note that for age groups below 60 years, there were, fortunately, none or very few events of severe illness and death, and thus estimates were omitted for these groups. The table shows that vaccine efficacy was quite similar in all age groups with some decrease in efficacy for the 80+ age category. Fitting a model without age-group/cohort interaction yielded overall vaccine efficacy for documented infection of 92·8% (CI: [92·6, 93·0]); hospitalization 94·2% (CI: [93·6, 94·7]); severe illness 94·4% (CI: [93·6, 95·0]); and death 93·7% (CI: [92·5, 94·7]). We repeated the analysis with full vaccination defined as 15 days or more after the second dose. The results are similar (not shown).

Table 5 presents the results for the Recovered Cohort when the past PCR-based individualized risk was set to one PCR cluster. Again, the protection was quite similar in all age groups with some decrease in efficacy for the 80+ age category, and quite similar to the results in Table 4. The overall estimated protection of prior SARS-CoV-2 infection for documented recurrent infection was 94·8% (CI: [94·4, 95·1]); hospitalization 94·1% (CI: [91·9, 95·7]); and severe illness 96·4% (CI: [92·5, 98·3]). As there were only 1 death cases in the Recovered Cohort, protection against death was not estimated.

As described above, we assigned the recovered individuals to the middle PCR risk group, so that the estimated protection of a prior infection is compared to unvaccinated individuals having a single PCR cluster in the past. The protection levels afforded by a prior infection compared to unvaccinated persons who had no or 2+ past PCR tests are given in a sensitivity analysis shown in Table S1. In addition, Table S1 presents results of a model without PCR, which can be interpreted as the overall protection of a prior infection. As expected, the protection of a prior infection compared to unvaccinated persons who did not have past PCR tests is estimated to be smaller and compared to those who had 2+ tests is larger. The results when omitting the PCR variable are very similar to the figures in Table 5.

The results for Cohorts 1A and 1B appear in Tables S2 and S3, respectively. The results up to two weeks after the first dose (Cohort 1A) suggest low but statistically significant efficacy. For Cohort 1B that comprises individuals at more than two weeks after the first dose, the efficacy is higher, being 57·7% (CI: [57·1, 58·4]) for documented infection; 69·4% (CI: [67·5, 71·2]) for hospitalization; 65·9% (CI: [63·1, 68·5]) for severe illness; and 62·7% (CI: [58·0, 66·8]) for death. The coefficients of all four models used for analyzing the data appear in Tables S4-S7.

Discussion

This population-based observational study demonstrates the high efficacy of the BNT162b2 vaccine and prior SARS-CoV-2 infection against both subsequent SARS-CoV-2 infection and other COVID-19–related outcomes. There are a few characteristics that make this study unique. First, it was a nationwide study and thus represented the real-world effectiveness of vaccination and prior infection on the full population. Second, it used individual-level data that enabled, at least to some degree, to mitigate biases caused by selection to get vaccinated, selection to undergo PCR testing, and time-changing level of risk, via adjustment for between-cohort differences in individuals' characteristics and municipality risk level. Third, the study included follow-up of the population for a period of three months, allowing follow-up of the fully vaccinated cohort over an extended duration. Fourth, this is the first large-scale study that has explored the protection due to prior SARS-CoV-2 infection compared to the Pfizer BNT162b2 vaccine.

There are some limitations to this observational study. One major source of confounding is related to possible population differences between individuals who were vaccinated compare to those who were not. This confounding is partially addressed by controlling for risk factors. Specifically, for each individual we adjusted for sex, age group, number of past PCR tests and the time-dependent environmental exposure. Another major source of potential bias is related to detection of SARS-CoV-2 infection. As apparent from the PCR test counts in Table 3, individuals who are fully vaccinated or were previously infected get tested less often than the unvaccinated cohort. Our results for the outcomes of

hospitalization, severe disease, and death do not suffer from this bias and thus are more reliable. The vaccine protection against infection might be biased upward as explained above, nevertheless the remarkable curtailing of the outbreak in Israel which followed the high vaccine uptake by the Israeli population further suggest that the vaccine is efficient in blocking transmission, see Figure 1.

The efficacy estimates of the BNT162b2 vaccine in this study are similar to those reported by previous large-scale studies. For the severe disease outcome, the randomized trial of BNT162b2[1] reported 89% efficacy for severe disease. A study by the Israeli Ministry of Health using aggregated data[5] reported 96% efficacy for people as defined in our Cohort 2. A study on data from Israel's largest HMO[6] split people as defined in our Cohort 1B and reported an efficacy of 62% and 80% for the third and fourth weeks after the first vaccine, respectively, and of 92% for their Cohort 2. In comparison, our analysis showed efficacy of 66% for Cohort 1B and 94% for Cohort 2. For other outcomes, the estimated vaccine efficacy for Cohort 2 in our study were 93% and 94%, for documented infection and hospitalization, respectively. These estimates are similar to previous studies[5,6] that estimated efficacy of 92% and 96% for documented infection, and of 87% and 96% for hospitalization. Our findings are based on a longer follow-up and a larger number of event than in the previous individual-level data reports. For example, the analysis of severe cases in the randomized clinical trial is based on only 10 cases, and that of Israel's largest HMO on 229.[6] In comparison, the analysis in our study is based on 8,463 cases, including 2,240 cases from Cohort 1 and 319 cases from Cohort 2. On the other hand, the other two studies[1,6] have the respective advantages of randomization and a detailed matching process which help in bias reduction.

The estimated protection against reinfection in this study is similar to that of the BNT162b2 vaccine. For documented SARS-CoV-2 reinfection, these results are similar to the results obtained in a large study from Qatar of 95% protection,[13] and suggest higher protection than reported by other previous studies. A large study from Denmark[14] suggested 80% protection against reinfection. A study on healthcare workers in the United Kingdom[16] reported that previous infection was associated with an 83% lower risk of infection. These

two studies are based on 11,727 and 6,614 previously infected individuals, with 72 and 44 reinfections, respectively. In comparison, the Recovered cohort in our study comprised 187,549 individuals, with 894 reinfections. One possible reason for the differences in the estimated protection against reinfection could be related to detection bias of SARS-CoV-2 infection. However, our estimated high levels of protection against hospitalization and serious disease after reinfection are unlikely to be affected by detection bias, and are reassuring.

An important assumption made here is that rates of infection or hazards are independent of time from vaccination. However, the rate of infection is expected to depend on time from vaccination or on time from first infection. Studying the hazard as a function of time is crucial for understanding waning immunity and for the need for additional booster vaccinations. Follow-up is currently too short to answer time-dependent questions, but this is a crucial and required next step that can be answered using the national Israeli data in the future. The hazard may also depend on calendar time, not only via environmental exposure, but also because of new variants appearing, against which, the vaccine may have different efficacy. During the period over which the data were collected, the COVID-19 variant B.1.1.7 was by far the most prevalent variant, and accounted for most of the documented cases, hence the approximation of a constant hazard is justified. Yet, it is of great importance to repeat this study in other populations in order to estimate the efficacy for other variants and vaccines.

This study suggests that both the BNT162b2 vaccine and prior SARS-CoV-2 infection are effective against both subsequent SARS-CoV-2 infection and other COVID-19–related outcomes. Moreover, the effectiveness seems similar for both cohorts. This puts into question the need to vaccinate recent (up to six month) previously-infected individuals.

References

1. Polack, F. P. *et al.* Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *New England Journal of Medicine* **383**, 2603–2615 (2020).

2. Tanne, J. H. Covid-19: Pfizer-BioNTech vaccine is rolled out in US. *BMJ* **371**, m4836 (2020).

3. dviraran. *Dviraran/covid_analyses*. (2021).

4. Rossman, H. *et al.* Patterns of COVID-19 pandemic dynamics following deployment of a broad national immunization program. *medRxiv* 2021.02.08.21251325 (2021) doi:10.1101/2021.02.08.21251325.

5. Haas, E. J. *et al. Nationwide Vaccination Campaign with BNT162b2 in Israel Demonstrates High Vaccine Effectiveness and Marked Declines in Incidence of SARS-CoV-2 Infections and COVID-19 Cases, Hospitalizations, and Deaths.* https://papers.ssrn.com/abstract=3811387 (2021).

6. Dagan, N. *et al.* BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *New England Journal of Medicine* (2021) doi:10.1056/NEJMoa2101765.

7. Chodick, G. *et al.* The effectiveness of the first dose of BNT162b2 vaccine in reducing SARS-CoV-2 infection 13-24 days after immunization: Real-world evidence. *medRxiv* 2021.01.27.21250612 (2021) doi:10.1101/2021.01.27.21250612.

8. Yelin, I. *et al.* Associations of the BNT162b2 COVID-19 vaccine effectiveness with patient age and comorbidities. *medRxiv* (2021).

9. Amit, S., Regev-Yochay, G., Afek, A., Kreiss, Y. & Leshem, E. Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients. *The Lancet* **397**, 875–877 (2021).

10. Benenson, S., Oster, Y., Cohen, M. J. & Nir-Paz, R. BNT162b2 mRNA Covid-19 Vaccine Effectiveness among Health Care Workers. *New England Journal of Medicine* **0**, null (2021).

11. Levine-Tiefenbrun, M. *et al.* Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine. *Nature Medicine* 1–3 (2021).

12. Petter, E. *et al.* Initial real world evidence for lower viral load of individuals who have been vaccinated by BNT162b2. (2021) doi:10.1101/2021.02.08.21251329.

13. SARS-CoV-2 reinfection in a cohort of 43,000 antibody-positive individuals followed for up to 35 weeks medRxiv.

14. Hansen, C. H., Michlmayr, D., Gubbels, S. M., Mølbak, K. & Ethelberg, S. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: A population-level observational study. *The Lancet* **397**, 1204–1212 (2021).

15. Lumley, S. F. *et al.* Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers. *New England Journal of Medicine* **384**, 533–540 (2021).

16. Hall, V. *et al.* Do antibody positive healthcare workers have lower SARS-CoV-2 infection rates than antibody negative healthcare workers? Large multi-centre prospective cohort study (the SIREN study), England: June to November 2020. *medRxiv* 2021.01.13.21249642 (2021) doi:10.1101/2021.01.13.21249642.

17. Caspi, G. *et al.* Socioeconomic Disparities and COVID-19 Vaccination Acceptance: Experience from Israel. *medRxiv* 2021.01.28.21250716 (2021) doi:10.1101/2021.01.28.21250716.

18. Clinical Spectrum. *COVID-19 Treatment Guidelines*.

19. Hougaard, P. *Analysis of multivariate survival data*. (Springer Science & Business Media, 2012).

20. Baden, L. R. *et al*. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *New England Journal of Medicine* **384**, 403–416 (2021).

21. Myers, R. H., Montgomery, D. C., Vining, G. G. & Robinson, T. J. *Generalized linear models: With applications in engineering and the sciences*. vol. 791 (John Wiley & Sons, 2012).

22. Skowronski, D. M. & De Serres, G. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *New England Journal of Medicine* (2021) doi:10.1056/NEJMc2036242.

Contributors

LF, YG, AH and MM were responsible for study design and for writing of the manuscript. RF, YG, MM, IN, YW, RY, and AZ analyzed the data. YW and AZ were responsible for collecting the data and for data management. LF, YG, AH and MM did the literature survey. LF, RF, YG, MM, and IN developed the mathematical model. YG and YW developed the software for analyzing the data. All authors interpreted the data and reviewed the draft and final versions of the manuscript.

Ethics statement

The study was approved by the Institutional Review Board of the Sheba Medical Center. Helsinki approval number: SMC-8228-21

Funding

None

Competing interests statement

All authors declare no competing interests.

Data sharing

The data used in this study are sensitive and will not be made publicly available.

Acknowledgments

The authors would like to thank Guy Katriel for fruitful discussions.

Table 1: Population level data. Columns Male, Female, and Total are in thousands. Columns PCR tests, Positive tests, Hospitalized, Severe, and Death, are the counts during the period December 20, 2020 to March 20, 2021.

Age	Male	Female	Total	PCR	Positive	Hospitalization	Severe	Death
16-39	1,513	1,484	2,997	2,414,803	183,617	2,722	684	44
40-49	531	542	1,073	810,988	49,373	1,614	814	64
50-59	404	423	827	575,853	34,411	1,978	1,252	153
60-69	345	386	731	399,149	21,073	2,242	1,528	406
70-79	207	249	456	207,538	10,410	2,358	1,757	674
80+	106	161	267	197,916	7,828	3,105	2,428	1,386
Total	3,107	3,245	6,352	4,606,247	306,712	14,019	8,463	2,727

Table 2: Person-day event counts. Person-day counts and event counts for the different cohorts during the period December 20, 2020 to March 20, 2021. Person-day counts are in millions. PCR, Positive, Hospitalized, Severe, and Death, are the actual counts.

Cohort	Age	Person Days	PCR	Positive	Hospitalization	Severe	Death
0	16-39	170.5	1,609,352	156,104	2,413	602	38
0	40-49	49.4	449,371	37,075	1,331	683	56
0	50-59	31.3	268,892	23,383	1,541	1,011	122
0	60-69	20.5	143,320	12,130	1,528	1,051	261
0	70-79	9.7	70,430	5,483	1,455	1,116	431
0	80+	7.1	64,035	3,908	1,789	1,425	841
1A	16-39	27.3	287,539	19,707	231	63	5
1A	40-49	11.4	107,441	7,619	201	99	6
1A	50-59	9.6	85,134	6,355	290	165	17
1A	60-69	8.8	61,433	4,638	400	269	74
1A	70-79	6.5	30,853	2,247	418	304	113
1A	80+	3.6	32,731	1,759	643	490	262
1B	16-39	25.5	265,444	6,185	54	11	1
1B	40-49	11.2	103,730	3,651	52	20	2
1B	50-59	9.6	84,936	3,655	96	52	11
1B	60-69	9.0	64,055	3,238	240	160	52
1B	70-79	6.7	32,475	1,904	339	244	94
1B	80+	3.7	32,244	1,440	467	363	204
2	16-39	32.9	224,106	1,002	12	2	0
2	40-49	21.7	142,540	903	26	12	0
2	50-59	22.5	130,718	931	44	21	3
2	60-69	27.0	126,381	1,030	69	45	19
2	70-79	21.3	72,091	764	140	92	36
2	80+	11.4	67,345	707	202	147	78
Recovered	16-39	9.0	28,362	619	12	6	0

Recovered	40-49	2.4	7,906	125	4	0	0
Recovered	50-59	1.8	6,173	87	7	3	0
Recovered	60-69	1.1	3,960	37	5	3	0
Recovered	70-79	0.5	1,689	12	6	1	0
Recovered	80+	0.2	1,561	14	4	3	1

Table 3: PCR tests per million person days.

Cohort	16-39	40-49	50-59	60-69	70-79	80+
0	9,439	9,097	8,591	6,991	7,261	9,019
1A	10,533	9,425	8,868	6,981	4,747	9,092
1B	10,410	9,262	8,848	7,117	4,847	8,715
2	6,812	6,569	5,810	4,681	3,385	5,908
Recovered	3,151	3,294	3,429	3,600	3,378	7,805

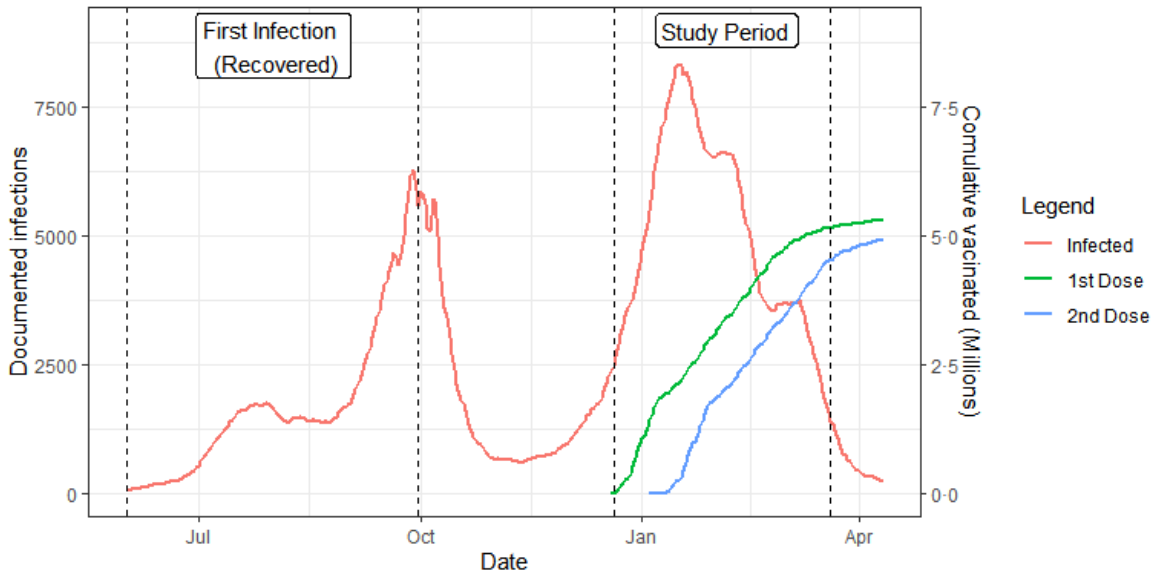
Table 4: Vaccination efficacy. Vaccination efficacy for the different age groups adjusted for sex, municipality risk, and past PCR. The overall estimates are based on models without cohort-age interaction. Estimates are not provided for Severe and Death outcomes for the lowest age groups due to very low case numbers in the vaccinated cohorts.

Age	Positive	Hospitalized	Severe	Death
16-39	95·1% [94·8, 95·4]	96·5% [93·8, 98·0]	—	—
40-49	92·5% [92·0, 93·0]	94·4% [91·7, 96·2]	—	—
50-59	92·7% [92·2, 93·1]	95·0% [93·3, 96·3]	—	—
60-69	92·4% [91·9, 92·9]	96·1% [95·1, 97·0]	96·4% [95·1, 97·3]	94·0% [90·4, 96·2]
70-79	92·2% [91·6, 92·8]	94·8% [93·8, 95·6]	95·5% [94·5, 96·4]	95·4% [93·5, 96·7]
80+	85·6% [84·3, 86·7]	91·2% [89·8, 92·4]	91·9% [90·4, 93·2]	92·6% [90·6, 94·1]
Overall	92·8% [92·6, 93·0]	94·2% [93·6, 94·7]	94·4% [93·6, 95·0]	93·7% [92·5, 94·7]

Table 5: Protection of prior SARS-CoV-2 infection. Protection of prior SARS-CoV-2 infection for the different age groups adjusted for sex, municipality risk, and past PCR. The overall estimates are based on models without cohort-age interaction. Estimates are not provided for Severe outcomes for the lowest age groups and for Death for all age groups due to very low case numbers in the previously-infected cohorts.

Age	Positive	Hospitalized	Severe
16-39	94·5% [94·1, 94·9]	92·8% [87·3, 95·9]	—
40-49	95·1% [94·2, 95·9]	95·4% [87·7, 98·3]	—
50-59	95·2% [94·1, 96·1]	93·9% [87·1, 97·1]	—
60-69	96·1% [94·6, 97·2]	95·7% [89·6, 98·2]	96·1% [87·8, 98·7]
70-79	97·0% [94·7, 98·3]	94·1% [86·8, 97·3]	98·7% [90·5, 99·8]
80+	91·4% [85·5, 94·9]	94·2% [84·5, 97·8]	94·2% [81·9, 98·1]
Overall	94·8% [94·4, 95·1]	94·1% [91·9, 95·7]	96·4% [92·5, 98·3]

Figure 1: Population dynamics. Documented new infections and cumulative vaccinated persons by date. The study period and the infection period of the recovered cohorts are marked by vertical lines.



Web Appendix: The Statistical Model

We define the efficacy of the vaccine in terms of hazard ratios. We use the following constant hazard models to describe the dynamics of an uninfected individual risk over time (calendar time and time from vaccination), where, in the most general model, each cohort has different coefficients:

$$h_i(x) = \exp\{\alpha_i + \beta_i^T x\} \;\; i = 0,\ 1A,\ 1B,\ 2,\ \text{Recovered}.$$

Here x indicates a set of risk factors of an individual, including time dependent variables (municipality risk). While the model above is quite general, enabling different coefficients for the different cohorts, our basic model restricts the coefficients of sex, past PCR tests and municipality risk to be equal among the cohorts. Specifically, let

$$\beta_i^T x = \beta_{i,age} \times \text{Age} + \beta_{i,sex} \times \text{Sex} + \beta_{i,ppcr} \times \text{Past PCR} + \beta_{i,risk} \times \text{Municipal risk},.$$

We assume that for $i = 0,\ 1A,\ 1B,\ 2,$ Recovered,

$$\beta_{i,sex} = \beta_{sex},\ \ \beta_{i,ppcr} = \beta_{ppcr},\ \ \text{and}\ \ \beta_{i,risk} = \beta_{risk}.$$

Thus, the effect of sex, past PCR test, and municipal risk on efficacy is multiplicative and identical among cohorts. However, efficacy may vary between different age groups.

The constant hazard assumption implies underlying exponential event-free models for these cohorts, with time-dependent covariates. The analysis can be carried out by performing Poisson regression with offsets for each risk profile. Specifically, consider a group of individuals' days in Cohort i with a certain risk profile x_0 (here the profile also includes time-dependent covariates, so only days satisfying x_0 count). The response variable is 'case count' – the number of cases among these individuals' days, and the exposure is the sum of all at-risk days for individuals with cohort and risk-profile combination (i, x_0). Thus, the model implies

$$\frac{\text{E}(\text{case count} \mid x_0, \text{at-risk days})}{\text{at-risk days}} = \exp\{\beta_i^T x_0\}.$$

In other words, the daily hazard for an event for an individual in Cohort i and risk profile x, denoted by $h_{i,x}$, is $e^{\beta_i^T x}$. The relative risk for Cohort $i = 2$ with risk profile x is defined as $h_{2,x}/h_{0,x}$, and the efficacy is defined as $1 - h_{2,x}/h_{0,x}$. Under the assumption of equal coefficients for sex, past PCR tests and municipality risk, the relative efficacy depends only on the age group.

Technically, in order to estimate the coefficients in the model, we create a working dataset as follows. For each combination of cohort, age group, sex, municipality risk level, and individualized risk level, we count the number of COVID-19 events and the number of at-risk days. Consider, for example, a 56-year-old male who lives in Tel Aviv, had 1 negative PCR test before December 20, 2020, received his first dose on January 1, 2021, and his second dose on January 23, 2020, and tested positive on February 8, 2021. Assume that the Tel Aviv risk level was category 1 during the period December 20, 2020 to January 20, 2021, category 2 from January 21, 2021 until the end of follow-up on February 8, 2021. This person contributes:

1. 11 days (Dec-20 to Dec-31) and 0 events to the group:
   cohort_0/50-60/male/mun_risk=1/past_pcr=1

2. 14 days (Jan-1 to Jan-14) and 0 events to the group:
   cohort_1A/50-60/male/mun_risk=1/past_pcr=1

3. 6 days (Jan-15 to Jan-20) and 0 events to the group:
   cohort_1B/50-60/male/mun_risk=1/past_pcr=1

4. 9 days (Jan-21 to Jan-29) and 0 events to the group:
   cohort_1B/50-60/male/mun_risk=2/past_pcr=1

5. 10 days (Jan-30 to Feb-8) and 1 event to the group:
   cohort_2/50-60/male/mun_risk=2/past_pcr=1

Figure S1: The dynamics of the cohort model. Solid arrows indicate possible transitions between cohorts. Dashed arrows indicate possible disease outcomes.

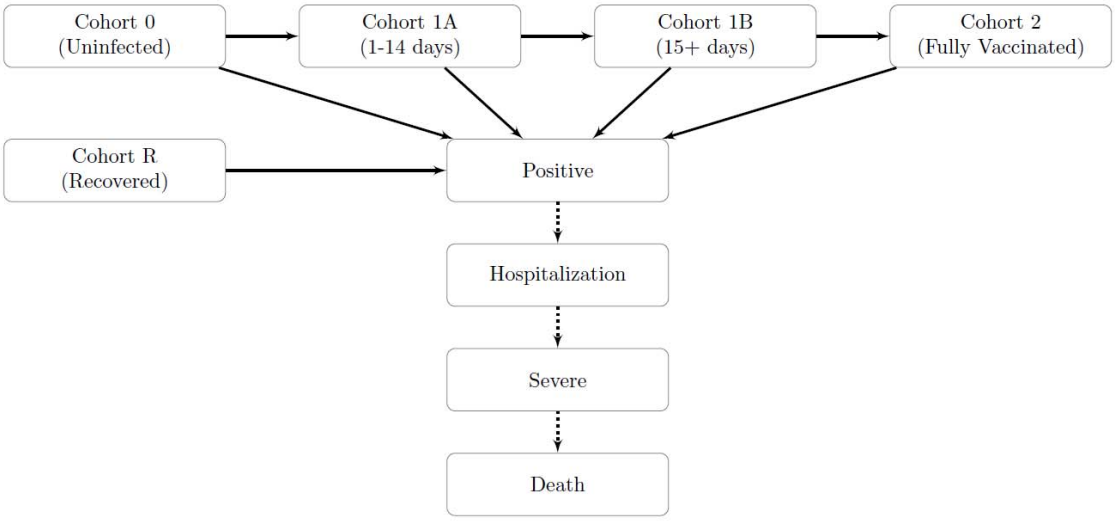


Figure S2: Length of follow-up for Cohort 2. Length of follow-up for Cohort 2 of the fully vaccinated, according to age group. Vaccination became available first to the 60+ age groups and then gradually to younger age groups as can be seen from the follow-up counts.

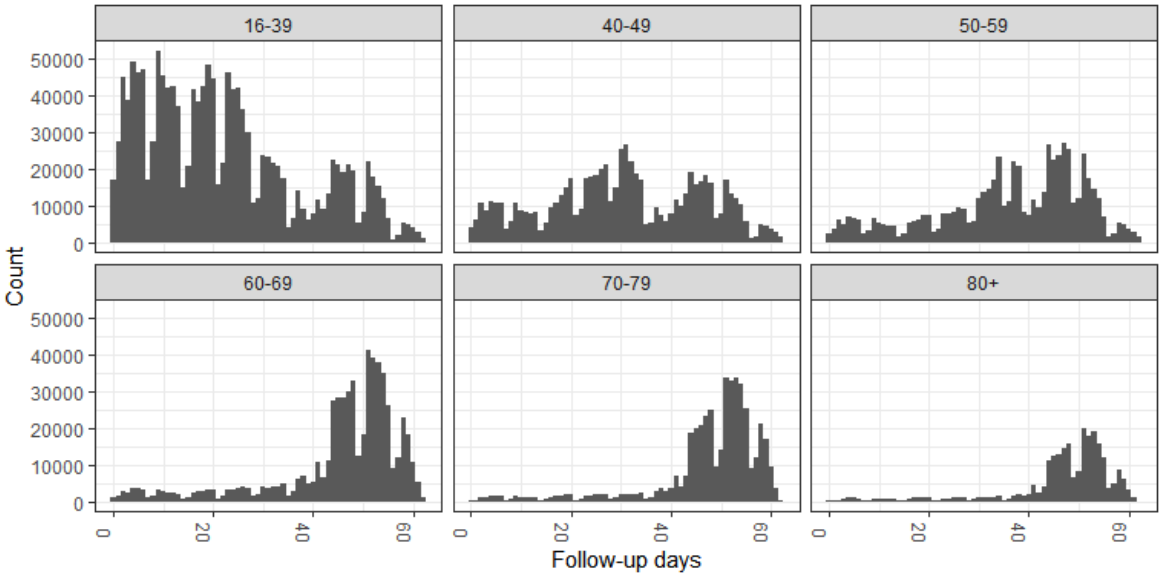


Figure S3: Length of follow-up for the Recovered Cohort. Length of follow-up from first positive PCR test for the Recovered Cohort, according to age group. This cohort included individuals that had a positive PCR test between June 1 and September 30, 2020. Note the sharp decrease in counts as a function of the follow-up. Note that each subfigure has a different scale.

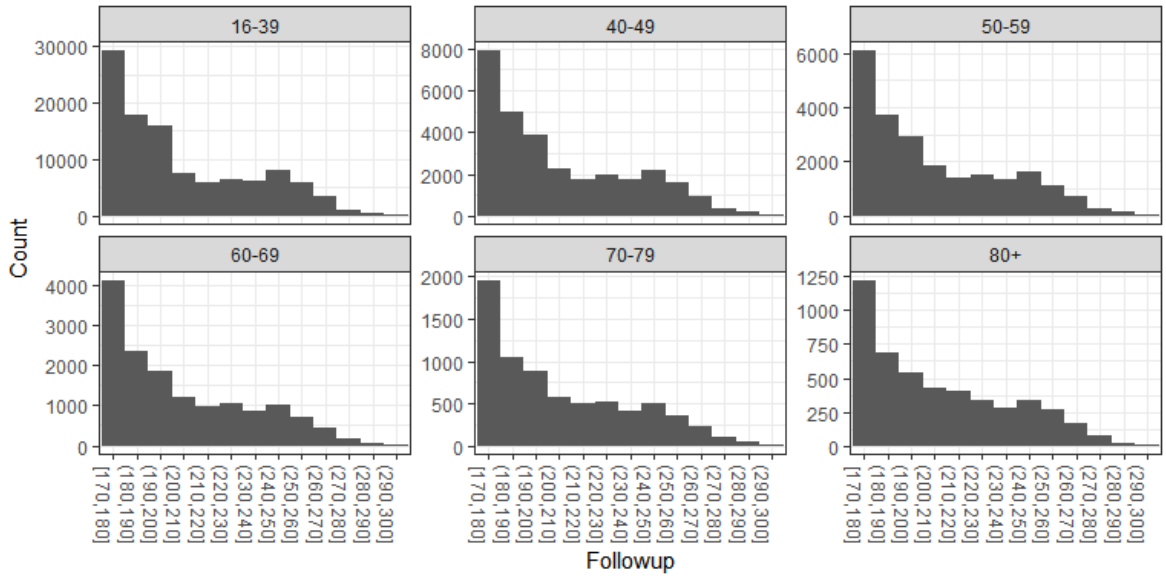


Figure S4: Vaccination by age. Percent of individuals vaccinated with the first and the second dose, by age group. The vaccination initiated in the 60+ age group. See text for details.

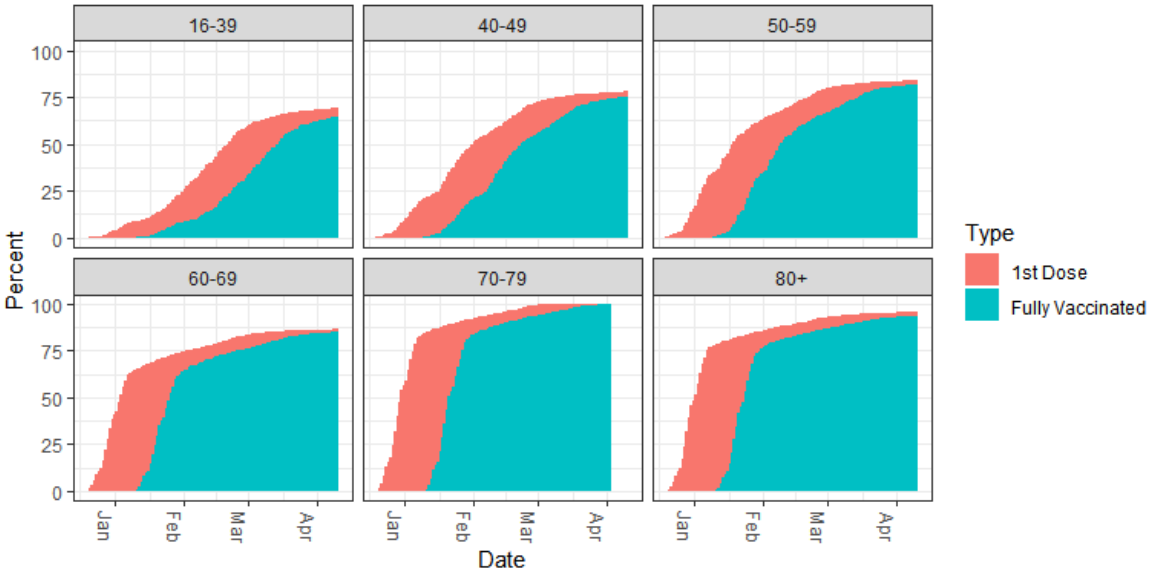


Figure S5: Vaccination by municipality risk. Percent of individuals vaccinated with the first and the second dose, by municipality risk group. The municipality risk was calculated as the median of the daily risk over the research period . Note that there is a negative correlation between vaccine coverage and risk group.

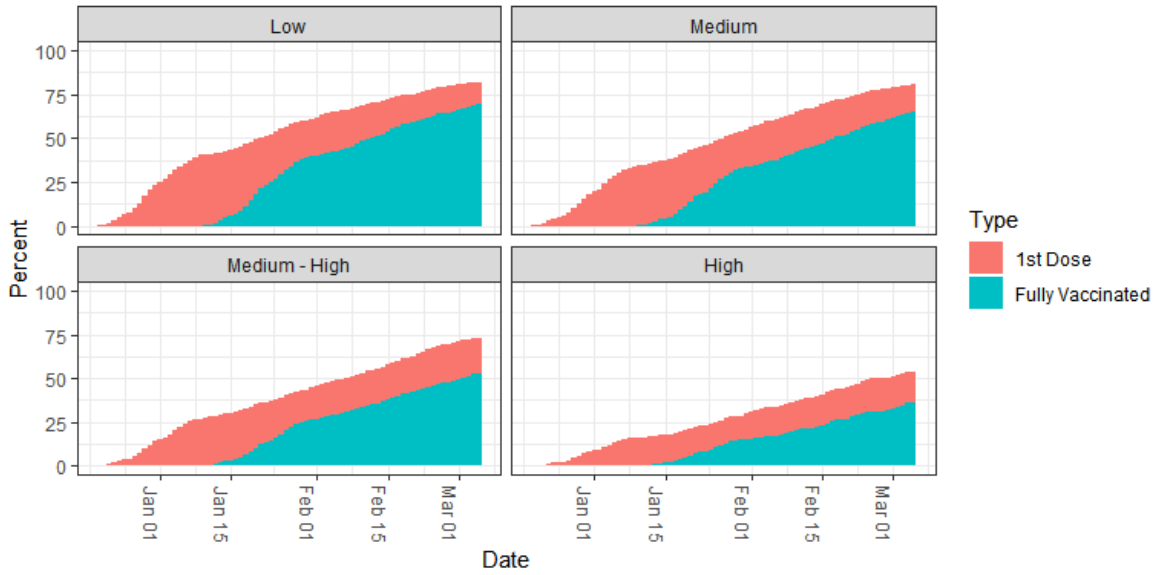


Figure S6: Events over time. Cases per 100,000, smoothed using seven-day moving average for the different age groups and the outcomes: PCR tests, documented infection cases, hospitalized cases, severe cases, and deaths.

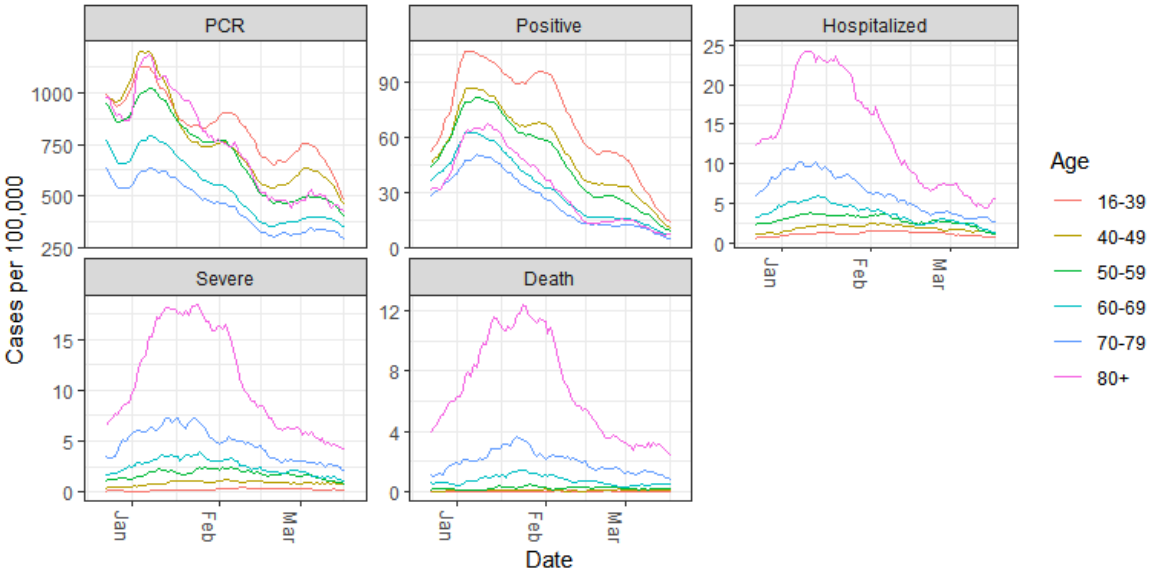


Table S1: Sensitivity analysis of past PCR on prior SARS-CoV-2 infection. Protection of prior SARS-CoV-2 infection for the different age groups. The model was fitted when the number of PCR clusters is assigned to be 0, 1, 2+, and omitted.

Analysis	Age	Positive	Hospitalized	Severe
PCR 0	16-39	91·9% [91·3, 92·6]	89·5% [81·5, 94·1]	—
PCR 0	40-49	92·8% [91·4, 93·9]	93·3% [82·0, 97·5]	—
PCR 0	50-59	92·9% [91·3, 94·3]	91·0% [81·2, 95·7]	—
PCR 0	60-69	94·2% [92·1, 95·8]	93·7% [84·8, 97·4]	94·6% [83·2, 98·3]
PCR 0	70-79	95·6% [92·2, 97·5]	91·4% [80·7, 96·1]	98·2% [86·9, 99·7]
PCR 0	80+	87·4% [78·7, 92·5]	91·6% [77·5, 96·8]	92·0% [75·1, 97·4]
PCR 1	16-39	94·5% [94·1, 94·9]	92·8% [87·3, 95·9]	—
PCR 1	40-49	95·1% [94·2, 95·9]	95·4% [87·7, 98·3]	—
PCR 1	50-59	95·2% [94·1, 96·1]	93·9% [87·1, 97·1]	—
PCR 1	60-69	96·1% [94·6, 97·2]	95·7% [89·6, 98·2]	96·1% [87·8, 98·7]
PCR 1	70-79	97·0% [94·7, 98·3]	94·1% [86·8, 97·3]	98·7% [90·5, 99·8]
PCR 1	80+	91·4% [85·5, 94·9]	94·2% [84·5, 97·8]	94·2% [81·9, 98·1]
PCR 2+	16-39	95·7% [95·4, 96·1]	95·4% [91·8, 97·4]	—
PCR 2+	40-49	96·2% [95·5, 96·8]	97·0% [92·0, 98·9]	—
PCR 2+	50-59	96·3% [95·4, 97·0]	96·0% [91·7, 98·1]	—
PCR 2+	60-69	97·0% [95·8, 97·8]	97·2% [93·3, 98·8]	97·9% [93·3, 99·3]
PCR 2+	70-79	97·7% [95·9, 98·7]	96·2% [91·5, 98·3]	99·3% [94·8, 99·9]
PCR 2+	80+	93·3% [88·7, 96·1]	96·3% [90·0, 98·6]	96·8% [90·2, 99·0]
No PCR	16-39	93·4% [92·9, 93·9]	91·7% [85·3, 95·3]	—
No PCR	40-49	94·0% [92·8, 95·0]	94·5% [85·4, 98·0]	—
No PCR	50-59	94·0% [92·6, 95·2]	92·6% [84·5, 96·5]	—
No PCR	60-69	95·1% [93·2, 96·4]	94·7% [87·3, 97·8]	95·5% [86·1, 98·6]
No PCR	70-79	96·4% [93·6, 97·9]	93·2% [84·8, 96·9]	98·6% [89·8, 99·8]
No PCR	80+	90·5% [84·0, 94·4]	94·0% [84·1, 97·8]	94·5% [83·0, 98·2]

Table S2: Vaccination efficacy for Cohort 1A. Vaccination efficacy for Cohort 1A adjusted for sex, municipality risk, and past PCR. The overall estimates are based on models without cohort-age interaction. Estimates are not provided for Severe and Death outcomes for the lowest age groups due to very low case numbers in the vaccinated cohorts.

Age	Positive	Hospitalized	Severe	Death
16-39	17·7% [16·4, 18·9]	39·7% [31·0, 47·4]	—	—
40-49	17·6% [15·5, 19·6]	40·7% [31·2, 48·9]	—	—
50-59	18·6% [16·3, 20·9]	44·6% [37·2, 51·1]	—	—
60-69	22·4% [19·7, 25·0]	47·3% [41·2, 52·8]	49·2% [42·0, 55·6]	44·7% [28·3, 57·3]
70-79	44·0% [41·2, 46·7]	60·5% [55·9, 64·6]	62·9% [57·8, 67·3]	63·6% [55·2, 70·4]
80+	17·2% [12·4, 21·7]	32·6% [26·3, 38·5]	36·2% [29·2, 42·4]	40·3% [31·3, 48·1]
Overall	20·6% [19·7, 21·4]	45·7% [43·1, 48·2]	49·3% [45·7, 52·7]	48·5% [42·8, 53·7]

Table S3: Vaccination efficacy for Cohort 1B. Vaccination efficacy for Cohort 1B adjusted for sex, municipality risk, and past PCR. The overall estimates are based on models without cohort-age interaction. Estimates are not provided for Severe and Death outcomes for the lowest age groups due to very low case numbers in the vaccinated cohorts.

Age	Positive	Hospitalized	Severe	Death
16-39	67·3% [66·4, 68·1]	82·4% [77·0, 86·6]	—	—
40-49	55·1% [53·6, 56·6]	82·8% [77·3, 87·0]	—	—
50-59	50·3% [48·5, 52·0]	80·7% [76·3, 84·3]	—	—
60-69	48·6% [46·6, 50·6]	70·0% [65·6, 73·8]	71·4% [66·3, 75·8]	63·3% [50·5, 72·7]
70-79	56·2% [53·9, 58·5]	70·4% [66·6, 73·7]	72·6% [68·5, 76·1]	72·1% [65·1, 77·7]
80+	36·6% [32·6, 40·3]	54·1% [49·2, 58·6]	55·8% [50·4, 60·6]	56·6% [49·3, 62·8]
Overall	57·7% [57·1, 58·4]	69·4% [67·5, 71·2]	65·9% [63·1, 68·5]	62·7% [58·0, 66·8]

Table S4: Model coefficients for the documented infection outcome.

term	estimate	std.error	statistic	p.value
Female	-9.760	0.030	-330.81	<0.001
Male	-9.847	0.030	-333.72	<0.001
Age 40-49	-0.104	0.006	-18.04	<0.001
Age 50-59	-0.118	0.007	-16.77	<0.001
Age 60-69	-0.270	0.009	-28.55	<0.001
Age 70-79	-0.309	0.014	-22.48	<0.001
Age 80+	-0.421	0.016	-25.91	<0.001
Municipal Risk 2	1.911	0.030	64.50	<0.001
Municipal Risk 4	3.490	0.030	118.21	<0.001
Municipal Risk 3	2.622	0.029	89.00	<0.001
Past PCR 1	0.388	0.004	91.55	<0.001
Past PCR 2+	0.639	0.005	132.02	<0.001
Age 16-39:Cohort 1A	-0.194	0.008	-25.61	<0.001
Age 40-49:Cohort 1A	-0.193	0.013	-15.36	<0.001
Age 50-59:Cohort 1A	-0.206	0.014	-14.56	<0.001
Age 60-69:Cohort 1A	-0.254	0.017	-14.69	<0.001
Age 70-79:Cohort 1A	-0.580	0.025	-23.16	<0.001
Age 80+:Cohort 1A	-0.188	0.029	-6.56	<0.001
Age 16-39:Cohort 1B	-1.117	0.013	-85.90	<0.001
Age 40-49:Cohort 1B	-0.802	0.017	-46.18	<0.001
Age 50-59:Cohort 1B	-0.699	0.018	-39.30	<0.001
Age 60-69:Cohort 1B	-0.666	0.020	-33.67	<0.001
Age 70-79:Cohort 1B	-0.826	0.027	-31.05	<0.001
Age 80+:Cohort 1B	-0.455	0.031	-14.75	<0.001
Age 16-39:Cohort 2	-3.014	0.032	-94.98	<0.001
Age 40-49:Cohort 2	-2.596	0.034	-77.00	<0.001
Age 50-59:Cohort 2	-2.612	0.033	-78.11	<0.001

Age 60-69:Cohort 2	-2.578	0.032	-79.42	<0.001
Age 70-79:Cohort 2	-2.551	0.039	-66.04	<0.001
Age 80+:Cohort 2	-1.935	0.041	-47.33	<0.001
Age 16-39:Cohort Recovered	-2.906	0.040	-71.98	<0.001
Age 40-49:Cohort Recovered	-3.016	0.090	-33.65	<0.001
Age 50-59:Cohort Recovered	-3.036	0.107	-28.25	<0.001
Age 60-69:Cohort Recovered	-3.243	0.165	-19.69	<0.001
Age 70-79:Cohort Recovered	-3.508	0.289	-12.14	<0.001
Age 80+:Cohort Recovered	-2.458	0.268	-9.18	<0.001

Table S5: Model coefficients for the hospitalization outcome.

term	estimate	std.error	statistic	p.value
Female	-13.605	0.114	-119.280	<0.001
Male	-13.469	0.114	-118.210	<0.001
Age 40-49	0.733	0.034	21.451	<0.001
Age 50-59	1.332	0.033	40.784	<0.001
Age 60-69	1.829	0.033	55.740	<0.001
Age 70-79	2.525	0.033	75.708	<0.001
Age 80+	2.940	0.032	92.933	<0.001
Municipal Risk 2	1.488	0.113	13.140	<0.001
Municipal Risk 4	2.902	0.113	25.636	<0.001
Municipal Risk 3	2.219	0.112	19.726	<0.001
Past PCR 1	0.377	0.021	18.111	<0.001
Past PCR 2+	0.815	0.021	38.294	<0.001
Age 16-39:Cohort 1A	-0.507	0.069	-7.349	<0.001
Age 40-49:Cohort 1A	-0.522	0.076	-6.901	<0.001
Age 50-59:Cohort 1A	-0.590	0.064	-9.219	<0.001
Age 60-69:Cohort 1A	-0.641	0.056	-11.402	<0.001
Age 70-79:Cohort 1A	-0.928	0.056	-16.705	<0.001
Age 80+:Cohort 1A	-0.395	0.046	-8.559	<0.001
Age 16-39:Cohort 1B	-1.740	0.138	-12.638	<0.001
Age 40-49:Cohort 1B	-1.760	0.141	-12.451	<0.001
Age 50-59:Cohort 1B	-1.645	0.105	-15.637	<0.001
Age 60-69:Cohort 1B	-1.204	0.069	-17.328	<0.001
Age 70-79:Cohort 1B	-1.216	0.060	-20.128	<0.001
Age 80+:Cohort 1B	-0.779	0.052	-14.943	<0.001
Age 16-39:Cohort 2	-3.353	0.289	-11.582	<0.001
Age 40-49:Cohort 2	-2.882	0.198	-14.546	<0.001
Age 50-59:Cohort 2	-3.005	0.153	-19.641	<0.001

Age 60-69:Cohort 2	-3.254	0.123	-26.432	<0.001
Age 70-79:Cohort 2	-2.949	0.089	-33.302	<0.001
Age 80+:Cohort 2	-2.425	0.074	-32.629	<0.001
Age 16-39:Cohort Recovered	-2.635	0.290	-9.093	<0.001
Age 40-49:Cohort Recovered	-3.074	0.501	-6.137	<0.001
Age 50-59:Cohort Recovered	-2.790	0.379	-7.359	<0.001
Age 60-69:Cohort Recovered	-3.138	0.448	-7.000	<0.001
Age 70-79:Cohort Recovered	-2.826	0.409	-6.903	<0.001
Age 80+:Cohort Recovered	-2.849	0.501	-5.689	<0.001

Table S6: Model coefficients for the severe disease outcome. Estimates are not provided for the lowest age groups due to very low event counts in the vaccinated cohorts.

term	estimate	std.error	statistic	p.value
Female	-12.258	0.177	-69.170	<0.001
Male	-11.829	0.177	-66.859	<0.001
Age 70-79	0.807	0.043	18.716	<0.001
Age 80+	1.261	0.041	30.411	<0.001
Municipal Risk 2	1.400	0.176	7.944	<0.001
Municipal Risk 4	2.902	0.176	16.445	<0.001
Municipal Risk 3	2.158	0.175	12.321	<0.001
Past PCR 1	0.321	0.035	9.285	<0.001
Past PCR 2+	0.929	0.032	29.362	<0.001
Age 60-69:Cohort 1A	-0.678	0.068	-9.914	<0.001
Age 70-79:Cohort 1A	-0.991	0.065	-15.281	<0.001
Age 80+:Cohort 1A	-0.449	0.053	-8.513	<0.001
Age 60-69:Cohort 1B	-1.253	0.085	-14.751	<0.001
Age 70-79:Cohort 1B	-1.293	0.071	-18.248	<0.001
Age 80+:Cohort 1B	-0.817	0.059	-13.808	<0.001
Age 60-69:Cohort 2	-3.313	0.152	-21.748	<0.001
Age 70-79:Cohort 2	-3.104	0.109	-28.587	<0.001
Age 80+:Cohort 2	-2.515	0.087	-28.962	<0.001
Age 60-69:Cohort Recovered	-3.237	0.579	-5.593	<0.001
Age 70-79:Cohort Recovered	-4.314	1.001	-4.311	<0.001
Age 80+:Cohort Recovered	-2.845	0.579	-4.918	<0.001

Table S7: Model coefficients for the death outcome. Estimates are not provided for the lowest age groups and the Recovered cohort due to very low event counts.

term	estimate	std.error	statistic	p.value
Female	-13.685	0.259	-52.938	<0.001
Male	-13.096	0.258	-50.798	<0.001
Age 70-79	1.227	0.079	15.612	<0.001
Age 80+	2.072	0.072	28.798	<0.001
Municipal Risk 2	1.284	0.253	5.066	<0.001
Municipal Risk 4	2.760	0.254	10.864	<0.001
Municipal Risk 3	2.023	0.252	8.038	<0.001
Past PCR 1	0.393	0.055	7.198	<0.001
Past PCR 2+	1.202	0.046	25.975	<0.001
Age 60-69:Cohort 1A	-0.592	0.132	-4.489	<0.001
Age 70-79:Cohort 1A	-1.010	0.106	-9.534	<0.001
Age 80+:Cohort 1A	-0.515	0.071	-7.218	<0.001
Age 60-69:Cohort 1B	-1.002	0.152	-6.593	<0.001
Age 70-79:Cohort 1B	-1.277	0.114	-11.191	<0.001
Age 80+:Cohort 1B	-0.834	0.079	-10.606	<0.001
Age 60-69:Cohort 2	-2.811	0.238	-11.823	<0.001
Age 70-79:Cohort 2	-3.081	0.174	-17.743	<0.001
Age 80+:Cohort 2	-2.599	0.119	-21.889	<0.001

EXHIBIT “B”

Title page

Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity: reinfections versus breakthrough infections

Sivan Gazit, MD MA[1,2*]; Roei Shlezinger, BA[1]; Galit Perez, MN MA[2]; Roni Lotan, PhD[2]; Asaf Peretz, MD[1,3]; Amir Ben-Tov, MD[1,4]; Dani Cohen, PhD[4]; Khitam Muhsen, PhD[4]; Gabriel Chodick, PhD MHA[2,4]; Tal Patalon, MD[1,2]

*Corresponding author.

[1]Kahn Sagol Maccabi (KSM) Research & Innovation Center, Maccabi Healthcare Services, Tel Aviv, 68125, Israel.
[2] Maccabitech Institute for Research and Innovation, Maccabi Healthcare Services, Israel.
[3]Internal Medicine COVID-19 Ward, Samson Assuta Ashdod University Hospital, Ashdod Israel.
[4]Sackler Faculty of Medicine, School of Public Health, Tel Aviv University, Tel Aviv, Israel.

The authors declare they have no conflict of interest.

Funding: There was no external funding for the project.

Corresponding author: Sivan Gazit, gazit_s@mac.org.il, 27 HaMared street, Tel Aviv, 68125, Israel

Abstract

Background:

Reports of waning vaccine-induced immunity against COVID-19 have begun to surface. With that, the comparable long-term protection conferred by previous infection with SARS-CoV-2 remains unclear.

Methods:

We conducted a retrospective observational study comparing three groups: (1)SARS-CoV-2-naïve individuals who received a two-dose regimen of the BioNTech/Pfizer mRNA BNT162b2 vaccine, (2)previously infected individuals who have not been vaccinated, and (3)previously infected *and* single dose vaccinated individuals. Three multivariate logistic regression models were applied. In all models we evaluated four outcomes: SARS-CoV-2 infection, symptomatic disease, COVID-19-related hospitalization and death. The follow-up period of June 1 to August 14, 2021, when the Delta variant was dominant in Israel.

Results:

SARS-CoV-2-naïve vaccinees had a 13.06-fold (95% CI, 8.08 to 21.11) increased risk for breakthrough infection with the Delta variant compared to those previously infected, when the first event (infection or vaccination) occurred during January and February of 2021. The increased risk was significant (P<0.001) for symptomatic disease as well. When allowing the infection to occur at any time before vaccination (from March 2020 to February 2021), evidence of waning natural immunity was demonstrated, though SARS-CoV-2 naïve vaccinees had a 5.96-fold (95% CI, 4.85 to

7.33) increased risk for breakthrough infection and a 7.13-fold (95% CI, 5.51 to 9.21) increased risk for symptomatic disease. SARS-CoV-2-naïve vaccinees were also at a greater risk for COVID-19-related-hospitalizations compared to those that were previously infected.

Conclusions:

This study demonstrated that natural immunity confers longer lasting and stronger protection against infection, symptomatic disease and hospitalization caused by the Delta variant of SARS-CoV-2, compared to the BNT162b2 two-dose vaccine-induced immunity. Individuals who were both previously infected with SARS-CoV-2 and given a single dose of the vaccine gained additional protection against the Delta variant.

Introduction

The heavy toll that SARS-CoV-2 infection has been taking on global health and healthcare resources has created an urgent need to estimate which part of the population is protected against COVID-19 at a given time in order to set healthcare policies such as lockdowns and to assess the possibility of herd immunity.

To date, there is still no evidence-based, long-term correlate of protection[1]. This lack of correlate of protection has led to different approaches in terms of vaccine resource allocation, namely the need for vaccine administration in recovered patients, the need for booster shots in previously vaccinated individuals or the need to vaccinate low-risk populations, potentially previously exposed.

The short-term effectiveness of a two-dose regimen of the BioNTech/Pfizer BNT162b2 mRNA COVID-19 vaccine was demonstrated in clinical trials[2] and in observational settings[3,4]. However, long term effectiveness across different variants is still unknown, though reports of waning immunity are beginning to surface, not merely in terms of antibody dynamics over time[5–7], but in real-world settings as well[8].

Alongside the question of long-term protection provided by the vaccine, the degree and duration to which previous infection with SARS-CoV-2 affords protection against repeated infection also remains unclear. Apart from the paucity of studies examining long-term protection against reinfection[9], there is a challenge in defining reinfection as opposed to prolonged viral shedding[10]. While clear-cut cases exist, namely two separate clinical events with two distinct sequenced viruses, relying solely on these cases will likely result in an under-estimation of the incidence of reinfection. Different criteria based on more widely-available information have been suggested[11], the Centers for Disease Control and Prevention's (CDC) guidelines refer to two positive SARS-CoV-2 polymerase chain reaction (PCR) test results at least 90 days

apart.[12] Using similar criteria, population-based studies demonstrated natural immunity[13,14] with no signs of waning immunity for at least 7 months, though protection was lower for those aged 65 or older[9].

The Delta (B.1.617.2) Variant of Concern (VOC), initially identified in India and today globally prevalent, has been the dominant strain in Israel since June 2021. The recent surge of cases in Israel[15], one of the first countries to embark on a nationwide vaccination campaign (mostly with the BioNTech/Pfizer BNT162b2 vaccine), has raised concerns about vaccine effectiveness against the Delta variant, including official reports of decreased protection[16]. Concomitantly, studies have demonstrated only mild differences in short-term vaccine effectiveness[17] against the Delta variant, as well as substantial antibody response[18]. Apart from the variant, the new surge was also explained by the correlation found between time-from-vaccine and breakthrough infection rates, as early vaccinees were demonstrated to be significantly more at risk than late vaccinees[8]. Now, when sufficient time has passed since both the beginning of the pandemic and the deployment of the vaccine, we can examine the long-term protection of natural immunity compared to vaccine-induced immunity.

To this end, we compared the incidence rates of breakthrough infections to the incidence rates of reinfection, leveraging the centralized computerized database of Maccabi Healthcare Services (MHS), Israel's second largest Health Maintenance Organization.

Methods

Study design and population

A retrospective cohort study was conducted, leveraging data from MHS' centralized computerized database. The study population included MHS members aged 16 or older who were vaccinated prior to February 28, 2021, who had a documented SARS-CoV-2 infection by February 28, 2021, or who had both a documented SARS-CoV-2 infection by February 28, 2021 *and* received one dose of the vaccine by May 25, 2021, at least 7 days before the study period. On March 2, 2021, The Israeli Ministry of Health revised its guidelines and allowed previously SARS-CoV-2 infected individuals to receive one dose of the vaccine, after a minimum 3-month-interval from the date of infection

Data Sources

Anonymized Electronic Medical Records (EMRs) were retrieved from MHS' centralized computerized database for the study period of March 1, 2020 to August 14, 2021.

MHS is a 2.5-million-member, state-mandated, non-for-profit, second largest health fund in Israel, which covers 26% of the population and provides a representative sample of the Israeli population. Membership in one of the four national health funds is mandatory, whereas all citizens must freely choose one of four funds, which are prohibited by law from denying membership to any resident. MHS has maintained a centralized database of EMRs for three decades, with less than 1% disengagement rate among its members, allowing for a comprehensive longitudinal medical follow-up. The centralized dataset 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.

Data extraction and definition of the study variables

COVID-19-related data

COVID-19-related information was captured as well, including dates of the first and second dose of the vaccine and results of any polymerase chain reaction (PCR) tests for SARS-CoV-2, given that all such tests are recorded centrally. Records of COVID-19-related hospitalizations were retrieved as well, and COVID-19-related mortality was screened for. Additionally, 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 phone visits with each infected individual.

Exposure variable: study groups

The eligible study population was divided into three groups: (1)fully vaccinated and SARS-CoV-2-naïve individuals, namely MHS members who received two doses of the BioNTech/Pfizer mRNA BNT162b2 vaccine by February 28, 2021, did not receive the third dose by the end of the study period and did not have a positive PCR test result by June 1, 2021; (2) unvaccinated previously infected individuals, namely MHS members who had a positive SARS-CoV-2 PCR test recorded by February 28, 2021 and who had not been vaccinated by the end of the study period; (3) previously infected *and* vaccinated individuals, including individuals who had a positive SARS-CoV-2 PCR test by February 28, 2021 and received one dose of the vaccine by May 25, 2021, at least 7 days before the study period. The fully vaccinated group was the comparison (reference) group in our study. Groups 2 and 3, were matched to the

comparison group 1 in a 1:1 ratio based on age, sex and residential socioeconomic status.

Dependent variables

We evaluated four SARS-CoV-2-related outcomes, or second events: documented RT-PCR confirmed SARS-CoV-2 infection, COVID-19, COVID-19-related hospitalization and death. Outcomes were evaluated during the follow-up period of June 1 to August 14, 2021, the date of analysis, corresponding to the time in which the Delta variant became dominant in Israel.

Covariates

Individual-level data of the study population included patient demographics, namely age, sex, socioeconomic status (SES) and a coded geographical statistical area (GSA, assigned by Israel's National Bureau of Statistics, corresponds to neighborhoods and is the smallest geostatistical unit of the Israeli census). The SES is measured on a scale from 1 (lowest) to 10, and the index is based on several parameters, including household income, educational qualifications, household crowding and car ownership. Data were also collected on last documented body mass index (BMI) and information about chronic diseases from MHS' automated registries, including cardiovascular diseases[19], hypertension[20], diabetes[21], chronic kidney disease[22], chronic obstructive pulmonary disease, immunocompromised conditions, and cancer from the National Cancer Registry[23].

Statistical analysis

Two multivariate logistic regression models were applied that evaluated the four aforementioned SARS-CoV-2-related outcomes as dependent variables, while the study groups were the main independent variables.

Model 1– previously infected vs. vaccinated individuals, with matching for time of first event

In model 1, we examined natural immunity and vaccine-induced immunity by comparing the likelihood of SARS-CoV-2-related outcomes between previously infected individuals who have never been vaccinated and fully vaccinated SARS-CoV-2-naïve individuals. These groups were matched in a 1:1 ratio by age, sex, GSA and time of first event. The first event (the preliminary exposure) was either the time of administration of the second dose of the vaccine *or* the time of documented infection with SARS-CoV-2 (a positive RT-PCR test result), both occurring between January 1, 2021 and February 28, 2021. Thereby, we matched the "immune activation" time of both groups, examining the long-term protection conferred when vaccination or infection occurred within the same time period. The three-month interval between the first event and the second event was implemented in order to capture reinfections (as opposed to prolonged viral shedding) by following the 90-day guideline of the CDC.

Model 2

In model 2, we compared the SARS-CoV-2 naïve vaccinees to unvaccinated previously infected individuals while intentionally *not* matching the time of the first event (i.e., either vaccination or infection), in order to compare vaccine-induced immunity to natural immunity, regardless of time of infection. Therefore, matching

was done in a 1:1 ratio based on age, sex and GSA alone. Similar to the model 1, either event (vaccination or infection) had to occur by February 28, to allow for the 90-day interval. The four SARS-CoV-2 study outcomes were the same for this model, evaluated during the same follow-up period.

Model 3

Model 3 examined previously infected individuals vs. previously-infected-and-once-vaccinated individuals, using "natural immunity" as the baseline group. We matched the groups in a 1:1 ratio based on age, sex and GSA. SARS-CoV-2 outcomes were the same, evaluated during the same follow-up period.

In all three models, we estimated natural immunity vs. vaccine-induced immunity for each SARS-CoV-2-related outcome, by applying logistic regression to calculate the odds ratio (OR) between the two groups in each model, with associated 95% confidence intervals (CIs). Results were then adjusted for underlying comorbidities, including obesity, cardiovascular diseases, diabetes, hypertension, chronic kidney disease, cancer and immunosuppression conditions.

Analyses were performed using Python version 3.73 with the stats model package. $P < 0.05$ was considered statistically significant.

Ethics declaration

This study was approved by the MHS (Maccabi Healthcare Services) Institutional Review Board (IRB). Due to the retrospective design of the study, informed consent was waived by the IRB, and all identifying details of the participants were removed before computational analysis.

Data availability statement

According to the Israel Ministry of Health regulations, individual-level data cannot be shared openly. Specific requests for remote access to de-identified community-level data should be directed to KSM, Maccabi Healthcare Services Research and Innovation Center.

Code availability

Specific requests for remote access to the code used for data analysis should be referred to KSM, Maccabi Healthcare Services Research and Innovation Center.

Results

Overall, 673,676 MHS members 16 years and older were eligible for the study group of fully vaccinated SARS-CoV-2-naïve individuals; 62,883 were eligible for the study group of unvaccinated previously infected individuals and 42,099 individuals were eligible for the study group of previously infected and single-dose vaccinees.

Model 1 – previously infected vs. vaccinated individuals, with matching for time of first event

In model 1, we matched 16,215 persons in each group. Overall, demographic characteristics were similar between the groups, with some differences in their comorbidity profile (Table 1a).

During the follow-up period, 257 cases of SARS-CoV-2 infection were recorded, of which 238 occurred in the vaccinated group (breakthrough infections) and 19 in the previously infected group (reinfections). After adjusting for comorbidities, we found a statistically significant 13.06-fold (95% CI, 8.08 to 21.11) increased risk for breakthrough infection as opposed to reinfection ($P<0.001$). Apart from age ≥60 years, there was no statistical evidence that any of the assessed comorbidities significantly affected the risk of an infection during the follow-up period (Table 2a).

As for symptomatic SARS-COV-2 infections during the follow-up period, 199 cases were recorded, 191 of which were in the vaccinated group and 8 in the previously infected group. Symptoms for all analyses were recorded in the central database within 5 days of the positive RT-PCR test for 90% of the patients, and included chiefly fever, cough, breathing difficulties, diarrhea, loss of taste or smell, myalgia, weakness, headache and sore throat. After adjusting for comorbidities, we found a 27.02-fold risk (95% CI, 12.7 to 57.5) for symptomatic breakthrough infection as

opposed to symptomatic reinfection (P<0.001) (Table 2b). None of the covariates were significant, except for age ≥60 years.

Nine cases of COVID-19-related hospitalizations were recorded, 8 of which were in the vaccinated group and 1 in the previously infected group (Table S1). No COVID-19-related deaths were recorded in our cohorts.

Model 2 –previously infected vs. vaccinated individuals, without matching for time of first event

In model 2, we matched 46,035 persons in each of the groups (previously infected vs. vaccinated). Baseline characteristics of the groups are presented in Table 1a. Figure 1 demonstrates the timely distribution of the first infection in reinfected individuals. When comparing the vaccinated individuals to those previously infected at any time (including during 2020), we found that throughout the follow-up period, 748 cases of SARS-CoV-2 infection were recorded, 640 of which were in the vaccinated group (breakthrough infections) and 108 in the previously infected group (reinfections). After adjusting for comorbidities, a 5.96-fold increased risk (95% CI, 4.85 to 7.33) increased risk for breakthrough infection as opposed to reinfection could be observed (P<0.001) (Table 3a). Apart from SES level and age ≥60, that remained significant in this model as well, there was no statistical evidence that any of the comorbidities significantly affected the risk of an infection.

Overall, 552 symptomatic cases of SARS-CoV-2 were recorded, 484 in the vaccinated group and 68 in the previously infected group. There was a 7.13-fold (95% CI, 5.51 to 9.21) increased risk for symptomatic breakthrough infection than symptomatic reinfection (Table 3b). COVID-19 related hospitalizations occurred in 4 and 21 of the reinfection and breakthrough infection groups, respectively. Vaccinated

individuals had a 6.7-fold (95% CI, 1.99 to 22.56) increased to be admitted compared to recovered individuals. Being 60 years of age or older significantly increased the risk of COVID-19-related hospitalizations (Table S2). No COVID-19-related deaths were recorded.

Model 3 - previously infected vs. vaccinated and previously infected individuals

In model 3, we matched 14,029 persons. Baseline characteristics of the groups are presented in Table 1b. Examining previously infected individuals to those who were both previously infected and received a single dose of the vaccine, we found that the latter group had a significant 0.53-fold (95% CI, 0.3 to 0.92) (Table 4a) decreased risk for reinfection, as 20 had a positive RT-PCR test, compared to 37 in the previously infected and unvaccinated group. Symptomatic disease was present in 16 single dose vaccinees and in 23 of their unvaccinated counterparts. One COVID-19-related hospitalization occurred in the unvaccinated previously infected group. No COVID-19-related mortality was recorded.

We conducted a further sub-analysis, compelling the single-dose vaccine to be administered *after* the positive RT-PCR test. This subset represented 81% of the previously-infected-and-vaccinated study group. When performing this analysis, we found a similar, though not significant, trend of decreased risk of reinfection, with an OR of 0.68 (95% CI, 0.38 to 1.21, *P*-value=0.188).

Discussion

This is the largest real-world observational study comparing natural immunity, gained through previous SARS-CoV-2 infection, to vaccine-induced immunity, afforded by the BNT162b2 mRNA vaccine. Our large cohort, enabled by Israel's rapid rollout of the mass-vaccination campaign, allowed us to investigate the risk for additional infection – either a breakthrough infection in vaccinated individuals or reinfection in previously infected ones – over a longer period than thus far described.

Our analysis demonstrates that SARS-CoV-2-naïve vaccinees had a 13.06-fold increased risk for breakthrough infection with the Delta variant compared to those previously infected, when the first event (infection or vaccination) occurred during January and February of 2021. The increased risk was significant for a symptomatic disease as well.

Broadening the research question to examine the extent of the phenomenon, we allowed the infection to occur at any time between March 2020 to February 2021 (when different variants were dominant in Israel), compared to vaccination only in January and February 2021. Although the results could suggest waning natural immunity against the Delta variant, those vaccinated are still at a 5.96-fold increased risk for breakthrough infection and at a 7.13-fold increased risk for symptomatic disease compared to those previously infected. SARS-CoV-2-naïve vaccinees were also at a greater risk for COVID-19-related-hospitalization compared to those who were previously infected.

Individuals who were previously infected with SARS-CoV-2 seem to gain additional protection from a subsequent single-dose vaccine regimen. Though this finding corresponds to previous reports[24,25], we could not demonstrate significance in our cohort.

The advantageous protection afforded by natural immunity that this analysis demonstrates could be explained by the more extensive immune response to the SARS-CoV-2 proteins than that generated by the anti-spike protein immune activation conferred by the vaccine[26,27]. However, as a correlate of protection is yet to be proven[1,28], including the role of B-Cell[29] and T-cell immunity[30,31], this remains a hypothesis.

Our study has several limitations. First, as the Delta variant was the dominant strain in Israel during the outcome period, the decreased long-term protection of the vaccine compared to that afforded by previous infection cannot be ascertained against other strains. Second, our analysis addressed protection afforded solely by the BioNTech/Pfizer mRNA BNT162b2 vaccine, and therefore does not address other vaccines or long-term protection following a third dose, of which the deployment is underway in Israel. Additionally, as this is an observational real-world study, where PCR screening was not performed by protocol, we might be underestimating asymptomatic infections, as these individuals often do not get tested.

Lastly, although we controlled for age, sex, and region of residence, our results might be affected by differences between the groups in terms of health behaviors (such as social distancing and mask wearing), a possible confounder that was not assessed. As individuals with chronic illness were primarily vaccinated between December and February, confounding by indication needs to be considered; however, adjusting for obesity, cardiovascular disease, diabetes, hypertension, chronic kidney disease, chronic obstructive pulmonary disease, cancer and immunosuppression had only a small impact on the estimate of effect as compared to the unadjusted OR. Therefore, residual confounding by unmeasured factors is unlikely.

This analysis demonstrated that natural immunity affords longer lasting and stronger protection against infection, symptomatic disease and hospitalization due to the Delta variant of SARS-CoV-2, compared to the BNT162b2 two-dose vaccine-induced immunity. Notably, individuals who were previously infected with SARS-CoV-2 and given a single dose of the BNT162b2 vaccine gained additional protection against the Delta variant. The long-term protection provided by a third dose, recently administered in Israel, is still unknown.

References

1. Krammer F. A correlate of protection for SARS-CoV-2 vaccines is urgently needed. Nat Med 2021 277 [Internet] 2021 [cited 2021 Aug 9];27(7):1147–8. Available from: https://www.nature.com/articles/s41591-021-01432-4

2. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med [Internet] 2020 [cited 2021 Mar 10];383(27):2603–15. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2034577

3. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med [Internet] 2021 [cited 2021 Apr 20];384(15). Available from: https://pubmed.ncbi.nlm.nih.gov/33626250/

4. Chodick G, Tene L, Rotem RS, et al. The Effectiveness of the Two-Dose BNT162b2 Vaccine: Analysis of Real-World Data. Clin Infect Dis [Internet] 2021 [cited 2021 Jul 22];Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab438/6276888

5. Seow J, Graham C, Merrick B, et al. Longitudinal observation and decline of neutralizing antibody responses in the three months following SARS-CoV-2 infection in humans. Nat Microbiol [Internet] 2020;5(12):1598–607. Available from: https://doi.org/10.1038/s41564-020-00813-8

6. Ruopp MD, Strymish J, Dryjowicz-Burek J, Creedon K, Gupta K. Durability of SARS-CoV-2 IgG Antibody Among Residents in a Long-Term Care Community. J Am Med Dir Assoc [Internet] 2021;22(3):510–1. Available from: https://pubmed.ncbi.nlm.nih.gov/33515497

7. Shrotri M, Navaratnam AMD, Nguyen V, et al. Spike-antibody waning after second dose of BNT162b2 or ChAdOx1. Lancet [Internet] 2021 [cited 2021 Jul 22];0(0). Available from: http://www.thelancet.com/article/S0140673621016421/fulltext

8. Mizrahi B, Lotan R, Kalkstein N, et al. Correlation of SARS-CoV-2 Breakthrough Infections to Time-from-vaccine; Preliminary Study. medRxiv [Internet] 2021 [cited 2021 Aug 12];2021.07.29.21261317. Available from: https://www.medrxiv.org/content/10.1101/2021.07.29.21261317v1

9. Hansen CH, Michlmayr D, Gubbels SM, Mølbak K, Ethelberg S. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. Lancet [Internet] 2021 [cited 2021 Aug 12];397(10280):1204–12. Available from: http://www.thelancet.com/article/S0140673621005754/fulltext

10. Iwasaki A. What reinfections mean for COVID-19. Lancet Infect Dis 2021;21(1):3–5.

11. Tomassini S, Kotecha D, Bird PW, Folwell A, Biju S, Tang JW. Setting the criteria for SARS-CoV-2 reinfection–six possible cases. J Infect 2020;

12. C CD. Reinfection [Internet]. 2020;(March 4, 2020). Available from: https://www.cdc.gov/coronavirus/2019-ncov/php/reinfection.html

13. Perez G, Banon T, Gazit S, et al. A 1 to 1000 SARS-CoV-2 reinfection proportion in members of a large healthcare provider in Israel: a preliminary report. medRxiv [Internet] 2021;2021.03.06.21253051. Available from: http://medrxiv.org/content/early/2021/03/08/2021.03.06.21253051.abstract

14. Lumley SF, O'Donnell D, Stoesser NE, et al. Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers. N Engl J Med [Internet] 2021

[cited 2021 Mar 15];384(6):533–40. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2034545

15. COVID-19 in Israel dashboard. 2021;

16. Decline in Vaccine Effectiveness Against Infection and Symptomatic Illness [Internet]. [cited 2021 Jul 22]. Available from: https://www.gov.il/en/Departments/news/05072021-03

17. Bernal JL, Andrews N, Gower C, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. https://doi.org/101056/NEJMoa2108891 [Internet] 2021 [cited 2021 Jul 22];NEJMoa2108891. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2108891

18. Lustig Y, Zuckerman N, Nemet I, et al. Neutralising capacity against Delta (B.1.617.2) and other variants of concern following Comirnaty (BNT162b2, BioNTech/Pfizer) vaccination in health care workers, Israel. Eurosurveillance [Internet] 2021 [cited 2021 Jul 22];26(26):2100557. Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.26.2100557

19. Shalev V, Chodick G, Goren I, Silber H, Kokia E, Heymann AD. The use of an automated patient registry to manage and monitor cardiovascular conditions and related outcomes in a large health organization. Int J Cardiol [Internet] 2011 [cited 2021 Jul 5];152(3):345–9. Available from: https://pubmed.ncbi.nlm.nih.gov/20826019/

20. D W, G C, V S, C G, E G. Prevalence and factors associated with resistant hypertension in a large health maintenance organization in Israel. Hypertens (Dallas, Tex 1979) [Internet] 2014 [cited 2021 Aug 16];64(3):501–7. Available from: https://pubmed.ncbi.nlm.nih.gov/24958503/

21. Chodick G, Heymann AD, Shalev V, Kookia E. The epidemiology of diabetes in a large Israeli HMO. Eur J Epidemiol [Internet] 2003 [cited 2021 Jul 4];18(12):1143–6. Available from: https://pubmed.ncbi.nlm.nih.gov/14758871/

22. Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA - J Am Med Assoc [Internet] 2014 [cited 2021 Jul 4];311(24):2518–31. Available from: https://pubmed.ncbi.nlm.nih.gov/24892770/

23. Israel Center for Disease Control. Jerusalem I. Data from: Israel national cancer registry.

24. Cavanaugh AM. Reduced Risk of Reinfection with SARS-CoV-2 After COVID-19 Vaccination — Kentucky, May–June 2021. MMWR Morb Mortal Wkly Rep [Internet] 2021 [cited 2021 Aug 13];70(32):1081–3. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/mm7032e1.htm

25. Stamatatos L, Czartoski J, Wan Y-H, et al. mRNA vaccination boosts cross-variant neutralizing antibodies elicited by SARS-CoV-2 infection. Science (80-) [Internet] 2021 [cited 2021 Aug 14];372(6549):1413–8. Available from: https://science.sciencemag.org/content/372/6549/1413

26. Bettini E, Locci M. SARS-CoV-2 mRNA Vaccines: Immunological Mechanism and Beyond. Vaccines [Internet] 2021 [cited 2021 Mar 15];9(2):147. Available from: /pmc/articles/PMC7918810/

27. Sette A, Crotty S. Leading Edge Adaptive immunity to SARS-CoV-2 and COVID-19. Cell [Internet] 2021 [cited 2021 Aug 21];184:861–80. Available from: https://doi.org/10.1016/j.cell.2021.01.007

28. Chia WN, Zhu F, Ong SWX, et al. Dynamics of SARS-CoV-2 neutralising antibody responses and duration of immunity: a longitudinal study. The Lancet

Microbe [Internet] 2021 [cited 2021 Aug 14];2(6):e240–9. Available from: http://www.thelancet.com/article/S2666524721000252/fulltext

29. Cho A, Muecksch F, Schaefer-Babajew D, et al. Antibody Evolution after SARS-CoV-2 mRNA Vaccination. bioRxiv [Internet] 2021 [cited 2021 Aug 21];2021.07.29.454333. Available from: https://www.biorxiv.org/content/10.1101/2021.07.29.454333v1

30. Cohen KW, Linderman SL, Moodie Z, et al. Longitudinal analysis shows durable and broad immune memory after SARS-CoV-2 infection with persisting antibody responses and memory B and T cells. Cell Reports Med 2021;2(7).

31. Lu Z, Laing ED, Pena-Damata J, et al. Durability of SARS-CoV-2-specific T cell responses at 12-months post-infection. bioRxiv [Internet] 2021 [cited 2021 Aug 21];2021.08.11.455984. Available from: https://www.biorxiv.org/content/10.1101/2021.08.11.455984v1

Tables and figures

Table 1a. Characteristics of study population, model 1 and 2.

	Model 1 – with matching of time of first event		**Model 2 – without matching of time of first event**	
Characteristics	Previously infected (n=16,215)	Vaccinated individuals (n=16,215)	Previously infected (n=46,035)	Previously infected *and* vaccinated (n =46,035)
Age years, mean (SD)	36.1 (13.9)	36.1 (13.9)	36.1 (14.7)	36.1 (14.7)
Age group – no. (%)				
16 to 39 yr	9,889 (61.0)	9,889 (61.0)	28,157 (61.2)	28,157 (61.2)
40 to 59 yr	5,536 (34.1)	5,536 (34.1)	14,973 (32.5)	14,973 (32.5)
≥60 yr	790 (4.9)	790 (4.9)	2,905 (6.3)	2,905 (6.3)
Sex – no. (%)				
Female	7,428 (45.8)	7,428 (45.8)	22,661 (49.2)	22,661 (49.2)
Male	8,787 (54.2)	8,787 (54.2)	23,374 (50.8)	23,374 (50.8)
SES, mean (SD)	5.5 (1.9)	5.5 (1.9)	5.3 (1.9)	5.3 (1.9)
Comorbidities – no. (%)				
Hypertension	1,276 (7.9)	1,569 (9.7)	4,009 (8.7)	4,301 (9.3)
CVD	551 (3.4)	647 (4.0)	1,875 (4.1)	1830 (4.0)
DM	635 (3.9)	877 (5.4)	2207 (4.8)	2300 (5.0)
Immunocompromised	164 (1.0)	420 (2.6)	527 (1.1)	849 (1.8)
Obesity (BMI ≥30)	3,076 (19.0)	3,073 (19.0)	9,117 (19.8)	8,610 (18.7)
CKD	196 (1.2)	271 (1.7)	659 (1.4)	814 (1.8)
COPD	65 (0.4)	97 (0.6)	218 (0.5)	292 (0.6)
Cancer	324 (2.0)	636 (3.9)	1,044 (2.3)	1,364 (3.0)

SD – Standard Deviation; SES – Socioeconomic status on a scale from 1 (lowest) to 10; CVD – Cardiovascular Diseases; DM – Diabetes Mellitus; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease.

Table 1b. Characteristics of study population, model 3.

Characteristics	Previously infected (n=14,029)	Previously infected and single dose vaccinated (n=14,029)
Age years, mean (SD)	33.2 (14.0)	33.2 (14.0)
Age group – no. (%)		
16 to 39 yr	9543 (68.0)	9543 (68.0)
40 to 59 yr	3919 (27.9)	3919 (27.9)
≥60 yr	567 (4.0)	567 (4.0)
Sex – no. (%)		
Female	7467 (53.2)	7467 (53.2)
Male	6562 (46.8)	6562 (46.8)
SES, mean (SD)	4.7 (1.9)	4.7 (1.9)
Comorbidities		
Hypertension	892 (6.4)	1004 (7.2)
CVD	437 (3.1)	386 (2.8)
DM	529 (3.8)	600 (4.3)
Immunocompromised	127 (0.9)	145 (1.0)
Obesity (BMI ≥30)	2599 (18.5)	2772 (19.8)
CKD	137 (1.0)	162 (1.2)
COPD	30 (0.2)	53 (0.4)
Cancer	241 (1.7)	267 (1.9)

SD – Standard Deviation; SES – Socioeconomic status on a scale from 1 (lowest) to 10; CVD – Cardiovascular Diseases; DM – Diabetes Mellitus; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease.

Table 2a. OR for SARS-CoV-2 infection, model 1, previously infected vs. vaccinated

Variable	Category	ß	OR	95%CI	P-value
Induced Immunity					
	Previously infected	Ref			
	Vaccinated	2.57	13.06	8.08 – 21.11	<0.001
SES		0.04	1.04	0.97 – 1.11	0.251
Age group, yr.					
	16-39	Ref			
	40-59	0.05	1.05	0.78 - 1.4	0.751
	≥60	0.99	2.7	1.68 – 4.34	<0.001
Sex					
	Female	Ref			
	Male	-0.03	0.97	0.76 – 1.25	0.841
Comorbidities					
	Obesity (BMI≥30)	0.01	1.01	0.73 – 1.39	0.967
	Diabetes mellitus	-0.36	0.7	0.39 – 1.25	0.229
	Hypertension	0.1	1.11	0.72 – 1.72	0.641
	Cancer	0.37	1.44	0.85 – 2.44	0.171
	CKD	0.53	1.7	0.83 – 3.46	0.146
	COPD	-0.46	0.63	0.15 – 2.66	0.529
	Immunosuppression	-0.1	0.91	0.42 – 1.97	0.803
	Cardiovascular diseases	0.26	1.3	0.75 – 2.25	0.343

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10; CVD – Cardiovascular Diseases; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease.

Table 2b. OR for Symptomatic SARS-CoV-2 infection, model 1, previously infected vs. vaccinated

Variable	Category	ß	OR	95%CI	P-value
Induced Immunity					
	Previously infected	Ref			
	Vaccinated	3.3	27.02	12.7 – 57.5	<0.001
SES		0.04	1.04	0.96 – 1.12	0.312
Age group, yr.					
	16-39	Ref			
	40-59	0.19	1.21	0.88 – 1.67	0.25
	≥60	1.06	2.89	1.68 – 4.99	<0.001
Sex					
	Female	Ref			
	Male	-0.19	0.82	0.62 – 1.1	0.185
Comorbidities					
	Obesity (BMI≥30)	0.02	1.02	0.71 – 1.48	0.899
	Diabetes mellitus	-0.31	0.73	0.37 – 1.43	0.361
	Hypertension	0.12	1.13	0.69 – 1.85	0.623
	Cancer	0.37	1.45	0.8 – 2.62	0.217
	CKD	0.1	1.1	0.42 – 2.87	0.846
	COPD	-0.78	0.46	0.06 – 3.41	0.445
	Immunosuppression	-0.37	0.69	0.25 – 1.89	0.468
	Cardiovascular diseases	0.03	1.03	0.52 – 2.03	0.941

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10; CVD – Cardiovascular Diseases; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease.

Table 3a. OR for SARS-CoV-2 infection, model 2, previously infected vs. vaccinated

Variable	Category	ß	OR	95%CI	P-value
Induced Immunity					
	Previously infected	Ref			
	Vaccinated	1.78	5.96	4.85 – 7.33	<0.001
SES		0.07	1.07	1.03 – 1.11	<0.001
Age group, yr.					
	16-39	Ref			
	40-59	0.06	1.06	0.9 – 1.26	0.481
	≥60	0.79	2.2	1.66 – 2.92	<0.001
Sex					
	Female	Ref			
	Male	-0.01	0.99	0.85 - 1.14	0.842
Comorbidities					
	Obesity (BMI≥30)	0.12	1.13	0.94 – 1.36	0.202
	Diabetes mellitus	-0.15	0.86	0.61 – 1.22	0.4
	Hypertension	-0.12	0.89	0.67 – 1.17	0.402
	Cancer	0.2	1.22	0.85 – 1.76	0.283
	CKD	0.3	1.35	0.85 – 2.14	0.207
	COPD	0.48	1.62	0.88 – 2.97	0.121
	Immunosuppression	-0.03	0.98	0.57 – 1.66	0.925
	Cardiovascular diseases	0.08	1.09	0.77 – 1.53	0.638

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10; CVD – Cardiovascular Diseases; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease.

Table 3b. OR for Symptomatic SARS-CoV-2 infection, model 2, previously infected vs. vaccinated

Variable	Category	ß	OR	95%CI	P-value
Induced Immunity					
	Previously infected	Ref			
	Vaccinated	1.96	7.13	5.51 – 9.21	<0.001
SES		0.07	1.07	1.02 – 1.12	0.003
Age group, yr.					
	16-39	Ref			
	40-59	0.09	1.1	0.9 – 1.33	0.35
	≥60	0.8	2.23	1.61 – 3.09	<0.001
Sex					
	Female	Ref			
	Male	-0.02	0.98	0.82 – 1.16	0.785
Comorbidities					
	Obesity (BMI≥30)	0.16	1.18	0.95 – 1.46	0.133
	Diabetes mellitus	-0.11	0.89	0.61 – 1.32	0.571
	Hypertension	-0.01	0.99	0.72 – 1.35	0.943
	Cancer	0.08	1.09	0.7 – 1.69	0.71
	CKD	0.13	1.14	0.65 – 1.98	0.654
	COPD	0.5	1.65	0.82 – 3.31	0.162
	Immunosuppression	0	1	0.54 – 1.85	0.999
	Cardiovascular diseases	0	1	0.67 – 1.5	0.99

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10; CVD – Cardiovascular Diseases; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease.

Table 4a. OR for SARS-CoV-2 infection, model 3, previously infected vs. previously infected and single-dose-vaccinated

Variable	Category	ß	OR	95%CI	P-value
Induced Immunity					
	Previously infected	Ref			
	Previously infected and vaccinated	-0.64	0.53	0.3 – 0.92	0.024
SES		0.11	1.12	0.98 – 1.28	0.096
Age group, yr.					
	16-59	Ref			
	≥60	-0.81	0.44	0.06 – 3.22	0.422
Comorbidities					
	Immunosuppression	0.72	2.06	0.28 – 15.01	0.475

SES – Socioeconomic status on a scale from 1 (lowest) to 10

Table 4b. OR for Symptomatic SARS-CoV-2 infection, model 2, previously infected vs. previously infected and vaccinated

Variable	Category	ß	OR	95%CI	P-value
Induced Immunity					
	Previously infected	Ref			
	Previously infected and vaccinated	-0.43	0.65	0.34 – 1.25	0.194
SES		0.06	1.06	0.9 – 1.24	0.508
Age group, yr.					
	16-59	Ref			
	≥60	-16.9	0	0.0 – inf	0.996
Comorbidities					
	Immunosuppression	1.15	3.14	0.43 – 23.01	0.26

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10.

Table S1. OR for COVID-19-related hospitalizations, model 1, previously infected vs. vaccinated

Variable	Category	ß	OR hospitalized	95%CI	*P*-value
Induced Immunity					
	Previously infected	Ref			
	Vaccinated	2.09	8.06	1.01 – 64.55	0.049
SES		0.05	1.05	0.72 – 1.53	0.81
Age ≥60 yrs (16-39, ref)		5.08	160.9	19.91 – 1300.44	<0.001

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10

Table S2. OR for COVID-19-related hospitalizations, model 2, previously infected vs. vaccinated

Variable	Category	ß	OR hospitalized	95%CI	*P*-value
Induced Immunity					
	Previously infected	Ref			
	Vaccinated	1.95	7.03	2.1 – 23.59	0.002
SES		-0.07	0.93	0.74 – 1.17	0.547
Age ≥60 yrs (16-39, ref)		4.3	73.5	25.09 – 215.29	<0.001

OR – Odds Ratio; SES – Socioeconomic status on a scale from 1 (lowest) to 10

Figure 1. Time of first infection in those reinfected between June and August 2021, model 2.

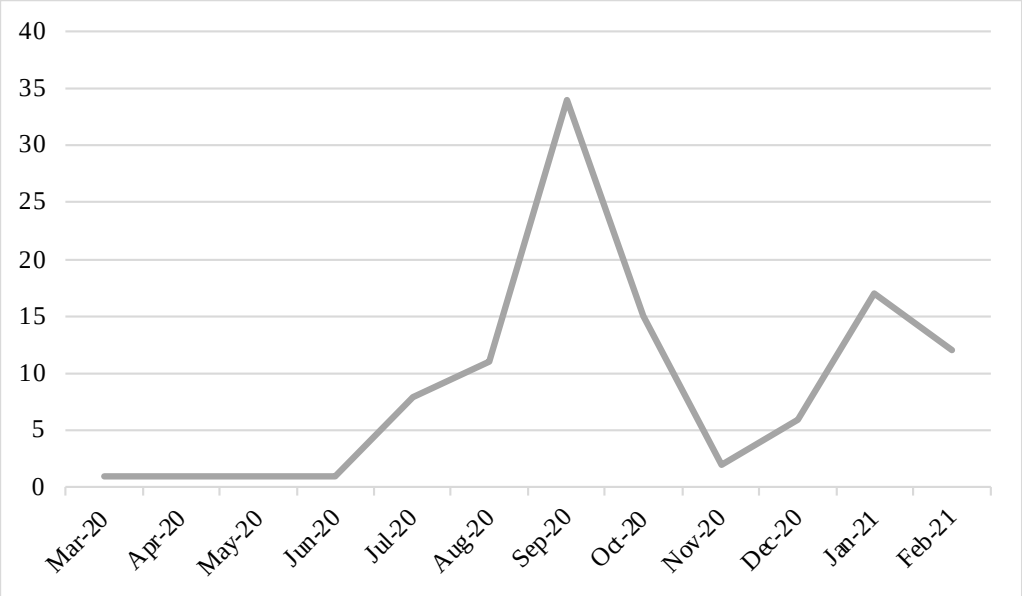


EXHIBIT “C”

ARTICLES
https://doi.org/10.1038/s41591-021-01583-4
nature medicine

BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar

Patrick Tang[1,13], Mohammad R. Hasan[1,13], Hiam Chemaitelly[2,3,13], Hadi M. Yassine[4,5], Fatiha M. Benslimane[4,5], Hebah A. Al Khatib[4,5], Sawsan AlMukdad[2,3], Peter Coyle[4,6,7], Houssein H. Ayoub[8], Zaina Al Kanaani[6], Einas Al Kuwari[6], Andrew Jeremijenko[6], Anvar Hassan Kaleeckal[6], Ali Nizar Latif[6], Riyazuddin Mohammad Shaik[6], Hanan F. Abdul Rahim[9], Gheyath K. Nasrallah[4,5], Mohamed Ghaith Al Kuwari[10], Hamad Eid Al Romaihi[11], Adeel A. Butt[6,12], Mohamed H. Al-Thani[11], Abdullatif Al Khal[6], Roberto Bertollini[11] and Laith J. Abu-Raddad[2,3,9,12] ✉

With the global expansion of the highly transmissible SARS-CoV-2 Delta (B.1.617.2) variant, we conducted a matched test-negative case–control study to assess the real-world effectiveness of COVID-19 messenger RNA vaccines against infection with Delta in Qatar's population. BNT162b2 effectiveness against any, symptomatic or asymptomatic, Delta infection was 45.3% (95% CI, 22.0–61.6%) ≥14 d after the first vaccine dose, but only 51.9% (95% CI, 47.0–56.4%) ≥14 d after the second dose, with 50% of fully vaccinated individuals receiving their second dose before 11 May 2021. Corresponding mRNA-1273 effectiveness ≥14 d after the first or second dose was 73.7% (95% CI, 58.1–83.5%) and 73.1% (95% CI, 67.5–77.8%), respectively. Notably, effectiveness against Delta-induced severe, critical or fatal disease was 93.4% (95% CI, 85.4–97.0%) for BNT162b2 and 96.1% (95% CI, 71.6–99.5%) for mRNA-1273 ≥ 14 d after the second dose. Our findings show robust effectiveness for both BNT162b2 and mRNA-1273 in preventing Delta hospitalization and death in Qatar's population, despite lower effectiveness in preventing infection, particularly for the BNT162b2 vaccine.

Appreciable community transmission of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Delta (B.1.617.2) variant was first noted in Qatar by end of March 2021 (refs. [1–3]). Although Delta incidence has increased along with a recent surge in cases and hovered at about 200 cases per day in the summer of 2021, it remains low compared to earlier variant incidences with no signal for an epidemic wave materializing as of 19 September 2021. Between 23 March 2021 and 7 September 2021, 43% of diagnosed infections were Delta infections (Methods)[1,3]. Delta dominance was, however, preceded by two large consecutive SARS-CoV-2 Alpha (B.1.1.7) and Beta (B.1.351) waves earlier in 2021 (refs. [1–5]). The rapid scale-up of Coronavirus Disease 2019 (COVID-19) vaccination in Qatar may have impeded efficient Delta transmission. As of 19 September 2021, it is estimated that over 80% of Qatar's resident population has received two doses of either the BNT162b2 (ref. [6]) (Pfizer-BioNTech) vaccine or the mRNA-1273 (ref. [7]) (Moderna) vaccine[8]. This study assessed BNT162b2 and mRNA-1273 vaccines' real-world effectiveness against the Delta variant in Qatar from 23 March 2021 to 7 September 2021 and compared these estimates to those in other countries.

Results

Study population. From 21 December 2020 to 7 September 2021, 950,232 people had at least one BNT162b2 vaccine dose (median date of first dose was 21 April 2021) and 916,290 were fully vaccinated (median date of second dose was 11 May 2021). Administration of the second dose was within a median of 21 d after the first dose (interquartile range (IQR) 21–22 d), with full-vaccination of 97.4% of individuals within 30 d of first dose.

Over this timeframe, 564,468 individuals had at least one mRNA-1273 vaccine dose (median date of first dose was 19 May 2021) and 509,322 were fully vaccinated (median date of second dose was 24 May 2021); distributions for both doses were skewed with means of 16 May 2021 and 11 June 2021, respectively. Administration of the second dose was within a median of 28 d after the first dose (IQR 28–31 d), with full-vaccination of 74.7% of individuals within 30 d of the first dose.

With greater and regular vaccine availability, coverage for BNT162b2 has been steadily increasing since December 2020. In contrast, coverage for mRNA-1273 depended on dispatch of large shipments and did not reach considerable levels before March 2021.

[1]Department of Pathology, Sidra Medicine, Doha, Qatar. [2]Infectious Disease Epidemiology Group, Weill Cornell Medicine-Qatar, Cornell University, Doha, Qatar. [3]World Health Organization Collaborating Centre for Disease Epidemiology Analytics on HIV/AIDS, Sexually Transmitted Infections, and Viral Hepatitis, Weill Cornell Medicine-Qatar, Cornell University, Qatar Foundation – Education City, Doha, Qatar. [4]Biomedical Research Center, Member of QU Health, Qatar University, Doha, Qatar. [5]Department of Biomedical Science, College of Health Sciences, Member of QU Health, Qatar University, Doha, Qatar. [6]Hamad Medical Corporation, Doha, Qatar. [7]Wellcome-Wolfson Institute for Experimental Medicine, Queens University, Belfast, UK. [8]Mathematics Program, Department of Mathematics, Statistics, and Physics, College of Arts and Sciences, Qatar University, Doha, Qatar. [9]Department of Public Health, College of Health Sciences, QU Health, Qatar University, Doha, Qatar. [10]Primary Health Care Corporation, Doha, Qatar. [11]Ministry of Public Health, Doha, Qatar. [12]Department of Population Health Sciences, Weill Cornell Medicine, Cornell University, New York, NY, USA. [13]These authors contributed equally: Patrick Tang, Mohammad R. Hasan, Hiam Chemaitelly. ✉e-mail: lja2002@qatar-med.cornell.edu

Table 1 | Demographic characteristics of cases (PCR-positive for SARS-CoV-2 Delta variant) and controls (PCR-negative) in the ≥14-d-after-first-dose analysis of vaccine effectiveness of sample A (BNT162b2), B (mRNA-1273) and C (BNT162b2 or mRNA-1273)

Study type	A Effectiveness of BNT162b2 vaccine		B Effectiveness of mRNA-1273 vaccine		C Effectiveness of BNT162b2 or mRNA-1273 vaccines	
Characteristics	Cases[a] (PCR-positive for Delta variant)	Controls[a] (PCR-negative)	Cases[a] (PCR-positive for Delta variant)	Controls[a] (PCR-negative)	Cases[a] (PCR-positive for Delta variant)	Controls[a] (PCR-negative)
	n = 2,783	*n* = 11,201	*n* = 2,781	*n* = 11,287	*n* = 2,934	*n* = 11,974
Median age (IQR) years	27 (11–35)	26 (10–34)	27 (12–35)	27 (10–35)	27 (12–36)	27 (11–35)
Age group no. (%)						
0–19 years	935 (33.6)	3,844 (34.3)	913 (32.8)	3,771 (33.4)	940 (32.0)	3,879 (32.4)
20–29 years	683 (24.5)	2,888 (25.8)	685 (24.6)	2,877 (25.5)	726 (24.7)	3,073 (25.7)
30–39 years	755 (27.1)	3,046 (27.2)	757 (27.2)	3,099 (27.5)	811 (27.6)	3,356 (28.0)
40–49 years	323 (11.6)	1,161 (10.4)	342 (12.3)	1,277 (11.3)	361 (12.3)	1,370 (11.4)
50–59 years	66 (2.4)	213 (1.9)	65 (2.3)	219 (1.9)	72 (2.5)	239 (2.0)
60–69 years	11 (0.4)	26 (0.2)	12 (0.4)	29 (0.3)	14 (0.5)	34 (0.3)
70+ years	10 (0.4)	23 (0.2)	7 (0.3)	15 (0.1)	10 (0.3)	23 (0.2)
Sex						
Male	1,810 (65.0)	7,832 (69.9)	1,820 (65.4)	7,941 (70.4)	1,899 (64.7)	8,273 (69.1)
Female	973 (35.0)	3,369 (30.1)	961 (34.6)	3,346 (29.6)	1,035 (35.3)	3,701 (30.9)
Nationality[b]						
Bangladeshi	207 (7.4)	954 (8.5)	224 (8.1)	1,022 (9.1)	242 (8.3)	1,107 (9.3)
Egyptian	76 (2.7)	316 (2.8)	79 (2.8)	315 (2.8)	84 (2.9)	343 (2.9)
Filipino	240 (8.6)	720 (6.4)	245 (8.8)	821 (7.3)	263 (9.0)	917 (7.7)
Indian	495 (17.8)	2,342 (20.9)	504 (18.1)	2,399 (21.3)	527 (18.0)	2,517 (21.0)
Nepalese	206 (7.4)	997 (8.9)	208 (7.5)	1,017 (9.0)	212 (7.2)	1,032 (8.6)
Pakistani	244 (8.8)	1,069 (9.5)	249 (9.0)	1,086 (9.6)	256 (8.7)	1,121 (9.4)
Qatari	749 (26.9)	3,090 (27.6)	709 (25.5)	2,904 (25.7)	752 (25.6)	3,117 (26.0)
Sri Lankan	44 (1.6)	168 (1.5)	45 (1.6)	181 (1.6)	50 (1.7)	193 (1.6)
Sudanese	44 (1.6)	143 (1.3)	43 (1.6)	137 (1.2)	46 (1.6)	148 (1.2)
Other nationalities[c]	478 (17.2)	1,402 (12.5)	475 (17.1)	1,405 (12.5)	502 (17.1)	1,479 (12.4)
Reason for PCR testing						
Clinical suspicion	1,277 (45.9)	5,061 (45.2)	1,278 (46.0)	5,150 (45.6)	1,370 (46.7)	5,588 (46.7)
Contact tracing	468 (16.8)	1,667 (14.9)	464 (16.7)	1,655 (14.7)	489 (16.7)	1,763 (14.7)
Survey	468 (16.8)	1,984 (17.7)	474 (17.0)	2,019 (17.9)	491 (6.7)	2,075 (17.3)
Individual request	449 (16.1)	2,083 (18.6)	449 (16.2)	2,080 (18.4)	456 (15.5)	2,115 (17.7)
Healthcare routine testing	97 (3.5)	372 (3.3)	96 (3.5)	356 (3.2)	103 (3.5)	396 (3.3)
Other	24 (0.9)	34 (0.3)	20 (0.7)	27 (0.2)	25 (0.9)	37 (0.3)

[a]Cases and controls were matched one-to-five by sex, 5-year age group, nationality, reason for PCR testing and calendar week of PCR test. [b]Nationalities were chosen to represent the most populous groups in Qatar. [c]These comprise 37 other nationalities in Qatar in sample A, 35 other nationalities in sample B and 37 other nationalities in sample C.

We defined a Delta 'case' as a PCR-positive swab with the Delta variant, irrespective of the reason for the PCR test or symptom presence or absence (Methods). Infections with other variants were excluded, except for Beta in an additional analysis. All records of vaccination for both BNT162b2 and mRNA-1273 were included. Extended Data Figs. 1–3 show flowcharts depicting the selection of study populations to estimate effectiveness of BNT162b2 (Extended Data Fig. 1), mRNA-1273 vaccine (Extended Data Fig. 2) and either of these vaccines (Extended Data Fig. 3) against the Delta variant. Tables 1 and 2 describe the samples used in estimation of effectiveness ≥14 d after the first dose and ≥14 d after the second dose, respectively. The median age of participants ranged from 26–30 years; only 9% of Qatar's residents are ≥50 years of age and 89% are residents from more than 150 countries[9,10].

Delta vaccine-breakthrough infections. Delta cases were ascertained using real-time PCR with reverse transcription (RT–qPCR) genotyping of randomly collected clinical samples (Methods)[1,3]. There were 88 and 1,126 Delta breakthrough infections between 23 March 2021 and 7 September 2021 among vaccinated individuals with one or two BNT162b2 doses, respectively and 60 and 187 Delta breakthrough infections among vaccinated individuals with one or two mRNA-1273 doses, respectively.

Additionally, by 7 September 2021, there were 4 and 15 severe Delta COVID-19 cases (acute care hospitalizations[11]; Methods)

Table 2 | Demographic characteristics of cases (PCR-positive for SARS-CoV-2 Delta variant) and controls (PCR-negative) in the ≥14-d-after-second-dose analysis of vaccine effectiveness of sample A (BNT162b2), B (mRNA-1273) and C (BNT162b2 or mRNA-1273)

Study type	A Effectiveness of BNT162b2 vaccine		B Effectiveness of mRNA-1273 vaccine		C Effectiveness of BNT162b2 or mRNA-1273 vaccines	
Characteristics	Cases[a] (PCR-positive for Delta variant)	Controls[a] (PCR-negative)	Cases[a] (PCR-positive for Delta variant)	Controls[a] (PCR-negative)	Cases[a] (PCR-positive for Delta variant)	Controls[a] (PCR-negative)
	n = 3,846	*n* = 15,977	*n* = 2,947	*n* = 12,151	*n* = 4,150	*n* = 17,490
Median age (IQR) years	30 (18–38)	29 (17–37)	28 (12–36)	28 (11–35)	30 (20–39)	30 (19–38)
Age group no. (%)						
0–19 years	1,025 (26.7)	4,383 (27.4)	919 (31.2)	3,799 (31.3)	1,034 (24.9)	4,430 (25.3)
20–29 years	891 (23.2)	3,900 (24.4)	720 (24.4)	3,071 (25.3)	966 (23.3)	4,253 (24.3)
30–39 years	1,076 (28.0)	4,564 (28.6)	825 (28.0)	3,470 (28. 6)	1,191 (28.7)	5,174 (29.6)
40–49 years	581 (15.1)	2,224 (13.9)	385 (13.1)	1,503 (12.4)	659 (15.9)	2,623 (15.0)
50–59 years	184 (4.8)	649 (4.1)	76 (2.6)	254 (2.1)	203 (4.9)	730 (4.2)
60–69 years	59 (1.5)	170 (1.1)	14 (0.5)	37 (0.3)	67 (1.6)	191 (1.1)
70+ years	30 (0.8)	87 (0.5)	8 (0.3)	17 (0.1)	30 (0.7)	89 (0.5)
Sex						
Male	2,316 (60.2)	10,057 (63.0)	1,879 (63.8)	8,223 (67.7)	2,464 (59.4)	10,808 (61.8)
Female	1,530 (39.8)	5,920 (37.1)	1,068 (36.2)	3,928 (32.3)	1,686 (40.6)	6,682 (38.2)
Nationality[b]						
Bangladeshi	228 (5.9)	1,054 (6.6)	230 (7.8)	1,061 (8.7)	266 (6.4)	1,237 (7.1)
Egyptian	129 (3.4)	543 (3.4)	91 (3.1)	374 (3.1)	150 (3.6)	637 (3.6)
Filipino	308 (8.0)	1,291 (8.1)	280 (9.5)	1,119 (9.2)	359 (8.7)	1,614 (9.2)
Indian	588 (15.3)	2,825 (17.7)	523 (17.8)	2,499 (20.6)	639 (15.4)	3,081 (17.6)
Nepalese	212 (5.5)	1,018 (6.4)	210 (7.1)	1,024 (8.4)	220 (5.3)	1,060 (6.1)
Pakistani	263 (6.8)	1,181 (7.4)	257 (8.7)	1,134 (9.3)	281 (6.8)	1,286 (7.4)
Qatari	1,307 (34.0)	5,594 (35.0)	745 (25.3)	3,060 (25.2)	1,336 (32.2)	5,771 (33.0)
Sri Lankan	55 (1.4)	195 (1.2)	47 (1.6)	193 (1.6)	63 (1.5)	237 (1.4)
Sudanese	56 (1.5)	202 (1.3)	48 (1.6)	157 (1.3)	63 (1.5)	228 (1.3)
Other nationalities[c]	700 (18.2)	2,074 (13.0)	516 (17.5)	1,530 (12.6)	773 (18.6)	2,339 (13.4)
Reason for PCR testing						
Clinical suspicion	1,932 (50.2)	7,933 (49.7)	1,356 (46.0)	5,573 (45.9)	2,092 (50.4)	8,788 (50.3)
Contact tracing	552 (14.4)	2,011 (12.6)	479 (16.3)	1,716 (14.1)	584 (14.1)	2,181 (12.5)
Survey	700 (18.2)	3,091 (19.4)	528 (17.9)	2,323 (19.1)	780 (18.8)	3,455 (19.8)
Individual request	495 (12.9)	2,328 (14.6)	457 (15.5)	2,136 (17.6)	510 (12.3)	2,403 (13.7)
Healthcare routine testing	133 (3.5)	551 (3.5)	102 (3.5)	371 (3.1)	145 (3.5)	589 (3.4)
Other	34 (0.9)	63 (0.4)	25 (0.9)	32 (0.3)	39 (0.9)	74 (0.4)

[a]Cases and controls were matched one-to-five by sex, 5-year age group, nationality, reason for PCR testing and calendar week of PCR test. [b]Nationalities were chosen to represent the most populous groups in Qatar. [c]These comprise 41 other nationalities in Qatar in sample A, 35 other nationalities in sample B and 41 other nationalities in sample C.

among vaccinated individuals with one or two BNT162b2 doses, respectively and 3 and 1 severe disease cases among vaccinated individuals with one or two mRNA-1273 doses, respectively.

Furthermore, there were one and two critical Delta COVID-19 cases (intensive care unit (ICU) hospitalization[11]; Methods) among vaccinated individuals with one or two BNT162b2 doses, respectively. The critical disease case reported after only one BNT162b2 vaccine dose also led to COVID-19 death (COVID-19 deaths[12]; Methods). There were no critical or fatal COVID-19 cases among those vaccinated with mRNA-1273.

Effectiveness ≥14 d after the first vaccine dose. Effectiveness against Delta infection ≥14 d after only one dose was estimated at 45.3% (95% confidence interval (CI), 22.0–61.6%) for BNT162b2, 73.7% (95% CI, 58.1–83.5%) for mRNA-1273 and 58.0% (95% CI, 44.4–68.2%) for either of these vaccines (Table 3).

Effectiveness against any Delta-induced severe[11], critical[11] or fatal[12] COVID-19 disease (Methods), 14 or more days after only one dose, ranged between 80–87% for BNT162b2, mRNA-1273 and either of these vaccines, but 95% confidence intervals were wide given the relatively small number of Delta disease cases (Table 3).

Effectiveness ≥14 d after the second vaccine dose. Effectiveness against Delta infection 14 or more days after the second dose was 51.9% (95% CI, 47.0–56.4%) for BNT162b2, 73.1% (95% CI,

Table 3 | Effectiveness of the BNT162b2 and mRNA-1273 vaccines against the Delta variant ≥14 d after the first dose and ≥14 d after the second dose

Sub-studies[a]	≥14 d after first dose and no second dose					≥14 d after second dose				
	Cases[b] (PCR-positive)		Controls[b] (PCR-negative)		Effectiveness in % (95% CI)[c]	Cases[b] (PCR-positive)		Controls[b] (PCR-negative)		Effectiveness in % (95% CI)[c]
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
Effectiveness against infection										
BNT162b2	39	2,744	254	10,947	45.3 (22.0; 61.6)	998	2,848	5,592	10,385	51.9 (47.0; 56.4)
mRNA-1273	21	2,760	259	11,028	73.7 (58.1; 83.5)	150	2,797	1,568	10,583	73.1 (67.5; 77.8)
BNT162b2 or mRNA-1273	61	2,873	508	11,466	58.0 (44.4; 68.2)	1,174	2,976	6,862	10,628	55.5 (51.2; 59.4)
Effectiveness against severity, criticality and fatality[d]										
BNT162b2	1	96	16	317	79.7 (−59.5; 97.4)	13	104	231	222	93.4 (85.4; 97.0)
mRNA-1273	1	100	23	334	86.7 (−1.4; 98.3)	1	103	71	305	96.1 (71.6; 99.5)
BNT162b2 or mRNA-1273	2	104	34	343	80.8 (18.3; 95.5)	14	113	256	252	93.6 (85.9; 97.1)

[a]In each time-since-vaccination stratum, for first and second doses, we analyzed only those vaccinated in this specific time-since-vaccination stratum and those unvaccinated (our reference group). Accordingly, the sample size for cases (and controls) varied in the different time-since-vaccination analyses. [b]Cases and controls were matched one-to-five by sex, 5-year age group, nationality, reason for PCR testing and calendar week of PCR test. [c]Vaccine effectiveness was estimated using the test-negative, case-control study design[43,44]. [d]Effectiveness against severe, critical or fatal COVID-19. Severity[11], criticality[11] and fatality[12] were defined as per World Health Organization (WHO) guidelines.

Table 4 | Sensitivity analyses for effectiveness of the BNT162b2 and mRNA-1273 vaccines against the Delta variant ≥14 d after the first dose and ≥14 d after the second dose, adjusting for previous infection and health worker status in conditional logistic regression analysis

Sub-studies[a]	≥14 d after first dose and no second dose					≥14 d after second dose				
	Cases[b] (PCR-positive)		Controls[b] (PCR-negative)		Effectiveness in % (95% CI)[c]	Cases[b] (PCR-positive)		Controls[b] (PCR-negative)		Effectiveness in % (95% CI)[c]
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
Effectiveness against infection										
BNT162b2	39	2,744	254	10,947	42.8 (18.2; 60.1)	998	2,848	5,592	10,385	50.6 (45.4; 55.3)
mRNA-1273	21	2,760	259	11,028	73.2 (57.3; 83.2)	150	2,797	1,568	10,583	72.0 (66.1; 76.9)
BNT162b2 or mRNA-1273	61	2,873	508	11,466	56.9 (42.8; 67.5)	1,174	2,976	6,862	10,628	54.1 (49.7; 58.2)
Effectiveness against severity, criticality and fatality[d]										
BNT162b2	1	96	16	317	84.5 (−25.2; 98.1)	13	104	231	222	94.1 (85.9; 97.6)
mRNA-1273	1	100	23	334	87.5 (4.8; 98.4)	1	103	71	305	96.1 (71.4; 99.5)
BNT162b2 or mRNA-1273	2	104	34	343	82.0 (23.4; 95.8)	14	113	256	252	93.4 (85.0; 97.1)

[a]In each time-since-vaccination stratum, for first and second doses, we analyzed only those vaccinated in this specific time-since-vaccination stratum and those unvaccinated (our reference group). Accordingly, the sample size for cases (and controls) varied in the different time-since-vaccination analyses. [b]Cases and controls were matched one-to-five by sex, 5-year age group, nationality, reason for PCR testing and calendar week of PCR test. [c]Vaccine effectiveness was estimated using the test-negative, case-control study design[43,44]. [d]Effectiveness against severe, critical or fatal COVID-19. Severity[11], criticality[11] and fatality[12] were defined as per WHO guidelines.

Table 5 | Effectiveness of the BNT162b2 and mRNA-1273 vaccines against symptomatic and asymptomatic infection with the Delta variant ≥14 d after the first dose and ≥14 d after the second dose

Sub-studies[a]	≥14 d after first dose and no second dose					≥14 d after second dose				
	Cases[b] (PCR-positive)		Controls[b] (PCR-negative)		Effectiveness in % (95% CI)[c]	Cases[b] (PCR-positive)		Controls[b] (PCR-negative)		Effectiveness in % (95% CI)[c]
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
Effectiveness against symptomatic infection[d]										
BNT162b2	23	1,254	181	4,880	56.2 (30.6; 72.4)	633	1,299	3,237	4,696	44.4 (37.0; 50.9)
mRNA-1273	10	1,268	161	4,989	82.5 (65.2; 91.2)	75	1,281	821	4,752	73.9 (65.9; 79.9)
BNT162b2 or mRNA-1273	33	1,337	342	5,246	67.3 (52.4; 77.6)	717	1,375	3,891	4,897	49.2 (42.8; 54.9)
Effectiveness against asymptomatic infection[e]										
BNT162b2	4	464	27	1,957	46.7 (−56.2; 81.8)	216	484	1,210	1,881	46.0 (32.3; 56.9)
mRNA-1273	4	470	38	1,981	61.8 (−9.6; 86.7)	53	475	368	1,955	53.6 (33.4; 67.6)
BNT162b2 or mRNA-1273	8	483	53	2,022	47.0 (−13.8; 75.3)	279	501	1,533	1,922	45.9 (33.3; 56.1)

[a]In each time-since-vaccination stratum, for first and second doses, we analyzed only those vaccinated in this specific time-since-vaccination stratum and those unvaccinated (our reference group). Accordingly, the sample size for cases (and controls) varied in the different time-since-vaccination analyses. [b]Cases and controls were matched one-to-five by sex, 5-year age group, nationality, reason for PCR testing and calendar week of PCR test. [c]Vaccine effectiveness was estimated using the test-negative, case-control study design[43,44]. [d]A symptomatic infection is defined as a PCR-positive test conducted because of clinical suspicion due to presence of symptoms compatible with a respiratory tract infection. [e]An asymptomatic infection is defined as a PCR-positive test conducted with no reported presence of symptoms compatible with a respiratory tract infection (PCR testing was conducted as part of a survey or a random testing campaign).

Table 6 | Effectiveness of the BNT162b2 and mRNA-1273 vaccines against the Beta variant ≥14 d after the first dose and ≥14 d after the second dose

Sub-studies[a]	≥14 d after first dose and no second dose					≥14 d after second dose				
	Cases[b] (PCR-positive)		Controls[b] (PCR-negative)		Effectiveness in % (95% CI)[c]	Cases[b] (PCR-positive)		Controls[b] (PCR-negative)		Effectiveness in % (95% CI)[c]
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
Effectiveness against infection										
BNT162b2	97	3,386	520	15,288	18.9 (−1.8; 35.4)	290	3,438	3,170	13,983	74.3 (70.3; 77.7)
mRNA-1273	64	3,278	707	14,336	66.3 (55.8; 74.2)	19	3,268	345	14,421	80.8 (69.0; 88.2)
BNT162b2 or mRNA-1273	166	4,235	1,243	18,956	44.9 (34.7; 53.5)	313	4,279	3,725	17,537	76.4 (72.9; 79.4)
Effectiveness against severity, criticality and fatality[d]										
BNT162b2	2	147	33	609	74.8 (−7.6; 94.1)	7	152	178	520	92.7 (81.5; 97.1)
mRNA-1273	3	143	42	581	72.5 (7.7; 91.8)	0	143	17	589	100.0 (Omitted)[e]
BNT162b2 or mRNA-1273	7	192	83	781	67.7 (28.6; 85.4)	7	196	201	697	93.4 (83.5; 97.4)

[a]In each time-since-vaccination stratum, for first and second doses, we analyzed only those vaccinated in this specific time-since-vaccination stratum and those unvaccinated (our reference group). Accordingly, the sample size for cases (and controls) varied in the different time-since-vaccination analyses. [b]Cases and controls were matched one-to-five by sex, 5-year age group, nationality, reason for PCR testing and calendar week of PCR test. [c]Vaccine effectiveness was estimated using the test-negative, case-control study design[43,44]. [d]Effectiveness against severe, critical or fatal COVID-19. Severity[11], criticality[11] and fatality[12] were defined as per WHO guidelines. [e]CI could not be estimated because of zero events among vaccinated.

67.5–77.8%) for mRNA-1273 and 55.5% (95% CI, 51.2–59.4%) for either of these vaccines (Table 3).

Effectiveness against any Delta-induced severe[11], critical[11] or fatal[12] COVID-19 disease 14 or more days after the second dose was 93.4% (95% CI, 85.4–97.0%) for BNT162b2, 96.1% (95% CI, 71.6–99.5%) for mRNA-1273 and 93.6% (95% CI, 85.9–97.1%) for either of these vaccines (Table 3).

Additional analyses. Sensitivity analyses adjusting for previous infection and health worker status in conditional logistic regression analysis confirmed the main findings (Table 4).

Vaccine effectiveness against Delta infection for those ≥50 years of age was lower than that for those <50 for both vaccines (Supplementary Table 1). However, this result should be seen in the context that those ≥50 years of age received their second dose earlier than those <50. The median date of second vaccine dose for those ≥50 years of age was 9 April 2021, but was 19 May 2021 for those <50 years.

Effectiveness against symptomatic Delta infection 14 or more days after the second dose was estimated at 44.4% (95% CI, 37.0–50.9%) for BNT162b2, 73.9% (95% CI, 65.9–79.9%) for mRNA-1273 and 49.2% (95% CI, 42.8–54.9%) for either of these vaccines (Table 5). Symptomatic infection was defined as a PCR-positive swab collected based on clinical suspicion (symptoms indicative of a respiratory tract infection).

Effectiveness against asymptomatic Delta infection 14 or more days after the second dose was estimated at 46.0% (95% CI, 32.3–56.9%) for BNT162b2, 53.6% (95% CI, 33.4–67.6%) for mRNA-1273 and 45.9% (95% CI, 33.3–56.1%) for either of these vaccines (Table 5). Asymptomatic infection was defined as a PCR-positive swab collected in the absence of reported respiratory tract symptoms, such as during a survey or a random testing campaign (data sources in Methods).

For comparison, vaccine effectiveness against Beta infection was also estimated over the same period 23 March 2021 to 7 September 2021. Beta cases were also ascertained using RT–qPCR genotyping of randomly collected clinical samples (Methods)[1,3]. Effectiveness against Beta infection was estimated for BNT162b2 at 18.9% (95% CI, −1.8–35.4%) 14 or more days after only one dose and at 74.3% (95% CI, 70.3–77.7%) 14 or more days after the second dose (Table 6). The corresponding effectiveness measures for mRNA-1273 were 66.3% (95% CI, 55.8–74.2%) and 80.8% (95% CI, 69.0–88.2%), respectively. Estimated effectiveness against any Beta-induced severe[11], critical[11] or fatal[12] COVID-19 disease was >90% for both vaccines (Table 6).

In comparing estimates for Beta to those for Delta, it must be noted that the median PCR diagnosis date was 15 April 2021 for Beta cases, but was 2 August 2021 for Delta cases. Beta dominated transmission earlier in the study, whereas Delta dominated transmission later in the study[1–5]. From 1 August 2021 to 7 September 2021, 83.6% of the RT–qPCR-genotyped cases were Delta cases (Methods).

Discussion

BNT162b2 and mRNA-1273 vaccines both showed robust effectiveness (≥90%) against Delta-related hospitalization and fatality, in line with studies from the United Kingdom[13,14], United States[15–18] and Israel[19]. Despite many breakthrough infections, particularly for BNT162b2, there were limited instances of severe or critical disease among vaccinated individuals. In BNT162b2 fully vaccinated individuals, only 15 severe disease cases, 2 critical disease cases and 1 COVID-19 death were due to Delta. For mRNA-1273, only 1 severe disease case and no critical or fatal disease cases were reported.

Notably, estimated BNT162b2 or mRNA-1273 effectiveness against Delta infection 14 or more days after the first dose or 14 or more days after the second dose, were comparable. Recent evidence pointed to considerable waning of vaccine effectiveness over time, particularly for BNT162b2 (refs. [14,20–23]). The high effectiveness against Alpha and Beta in Qatar in our previous studies (≥75%)[4,5,24,25] as well as against Beta in this study (Table 6) were estimated when most residents in Qatar were recently vaccinated with BNT162b2 or mRNA-1273. Conversely, effectiveness against Delta was estimated here after several months have passed since the second vaccine dose for a large proportion of residents. This unexpectedly low effectiveness against Delta in fully vaccinated individuals could be therefore reflecting gradual waning of vaccine protection.

This observation is consistent with the pattern seen in reported effectiveness estimates against Delta elsewhere. Our estimate of 51.9% in BNT162b2 fully vaccinated individuals is lower than that reported in the United Kingdom[14,26,27] and Canada[28], where effectiveness was estimated at >75%, but similar to that reported in Israel[19] and the United States[18,29–31], where effectiveness was estimated between 39% and 66%. The delay in administering the second dose in the United Kingdom and Canada led to most persons being fully vaccinated ~3 months more recently than in Israel, the United States and Qatar, where vaccinated persons received their second dose 3 weeks after the first dose. The lower effectiveness in Israel, the United States and Qatar may therefore signal waning of vaccine protection in those who were fully vaccinated by the end of 2020 or early in 2021, as also suggested in a recent analysis of waning of BNT162b2 protection over time in Qatar[23]. Notably, mass vaccination in Qatar started shortly after that in Israel and the United States.

Another potential explanation pertains to the gradual easing of public health restrictions in Qatar in the last few months, at a time when Delta incidence has been slowly increasing. With more restrictions eased based on vaccination status, which is implemented through a mandatory mobile app (the Ehteraz app), vaccinated individuals may have had higher social contact rates than unvaccinated persons and may have adhered less strictly to safety measures, such as masks, due to their perception of lower risk[32–34]. Such risk compensation may even increase over time after completing the second dose, resulting in further normalization of behavior[33–35]. Vaccinated persons may therefore have higher risk of exposure to the virus than unvaccinated individuals, leading to increased infection incidence among those vaccinated, thereby reducing the observed real-world vaccine effectiveness.

Higher effectiveness against infection with Delta after the second dose was estimated for mRNA-1273 compared to BNT162b2 ($P=0.009$), in line with studies indicating a stronger induced immune response and protection for mRNA-1273 (refs. [5,36–38]).

This study found higher vaccine effectiveness for more serious COVID-19 disease (greater protection against symptomatic or severe infections), as observed earlier for BNT162b2 and mRNA-1273 effectiveness against the Alpha and Beta variants[4,5,24,28].

This study has limitations. With the relatively small number of severe and critical disease cases and fatal cases in Qatar's young population[9,39], some of the effectiveness estimates against hospitalization and death had wide 95% confidence intervals. Data on comorbid conditions were not available to be included in the analysis. With the young population of Qatar[9,10], the part of the population with serious comorbid conditions is small. In the national list of vaccine prioritization, there were only 19,800 individuals of all age groups with serious comorbid conditions. Accordingly, our findings may not apply to settings where the elderly population constitutes a considerable part of the population.

Data on occupation were not available to study investigators. The matching by nationality may have controlled in part for the occupational risk, considering the labor force structure in Qatar[40–42]. Infection incidence and vaccination were broadly distributed across the country's neighborhoods or areas and population social substrata. Therefore, it is not likely that the results could be explained by clustering of vaccination or infection in specific geographies or social strata.

Vaccine effectiveness was investigated using a test-negative case–control study design[43,44], rather than a randomized clinical trial design or a cohort study design that followed vaccinated and unvaccinated cohorts. However, the cohort study design applied to the same population of Qatar previously resulted in similar findings to the test-negative case–control study design[4,5,45] (Extended Data Fig. 4), supporting the reliability of the test-negative case–control study design that has been of wide application for vaccine effectiveness studies of respiratory tract infections[43,44].

In conclusion, both the BNT162b2 and mRNA-1273 vaccines are highly effective in preventing hospitalization and death due to infection with the Delta variant. However, effectiveness against infection was considerably lower than that against serious COVID-19 disease, particularly for the BNT162b2 vaccine. The reasons for the inferior protection against infection remain to be determined and may not necessarily relate to immune evasion by the Delta variant. The lower effectiveness may reflect some waning of vaccine protection over time[23] or higher risk of exposure to the virus among vaccinated individuals compared to unvaccinated individuals, due to higher social contact rate and less adherence to safety measures. These findings indicate the need for more follow-up of vaccinated cohorts to investigate waning of vaccine immunity and for studies that investigate the effect of risk compensation on biasing vaccine effectiveness estimates.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-021-01583-4.

Received: 10 August 2021; Accepted: 18 October 2021;
Published online: 2 November 2021

References

1. National Project of Surveillance for Variants of Concern and Viral Genome Sequencing. Qatar viral genome sequencing data. Data on randomly collected samples. https://www.gisaid.org/phylodynamics/global/nextstrain/ (2021).
2. Benslimane, F. M. et al. One year of SARS-CoV-2: genomic characterization of COVID-19 outbreak in Qatar. Preprint at *medRxiv* https://doi.org/10.1101/2021.05.19.21257433 (2021).
3. Hasan, M. R. et al. Real-time SARS-CoV-2 genotyping by high-throughput multiplex PCR reveals the epidemiology of the variants of concern in Qatar. *Int J. Infect. Dis.* **112**, 52–54 (2021).
4. Abu-Raddad, L. J., Chemaitelly, H., Butt, A. A. & National Study Group for COVID-19 Vaccination. Effectiveness of the BNT162b2 Covid-19 vaccine against the B.1.1.7 and B.1.351 variants. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMc2104974 (2021).
5. Chemaitelly, H. et al. mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. *Nat. Med* **27**, 1614–1621 (2021).
6. Polack, F. P. et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N. Engl. J. Med.* **383**, 2603–2615 (2020).
7. Baden, L. R. et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N. Engl. J. Med.* **384**, 403–416 (2021).
8. Ministry of Public Health. National Covid-19 Testing and Vaccination Program Data. https://covid19.moph.gov.qa/EN/Pages/Vaccination-Program-Data.aspx (2021).
9. Abu-Raddad, L. J. et al. Characterizing the Qatar advanced-phase SARS-CoV-2 epidemic. *Sci. Rep.* **11**, 6233 (2021).
10. Planning and Statistics Authority-State of Qatar. Qatar Monthly Statistics. https://www.psa.gov.qa/en/pages/default.aspx (2020).
11. World Health Organization. COVID-19 clinical management: living guidance. https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1 (2021).
12. World Health Organization. International guidelines for certification and classification (coding) of COVID-19 as cause of death. https://www.who.int/classifications/icd/Guidelines_Cause_of_Death_COVID-19-20200420-EN.pdf?ua=1 (2020).
13. Stowe, J. et al. Effectiveness of COVID-19 vaccines against hospital admission with the Delta (B.1.617.2) variant. https://khub.net/web/phe-national/public-library/-/document_library/v2WsRK3ZlEig/view_file/479607329?_com_liferay_document_library_web_portlet_DLPortlet_INSTANCE_v2WsRK3ZlEig_redirect=https%253A%252F%252Fkhub.net%253A443%252Fweb%252Fphe-national%252Fpublic-library%252F-%25 (2021).
14. Andrews, N. et al. Vaccine effectiveness and duration of protection of Comirnaty, Vaxzevria and Spikevax against mild and severe COVID-19 in the UK. https://khub.net/documents/135939561/338928724/Vaccine+effectiveness+and+duration+of+protection+of+covid+vaccines+against+mild+and+severe+COVID-19+in+the+UK.pdf/10dcd99c-0441-0403-dfd8-11ba2c6f5801 (2021).
15. Tenforde, M. W. et al. Sustained effectiveness of Pfizer-BioNTech and Moderna vaccines against COVID-19 associated hospitalizations among adults - United States, March–July 2021. *Morb. Mortal. Wkly Rep.* **70**, 1156–1162 (2021).
16. Bajema, K. L. et al. Effectiveness of COVID-19 mRNA vaccines against COVID-19-associated hospitalization - five Veterans Affairs Medical Centers, United States, February 1–August 6, 2021. *Morb. Mortal. Wkly Rep.* **70**, 1294–1299 (2021).
17. Grannis, S. J. et al. Interim estimates of COVID-19 vaccine effectiveness against COVID-19-associated emergency department or urgent care clinic encounters and hospitalizations among adults during SARS-CoV-2 B.1.617.2 (Delta) variant predominance - nine states, June–August 2021. *Morb. Mortal. Wkly Rep.* **70**, 1291–1293 (2021).
18. Tartof, S.Y. et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. *Lancet* https://doi.org/10.1016/S0140-6736(21)02183-8 (2021).
19. Israel Ministry of Health. *COVID-19 vaccine effectiveness against the Delta variant. Israel's Ministry of Health Report* https://www.gov.il/BlobFolder/reports/vaccine-efficacy-safety-follow-up-committee/he/files_publications_corona_two-dose-vaccination-data.pdf (2021).
20. Israel, A. et al. Elapsed time since BNT162b2 vaccine and risk of SARS-CoV-2 infection in a large cohort. Preprint at *medRxiv* https://doi.org/10.1101/2021.08.03.21261496 (2021).
21. Thomas, S. J. et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine through 6 months. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2110345 (2021).
22. Mizrahi, B. et al. Correlation of SARS-CoV-2 breakthrough infections to time-from-vaccine: preliminary study. Preprint at *medRxiv* https://doi.org/10.1101/2021.07.29.21261317 (2021).
23. Chemaitelly, H. et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2114114 (2021).
24. Abu-Raddad, L. J. et al. Pfizer-BioNTech mRNA BNT162b2 Covid-19 vaccine protection against variants of concern after one versus two doses. *J. Travel Med.* https://doi.org/10.1093/jtm/taab083 (2021).
25. Bertollini, R. et al. Associations of vaccination and of prior infection with positive PCR test results for SARS-CoV-2 in airline passengers arriving in Qatar. *JAMA* **326**, 185–188 (2021).
26. Lopez Bernal, J. et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) variant. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2108891 (2021).
27. Sheikh, A., McMenamin, J., Taylor, B. & Robertson, C. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. *Lancet* **397**, 2461–2462 (2021).
28. Nasreen, S. et al. Effectiveness of COVID-19 vaccines against variants of concern, Canada. Preprint at *medRxiv* https://doi.org/10.1101/2021.06.28.21259420 (2021).
29. Puranik, A. et al. Comparison of two highly effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. Preprint at *medRxiv* https://doi.org/10.1101/2021.08.06.21261707 (2021).
30. Fowlkes, A. et al. Effectiveness of COVID-19 vaccines in preventing SARS-CoV-2 infection among frontline workers before and during B.1.617.2 (Delta) variant predominance - eight US locations, December 2020–August 2021. *Morb. Mortal. Wkly Rep.* **70**, 1167–1169 (2021).
31. Nanduri, S. et al. Effectiveness of Pfizer-BioNTech and Moderna vaccines in preventing SARS-CoV-2 infection among nursing home residents before and during widespread circulation of the SARS-CoV-2 B.1.617.2 (Delta) variant - National Healthcare Safety Network, March 1–August 1, 2021. *Morb. Mortal. Wkly Rep.* **70**, 1163–1166 (2021).
32. Makhoul, M. et al. Epidemiological impact of SARS-CoV-2 vaccination: mathematical modeling analyses. *Vaccines* https://doi.org/10.3390/vaccines8040668 (2020).
33. Usherwood, T., LaJoie, Z. & Srivastava, V. A model and predictions for COVID-19 considering population behavior and vaccination. *Sci. Rep.* **11**, 12051 (2021).
34. Andersson, O., Campos-Mercade, P., Meier, A.N. & Wengström, E. Anticipation of COVID-19 vaccines reduces social distancing. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3765329 (2021).

35. Cassell, M. M., Halperin, D. T., Shelton, J. D. & Stanton, D. Risk compensation: the Achilles' heel of innovations in HIV prevention? *BMJ* **332**, 605–607 (2006).
36. Abu-Raddad, L. J. et al. Effect of vaccination and of prior infection on infectiousness of vaccine-breakthrough infections and reinfections. Preprint at *medRxiv* https://doi.org/10.1101/2021.07.28.21261086 (2021).
37. Abu-Raddad, L. J. et al. Association of prior SARS-CoV-2 infection with risk of breakthrough infection following mRNA vaccination in Qatar. *JAMA* (in the press).
38. Khoury, D. S. et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat. Med.* **27**, 1205–1211 (2021).
39. Seedat, S. et al. SARS-CoV-2 infection hospitalization, severity, criticality, and fatality rates in Qatar. *Sci. Rep.* **11**, 18182 (2021).
40. Jeremijenko, A. et al. Herd immunity against severe acute respiratory syndrome coronavirus 2 infection in 10 communities, Qatar. *Emerg. Infect. Dis.* **27**, 1343–1352 (2021).
41. Al-Thani, M. H. et al. SARS-CoV-2 infection is at herd immunity in the majority segment of the population of Qatar. *Open Forum Infect. Dis.* **8**, ofab221 (2021).
42. Coyle, P. V. et al. SARS-CoV-2 seroprevalence in the urban population of Qatar: an analysis of antibody testing on a sample of 112,941 individuals. *Iscience* **24**, 102646 (2021).
43. Jackson, M. L. & Nelson, J. C. The test-negative design for estimating influenza vaccine effectiveness. *Vaccine* **31**, 2165–2168 (2013).
44. Verani, J. R. et al. Case–control vaccine effectiveness studies: preparation, design, and enrollment of cases and controls. *Vaccine* **35**, 3295–3302 (2017).
45. Butt, A. A. et al. SARS-CoV-2 vaccine effectiveness in preventing confirmed infection in pregnant women. *J. Clin. Invest.* https://doi.org/10.1172/JCI153662 (2021).

Methods

Hamad Medical Corporation and Weill Cornell Medicine-Qatar Institutional Review Boards approved the study with waiver of informed consent. A STROBE checklist is included in Supplementary Table 2.

Data sources, study population and study design. This study was conducted in the resident population of Qatar. COVID-19 laboratory testing, vaccination, clinical infection data and related demographic details were extracted from the integrated, nationwide, digital-health information platform at Hamad Medical Corporation, the main public healthcare provider and the nationally designated provider for all COVID-19 healthcare needs. This platform hosts the national, federated SARS-CoV-2 databases. Data access was provided by the Ministry of Public Health for analyses to inform the national COVID-19 response. These databases include complete information for PCR testing, vaccinations, hospitalizations and demographic characteristics from epidemic onset.

Almost all vaccinations were provided at no cost in Qatar rather than abroad, through the universal public healthcare system for all nationals and residents of Qatar. In occasional episodes of vaccination abroad, details were still incorporated into the health system upon arrival to Qatar (at airport), for compliance with national regulations and to take advantage of travel-related privileges, such as quarantine exemption[25].

All PCR tests in Qatar, irrespective of test-center location, are classified with respect to symptoms and the reason for testing (clinical symptoms, contact tracing, surveys or random testing campaigns, individual requests, routine healthcare testing, pre-travel, at port of entry or other). Only 9% of residents of Qatar are aged ≥50 years and 89% are incomers from over 150 countries[9,10]. Most of these expatriates are male craft and manual workers[9,10,11].

We estimated vaccine effectiveness using a test-negative, case–control study design, a widely used design for appraising influenza vaccine effectiveness[43,44]. This design controls for potential bias due to infection misclassification or to healthcare-seeking differentials between vaccinated and unvaccinated individuals[43,44]. To maximize statistical power, all cases (PCR-positive individuals with confirmed SARS-CoV-2 Delta infection) and controls (PCR-negative individuals) in Qatar, between 23 March 2021 and 7 September 2021, were included in the study.

To adjust for underlying differences in the risk of exposure to infection[9,10–12], we exact-matched cases and controls in a one-to-five ratio by sex, 5-year age group, nationality, reason for PCR testing and calendar week of PCR test. By virtue of having many more PCR-negative tests than PCR-positive tests, it was generally possible to find exact PCR-negative matches for most age groups for the PCR-positive Delta cases included in this study.

For each case, we considered the first PCR-positive test with confirmed Delta infection during the study from 23 March 2021 to 7 September 2021. After excluding all other PCR tests on individuals with infection, we considered the first PCR-negative test for each control during this period. This yielded an independent sample of unique cases and controls. This strategy was used to control for potential bias due to repeat testing in PCR-positive individuals seeking to check for infection clearance or bias arising from repeat testers among controls (persons with a higher level of healthcare-seeking behavior and presumably lower risk of infection).

PCR tests conducted for pre-travel or at the port of entry were excluded from analysis. This type of testing could possibly be affected by different test-seeking behavior among those vaccinated versus unvaccinated individuals given travel-related benefits extended only to vaccinated individuals, such as exemption from quarantine[25].

We estimated effectiveness against Delta (B.1.617.2) documented infection (defined as a PCR-positive test with the Delta variant irrespective of the reason for the test or presence of symptoms) and against related severe, critical or fatal disease. Classification of case severity (acute care hospitalizations)[11], criticality (ICU hospitalizations)[11] and fatality[12] was per WHO classification using individual chart reviews (details below).

We reviewed all PCR testing records for vaccinated and unvaccinated individuals. We excluded individuals with mixed vaccinations or with a vaccine record other than BNT162b2 or mRNA-1273. Every Delta case fulfilling the inclusion criteria, regardless of vaccination status and that could be matched to one or more controls was retained for the analysis. Infection and vaccination statuses were both ascertained at the time of PCR test. Each hospitalized individual underwent an infection severity assessment every 3 d from hospital admission up to discharge or death. Hospitalized individuals were classified according to their worst outcome (death[12]), followed by critical disease[11] and severe disease[11] (details below).

COVID-19 severity, criticality and fatality classification. WHO defines severe COVID-19 as a SARS-CoV-2-infected individual with 'oxygen saturation of <90% on room air and/or respiratory rate of >30 breaths min^{-1} in adults and children >5 years old (or ≥60 breaths min^{-1} in children <2 months old or ≥50 breaths min^{-1} in children 2–11 months old or ≥40 breaths min^{-1} in children 1–5 years old) and/or signs of severe respiratory distress (accessory muscle use and inability to complete full sentences and, in children, very severe chest wall indrawing, grunting, central cyanosis or presence of any other general danger signs)'[11]. Detailed criteria are in the WHO technical report[11].

Critical COVID-19 is defined as a SARS-CoV-2-infected individual with 'acute respiratory distress syndrome, sepsis, septic shock or other conditions that would normally require the provision of life sustaining therapies such as mechanical ventilation (invasive or noninvasive) or vasopressor therapy'[11]. Detailed criteria are in the WHO technical report[11].

COVID-19 death is defined as 'a death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID-19 disease (for example, trauma). There should be no period of complete recovery from COVID-19 between illness and death. A death due to COVID-19 may not be attributed to another disease (such as cancer) and should be counted independently of preexisting conditions that are suspected of triggering a severe course of COVID-19'. Detailed criteria are in the WHO technical report[12].

Laboratory methods. Nasopharyngeal and/or oropharyngeal swabs were collected for PCR testing and placed in Universal Transport Medium (UTM). Aliquots of UTM were extracted on a QIAsymphony platform (QIAGEN) and tested with real-time RT–qPCR using TaqPath COVID-19 Combo kits (Thermo Fisher Scientific) on an ABI 7500 FAST (Thermo Fisher); tested directly on the Cepheid GeneXpert system using the Xpert Xpress SARS-CoV-2 (Cepheid); or loaded directly into a Roche cobas 6800 system and assayed with a cobas SARS-CoV-2 Test (Roche). The first assay targets the viral S, N and ORF1ab gene regions. The second targets the viral N and E-gene regions and the third targets the ORF1ab and E-gene regions.

Tests were performed at the HMC Central Laboratory or Sidra Medicine Laboratory, following standardized protocols.

Classification of infections by variant type. Viral genome sequencing and multiplex RT–qPCR were used to screen for variants[16] in randomly collected positive clinical samples[1–5], supplemented by deep wastewater sequencing[1,47]. The latter is used to compare the distribution of variants in wastewater to that in clinical samples collected from patients with SARS-CoV-2.

Ascertainment of Delta (B.1.617.2) and Beta (B.1.351) cases in this study was through weekly RT–qPCR genotyping of positive clinical samples[1,3]. From 23 March 2021 to 7 September 2021, RT–qPCR genotyping identified 6,005 (35.5%) Beta (B.1.351)-like cases, 3,658 (21.6%) Alpha (B.1.1.7)-like cases, 7,218 (42.6%) 'other' variant cases and 51 (0.3%) B.1.375-like or B.1.258-like cases in 16,932 randomly collected specimens[1,3]. Since RT–qPCR genotyping started on 23 March 2021, the proportion of all diagnosed infections in Qatar that have been RT–qPCR genotyped is 12.0%, with the proportion of infections genotyped increasing with time, especially in the summer of 2021.

RT–qPCR genotyping accuracy was contrasted against results of Sanger sequencing of the receptor-binding domain of SARS-CoV-2 surface glycoprotein (S) gene or by viral whole-genome sequencing on a Nanopore GridION sequencing device. From 236 random samples (27 Alpha-like, 186 Beta-like and 23 'other' variants), PCR genotyping results for Alpha-like, Beta-like and 'other' variants were in 88.8% (23 out of 27), 99.5% (185 out of 186) and 100% (23 out of 23) agreement with the SARS-CoV-2 lineages assigned by sequencing.

Within the 'other' variant category, Sanger sequencing and/or Illumina sequencing of the receptor-binding domain of SARS-CoV-2 spike gene on 728 random samples, between 23 March 2021 and 7 September 2021, confirmed that 701 (96.3%) were Delta cases and 17 (2.3%) were other variant cases, with 10 (1.4%) samples failing lineage assignment.[6,8] Consequently, a Delta infection was proxied as any 'other' case based on the RT–qPCR-based variant screening result.

Statistical analysis. Study samples were described using frequency distributions and measures of central tendency. The odds ratio (and 95% CI, comparing odds of vaccination among cases to that among controls), was estimated using conditional logistic regression factoring the matching in the study design. This analytical approach was implemented to reduce potential bias due to variation in epidemic phase[43,48], gradual vaccination roll-out[43,48] and other confounders[9,10–12,49,50]. CIs did not factor multiplicity. Interactions were not examined. Vaccine effectiveness at different time frames and its associated 95% CI were then estimated using[43,44]:

$$\text{Vaccine effectiveness} = 1 - \text{odds ratio of vaccination among cases versus controls}$$

In each time-since-vaccination stratum, for first and second doses, we analyzed only those vaccinated in this specific time-since-vaccination stratum and those unvaccinated (our reference group). Accordingly, the sample size for cases (and controls) varied in the different time-since-vaccination analyses. As we used a test-negative study design, some individuals were tested PCR-positive or PCR-negative after their first dose and before the second dose. This allowed us to estimate effectiveness after only the first vaccination dose.

A sensitivity analysis was implemented to control for previous infection and health worker status in the conditional logistic regression, because health workers are potentially at higher risk of infection exposure and were prioritized for vaccination.

Additional analyses were performed to estimate vaccine effectiveness stratified by age (<50 versus ≥50 years of age). We also estimated vaccine effectiveness against symptomatic infection, defined as a PCR-positive swab collected based on clinical suspicion (symptoms indicative of a respiratory tract infection) and against asymptomatic infection, defined as a PCR-positive swab collected in the absence of

reported respiratory tract infection symptoms (during a survey or a random testing campaign). For comparison, vaccine effectiveness was further estimated against the Beta variant, the only other variant with an appreciable incidence concurrent with the Delta incidence[1–3].

A two-sided P value derived from logistic regression analyses was used to compare effectiveness of both vaccines with $P < 0.05$ showing statistical significance. Statistical analyses were conducted in STATA/SE version 17.0 (ref. [51]).

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The dataset of this study is the property of the Qatar Ministry of Public Health and was provided to the researchers through a restricted-access agreement that prevents sharing the dataset with a third party or publicly for preservation of confidentiality of patient data. Access to this dataset is at the discretion of the Qatar Ministry of Public Health. Access to the dataset may be granted following a direct application for data access to Her Excellency the Minister of Public Health (https://www.moph.gov.qa/english/Pages/default.aspx). Aggregate data are available within the manuscript and its supplementary information.

Code availability

Standard epidemiological analyses were conducted using standard commands in STATA/SE 17.0 (ref. [51]). The commands/code are accessible at https://github.com/IDEGWCMQ/Delta/blob/main/Code.do.

References

46. Vogels, C., Fauver, J. & Grubaugh, N. Multiplexed RT–qPCR to screen for SARS-COV-2 B.1.1.7, B.1.351, and P.1 variants of concern v3 *ProtocolsIO* https://doi.org/10.17504/protocols.io.br9vm966 (2021).
47. Saththasivam, J. et al. COVID-19 (SARS-CoV-2) outbreak monitoring using wastewater-based epidemiology in Qatar. *Sci. Total Environ.* **774**, 145608 (2021).
48. Jacoby, P. & Kelly, H. Is it necessary to adjust for calendar time in a test-negative design? Responding to: Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. Vaccine 2013;31(April (17)):2165-8. *Vaccine* **32**, 2942 (2014).
49. Pearce, N. Analysis of matched case–control studies. *BMJ* **352**, i969 (2016).
50. Rothman, K. J., Greenland, S. & Lash, T. L. *Modern Epidemiology* (Wolters Kluwer Health/Lippincott Williams & Wilkins, 2008).
51. StataCorp. Stata Statistical Software release 17 (StataCorp, 2021).

Acknowledgements

We acknowledge the many dedicated individuals at Hamad Medical Corporation, the Ministry of Public Health, the Primary Health Care Corporation, Qatar Biobank, Sidra Medicine and Weill Cornell Medicine-Qatar for their diligent efforts and contributions to make this study possible. The authors are grateful for institutional salary support from the Biomedical Research Program and the Biostatistics, Epidemiology and Biomathematics Research Core, both at Weill Cornell Medicine-Qatar, as well as for institutional salary support provided by the Ministry of Public Health and Hamad Medical Corporation. The authors are also grateful for the Qatar Genome Programme, which provided institutional support for the reagents needed for viral genome sequencing. The funders of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the article. Statements made herein are solely the responsibility of the authors.

Author contributions

P.T. and M.R.H. conducted the multiplex RT–qPCR variant screening and viral genome sequencing. H.C. co-designed the study, performed statistical analyses and co-wrote the first draft of the article. L.J.A. conceived and co-designed the study, led statistical analyses and co-wrote the first draft of the article. H.Y., F.M.B. and H.A.K. conducted viral genome sequencing. All authors contributed to data collection and acquisition, database development, discussion and interpretation of results and to writing the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

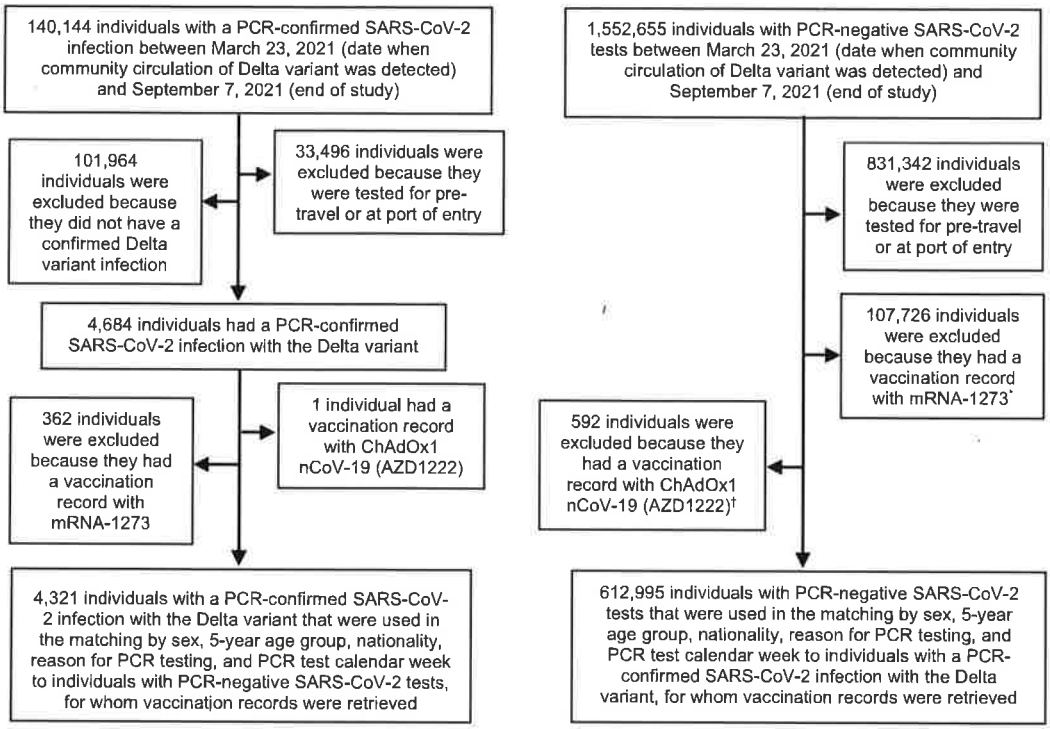
Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-021-01583-4.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-021-01583-4.

Correspondence and requests for materials should be addressed to Laith J. Abu-Raddad.

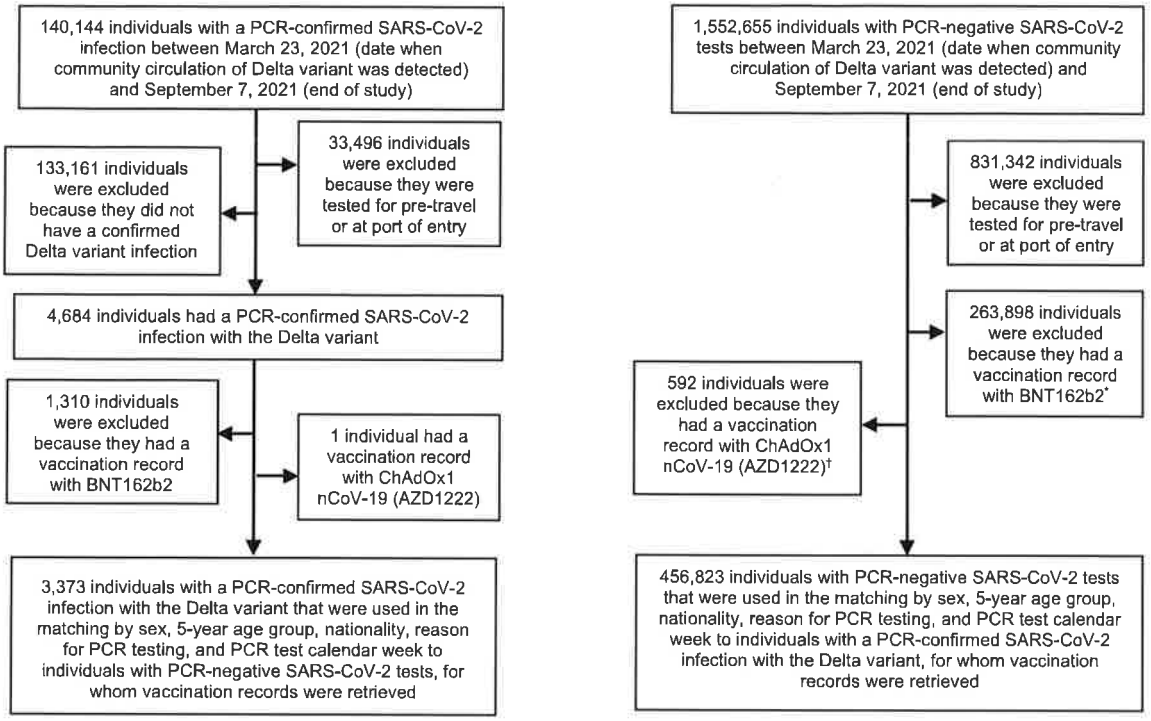
Peer review information *Nature Medicine* thanks Ben Lopman and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Alison Farrell was the primary editor on this article and managed its editorial process and peer review in collaboration with the rest of the editorial team.



*Sample includes 41 persons who had another vaccination with mRNA-1273
†Sample includes 1 person who had another vaccination with BNT162b2 and 1 person who had another vaccination with mRNA-1273

Note: In each analysis for a specific time-since-vaccination stratum, we included only those vaccinated in this specific time-since-vaccination stratum and those unvaccinated (our reference group). Thus, the number of cases (and controls) varied across time-since-vaccination analyses.

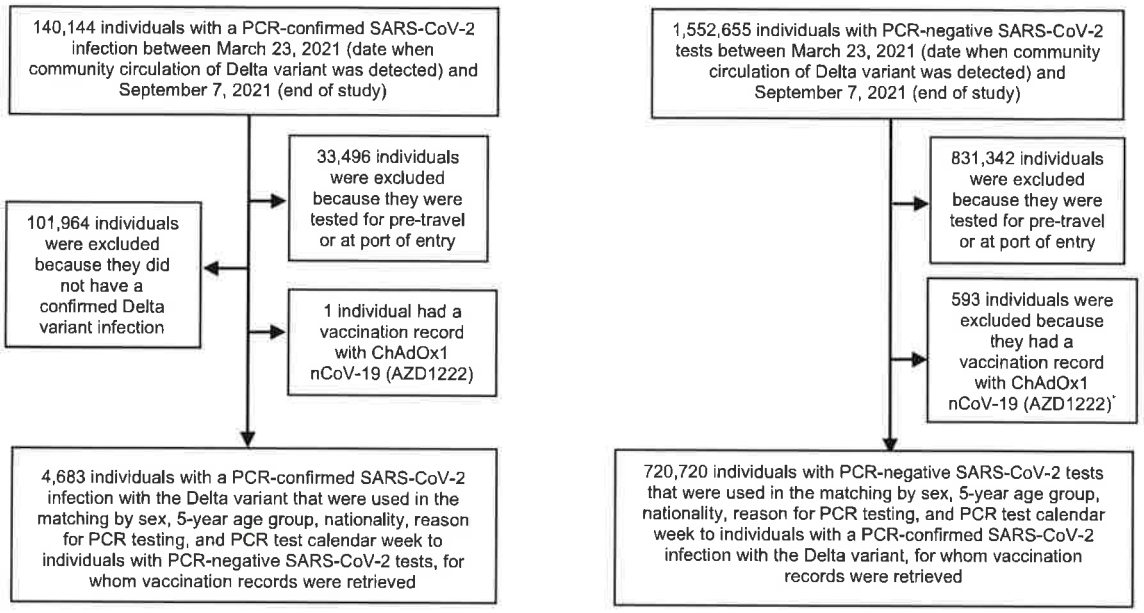
Extended Data Fig. 1 | Population selection process for investigating BNT162b2 vaccine effectiveness. Flowchart describing the population selection process for investigating BNT162b2 vaccine effectiveness against infection with the SARS-CoV-2 Delta variant.



*Sample includes 41 persons who had another vaccination with BNT162b2
†Sample includes 1 person who had another vaccination with BNT162b2 and 1 person who had another vaccination with mRNA-1273

Note: In each analysis for a specific time-since-vaccination stratum, we included only those vaccinated in this specific time-since-vaccination stratum and those unvaccinated (our reference group). Thus, the number of cases (and controls) varied across time-since-vaccination analyses.

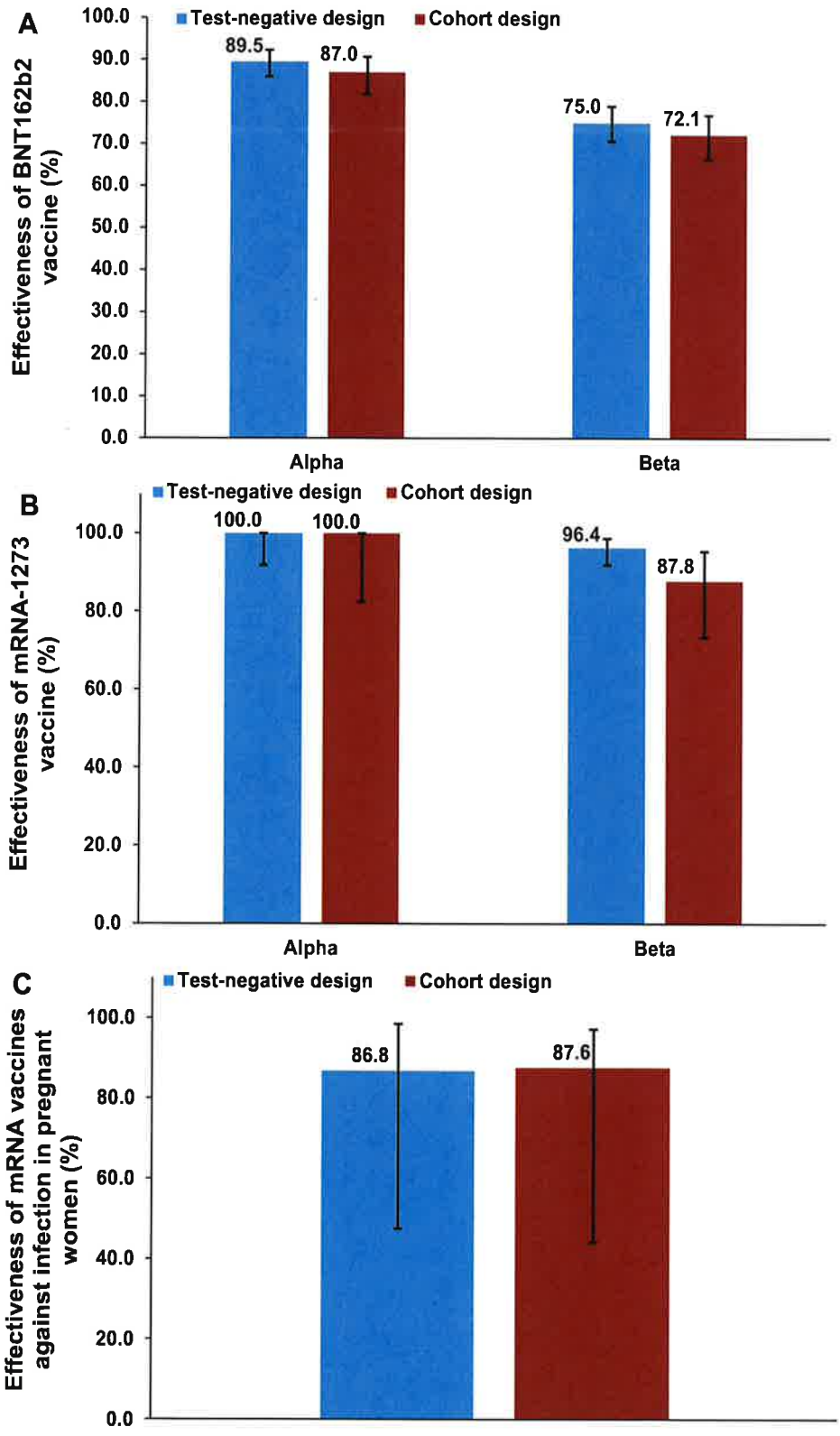
Extended Data Fig. 2 | Population selection process for investigating mRNA-1273 vaccine effectiveness. Flowchart describing the population selection process for investigating mRNA-1273 vaccine effectiveness against infection with the SARS-CoV-2 Delta variant.



*Sample includes 1 person who had another vaccination with BNT162b2 and 1 person who had another vaccination with mRNA-1273

Note: In each analysis for a specific time-since-vaccination stratum, we included only those vaccinated in this specific time-since-vaccination stratum and those unvaccinated (our reference group). Thus, the number of cases (and controls) varied across time-since-vaccination analyses.

Extended Data Fig. 3 | Population selection process for investigating the BNT162b2 and mRNA-1273 vaccines effectiveness. Flowchart describing the population selection process for investigating the BNT162b2 and mRNA-1273 vaccines effectiveness against infection with the SARS-CoV-2 Delta variant.



Extended Data Fig. 4 | See next page for caption.

Extended Data Fig. 4 | Comparison of vaccine effectiveness estimates using the test-negative case-control study design versus the cohort study design in previous assessments of vaccine effectiveness in Qatar. Effectiveness of A) BNT162b2 vaccine against each of the SARS-CoV-2 Alpha (independent samples of n = 20,195 PCR-positive cases and n = 20,195 PCR-negative controls) and Beta (independent samples of n = 23,718 PCR-positive cases and n = 23,718 PCR-negative controls) variants, B) mRNA-1273 vaccine against each of the SARS-CoV-2 Alpha (independent samples of n = 25,034 PCR-positive cases and n = 25,034 PCR-negative controls) and Beta (independent samples of n = 52,442 PCR-positive cases and n = 52,442 PCR-negative controls) variants and C) BNT162b2 or mRNA-1273 vaccines against any SARS-CoV-2 infection in pregnant women (independent samples of n = 386 PCR-positive cases and n = 834 PCR-negative controls). Data are presented as effectiveness point estimates with error bars indicating the corresponding 95% confidence intervals.

nature research

Corresponding author(s): Laith J Abu-Raddad

Last updated by author(s): October 14, 2021

Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Data were available to authors through .csv files downloaded from the CERNER database system.
Data analysis	Analyses were conducted in STATA/SE 17.0. The commands/code are accessible using URL: https://github.com/IDEGWCMQ/Delta/blob/main/Code.do

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The dataset of this study is a property of the Qatar Ministry of Public Health that was provided to the researchers through a restricted-access agreement that prevents sharing the dataset with a third party or publicly for preservation of confidentiality of patient data. Access to this dataset is at the discretion of the Qatar Ministry of Public Health. Access to the dataset can be considered through a direct application for data access to Her Excellency the Minister of Public Health (https://www.moph.gov.qa/english/Pages/default.aspx). Aggregate data are available within the manuscript and its supplementary information.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Coronavirus Disease 2019 (COVID-19) laboratory testing, vaccination, clinical infection data, and related demographic details were extracted from the integrated nationwide digital-health information platform that hosts the national, federated SARS-CoV-2 databases. These databases are complete and have captured all SARS-CoV-2-related data since epidemic onset. The data is based on a national cohort that includes every single individual tested using PCR in Qatar. Sample size varied depending on the definition used for cases [PCR-positive swab regardless of the reason for PCR testing or presence of symptoms with the Delta (B.1.617.2) variant, as well as severe, critical, or fatal COVID-19 disease due to Delta infection] and controls (PCR-negative swab). Cases and controls were matched one-to-five by sex, 5-year age group, nationality, reason for SARS-CoV-2 polymerase chain reaction (PCR) testing, and calendar week of PCR test. In each analysis for a specific time-since-vaccination stratum, we included only those vaccinated in this specific time-since-vaccination stratum and those unvaccinated (our reference group). Thus, the number of cases (and controls) varied across time-since-vaccination analyses. Given that the sample sizes were based on national cohorts with only individuals that do not fit the eligibility criteria excluded, the sample size for each sub-study can be considered sufficient. Detailed sample sizes can be found in Extended Data 1-3.
Data exclusions	Exclusion criteria were specified for cases and controls in each study group a priori. For each vaccine effectiveness study, PCR-positive individuals (cases) were excluded if they did not have a PCR confirmed infection with the Delta variant. Only the first PCR-positive test with confirmed Delta infection during the study, January 1, 2021 to September 7, 2021 , was included for each case, and only the first PCR-negative test during the study was included for each control. All PCR tests done for pre-travel or at the port of entry were excluded from analysis. Additionally, cases and controls were excluded if they received a different vaccine from that under study.
Replication	For replication, additional analyses were conducted to estimate vaccine effectiveness after 1) adjusting for prior infection and health worker status in conditional logistic regression analyses, 2) restricting the analysis to either symptomatic infection (defined as a PCR-positive test conducted because of clinical suspicion due to presence of symptoms compatible with a respiratory tract infection) or asymptomatic infection (defined as a PCR-positive test conducted with no reported presence of symptoms compatible with a respiratory tract infection, that is the PCR testing was done as part of a survey or a random testing campaign), and 3) stratifying the analysis by age (<50 versus >=50 years). All analyses confirmed/reproduced estimates of vaccine effectiveness obtained in the main analysis.
Randomization	Not applicable as this is an observational case-control study where individuals are aware of both their infection status and their vaccination status. However, to ensure control confounding, cases and controls were matched one-to-five by sex, 5-year age group, nationality, reason for SARS-CoV-2 polymerase chain reaction (PCR) testing, and calendar week of PCR test. To ensure that vaccine effectiveness estimates were not biased, conditional logistic regression analyses were applied and a sensitivity analysis was conducted by additionally adjusting for prior infection and health worker status in conditional logistic regression analyses.
Blinding	Not applicable as this is an observational study case-control study where individuals are aware of both their infection status and their vaccination status.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	The demographic characteristics of the different study populations can be found in Tables 1 and 2.
Recruitment	This is a retrospective study where COVID-19 laboratory testing, vaccination, clinical infection data, and related demographic details were extracted from the integrated nationwide digital-health information platform that hosts the national, federated SARS-CoV-2 databases. These databases are complete with no missing information for PCR testing, COVID-19 vaccinations, COVID-19 hospitalizations, and basic demographic details, and have captured all SARS-CoV-2-related data since epidemic onset. Cases and controls were defined based on analysis for these data. Cases were defined as a PCR-positive swab or presence of symptoms with the B.1.617.2 variant, as well as against severe, critical, or fatal COVID-19 disease due to Delta infection. While controls were defined as a PCR-negative swab. Classification of COVID-19 case severity (acute-care hospitalizations), criticality (ICU hospitalizations), and fatality, followed the World Health Organization guidelines, and assessments were made by trained medical personnel using individual chart reviews. All records of PCR testing for those vaccinated and unvaccinated during the study duration were examined.
Ethics oversight	The study was approved by the Hamad Medical Corporation and Weill Cornell Medicine-Qatar Institutional Review Boards with waiver of informed consent.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

EXHIBIT “D”

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study

Sara Y Tartof, Jeff M Slezak, Heidi Fischer, Vennis Hong, Bradley K Ackerson, Omesh N Ranasinghe, Timothy B Frankland, Oluwaseye A Ogun, Joann M Zamparo, Sharon Gray, Srinivas R Valluri, Kaije Pan, Frederick J Angulo, Luis Jodar, John M McLaughlin

Summary

Background Vaccine effectiveness studies have not differentiated the effect of the delta (B.1.617.2) variant and potential waning immunity in observed reductions in effectiveness against SARS-CoV-2 infections. We aimed to evaluate overall and variant-specific effectiveness of BNT162b2 (tozinameran, Pfizer–BioNTech) against SARS-CoV-2 infections and COVID-19-related hospital admissions by time since vaccination among members of a large US health-care system.

Methods In this retrospective cohort study, we analysed electronic health records of individuals (≥12 years) who were members of the health-care organisation Kaiser Permanente Southern California (CA, USA), to assess BNT162b2 vaccine effectiveness against SARS-CoV-2 infections and COVID-19-related hospital admissions for up to 6 months. Participants were required to have 1 year or more previous membership of the organisation. Outcomes comprised SARS-CoV-2 PCR-positive tests and COVID-19-related hospital admissions. Effectiveness calculations were based on hazard ratios from adjusted Cox models. This study was registered with ClinicalTrials.gov, NCT04848584.

Findings Between Dec 14, 2020, and Aug 8, 2021, of 4 920 549 individuals assessed for eligibility, we included 3 436 957 (median age 45 years [IQR 29–61]; 1 799 395 [52·4%] female and 1 637 394 [47·6%] male). For fully vaccinated individuals, effectiveness against SARS-CoV-2 infections was 73% (95% CI 72–74) and against COVID-19-related hospital admissions was 90% (89–92). Effectiveness against infections declined from 88% (95% CI 86–89) during the first month after full vaccination to 47% (43–51) after 5 months. Among sequenced infections, vaccine effectiveness against infections of the delta variant was high during the first month after full vaccination (93% [95% CI 85–97]) but declined to 53% [39–65] after 4 months. Effectiveness against other (non-delta) variants the first month after full vaccination was also high at 97% (95% CI 95–99), but waned to 67% (45–80) at 4–5 months. Vaccine effectiveness against hospital admissions for infections with the delta variant for all ages was high overall (93% [95% CI 84–96]) up to 6 months.

Interpretation Our results provide support for high effectiveness of BNT162b2 against hospital admissions up until around 6 months after being fully vaccinated, even in the face of widespread dissemination of the delta variant. Reduction in vaccine effectiveness against SARS-CoV-2 infections over time is probably primarily due to waning immunity with time rather than the delta variant escaping vaccine protection.

Funding Pfizer.

Lancet 2021; 398: 1407–16

Published Online October 4, 2021 https://doi.org/10.1016/S0140-6736(21)02183-8

See Comment page 1382

Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA, USA (S Y Tartof PhD, J M Slezak MS, H Fischer PhD, V Hong MPH, O N Ranasinghe MPH, O A Ogun MD); **Department of Pediatric Infectious Diseases, Southern California Permanente Medical Group, Harbor City, CA, USA** (B K Ackerson MD); **Kaiser Permanente Center for Integrated Health Care Research, Honolulu, HI, USA** (T B Frankland MA); **Pfizer, Collegeville, PA, USA** (J M Zamparo MPH, S Gray MS, S R Valluri PhD, K Pan MS, F J Angulo PhD, L Jodar PhD, J M McLaughlin PhD); **Department of Health Systems Science, Kaiser Permanente Bernard J Tyson School of Medicine, Pasadena, CA, USA** (S Y Tartof)

Correspondence to: Dr Sara Y Tartof, Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA 91101, USA **sara.y.tartof@kp.org**

Introduction

In a pivotal randomised controlled trial, the BNT162b2 mRNA vaccine (tozinameran, Pfizer–BioNTech) showed 95% or greater efficacy against symptomatic and severe COVID-19 disease due to SARS-CoV-2.[1] In the early months after its introduction, BNT162b2 has been shown to be highly effective in the real-world setting and to have had a large public health effect on reducing infections, hospital admissions, and deaths at a time when the alpha (B.1.1.7) variant was the predominant strain in Israel,[2–4] the USA,[5–8] Canada,[9] the UK,[10–16] and Qatar.[17,18]

The continual emergence of SARS-CoV-2 variants has raised concern that COVID-19 vaccines could have reduced effectiveness against new viral strains; however, BNT162b2 has shown robust amounts of neutralising antibodies against all variants of concern evaluated to date.[19–21] Moreover, confirmatory, real-world studies have shown high effectiveness of two doses of BNT162b2 against COVID-19, especially severe disease, caused by variants of concern alpha,[3,17] beta (B.1.351),[17,22] and delta[9,14–16,23,24] in various settings.

After global transmission of the delta variant in June and July, 2021, reports describing reduced effectiveness of BNT162b2 (and other COVID-19 vaccines) against SARS-CoV-2 infections caused by the delta variant began to surface from Israel,[25] Qatar,[23] and the USA.[26,27]

The emergence of the delta variant, however, might not be the primary driver of reported declines in effectiveness

Research in context

Evidence before this study

After global transmission of the delta (B.1.617.2) variant in June and July, 2021, reports describing reduced effectiveness of BNT162b2 (and other COVID-19 vaccines) against SARS-CoV-2 infections caused by the delta variant began to surface from Israel, Qatar, and the USA. Vaccine effectiveness studies in the setting of widespread prevalence of the delta variant, however, have not adequately differentiated the effect of the variant from potential waning immunity on observed reductions in effectiveness against SARS-CoV-2 infections. To help answer this urgent public health question, we evaluated overall and variant-specific real-world effectiveness of BNT162b2 against SARS-CoV-2 infections and COVID-19-related hospital admissions by time since vaccination among members of a large integrated health-care system in the USA up until 6 months after full vaccination.

Added value of this study

Our variant-specific analysis suggests that reductions in BNT162b2 effectiveness over time are likely to be primarily due to waning vaccine effectiveness rather than the delta variant escaping vaccine protection given that effectiveness against delta variant infections was more than 90% within 1 month of full vaccination, reductions in effectiveness in infections by time since being fully vaccinated were observed irrespective of SARS-CoV-2 variant, and effectiveness against hospital admissions due to the delta variant was very high over the entire study period.

Implications of all the available evidence

Related to other findings from Israel, the USA, and other countries, our findings underscore the importance of monitoring vaccine effectiveness over time and suggest that booster doses are likely to be needed to restore the initial high amounts of protection observed early in the vaccination programme.

against SARS-CoV-2 infections and increasing rates of breakthrough infections among individuals who are fully vaccinated.[23] In Israel, Qatar, and the USA, for example, widespread dissemination of the delta variant also coincided with the time period during which many individuals at high risk who were fully vaccinated first (eg, health-care workers, individuals who were immunocompromised, and older people) were approaching 6 months since the receipt of their second dose. Thus, waning of vaccine-induced immunity, which was observed in the pivotal randomised controlled trial before the emergence of the delta variant,[28] is an important factor to consider in the context of reported declines in effectiveness.

Vaccine effectiveness studies in the setting of high prevalence of the delta variant have not adequately differentiated the effect of the delta variant from potential waning immunity on observed reductions in effectiveness against SARS-CoV-2 infections. This distinction is essential to inform the need for booster doses and to establish what the antigenic composition of future vaccines should be. To help answer this urgent public-health question, we aimed to evaluate overall and variant-specific real-world effectiveness of BNT162b2 against SARS-CoV-2 infections and COVID-19-related hospital admissions by time since vaccination among members of a large integrated health-care system in the USA.

Methods

Study design and participants

In this retrospective cohort study, we analysed electronic health records from the Kaiser Permanente Southern California (KPSC) health-care system (CA, USA) to assess the effectiveness of the BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19-related hospital admissions. The study population consisted of all KPSC members aged 12 years and older. The start of the study period corresponded to the date the first doses of BNT162b2 were administered to KPSC members. The test-negative design described in the study protocol will be performed in future work.

KPSC is an integrated health-care organisation with more than 4·7 million members, representative of the socioeconomic and racial and ethnic diversity of the area's population.[29] KPSC electronic health records integrate clinical data including diagnostic, pharmacy, laboratory, and vaccination history information across all settings of care. Care delivered to members outside of the KPSC system is also captured, as outside providers must submit detailed claims to KPSC for reimbursement by the health plan.

Participants were required to have 1 year or more of membership (allowing a 31-day gap during previous membership to allow for potential delays in renewal) to determine comorbidities and medical history. Patients with documentation requesting removal from all research studies were excluded. The study protocol was reviewed and approved by the KPSC institutional review board, which waived requirement for informed consent (number 12816).

Procedures

COVID-19 vaccines were provided to KPSC members at no cost following emergency use authorisation. Any COVID-19 vaccines administered to members outside of the KPSC system during the study period were captured using batch queries to the California Immunization Registry. California providers are required by law to report all COVID-19 vaccine administrations to the registry every 24 h. KPSC followed the state of California guidance in rolling out COVID-19 vaccines, first making vaccines available to health-care workers in December, 2020.

Vaccines were then progressively made available to older people, individuals with underlying health conditions, and essential workers. By April, 2021, anyone aged 16 years or older was eligible to receive the vaccine. Those aged 12–15 years became eligible in May, 2021.

The primary exposure was full vaccination with BNT162b2, defined as receiving two doses of BNT162b2 with 7 days or more after the second dose. Individuals were considered partially vaccinated if they received only one dose with 14 days or more after the first dose or if they received two doses with less than 7 days after the second dose. Individuals were considered unvaccinated until receipt of their first dose of BNT162b2, or until censoring at disenrolment, death, or receipt of another COVID-19 vaccine.

Outcomes

Outcomes comprised SARS-CoV-2 infection defined as testing positive for SARS-CoV-2 via a PCR test from any sample (ie, bronchial lavage, nasopharyngeal or nasal swab, oropharyngeal swab, throat swab, saliva, sputum, or tracheal aspirate) in any clinical setting regardless of the presence of symptoms (see appendix p 1), and COVID-19-related hospital admission defined as a hospital admission with a positive SARS-CoV-2 PCR test that was conducted between 14 days before and 3 days after the date of hospital admission.

All PCR-positive SARS-CoV-2 laboratory specimens collected between March 4 and July 21, 2021, were processed for whole genome sequencing and viral lineage designation (appendix p 1). A small number of archived specimens (n=148) collected before March 4, 2021, were also included. For those with multiple positive samples, the first successfully sequenced sample was included in analyses.

Statistical analysis

Using descriptive statistics, we described the distribution of demographic and clinical characteristics of the study cohort by BNT162b2 vaccination status and history of SARS-CoV-2 infection. Among those who tested positive for SARS-CoV-2, we described study population characteristics by infecting strain (ie, delta, other variant, failed sequencing). Analyses of specimens that failed sequencing were not specified in the protocol but were added due to sufficient sample size and to better understand potential bias in the sequenced sub-sample. Median time since full vaccination was also described. Hazard ratios (HRs) with 95% CIs from an unadjusted Cox model with time-varying covariates were estimated comparing rates of SARS-CoV-2 infection and COVID-19-related hospital admissions among fully vaccinated and partially vaccinated individuals to those who were unvaccinated. BNT162b2 vaccination status was categorised as time-varying, with all participants entering the cohort as unvaccinated. Follow-up time was censored at the time of disenrolment from KPSC, death, receipt of any other newly licensed or investigational COVID-19 vaccine or prophylactic agent other than BNT162b2, or receipt of more than two doses of BNT162b2. Unexposed person-time consisted of follow-up time of those never vaccinated against COVID-19, as well as time contributed by participants before being vaccinated or censored. To assess durability, vaccine effectiveness was estimated at monthly intervals after participants were fully vaccinated with BNT162b2. Sufficient sample size allowed for monthly estimates rather than the 3-month intervals specified in the protocol. Calendar time was included in all models (crude and adjusted) as the underlying time scale to allow the baseline hazard to vary flexibly as vaccine eligibility, testing practices, non-pharmaceutical interventions, lockdown requirements, disease activity, and COVID-19 treatment changed over time. The estimated hazard for a model with time-varying covariates does not have the direct relationship with cumulative incidence that the standard Cox model does, as cumulative incidence depends on the entire history of the time-varying covariate for all patients. Thus, the vaccine effectiveness estimates from these models will not match a crude rate ratio calculated using events or person-time (appendix pp 7–8). With calendar time as the timescale, both unadjusted and adjusted models compare those who are unvaccinated on each calendar date to those who are vaccinated on that same date. The adjusted Cox model extends this, effectively comparing each vaccinated person on a given date to a person with the same covariates who is unvaccinated as of that date.

See Online for appendix

Adjusted HRs and 95% CIs were estimated by including all measured covariates in the Cox models with time-varying vaccination status. Variables included in the multivariable models were age, sex, race and ethnicity, previous PCR-positive SARS-CoV-2, previous health-care utilisation (inpatient, outpatient, emergency department, or virtual), body-mass index, acute myocardial infarction, congestive heart failure, cerebrovascular disease, peripheral vascular disease, organ transplant, diabetes, malignancy, renal disease, chronic obstructive pulmonary disease, hypertension, Charlson comorbidity index, influenza vaccination in the year before index date, pneumococcal vaccination in the 5 years before index date, and neighbourhood deprivation index[30] to capture differences in neighbourhood level socioeconomic status. The inclusion of all pre-specified covariates, as requested by the US Food and Drug Administration, differs from the backward selection method outlined in the protocol. Robust variance was computed to account for clustering introduced by including neighbourhood deprivation index in the model. For all models, vaccine effectiveness was calculated as: (1–HR) multiplied by 100%. Due to limitations in sample size, variant-specific vaccine effectiveness analyses were not stratified by age, were estimated only up to 4 months for SARS-CoV-2 infections, and were not stratified by month for COVID-19-related hospital admissions. Statistical

	BNT162b2 vaccination status				SARS-CoV-2 outcomes			
	Unvaccinated* (n=2 290 189)	One dose plus <14 days (n=27 274)	One dose plus ≥14 days or two doses plus <7 days (n=76 205)	Two doses plus ≥7 days (n=1 043 289)	Uninfected (n=3 252 916)	SARS-CoV-2 infection (n=184 041)	COVID-19 hospital admission (n=12 130)	Total (N=3 436 957)
Age, years								
12–15	104 918 (4·6%)	7164 (26·3%)	10 697 (14·0%)	78 843 (7·6%)	192 999 (5·9%)	8623 (4·7%)	45 (0·4%)	201 622 (5·9%)
16–44	1 038 609 (45·4%)	12 943 (47·5%)	35 876 (47·1%)	420 393 (40·3%)	1 417 518 (43·6%)	90 303 (49·1%)	2366 (19·5%)	1 507 821 (43·9%)
45–64	709 815 (31·0%)	5808 (21·3%)	20 709 (27·2%)	314 911 (30·2%)	990 866 (30·5%)	60 377 (32·8%)	4302 (35·5%)	1 051 243 (30·6%)
≥65	436 847 (19·1%)	1359 (5·0%)	8923 (11·7%)	229 142 (22·0%)	651 533 (20·0%)	24 738 (13·4%)	5417 (44·7%)	676 271 (19·7%)
Median	45 (29–61)	29 (15–45)	37 (21–54)	46 (29–62)	45 (29–61)	42 (29–57)	62 (49–74)	45 (29–61)
Sex								
Male	1 115 148 (48·7%)	12 694 (46·5%)	36 843 (48·3%)	472 709 (45·3%)	1 552 606 (47·7%)	84 788 (46·1%)	6608 (54·5%)	1 637 394 (47·6%)
Female	1 174 921 (51·3%)	14 579 (53·5%)	39 355 (51·6%)	570 540 (54·7%)	1 700 146 (52·3%)	99 249 (53·9%)	5522 (45·5%)	1 799 395 (52·4%)
Other or unknown	120 (<0·1%)	1 (<0·1%)	7 (<0·1%)	40 (<0·1%)	164 (<0·1%)	4 (<0·1%)	0	168 (<0·1%)
Race and ethnicity								
Hispanic	924 696 (40·4%)	14 683 (53·8%)	35 991 (47·2%)	415 217 (39·8%)	1 284 467 (39·5%)	106 120 (57·7%)	6691 (55·2%)	1 390 587 (40·5%)
Black	197 993 (8·6%)	3465 (12·7%)	6350 (8·3%)	68 391 (6·6%)	262 682 (8·1%)	13 517 (7·3%)	1201 (9·9%)	276 199 (8·0%)
White	759 438 (33·2%)	5563 (20·4%)	19 422 (25·5%)	324 033 (31·1%)	1 066 792 (32·8%)	41 664 (22·6%)	2752 (22·7%)	1 108 456 (32·3%)
Asian or Pacific Islander	226 149 (9·9%)	1734 (6·4%)	8355 (11·0%)	162 948 (15·6%)	385 995 (11·9%)	13 191 (7·2%)	1268 (10·5%)	399 186 (11·6%)
Other	52 505 (2·3%)	602 (2·2%)	1906 (2·5%)	25 431 (2·4%)	76 892 (2·4%)	3552 (1·9%)	117 (1·0%)	80 444 (2·3%)
Unknown	129 408 (5·7%)	1227 (4·5%)	4181 (5·5%)	47 269 (4·5%)	176 088 (5·4%)	5997 (3·3%)	101 (0·8%)	182 085 (5·3%)
Body-mass index, kg/m²								
<18·5	62 618 (2·7%)	2127 (7·8%)	3953 (5·2%)	38 136 (3·7%)	103 360 (3·2%)	3474 (1·9%)	132 (1·1%)	106 834 (3·1%)
18·5–24·9	607 399 (26·5%)	8366 (30·7%)	22 675 (29·8%)	307 811 (29·5%)	907 630 (27·9%)	38 621 (21%)	1750 (14·4%)	946 251 (27·5%)
25·0–29·9	687 057 (30·0%)	7167 (26·3%)	21 499 (28·2%)	318 164 (30·5%)	978 156 (30·1%)	55 731 (30·3%)	3436 (28·3%)	1 033 887 (30·1%)
30·0–34·9	439 367 (19·2%)	4634 (17·0%)	13 359 (17·5%)	191 486 (18·4%)	605 962 (18·6%)	42 884 (23·3%)	3101 (25·6%)	648 846 (18·9%)
35·0–39·9	203 208 (8·9%)	2272 (8·3%)	6232 (8·2%)	86 551 (8·3%)	276 414 (8·5%)	21 849 (11·9%)	1803 (14·9%)	298 263 (8·7%)
≥40·0	137 456 (6·0%)	1497 (5·5%)	3854 (5·1%)	54 839 (5·3%)	181 492 (5·6%)	16 154 (8·8%)	1691 (13·9%)	197 646 (5·8%)
Unknown	153 084 (6·7%)	1211 (4·4%)	4633 (6·1%)	46 302 (4·4%)	199 902 (6·1%)	5328 (2·9%)	217 (1·8%)	205 230 (6·0%)
Comorbidities								
Congestive heart failure	43 875 (1·9%)	218 (0·8%)	995 (1·3%)	20 120 (1·9%)	61 451 (1·9%)	3757 (2·0%)	1357 (11·2%)	65 208 (1·9%)
Coronary artery disease	26 661 (1·2%)	120 (0·4%)	568 (0·7%)	12 379 (1·2%)	37 662 (1·2%)	2066 (1·1%)	613 (5·1%)	39 728 (1·2%)
Peripheral vascular disease	179 305 (7·8%)	539 (2·0%)	3538 (4·6%)	96 772 (9·3%)	268 007 (8·2%)	12 147 (6·6%)	3316 (27·3%)	280 154 (8·2%)
Cerebrovascular disease	34 513 (1·5%)	147 (0·5%)	846 (1·1%)	16 661 (1·6%)	49 626 (1·5%)	2541 (1·4%)	730 (6·0%)	52 167 (1·5%)
Organ transplant	3111 (0·1%)	18 (0·1%)	63 (0·1%)	1638 (0·2%)	4408 (0·1%)	422 (0·2%)	160 (1·3%)	4830 (0·1%)
Diabetes with unknown glycated haemoglobin	25 942 (1·1%)	195 (0·7%)	725 (1·0%)	9648 (0·9%)	34 427 (1·1%)	2083 (1·1%)	329 (2·7%)	36 510 (1·1%)
Diabetes with glycated haemoglobin <7·5%	157 336 (6·9%)	814 (3·0%)	3693 (4·8%)	81 669 (7·8%)	229 185 (7·0%)	14 327 (7·8%)	2566 (21·2%)	243 512 (7·1%)
Diabetes with glycated haemoglobin ≥7·5%	86 318 (3·8%)	644 (2·4%)	2254 (3·0%)	38 732 (3·7%)	117 845 (3·6%)	10 103 (5·5%)	1966 (16·2%)	127 948 (3·7%)
Chronic obstructive pulmonary disease	204 050 (8·9%)	2338 (8·6%)	6298 (8·3%)	101 486 (9·7%)	295 394 (9·1%)	18 778 (10·2%)	2209 (18·2%)	314 172 (9·1%)
Renal disease	106 351 (4·6%)	420 (1·5%)	2137 (2·8%)	53 200 (5·1%)	154 006 (4·7%)	8102 (4·4%)	2579 (21·3%)	162 108 (4·7%)
Malignancy	52 934 (2·3%)	288 (1·1%)	1194 (1·6%)	27 092 (2·6%)	77 528 (2·4%)	3980 (2·2%)	792 (6·5%)	81 508 (2·4%)
Hypertension	465 109 (20·3%)	2637 (9·7%)	10 930 (14·3%)	231 754 (22·2%)	673 564 (20·7%)	36 866 (20·0%)	6227 (51·3%)	710 430 (20·7%)
Charlson comorbidity index								
0	1 685 257 (73·6%)	22 609 (82·9%)	60 171 (79%)	743 248 (71·2%)	2 379 993 (73·2%)	131 292 (71·3%)	4460 (36·8%)	2 511 285 (73·1%)
1	303 977 (13·3%)	3213 (11·8%)	9266 (12·2%)	149 201 (14·3%)	437 558 (13·5%)	28 099 (15·3%)	2171 (17·9%)	465 657 (13·5%)
2	126 645 (5·5%)	713 (2·6%)	3047 (4·0%)	62 764 (6·0%)	182 559 (5·6%)	10 610 (5·8%)	1499 (12·4%)	193 169 (5·6%)
3	57 517 (2·5%)	254 (0·9%)	1240 (1·6%)	30 419 (2·9%)	85 034 (2·6%)	4396 (2·4%)	885 (7·3%)	89 430 (2·6%)
≥4	116 793 (5·1%)	485 (1·8%)	2481 (3·3%)	57 657 (5·5%)	167 772 (5·2%)	9644 (5·2%)	3115 (25·7%)	177 416 (5·2%)

(Table continues on next page)

	BNT162b2 vaccination status				SARS-CoV-2 outcomes			
	Unvaccinated* (n=2 290 189)	One dose plus <14 days (n=27 274)	One dose plus ≥14 days or two doses plus <7 days (n=76 205)	Two doses plus ≥7 days (n=1 043 289)	Uninfected (n=3 252 916)	SARS-CoV-2 infection (n=184 041)	COVID-19 hospital admission (n=12 130)	Total (N=3 436 957)
(Continued from previous page)								
Previous positive SARS-CoV-2 PCR test								
1	47 993 (2·1%)	668 (2·4%)	1681 (2·2%)	18 356 (1·8%)	68 258 (2·1%)	440 (0·2%)	71 (0·6%)	68 698 (2·0%)
≥2	3827 (0·2%)	53 (0·2%)	116 (0·2%)	1590 (0·2%)	5537 (0·2%)	49 (<0·1%)	6 (<0·1%)	5586 (0·2%)
Previous positive SARS-CoV-2 serology								
1	2466 (0·1%)	41 (0·2%)	56 (0·1%)	1231 (0·1%)	3764 (0·1%)	30 (<0·1%)	4 (<0·1%)	3794 (0·1%)
≥2	69 (<0·1%)	0	0	45 (<0·1%)	113	1 (<0·1%)	0	114 (<0·1%)

Data are n (%) or median (IQR). Characteristics of Kaiser Permanente Southern California members (n=3 436 957), by BNT162b2 vaccination status (as of Aug 8, 2021), and by SARS-CoV-2 outcomes (Dec 14, 2020, to Aug 8, 2021). *Unvaccinated group includes those not vaccinated with BNT162b2 as of Aug 8, 2021, and those vaccinated with other COVID-19 vaccines. Those vaccinated with COVID-19 vaccines other than BNT162b2 are censored in the vaccine effectiveness modelling at vaccination date.

Table: **Baseline characteristics**

comparisons of vaccine effectiveness by time since vaccination were made using Wald χ^2 tests for contrasts within Cox models. Vaccine effectiveness for delta and other variants could not be directly compared in the same regression model. The difference between delta variant vaccine effectiveness versus other variant vaccine effectiveness was compared using independent Z tests on the log HRs, which are conservative as the vaccine effectiveness for COVID-19 variants is positively correlated in the same population. All analyses were performed using SAS Enterprise Guide statistical software, version 7.1. This study was registered with ClinicalTrials.gov, NCT04848584.

Role of the funding source

The funder of the study approved the study design, and participated in data interpretation and writing of the report.

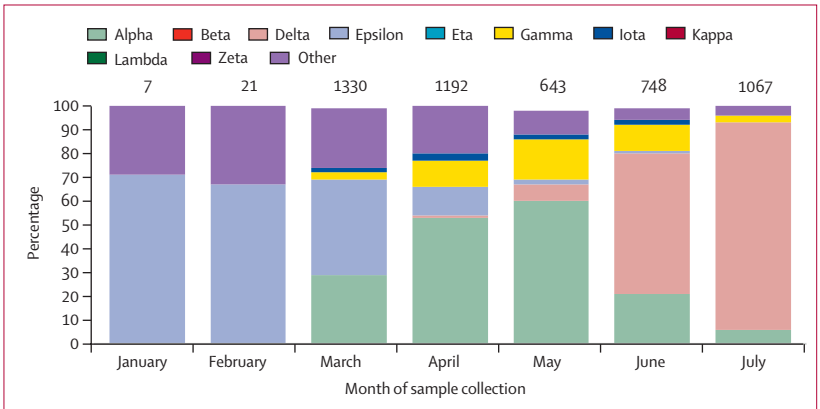
Results

The study period ran from Dec 14, 2020, to Aug 8, 2021. As of Dec 14, 2020, of 4 920 549 individuals assessed for eligibility there were 3 436 957 members of KPSC who fulfilled the inclusion criteria of age 12 years or older with membership of 1 year or longer who were included in the study cohort. Median age was 45 years (IQR 29–61), 1 799 395 [52·4%] participants were female and 1 637 394 [47·6%] were male. 1 390 587 (40·5%) participants were Hispanic, 1 108 456 (32·3%) were white, 399 186 (11·6%) were Asian or a Pacific Islander, and 276 199 (8·0%) were Black. In the year before the study start date, 74 284 (2·2%) of 3 436 957 participants had one or more positive SARS-CoV-2 PCR tests, and 543 628 (15·8%) had one or more negative PCR tests (table).

During the study period, 184 041 (5·4%) of 3 436 957 participants were infected with SARS-CoV-2, among whom 12 130 (6·6%) were admitted to hospital. A higher proportion of the individuals infected with SARS-CoV-2 were younger (median age 42 years *vs* 45 years), Hispanic (57·7% *vs* 39·5%), and obese (>30 kg/m²; 43·9% *vs* 32·7%) than those who were not infected. Among those infected with SARS-CoV-2, a higher proportion of those who were admitted to hospital for COVID-19 were older, male, had comorbidities, and had greater previous health-care utilisation than those not admitted to hospital (table, appendix p 2).

Of 9147 specimens sent for whole genome sequencing, 236 were excluded from analyses (42 were the second sequenced samples from the same individual; 194 were the second failed samples from the same individual). Therefore, 8911 specimens were included for analyses and 5008 (56·2%) of 8911 had a sequence determined (appendix pp 3–4). We systematically submitted all PCR-positive specimens for sequencing starting March 4, 2021; however, the overall count of submitted specimens (n=8911) was 4·8% of all positive SARS-CoV-2 cases in the study (n=184 041). Specimens for which a sequence could not be determined were more likely to have high cycle threshold (Ct) values (appendix p 5). The median Ct values of sequenced N, ORF1ab, and S genes were 23·0 cycles for N, 23·3 cycles for ORF1ab, and 23·4 cycles for S; the median Ct values for specimens for which a sequence could not be determined were 30·7 cycles for N, 32·4 cycles for ORF1ab, and 28·8 cycles for S. Over the study period, 1422 (28·4%) of 5008 specimens for which a sequence could be determined were the delta variant. The proportion of sequenced specimens that were delta increased from 0·6% (seven of 1192) in April, 2021, to 86·5% (923 of 1067) in July, 2021 (figure 1). The distribution of comorbidities and previous health-care utilisation was generally consistent between the variant groups in our cohort (appendix pp 3–4).

By Aug 8, 2021, 1 146 768 (33·4%) of 3 436 957 cohort members had received one or more doses of BNT162b2 (1 010 516 received ≥1 dose of mRNA-1273 [Moderna],



	January	February	March	April	May	June	July
Alpha	0	0	383 (28·8%)	632 (53·0%)	389 (60·5%)	158 (21·1%)	60 (5·6%)
Beta	0	0	2 (0·2%)	5 (0·4%)	2 (0·3%)	1 (0·1%)	1 (0·1%)
Delta	0	0	0	7 (0·6%)	47 (7·3%)	445 (59·5%)	923 (86·5%)
Epsilon	5 (71·4%)	14 (66·7%)	532 (40·0%)	139 (11·7%)	11 (1·7%)	4 (0·5%)	0
Eta	0	0	2 (0·2%)	2 (0·2%)	1 (0·2%)	1 (0·1%)	0
Gamma	0	0	40 (3·0%)	131 (11·0%)	107 (16·6%)	82 (11·0%)	33 (3·1%)
Iota	0	0	25 (1·9%)	33 (2·8%)	16 (2·5%)	17 (2·3%)	1 (0·1%)
Kappa	0	0	1 (0·1%)	1 (0·1%)	0	0	0
Lambda	0	0	1 (0·1%)	4 (0·3%)	3 (0·5%)	0	1 (0·1%)
Zeta	0	0	6 (0·5%)	0	0	0	0
Other	2 (28·6%)	7 (33·3%)	338 (25·4%)	238 (20·0%)	67 (10·4%)	40 (5·3%)	48 (4·5%)
All	7 (100%)	21 (100%)	1330 (100%)	1192 (100%)	643 (100%)	748 (100%)	1067 (100%)
Failed sequence	9/16 (56·3%)	13/34 (38·2%)	993/2323 (42·7%)	882/2074 (42·5%)	648/1291 (50·2%)	720/1468 (49·0%)	638/1705 (37·4%)

Figure 1: **Distribution of variants from January to July, 2021**
n=5008. Failed sequence counts are not included.

109 911 Ad26.COV2.S [Janssen], 2972 other COVID-19 vaccines or mixed regimens, and 1 166 790 remained unvaccinated). Of these, 1 043 289 (91·0%) of 1 146 768 patients were fully vaccinated, and 76 205 (6·6%) of 1 146 768 were partially vaccinated with BNT162b2 (table). Mean time since being fully vaccinated (7 days after second dose) was 3·4 months (SD 1·8); 752 562 (72·1%) of 1 043 289 of the fully vaccinated individuals were fully vaccinated at least 3 months before.

Over the entire study period, fully vaccinated individuals had an adjusted vaccine effectiveness of 73% (95% CI 72–74) against SARS-CoV-2 infections and 90% (89–92) against COVID-19-related hospital admissions (appendix pp 6–7). Stratified by age group, the vaccine effectiveness against infection of those who were fully vaccinated was 91% (95% CI 88–93) for those aged 12–15 years and 61% (57–65) for those aged 65 years and older (appendix p 6). The age stratified vaccine effectiveness against hospital admissions was 92% (95% CI 88–95) for those aged 16–44 years, and 86% (82–88) for those aged 65 years and older (appendix p 6).

Vaccine effectiveness against infection for the fully vaccinated decreased with increasing time since vaccination, declining from 88% (95% CI 86–89) during the first month after full vaccination to 47% (43–51) after 5 months (≥157 days after second dose, p<0·0001; figure 2A; appendix p 9). Individuals aged 65 years and older had a vaccine effectiveness of 80% (95% CI 73–85) within 1 month after being fully vaccinated, decreasing to 43% (30–54; p<0·0001) at 5 months after full vaccination (figure 2A; appendix p 9). Among fully vaccinated individuals of all ages, overall adjusted vaccine effectiveness estimates for COVID-19 hospital admissions were 87% (95% CI 82–91) within 1 month after being fully vaccinated, and 88% (82–92) at 5 months after full vaccination, showing no significant waning (p=0·80; figure 2B; appendix pp 9–10).

Overall vaccine effectiveness against infection with the delta variant for the fully vaccinated was 75% (95% CI 71–78), while overall vaccine effectiveness for other variants was 91% (88–92; appendix pp 9–10). Estimates against both delta and other variants were high within 1 month after full vaccination (vaccine effectiveness against delta 93% [95% CI 85–97] *vs* other variants 97% [95–99]; p=0·29). At 4 months after full vaccination, vaccine effectiveness against delta infections declined to 53% (95% CI 39–65) and vaccine effectiveness against other variants declined to 67% (45–80; p=0·25). The difference in rate of decline in vaccine effectiveness between delta and other variants was not significant (p=0·30). For specimens in which a sequence could not be determined, adjusted vaccine effectiveness after full vaccination declined from 84% [95% CI 78–88]) at less than 1 month to 47% (30–59) after 4 months (figure 3; appendix pp 10–11). Among the fully vaccinated, vaccine effectiveness against hospital admissions was 93% (95% CI 84–96) for delta and 95% (90–98) for other variants. Effectiveness against hospital admissions was lower among specimens that failed sequencing (vaccine effectiveness 77% [95% CI 67–85]; appendix pp 10–11).

Discussion

This retrospective cohort study conducted in a large integrated health-care system showed that individuals who were fully vaccinated with BNT162b2 had 73% (95% CI 72–74) overall effectiveness against SARS-CoV-2 infections and 90% (89–92) effectiveness against COVID-19-related hospital admissions after a mean time since being fully vaccinated of 3·4 months. Effectiveness against SARS-CoV-2 infections waned during the 6 months of this study. Effectiveness against hospital admissions in all age groups did not wane over the duration of the study. These findings are consistent with preliminary reports from the Israel Ministry of Health and US Centers for Disease Control and Prevention showing reductions in effectiveness of BNT162b2 against infections 5 months or longer after being fully vaccinated, but consistently high estimates against COVID-19-related hospital admissions and severe disease up until July, 2021.[24–27] The most recent report from August, 2021, from Israel, however, suggests that some reduction in effectiveness against hospital admissions has been

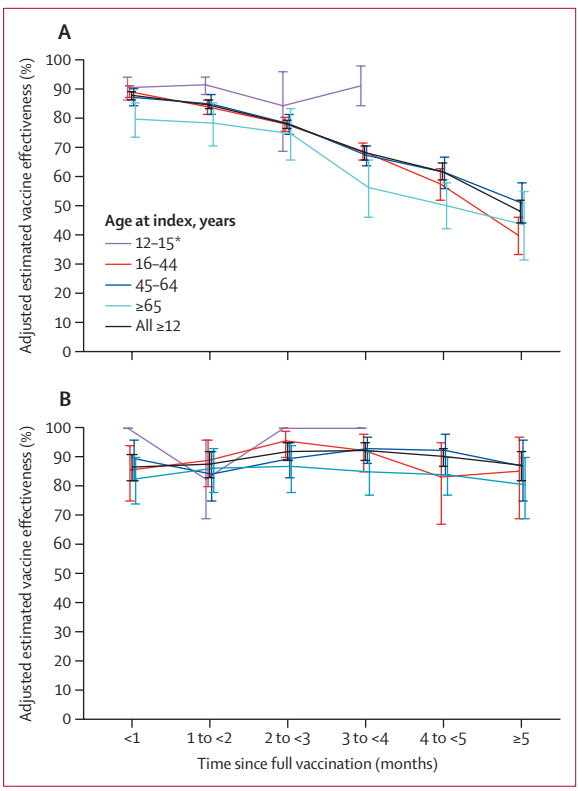


Figure 2: **Adjusted estimated vaccine effectiveness against SARS-CoV-2 infection and hospital admissions**
Vaccine effectiveness (95% CI) against SARS-CoV-2 infection (A) and COVID-19 hospital admission (B) by age group and number of months since being fully vaccinated with BNT162b2. *BNT162b2 authorised for those aged 12–15 years in May, 2021, limiting follow-up time for this age group.

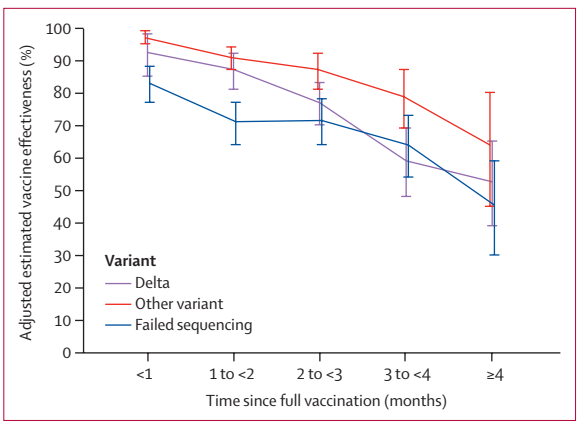


Figure 3: **Adjusted estimated vaccine effectiveness against SARS-CoV-2 infection by variant**
Data are shown for number of months since being fully vaccinated with BNT162b2 with 95% CIs.

observed among older people (≥65 years) roughly 6 months after receiving the second dose of BNT162b2.[31] Thus, long-term effectiveness data against severe outcomes should be continuously monitored in our study population and globally.

Effectiveness of BNT162b2 against infections caused by the delta variant, which became the predominant strain in KPSC by July, 2021, was 75% (95% CI 71–78) over the study period. Effectiveness against delta infections at 1 month after being fully vaccinated was high at 93% (85–97) but fell to 53% (39–65) up to 5 months after being fully vaccinated. Effectiveness against other (non-delta) variants within 1 month of being fully vaccinated was also high at 97% (95–99) and also waned, to 67% (45–80) up to 5 months after being fully vaccinated. Effectiveness against delta-related hospital admissions over the entire study period was high, at 93% (84–96) and was similar to effectiveness against hospital admissions for other (non-delta) variants. These findings are consistent with reports from the USA[24,26,27] and Qatar.[23] Our variant-specific analyses suggest that reductions in vaccine effectiveness over time are likely to be primarily due to waning vaccine effectiveness rather than the delta variant escaping vaccine protection given that vaccine effectiveness against delta infections was more than 90% soon after vaccination, vaccine effectiveness against delta and other variants for hospital admissions was very high over the entire study period, and reductions in vaccine effectiveness against infection by time since being fully vaccinated were observed irrespective of the variant. We did not observe a difference in waning between variant types; however, the number of events at 3–4 months was low for analyses by variant. As such, analyses with longer follow-up to measure the rate of waning for the delta versus other variants are warranted. Related to our findings, studies from Canada[9] and the UK[14,15] have shown high effectiveness of BNT162b2 against symptomatic COVID-19 caused by the delta variant in a vaccine schedule that separates the first and second doses by 2–3 months instead of 3 weeks. This longer interval between doses could lead to higher immunological responses;[32,33] however, duration of follow-up in these studies (<3 months)[9,14,15] was insufficient to establish the effects of waning. Moreover, given the lower effectiveness after only one dose observed in our study and in other reports of one-dose effectiveness against variants of concern like beta or delta,[14,17,23] delaying the second dose is not without risk.

Our results reiterate in a real-world US setting that vaccination with BNT162b2 remains an essential tool for preventing COVID-19, especially COVID-19-associated hospital admissions, caused by all current variants of concern. Along with other emerging evidence,[9,14–16,23] our results suggest that despite early effectiveness of BNT162b2 against delta and other variants of concern, effectiveness against infection erodes steadily in the months after receipt of the second dose. Waning effectiveness and an increased number of infections 6–12 months after the second dose—along with the potential need for booster doses—was expected given that lower neutralising antibody titres during this time period have been observed in immunogenicity studies.[34–36]

Waning has been observed for both mRNA-based (Pfizer–BioNTech and Moderna) COVID-19 vaccines,[26,27] and is consistent with studies of other coronaviruses.[37] Reassuringly, early phase 1 data show that a third booster dose of the current BNT162b2 vaccine given 6 months after the second dose elicited neutralising antibody titres against the original SARS-CoV-2 wild-type strain, beta, and delta, which were several times higher than after two primary doses.[34,35] Modelling studies have predicted that these increases in neutralising antibody titres will restore high amounts of vaccine effectiveness.[36] Moreover, early unpublished data from an Israeli health maintenance organisation (Maccabi Health Services) suggest that a third booster dose is highly effective in a setting in which the delta variant accounts for nearly all cases.[38,39] These findings suggest that boosting with the current BNT162b2 vaccine rather than a delta-specific construct might be effective. Considerations of booster doses should also account for COVID-19 supply, as priority populations in some countries or subnational settings have not yet received a primary vaccination series.[40]

Our study has potential limitations. We were unable to establish causal relationships between vaccination and COVID-19 outcomes in this observational study. Further, it is difficult to achieve a perfect balance of testing patterns and other characteristics between vaccinated and unvaccinated patients in this real-world observational study design. We attempt to address this issue by adjusting for proxies for general health-care seeking behaviour (visits across health-care settings before baseline), prior vaccination behaviour, demographics, comorbidities, and neighbourhood-level socioeconomic status. However, we did not have data for adherence to masking guidelines, social interactions, and occupation, which are likely to also affect likelihood of testing for SARS-CoV-2 either when experiencing symptoms or routinely as a preventive measure. KPSC maintained several drive-through testing clinics, did not have resource limitations on COVID-19 testing, and provided free testing to all members during the study period. We compared vaccinated and unvaccinated individuals at the same point in time, which balances the availability of testing, infection rates, and other secular inputs that might affect testing behaviours between vaccinated and unvaccinated patients to the extent possible in observational research. Effectiveness was lowest for PCR-positive specimens for which a sequence could not be determined. These specimens had higher Ct values than other PCR-positive specimens, which probably corresponded to milder or asymptomatic infections. Thus, our vaccine effectiveness estimates against SARS-CoV-2 infections and hospital admissions could be muted by mild or asymptomatic infections and are not directly comparable to estimates of effectiveness against symptomatic disease. Sequencing was more likely to fail in samples from vaccinated individuals due to lower viral loads, which could lead to an overestimate of variant-specific effectiveness. Finally, although the KPSC electronic health records might miss some vaccinations administered outside of the health system, our data capture through the California Immunization Registry minimised this effect.

Our results show high effectiveness of BNT162b2 against hospital admissions up until 6 months after being fully vaccinated in a large, diverse cohort under real-world vaccination conditions, even in the face of widespread dissemination of the delta variant. These findings underscore the importance of continuing to prioritise improving COVID-19 vaccination rates, including in hard-to-reach communities. Effectiveness against infections was high soon after full vaccination, both for delta and other variants of concern, but waned over the study period. Although waning effectiveness against hospital admissions was not observed in our study population to date, this possibility should be carefully monitored.[31] Our findings underscore the importance of monitoring vaccine effectiveness over time and suggest that booster doses might eventually be needed to restore the high levels of protection observed early in the vaccination programme. These factors are especially important to help control heightened transmission of the delta variant as we enter the upcoming autumn and winter viral respiratory season.

Contributors

SYT, FJA, LJ, and JMM conceived this study. JMS, HF, VH, and ONR conducted the analysis. SYT, FJA, JMS, HF, and JMM wrote the first draft of the protocol. SYT and JMM wrote the first draft of the manuscript. All authors contributed to the study design, drafting the protocol, and edited the manuscript for important intellectual content. All authors gave final approval of the version to be published. All authors had full access to all the data and had final responsibility for the decision to submit for publication.

Declaration of interests

JMZ, SG, KP, FJA, LJ, SRV, and JMM are employees of and hold stock and stock options in Pfizer. TBF holds shares of Pfizer stock. SYT, JMS, HF, VH, BKA, ONR, TBF, and OAO received research support from Pfizer during the conduct of this study that was paid directly to KPSC. For work unrelated to this project, SYT received research funding from Gilead, GlaxoSmithKline, and Genentech; BKA received research funding from GlaxoSmithKline, Novavax, Dynavax, Genentech, Novartis, Seqirus, and Moderna; JMS received research funding from Novavax, Dynavax, and ALK; and HF received research funding from Genentech. All other authors declare no competing interests.

Data sharing

Individual-level testing and clinical outcomes data reported in this study are not publicly shared. Individuals wishing to access disaggregated data, including data reported in this study, should submit requests for access to the corresponding author (sara.y.tartof@kp.org). De-identified data (including, as applicable, participant data and relevant data dictionaries) will be shared upon approval of analysis proposals with signed data-access agreements in place.

Acknowledgments

We acknowledge the following KPSC staff: Harpreet S Takhar, Michael Aragones, Soon Kyu Choi, Jennifer Charter, Lee Childs, Joy Gelfond, Radha Bathala, Raul Calderon, Kourtney Kottman, Ana Acevedo, Elmer Ayala, and Jonathan Arguello for their technical and laboratory support processing SARS-CoV-2 specimens. We thank KPSC members for their contributions through our electronic health record systems. Finally, we thank Helix OpCo for whole genome sequencing of

SARS-CoV-2 and acknowledge Uğur Şahin and Özlem Türeci from BioNTech, the holders of the emergency use authorisation for BNT162b2 in Israel; BNT162b2 is produced using BioNTech proprietary mRNA technology and was developed by BioNTech and Pfizer. The study design was developed by KPSC and approved by KPSC and Pfizer. KPSC collected and analysed the data; Pfizer did not participate in the collection or analysis of data. KPSC and Pfizer participated in the interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

References

1 Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020; **383:** 2603–15.

2 Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med* 2021; **384:** 1412–23.

3 Haas EJ, Angulo FJ, McLaughlin JM, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. *Lancet* 2021; **397:** 1819–29.

4 Haas EJ, McLaughlin JM, Khan F, et al. Infections, hospitalizations, and deaths averted via direct effects of the Pfizer–BioNTech BNT162b2 mRNA COVID-19 vaccine in a nationwide vaccination campaign, Israel. *Lancet Infect Dis* 2021; published online Sept 22. https://doi.org/10.1016/S1473-3099(21)00566-1.

5 Britton A, Jacobs Slifka KM, Edens C, et al. Effectiveness of the Pfizer–BioNTech COVID-19 vaccine among residents of two skilled nursing facilities experiencing COVID-19 outbreaks—Connecticut, December 2020–February 2021. *MMWR Morb Mortal Wkly Rep* 2021; **70:** 396–401.

6 Thompson MG, Burgess JL, Naleway AL, et al. Interim estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines in preventing SARS-CoV-2 infection among health care personnel, first responders, and other essential and frontline workers—eight U.S. locations, December 2020–March 2021. *MMWR Morb Mortal Wkly Rep* 2021; **70:** 495–500.

7 Pilishvili T, Fleming-Dutra KE, Farrar JL, et al. Interim estimates of vaccine effectiveness of Pfizer–BioNTech and Moderna COVID-19 vaccines among health care personnel—33 US sites, January-March 2021. *MMWR Morb Mortal Wkly Rep* 2021; **70:** 753–58.

8 Tenforde MW, Olson SM, Self WH, et al. Effectiveness of Pfizer–BioNTech and Moderna vaccines against COVID-19 among hospitalized adults aged ≥65 years—United States, January–March 2021. *MMWR Morb Mortal Wkly Rep* 2021; **70:** 674–79.

9 Nasreen S, Chung H, He S, et al. Effectiveness of COVID-19 vaccines against variants of concern in Ontario, Canada. *medRxiv* 2021; published online July 3. https://doi.org/10.1101/2021.06.28.21259420 (preprint).

10 Hall VJ, Foulkes S, Saei A, et al. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. *Lancet* 2021; **397:** 1725–35.

11 Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) variant. *N Engl J Med* 2021; **385:** 585–94.

12 Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the Pfizer–BioNTech and Oxford–AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *BMJ* 2021; **373:** n1088.

13 Vasileiou E, Simpson CR, Shi T, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. *Lancet* 2021; **397:** 1646–57.

14 Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (delta) variant. *N Engl J Med* 2021; **385:** 585–94.

15 Sheikh A, McMenamin J, Taylor B, Robertson C. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. *Lancet* 2021; **397:** 2461–62.

16 Stowe J, Andrews N, Gower C, et al. Effectiveness of COVID-19 vaccines against hospital admission with the Delta (B.1.617.2) variant. Public Health England. 2021 https://media.tghn.org/articles/Effectiveness_of_COVID-19_vaccines_against_hospital_admission_with_the_Delta_B._G6gnnqJ.pdf (accessed Aug 15, 2021).

17 Abu-Raddad LJ, Chemaitelly H, Butt AA. Effectiveness of the BNT162b2 Covid-19 vaccine against the B.1.1.7 and B.1.351 variants. *N Engl J Med* 2021; **385:** 187–89.

18 Chemaitelly H, Yassine HM, Benslimane FM, et al. mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. *Nat Med* 2021; **27:** 1614–21.

19 Liu J, Liu Y, Xia H, et al. BNT162b2-elicited neutralization of B.1.617 and other SARS-CoV-2 variants. *Nature* 2021; **596:** 273–75.

20 Liu Y, Liu J, Xia H, et al. Neutralizing activity of BNT162b2-elicited serum. *N Engl J Med* 2021; **384:** 1466–68.

21 Liu Y, Liu J, Xia H, et al. BNT162b2-elicited neutralization against new SARS-CoV-2 spike variants. *N Engl J Med* 2021; **385:** 472–74.

22 Singer SR, Angulo FJ, Swerdlow D, et al. Effectiveness of BNT162b2 mRNA COVID-19 vaccine against SARS-CoV-2 variant beta (B.1.351) among persons identified through contact tracing in Israel. SSRN 2021; published online Aug 13. http://dx.doi.org/10.2139/ssrn.3904701 (preprint).

23 Tang P, Hasan MR, Chemaitelly H, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the Delta (B.1.617.2) variant in Qatar. *medRxiv* 2021; puyblished online Aug 11. https://doi.org/10.1101/2021.08.11.21261885 (preprint).

24 Tenforde MW, Self WH, Naioti EA, et al. Sustained effectiveness of Pfizer–BioNTech and Moderna vaccines against COVID-19 associated hospitalizations among adults - United States, March–July 2021. *MMWR Morb Mortal Wkly Rep* 2021; **70:** 1156–62.

25 Committee IMoHC-VCE. Vaccine effectiveness data on a cohort of persons vaccinated by 31-Jan-2021 with two doses. Presented at Israel Ministry of Health COVID-19 Vaccines Campaign Effectiveness Committee Meeting on 20-Jul-2021. 2021. https://www.gov.il/BlobFolder/reports/vaccine-efficacy-safety-follow-up-committee/he/files_publications_corona_two-dose-vaccination-data.pdf (accessed Aug 1, 2021).

26 Nanduri SA, Pilishvili T, Derado G, et al. Effectiveness of Pfizer–BioNTech and Moderna vaccines in preventing SARS-CoV-2 infection among nursing home residents before and during widespread circulation of the SARS-CoV-2 B.1.617.2 (delta) variant—National Healthcare Safety Network, March 1–August 1, 2021. *MMWR Morb Mortal Wkly Rep* 2021; 70: 1163–66.

27 Rosenberg ES, Holtgrave DR, Dorabawila V, et al. New COVID-19 cases and hospitalizations among adults, by vaccination status—New York, May 3–July 25, 2021. *MMWR Morb Mortal Wkly Rep* 2021; **70:** 1150–55.

28 Thomas SJ, Moreira ED, Kitchin N, et al. Six month safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *medRxiv* 2021; published online July 28. https://doi.org/10.1101/2021.07.28.21261159 (preprint).

29 Koebnick C, Langer-Gould AM, Gould MK, et al. Sociodemographic characteristics of members of a large, integrated health care system: comparison with US Census Bureau data. *Perm J* 2012; **16:** 37–41.

30 Messer LC, Laraia BA, Kaufman JS, et al. The development of a standardized neighborhood deprivation index. *J Urban Health* 2006; **83:** 1041–62.

31 Israel Ministry of Health Epidemiology Division. COVID-19 Weekly Data Update, 11-Aug-2021. 2021. https://www.gov.il/BlobFolder/reports/vpb-12082021/he/files_publications_corona_vpb-12082021-01.pdf (accessed Aug 11, 2021).

32 Parry H, Bruton R, Tut G, et al. Immunogenicity of single vaccination with BNT162b2 or ChAdOx1 nCoV-19 at 5–6 weeks post vaccine in participants aged 80 years or older: an exploratory analysis. *Lancet Healthy Longev* 2021; **2:** e554–60.

33 Parry H, Bruton R, Stephens C, et al. Extended interval BNT162b2 vaccination enhances peak antibody generation in older people. *medRxiv* 2021; published online May 17. https://doi.org/10.1101/2021.05.15.21257017 (preprint).

34 Pfizer–BioNTech. Pfizer and BioNTech provide update on booster program in light of the delta-variant New York and Mainz, Germany, July 8, 2021. https://cdn.pfizer.com/pfizercom/2021-07/Delta_Variant_Study_Press_Statement_Final_7.8.21.pdf (accessed Aug 15, 2021).

35 Pfizer. Pfizer second quarter 2021 earning teleconference, July 28, 2021. https://s21.q4cdn.com/317678438/files/doc_financials/2021/q2/Q2-2021-Earnings-Charts-FINAL.pdf (accessed Aug 15, 2021).

36 Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021; **27:** 1205–11.

37 Callow KA, Parry HF, Sergeant M, Tyrrell DA. The time course of the immune response to experimental coronavirus infection of man. *Epidemiol Infect* 1990; **105:** 435–46.

38 Reuters. Update 1-Third Pfizer dose 86% effective in over 60s, Israeli HMO says August 18, 2021. https://www.reuters.com/article/health-coronavirus-israel-vaccine-idCNL1N2PP0XD (accessed Aug 20, 2021).

39 Spiro A. COVID booster shots raise protection against severe illness to 97%. The Times of Israel. https://www.timesofisrael.com/covid-booster-shots-raise-protection-against-severe-illness-to-97-tv/ (accessed Aug 28, 2021).

40 WHO. Interim statement on COVID-19 vaccine booster doses 2021. Geneva: World Health Organization, 2021. https://www.who.int/news/item/10-08-2021-interim-statement-on-covid-19-vaccine-booster-doses (accessed Aug 15, 2021).

EXHIBIT “E”

Community transmission and viral load kinetics of the SARS-CoV-2 delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study

Anika Singanayagam, Seran Hakki*, Jake Dunning*, Kieran J Madon, Michael A Crone, Aleksandra Koycheva, Nieves Derqui-Fernandez, Jack L Barnett, Michael G Whitfield, Robert Varro, Andre Charlett, Rhia Kundu, Joe Fenn, Jessica Cutajar, Valerie Quinn, Emily Conibear, Wendy Barclay, Paul S Freemont, Graham P Taylor, Shazaad Ahmad, Maria Zambon, Neil M Ferguson†, Ajit Lalvani†, on behalf of the ATACCC Study Investigators‡*

Summary

Background The SARS-CoV-2 delta (B.1.617.2) variant is highly transmissible and spreading globally, including in populations with high vaccination rates. We aimed to investigate transmission and viral load kinetics in vaccinated and unvaccinated individuals with mild delta variant infection in the community.

Methods Between Sept 13, 2020, and Sept 15, 2021, 602 community contacts (identified via the UK contract-tracing system) of 471 UK COVID-19 index cases were recruited to the Assessment of Transmission and Contagiousness of COVID-19 in Contacts cohort study and contributed 8145 upper respiratory tract samples from daily sampling for up to 20 days. Household and non-household exposed contacts aged 5 years or older were eligible for recruitment if they could provide informed consent and agree to self-swabbing of the upper respiratory tract. We analysed transmission risk by vaccination status for 231 contacts exposed to 162 epidemiologically linked delta variant-infected index cases. We compared viral load trajectories from fully vaccinated individuals with delta infection (n=29) with unvaccinated individuals with delta (n=16), alpha (B.1.1.7; n=39), and pre-alpha (n=49) infections. Primary outcomes for the epidemiological analysis were to assess the secondary attack rate (SAR) in household contacts stratified by contact vaccination status and the index cases' vaccination status. Primary outcomes for the viral load kinetics analysis were to detect differences in the peak viral load, viral growth rate, and viral decline rate between participants according to SARS-CoV-2 variant and vaccination status.

Findings The SAR in household contacts exposed to the delta variant was 25% (95% CI 18–33) for fully vaccinated individuals compared with 38% (24–53) in unvaccinated individuals. The median time between second vaccine dose and study recruitment in fully vaccinated contacts was longer for infected individuals (median 101 days [IQR 74–120]) than for uninfected individuals (64 days [32–97], p=0·001). SAR among household contacts exposed to fully vaccinated index cases was similar to household contacts exposed to unvaccinated index cases (25% [95% CI 15–35] for vaccinated *vs* 23% [15–31] for unvaccinated). 12 (39%) of 31 infections in fully vaccinated household contacts arose from fully vaccinated epidemiologically linked index cases, further confirmed by genomic and virological analysis in three index case–contact pairs. Although peak viral load did not differ by vaccination status or variant type, it increased modestly with age (difference of 0·39 [95% credible interval –0·03 to 0·79] in peak $\log_{10}$ viral load per mL between those aged 10 years and 50 years). Fully vaccinated individuals with delta variant infection had a faster (posterior probability >0·84) mean rate of viral load decline (0·95 $\log_{10}$ copies per mL per day) than did unvaccinated individuals with pre-alpha (0·69), alpha (0·82), or delta (0·79) variant infections. Within individuals, faster viral load growth was correlated with higher peak viral load (correlation 0·42 [95% credible interval 0·13 to 0·65]) and slower decline (–0·44 [–0·67 to –0·18]).

Interpretation Vaccination reduces the risk of delta variant infection and accelerates viral clearance. Nonetheless, fully vaccinated individuals with breakthrough infections have peak viral load similar to unvaccinated cases and can efficiently transmit infection in household settings, including to fully vaccinated contacts. Host–virus interactions early in infection may shape the entire viral trajectory.

Funding National Institute for Health Research.

Lancet Infect Dis 2022; 22: 183–95

Published Online October 28, 2021 https://doi.org/10.1016/S1473-3099(21)00648-4

This online publication has been corrected. The corrected version first appeared at thelancet.com/infection on November 2, 2021

See Comment page 152

*Joint first authors

†Contributed equally

‡Investigators are listed at the end of the article

NIHR Health Protection Research Unit in Respiratory Infections, National Heart and Lung Institute (A Singanayagam PhD, S Hakki PhD, K J Madon MSc, A Koycheva BSc, N Derqui-Fernandez MSc, J L Barnett MPhys, M G Whitfield PhD, R Varro MSc, R Kundu PhD, J Fenn PhD, J Cutajar BSc, V Quinn BSc, E Conibear MSc, Prof A Lalvani DM), **Department of Infectious Disease** (A Singanayagam, Prof W Barclay PhD, Prof G P Taylor DSc, M A Crone MBBCh, Prof P S Freemont PhD), **NIHR Health Protection Research Unit in Modelling and Health Economics, MRC Centre for Global Infectious Disease Analysis, Jameel Institute** (Prof N M Ferguson DPhil), **and UK Dementia Research Institute Centre for Care Research and Technology** (M A Crone, Prof P S Freemont), **Imperial College London, London, UK; NIHR Health Protection Research Unit in Emerging and Zoonotic Infections, University of Oxford, Oxford, UK** (J Dunning PhD);

Introduction

While the primary aim of vaccination is to protect individuals against severe COVID-19 disease and its consequences, the extent to which vaccines reduce onward transmission of SARS-CoV-2 is key to containing the pandemic. This outcome depends on the ability of

London Biofoundry, Imperial College Translation and Innovation Hub, London, UK (M A Crone, Prof P S Freemont); **National Infection Service** (A Singanayagam, J Dunning, Prof M Zambon FRCPath) **and Data and Analytical Services** (A Charlett PhD), **Public Health England, London, UK; Department of Virology, Manchester Medical Microbiology Partnership, Manchester Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, UK** (S Ahmad FRCPath)

Correspondence to: Prof Ajit Lalvani, NIHR Health Protection Research Unit in Respiratory Infections, National Heart and Lung Institute, Imperial College London, London, W2 1PG, UK
a.lalvani@imperial.ac.uk

Research in context

Evidence before this study

The SARS-CoV-2 delta variant is spreading globally, including in populations with high vaccination coverage. While vaccination remains highly effective at attenuating disease severity and preventing death, vaccine effectiveness against infection is reduced for delta. Determining the extent of transmission from vaccinated delta-infected individuals to their vaccinated contacts is a public health priority. Comparing the upper respiratory tract (URT) viral load kinetics of delta infections with those of other variants gives insight into potential mechanisms for its increased transmissibility. We searched PubMed and *medRxiv* for articles published between database inception and Sept 20, 2021, using search terms describing "SARS-CoV-2, delta variant, viral load, and transmission". Two studies longitudinally sampled the URT in vaccinated and unvaccinated delta variant-infected individuals to compare viral load kinetics. In a retrospective study of a cohort of hospitalised patients in Singapore, more rapid viral load decline was found in vaccinated individuals than unvaccinated cases. However, the unvaccinated cases in this study had moderate-to-severe infection, which is known to be associated with prolonged shedding. The second study longitudinally sampled professional USA sports players. Again, clearance of delta viral RNA in vaccinated cases was faster than in unvaccinated cases, but only 8% of unvaccinated cases had delta variant infection, complicating interpretation. Lastly, a report of a single-source nosocomial outbreak of a distinct delta sub-lineage in Vietnamese health-care workers plotted viral load kinetics (without comparison with unvaccinated delta infections) and demonstrated transmission between fully vaccinated health-care workers in the nosocomial setting. The findings might therefore not be generalisable beyond the particular setting and distinct viral sub-lineage investigated.

Added value of this study

The majority of SARS-CoV-2 transmission occurs in households, but transmission between fully vaccinated individuals in this setting has not been shown to date. To ascertain secondary transmission with high sensitivity, we longitudinally followed index cases and their contacts (regardless of symptoms) in the community early after exposure to the delta variant of SARS-CoV-2, performing daily quantitative RT-PCR on URT samples for 14–20 days. We found that the secondary attack rate in fully vaccinated household contacts was high at 25%, but this value was lower than that of unvaccinated contacts (38%). Risk of infection increased with time in the 2–3 months since the second dose of vaccine. The proportion of infected contacts was similar regardless of the index cases' vaccination status. We observed transmission of the delta variant between fully vaccinated index cases and their fully vaccinated contacts in several households, confirmed by whole-genome sequencing. Peak viral load did not differ by vaccination status or variant type but did increase modestly with age. Vaccinated delta cases experienced faster viral load decline than did unvaccinated alpha or delta cases. Across study participants, faster viral load growth was correlated with higher peak viral load and slower decline, suggesting that host–virus interactions early in infection shape the entire viral trajectory. Since our findings are derived from community household contacts in a real-life setting, they are probably generalisable to the general population.

Implications of all the available evidence

Although vaccines remain highly effective at preventing severe disease and deaths from COVID-19, our findings suggest that vaccination is not sufficient to prevent transmission of the delta variant in household settings with prolonged exposures. Our findings highlight the importance of community studies to characterise the epidemiological phenotype of new SARS-CoV-2 variants in increasingly highly vaccinated populations. Continued public health and social measures to curb transmission of the delta variant remain important, even in vaccinated individuals.

vaccines to protect against infection and the extent to which vaccination reduces the infectiousness of breakthrough infections.

Vaccination was found to be effective in reducing household transmission of the alpha variant (B.1.1.7) by 40–50%,[1] and infected, vaccinated individuals had lower viral load in the upper respiratory tract (URT) than infections in unvaccinated individuals,[2] which is indicative of reduced infectiousness.[3,4] However, the delta variant (B.1.617.2), which is more transmissible than the alpha variant,[5,6] is now the dominant strain worldwide. After a large outbreak in India, the UK was one of the first countries to report a sharp rise in delta variant infection. Current vaccines remain highly effective at preventing admission to hospital and death from delta infection.[7] However, vaccine effectiveness against infection is reduced for delta, compared with alpha,[8,9] and the delta variant continues to cause a high burden of cases even in countries with high vaccination coverage. Data are scarce on the risk of community transmission of delta from vaccinated individuals with mild infections.

Here, we report data from a UK community-based study, the Assessment of Transmission and Contagiousness of COVID-19 in Contacts (ATACCC) study, in which ambulatory close contacts of confirmed COVID-19 cases underwent daily, longitudinal URT sampling, with collection of associated clinical and epidemiological data. We aimed to quantify household transmission of the delta variant and assess the effect of vaccination status on contacts' risk of infection and index cases' infectiousness, including (1) households with unvaccinated contacts and index cases and (2) households with fully vaccinated contacts and fully vaccinated index cases. We also compared sequentially sampled

URT viral RNA trajectories from individuals with non-severe delta, alpha, and pre-alpha SARS-CoV-2 infections to infer the effects of SARS-CoV-2 variant status—and, for delta infections, vaccination status—on transmission potential.

Methods

Study design and participants

ATACCC is an observational longitudinal cohort study of community contacts of SARS-CoV-2 cases. Contacts of symptomatic PCR-confirmed index cases notified to the UK contact-tracing system (National Health Service Test and Trace) were asked if they would be willing to be contacted by Public Health England to discuss participation in the study. All contacts notified within 5 days of index case symptom onset were selected to be contacted within our recruitment capacity. Household and non-household contacts aged 5 years or older were eligible for recruitment if they could provide written informed consent and agree to self-swabbing of the URT. Further details on URT sampling are given in the appendix (p 13).

The ATACCC study is separated into two study arms, ATACCC1 and ATACCC2, which were designed to capture different waves of the SARS-CoV-2 pandemic. In ATACCC1, which investigated alpha variant and pre-alpha cases in Greater London, only contacts were recruited between Sept 13, 2020, and March 13, 2021. ATACCC1 included a pre-alpha wave (September to November, 2020) and an alpha wave (December, 2020, to March, 2021). In ATACCC2, the study was relaunched specifically to investigate delta variant cases in Greater London and Bolton, and both index cases and contacts were recruited between May 25, and Sept 15, 2021. Early recruitment was focused in West London and Bolton because UK incidence of the delta variant was highest in these areas.[10] Based on national and regional surveillance data, community transmission was moderate-to-high throughout most of our recruitment period.

This study was approved by the Health Research Authority. Written informed consent was obtained from all participants before enrolment. Parents and caregivers gave consent for children.

Data collection

Demographic information was collected by the study team on enrolment. The date of exposure for non-household contacts was obtained from Public Health England. COVID-19 vaccination history was determined from the UK National Immunisation Management System, general practitioner records, and self-reporting by study participants. We defined a participant as unvaccinated if they had not received a single dose of a COVID-19 vaccine at least 7 days before enrolment, partially vaccinated if they had received one vaccine dose at least 7 days before study enrolment, and fully vaccinated if they had received two doses of a COVID-19 vaccine at least 7 days before study enrolment. Previous literature was used to determine the 7-day threshold for defining vaccination status.[11–13] We also did sensitivity analyses using a 14-day threshold. The time interval between vaccination and study recruitment was calculated. We used WHO criteria[14] to define symptomatic status up to the day of study recruitment. Symptomatic status for incident cases—participants who were PCR-negative at enrolment and subsequently tested positive—was defined from the day of the first PCR-positive result.

Laboratory procedures

SARS-CoV-2 quantitative RT-PCR, conversion of ORF1ab and envelope (E-gene) cycle threshold values to viral genome copies, whole-genome sequencing, and lineage assignments are described in the appendix (pp 13–14).

Outcomes

Primary outcomes for the epidemiological analysis were to assess the secondary attack rate (SAR) in household contacts stratified by contact vaccination status and the index cases' vaccination status. Primary outcomes for the viral load kinetics analysis were to detect differences in the peak viral load, viral growth rate, and viral decline rate between participants infected with pre-alpha versus alpha versus delta variants and between unvaccinated delta-infected participants and vaccinated delta-infected participants.

See Online for appendix

We assessed vaccine effectiveness and susceptibility to SARS-CoV-2 infection stratified by time elapsed since receipt of second vaccination as exploratory analyses.

Statistical analysis

To model viral kinetics, we used a simple phenomenological model of viral titre[15] during disease pathogenesis. Viral kinetic parameters were estimated on a participant-specific basis using a Bayesian hierarchical model to fit this model to the entire dataset of sequential cycle threshold values measured for all participants. For the 19 participants who were non-household contacts of index cases and had a unique date of exposure, the cycle threshold data were supplemented by a pseudo-absence data point (ie, undetectable virus) on the date of exposure. Test accuracy and model misspecification were modelled with a mixture model by assuming there was a probability p of a test giving an observation drawn from a (normal) error distribution and probability $1-p$ of it being drawn from the true distribution.

The hierarchical structure was represented by grouping participants based on the infecting variant and their vaccination status. A single-group model was fitted, which implicitly assumes that viral kinetic parameters vary by individual but not by variant or vaccination status. A four-group model was also explored, where groups 1, 2, 3, and 4 represent pre-alpha, alpha, unvaccinated delta, and fully vaccinated delta, respectively. We fitted a correlation matrix between

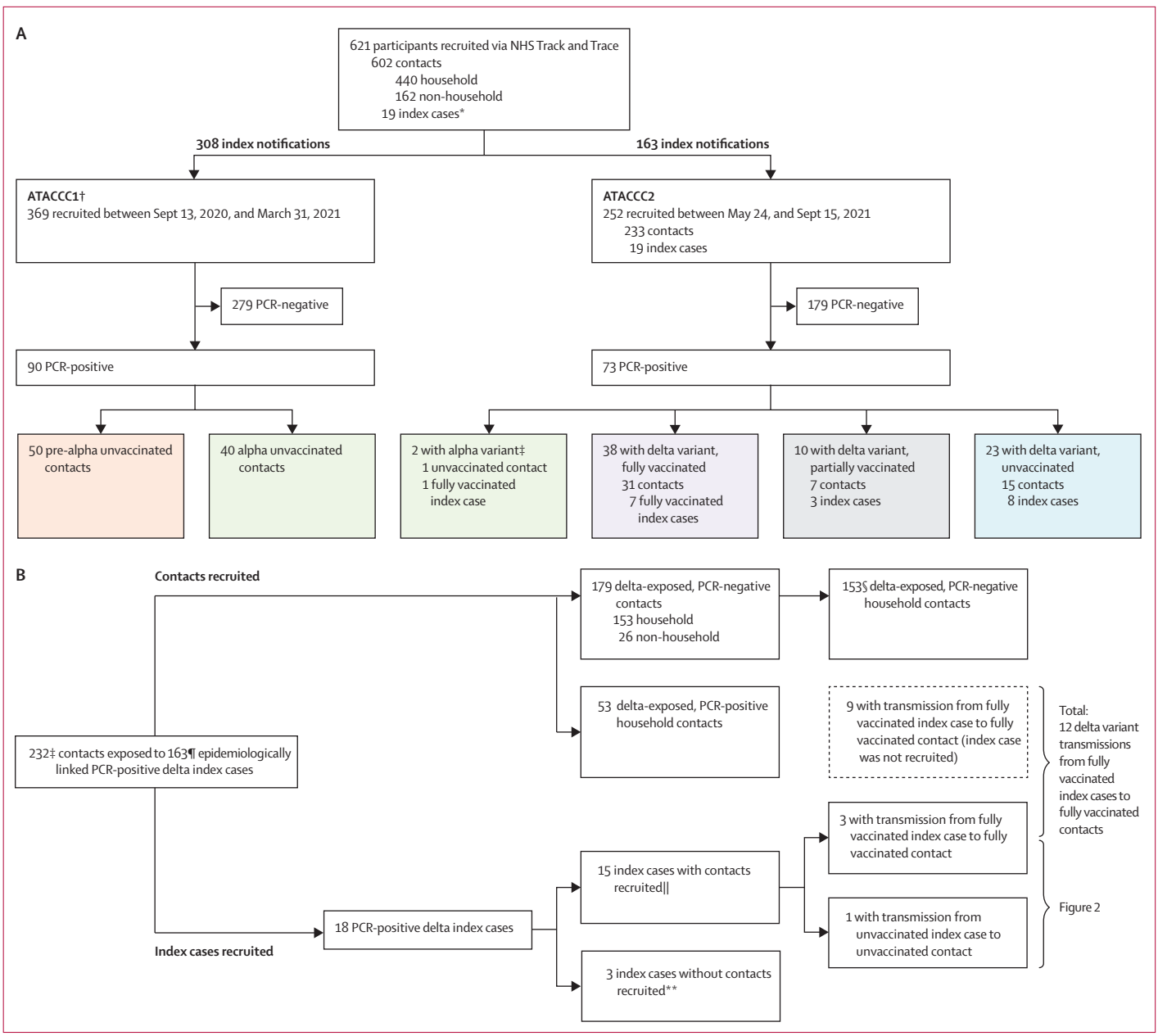


Figure 1: **Recruitment, SARS-CoV-2 infection, variant status, and vaccination history for ATACCC study participants**
(A) Study recruitment and variant status confirmed by whole-genome sequencing (ATACCC1 and ATACCC2 combined). (B) ATACCC2: delta-exposed contacts included in secondary attack rate calculation (table 1) and transmission assessment (table 2). NHS=National Health Service. *All index cases were from ATACCC2. †All contacts. ‡The two earliest PCR-positive cases from the ATACCC2 cohort (one index case and one contact) were confirmed as having the alpha variant on whole-genome sequencing (recruited on May 28, 2021). This alpha variant-exposed, PCR-positive contact is excluded from figure 1B. §One PCR-negative contact had no vaccination status data available and one PCR-negative contact's index case had no vaccination data available. ¶Vaccination data were available for 138 index cases of 163. ||The contacts of these 15 index cases are included within the 232 total contacts. **These three index cases without contacts are only included in the viral load kinetics analysis (figure 3) and are not included in tables 1 and 2.

participant-specific kinetic parameters to allow us to examine whether there is within-group correlation between peak viral titre, viral growth rate, and viral decline rate. Our initial model selection, using leave-one-out cross-validation, selected a four-group hierarchical model with fitted correlation coefficients between individual-level parameters determining peak viral load and viral load growth and decline rates (appendix p 5). However, resulting participant-specific estimates of peak viral load (but not growth and decline rates) showed a marked and significant correlation with age in the exploratory analysis, which motivated examination of models where mean peak viral load could vary with age. The most predictive model overall allowed mean viral

load growth and decline rates to vary across the four groups, with mean peak viral load common to all groups but assumed to vary linearly with the logarithm of age (appendix p 5). We present peak viral loads for the reference age of 50 years with 95% credible intervals (95% CrIs). 50 years was chosen as the reference age as it is typical of the ages of the cases in the whole dataset and the choice of reference age made no difference in the model fits or judgment of differences between the groups.

We computed group-level population means and within-sample group means of log peak viral titre, viral growth rate, and viral decline rate. Since posterior estimates of each of these variables are correlated across groups, overlap in the credible intervals of an estimate for one group with that for another group does not necessarily indicate no significant difference between those groups. We, therefore, computed posterior probabilities, *pp*, that these variables were larger for one group than another. For our model, Bayes factors can be computed as *pp*/(1–*pp*). We only report population (group-level) posterior probabilities greater than 0·75 (corresponding to Bayes factors >3) as indicating at least moderate evidence of a difference.

For vaccine effectiveness, we defined the estimated effectiveness at preventing infection, regardless of symptoms, with delta in the household setting as 1 – SAR (fully vaccinated) / SAR (unvaccinated).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Sept 13, 2020, and Sept 15, 2021, 621 community-based participants (602 contacts and 19 index cases) from 471 index notifications were prospectively enrolled in the ATACCC1 and ATACCC2 studies, and contributed 8145 URT samples. Of these, ATACCC1 enrolled 369 contacts (arising from 308 index notifications), and ATACCC2 enrolled 233 contacts (arising from 163 index notifications) and 19 index cases. SARS-CoV-2 RNA was detected in 163 (26%) of the 621 participants. Whole-genome sequencing of PCR-positive cases confirmed that 71 participants had delta variant infection (18 index cases and 53 contacts), 42 had alpha variant infection (one index case and 41 contacts), and 50 had pre-alpha variant infection (all contacts; figure 1A).

Of 163 PCR-positive participants, 89 (55%) were female and 133 (82%) were White. Median age was 36 years (IQR 26–50). Sex, age, ethnicity, body-mass index (BMI) distribution, and the frequency of comorbidities were similar among those with delta, alpha, and pre-alpha infection, and for vaccinated and unvaccinated delta-infected participants, except for age and sex (appendix pp 2–3). There were fewer unvaccinated females than males (p=0·04) and, as expected from the age-prioritisation of the UK vaccine roll-out, unvaccinated participants infected with the delta variant were significantly younger (p<0·001; appendix p 3). Median time between exposure to the index case and study enrolment was 4 days (IQR 4–5). All participants had non-severe ambulatory illness or were asymptomatic. The proportion of asymptomatic cases did not differ among fully vaccinated, partially vaccinated, and unvaccinated delta groups (appendix p 3).

No pre-alpha-infected and only one alpha-infected participant had received a COVID-19 vaccine before study enrolment. Of 71 delta-infected participants (of whom 18 were index cases), 23 (32%) were unvaccinated, ten (14%) were partially vaccinated, and 38 (54%) were fully vaccinated (figure 1A; appendix p 3). Of the 38 fully vaccinated delta-infected participants, 14 had received the BNT162b2 mRNA vaccine (Pfizer–BioNTech), 23 the ChAdOx1 nCoV-19 adenovirus vector vaccine (Oxford–AstraZeneca), and one the CoronaVac inactivated whole-virion vaccine (Sinovac).

It is highly probable that all but one of the 233 ATACCC2 contacts were exposed to the delta variant because they were recruited when the regional prevalence of delta was at least 90%, and mostly 95–99% (figure 1B).[10] Of these, 206 (89%) were household contacts (in 127 households), and 26 (11%) were non-household contacts. Distributions of age, ethnicity, BMI, smoking status, and comorbidities were similar between PCR-positive and PCR-negative contacts (appendix p 4). The median time between second vaccine dose and study recruitment in fully vaccinated contacts with delta variant infection was 74 days (IQR 35–105; range 16–201), and this was significantly longer in PCR-positive contacts than in PCR-negative contacts (101 days [IQR 74–120] *vs* 64 days [32–97], respectively, p=0·001; appendix p 4). All 53 PCR-positive contacts were exposed in household settings and the SAR for all delta variant-exposed household contacts was 26% (95% CI 20–32). SAR was

	Total	PCR positive	PCR negative	SAR (95% CI)	p value
Contacts					
All	231	53	178	23 (18–29)	NA
Fully vaccinated	140	31	109	22 (16–30)	0·16
Unvaccinated	44	15	29	34 (22–49)	..
Partially vaccinated	47	7	40	15 (7–28)	NA
Household contacts					
All	205	53	152	26 (20–32)	NA
Fully vaccinated	126	31	95	25 (18–33)	0·17
Unvaccinated	40	15	25	38 (24–53)	..
Partially vaccinated	39	7	32	18 (9–33)	NA

χ^2 test was performed to calculate p values for differences in SAR between fully vaccinated and unvaccinated cases. One PCR-negative contact who withdrew from the study without vaccination status information was excluded. NA=not applicable. SAR=secondary attack rate.

Table 1: **SAR in contacts of delta-exposed index cases recruited to the ATACCC2 study**

	All household contacts (n=204)*	Fully vaccinated contacts (n=125)		Partially vaccinated contacts (n=39)		Unvaccinated contacts (n=40)	
		PCR positive (n=31)	PCR negative (n=94)	PCR positive (n=7)	PCR negative (n=32)	PCR positive (n=15)	PCR negative (n=25)
Fully vaccinated index cases (n=50)	69	12	31	1	8	4	13
Partially vaccinated index cases (n=25)	35	7	12	3	10	3	0
Unvaccinated index cases (n=63)	100	12	51	3	14	8	12

Non-household exposed contacts (n=24, all PCR negative) were excluded. One PCR-negative household contact who withdrew from the study without vaccination status information was excluded. One PCR-negative household contact who could not be linked to their index case was also excluded. *The rows below show the number of contacts exposed to each category of index case.

Table 2: **Comparison of vaccination status of the 138 epidemiologically linked PCR-positive index cases for 204 delta variant-exposed household contacts**

not significantly higher in unvaccinated (38%, 95% CI 24–53) than fully vaccinated (25%, 18–33) household contacts (table 1). We estimated vaccine effectiveness at preventing infection (regardless of symptoms) with delta in the household setting to be 34% (bootstrap 95% CI –15 to 60). Sensitivity analyses using a 14 day threshold for time since second vaccination to study recruitment to denote fully vaccinated did not materially affect our estimates of vaccine effectiveness or SAR (data not shown). Although precision is restricted by the small sample size, this estimate is broadly consistent with vaccine effectiveness estimates for delta variant infection based on larger datasets.[9,16,17]

The vaccination status of 138 epidemiologically linked index cases of 204 delta variant-exposed household contacts was available (figure 1B, table 2). The SAR in household contacts exposed to fully vaccinated index cases was 25% (95% CI 15–35; 17 of 69), which is similar to the SAR in household contacts exposed to unvaccinated index cases (23% [15–31]; 23 of 100; table 2). The 53 PCR-positive contacts arose from household exposure to 39 PCR-positive index cases. Of these index cases who gave rise to secondary transmission, the proportion who were fully vaccinated (15 [38%] of 39) was similar to the proportion who were unvaccinated (16 [41%] of 39). The median number of days from the index cases' second vaccination to the day of recruitment for their respective contacts was 73 days (IQR 38–116). Time interval did not differ between index cases who transmitted infection to their contacts and those who did not (94 days [IQR 62–112] and 63 days [35–117], respectively; p=0·43).

18 of the 163 delta variant-infected index cases that led to contact enrolment were themselves recruited to ATACCC2 and serial URT samples were collected from them, allowing for more detailed virology and genome analyses. For 15 of these, their contacts were also recruited (13 household contacts and two non-household contacts). A corresponding PCR-positive household contact was identified for four of these 15 index cases (figure 1B). Genomic analysis showed that index–contact pairs were infected with the same delta variant sub-lineage in these instances, with one exception (figure 2A). In one household (number 4), an unvaccinated index case transmitted the delta variant to an unvaccinated contact, while another partially vaccinated contact was infected with a different delta sub-lineage (which was probably acquired outside the household). In the other three households (numbers 1–3), fully vaccinated index cases transmitted the delta variant to fully vaccinated household contacts, with high viral load in all cases, and temporal relationships between the viral load kinetics that were consistent with transmission from the index cases to their respective contacts (figure 2B).

Inclusion criteria for the modelling analysis selected 133 participant's viral load RNA trajectories from 163 PCR-positive participants (49 with the pre-alpha variant, 39 alpha, and 45 delta; appendix p 14). Of the 45 delta cases, 29 were fully vaccinated and 16 were unvaccinated; partially vaccinated cases were excluded. Of the 133 included cases, 29 (22%) were incident (ie, PCR negative at enrolment converting to PCR positive subsequently) and 104 (78%) were prevalent (ie, already PCR positive at enrolment). 15 of the prevalent cases had a clearly resolvable peak viral load. Figure 3 shows modelled viral RNA (ORF1ab) trajectories together with the viral RNA copy numbers measured for individual participants. The E-gene equivalent is shown in the appendix (p 2). Estimates derived from E-gene cycle threshold value data (appendix pp 5, 7, 9, 11) were similar to those for ORF1ab.

Although viral kinetics appear visually similar for all four groups of cases, we found quantitative differences in estimated viral growth rates and decline rates (tables 3, 4). Population (group-level) estimates of mean viral load decline rates based on ORF1ab cycle threshold value data varied in the range of 0·69–0·95 $\log_{10}$ units per mL per daxes 4; appendix p 10), indicating that a typical 10-day period was required for viral load to decline from peak to undetectable. A faster decline was seen in the alpha (*pp*=0·93), unvaccinated delta (*pp*=0·79), and fully vaccinated delta (*pp*=0·99) groups than in the pre-alpha group. The mean viral load decline rate of the fully vaccinated delta group was also faster than those of the alpha group (*pp*=0·84) and the unvaccinated delta group (*pp*=0·85). The differences in decline rates translate into a difference of about 3 days in the mean duration of the decline phase between the pre-alpha and delta vaccinated groups.

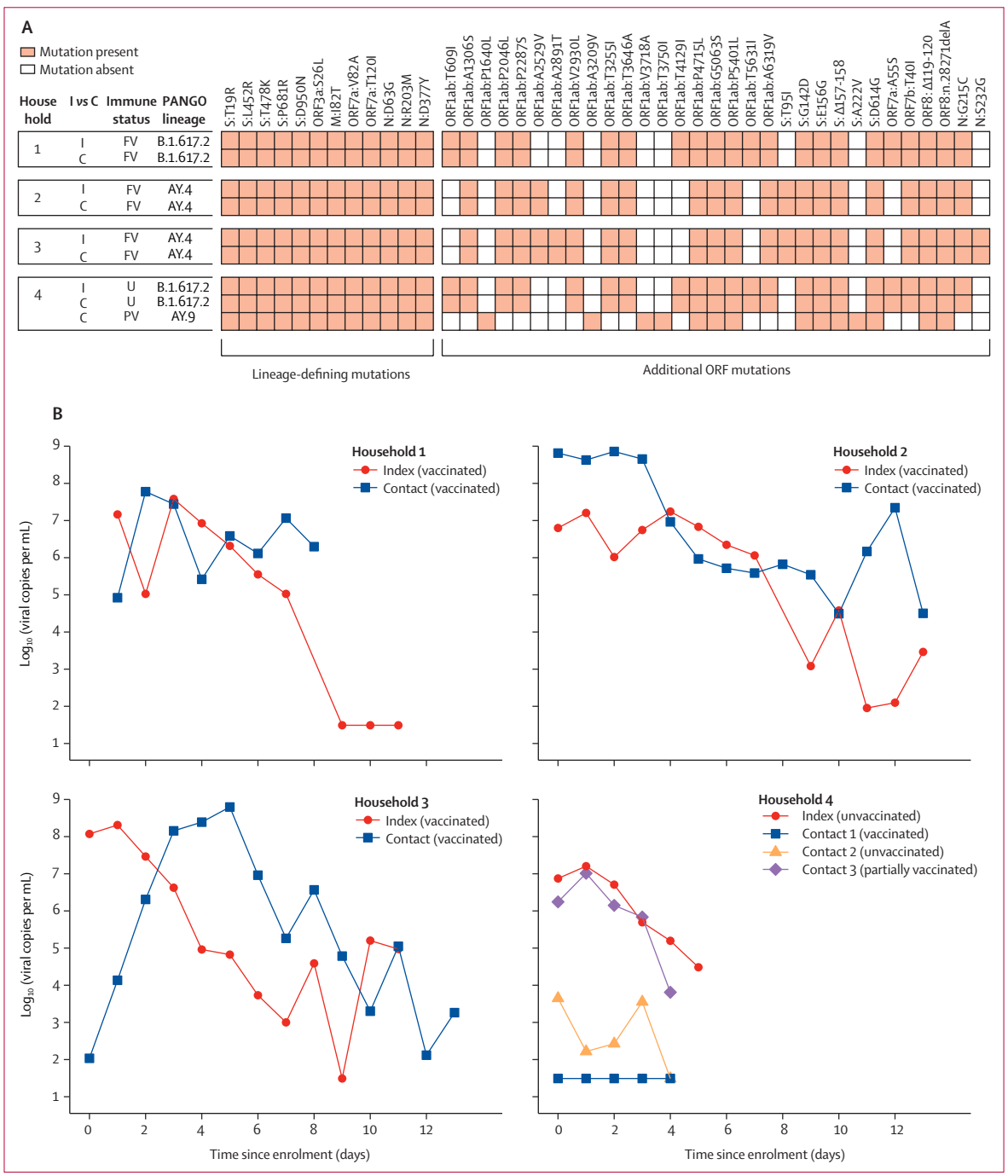
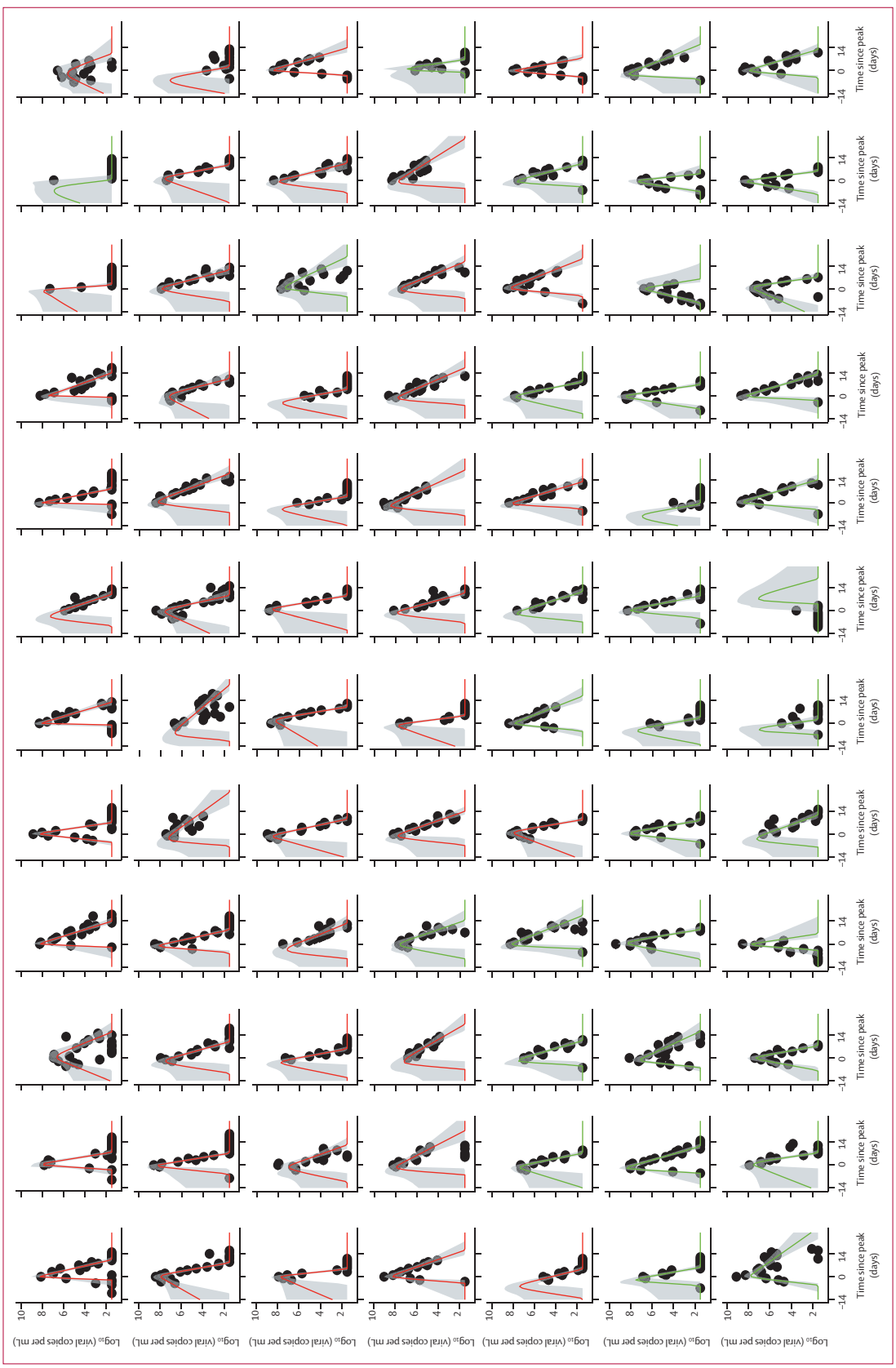


Figure 2: **Virological, epidemiological, and genomic evidence for transmission of the SARS-CoV-2 delta variant (B.1.617.2) in households**
(A) Genomic analysis of the four households with lineage-defining mutations for delta[18] and additional mutations within ORFs displayed to give insight into whether strains from individuals within the household are closely related. Lineages AY.4 and AY.9 are sub-lineages of delta. (B) Viral trajectories and vaccination status of the four index cases infected with the delta variant for whom infection was detected in their epidemiologically linked household contacts. All individuals had non-severe disease. Each plot shows an index case and their household contacts. Undetectable viral load measurements are plotted at the limit of detection ($10^{1\cdot49}$). C=contact. I=index case. FV=fully vaccinated. ORF=open reading frame. PV=partially vaccinated. U=unvaccinated.

Viral load growth rates were substantially faster than decline rates, varying in the range of 2·69–3·24 $\log_{10}$ units per mL per day between groups, indicating that a typical 3-day period was required for viral load to grow from undetectable to peak. Our power to infer differences in growth rates between groups was more restricted than for viral decline, but there was moderate evidence (*pp*=0·79) that growth rates were lower for



(Figure 3 continues on next page)

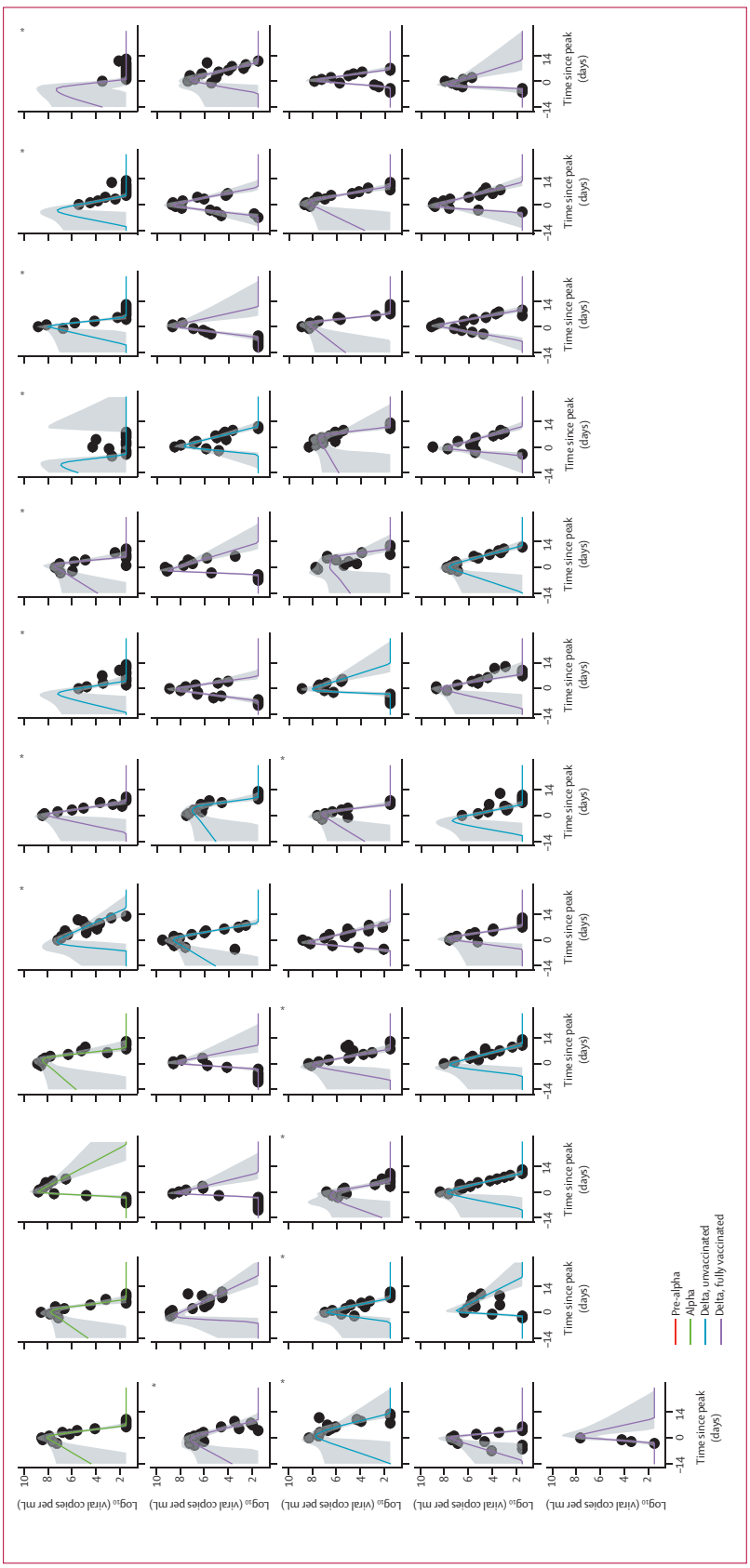


Figure 3: **ORF1ab viral load trajectories from 14 days before to 28 days after peak for 133 participants infected with pre-alpha or alpha variants (uncaccinated), or the delta variant (vaccinated and unvaccinated) variants**
Black circles are measured values, with the first datapoint for each participant being taken to the day of enrolment. Plots are rooted on the day of peak viral load for each participant, denoted as day 0 on the x-axis. Curves show the model posterior median estimate, with a 95% credible interval shading. 133 infected participants, comprising 114 contacts and 19 index cases. *Index cases.

	VL growth rate (95% CrI), log_{10} units per day	Posterior probability estimate is less than pre-alpha	Posterior probability estimate is less than alpha	Posterior probability estimate is less than delta (unvaccinated)	Posterior probability estimate is less than delta (fully vaccinated)
Pre-alpha (n=49)	3·24 (1·78–6·14)	..	0·44	0·27	0·21
Alpha (n=39)	3·13 (1·76–5·94)	0·56	..	0·32	0·25
Delta, unvaccinated (n=16)	2·81 (1·47–5·47)	0·73	0·68	..	0·44
Delta, fully vaccinated (n=29)	2·69 (1·51–5·17)	0·79	0·75	0·56	..

VL growth rates are shown as within-sample posterior mean estimates. Remaining columns show population (group-level) posterior probabilities that the estimate on that row is less than an estimate for a different group. Posterior probabilities are derived from 20 000 posterior samples and have sampling errors of <0·01. VL=viral load. CrI=credible interval.

Table 3: **Estimates of VL growth rates for pre-alpha, alpha, and delta (unvaccinated and fully vaccinated) cases, derived from ORF1ab cycle threshold data**

	VL decline rate (95% CrI), log_{10} units per day	Posterior probability estimate is larger than pre-alpha	Posterior probability estimate is larger than alpha	Posterior probability estimate is larger than delta (unvaccinated)	Posterior probability estimate is larger than delta (fully vaccinated)
Pre-alpha (n=49)	0·69 (0·58–0·81)	..	0·07	0·21	0·01
Alpha (n=39)	0·82 (0·67–1·01)	0·93	..	0·60	0·16
Delta, unvaccinated (n=16)	0·79 (0·59–1·04)	0·79	0·40	..	0·15
Delta, fully vaccinated (n=29)	0·95 (0·76–1·18)	0·99	0·84	0·85	..

VL decline rates are shown as within-sample posterior mean estimates. Remaining columns show population (group-level) posterior probabilities that the estimate on that row is less than an estimate for a different group. Posterior probabilities are derived from 20 000 posterior samples and have sampling errors of <0·01. VL=viral load. CrI=credible interval.

Table 4: **Estimates of VL decline rates for pre-alpha, alpha, and delta (unvaccinated and fully vaccinated) cases, derived from ORF1ab cycle threshold data**

those in the vaccinated delta group than in the pre-alpha group.

We estimated mean peak viral load for 50-year-old adults to be 8·14 (95% CrI 7·95 to 8·32) log_{10} copies per mL, but peak viral load did not differ by variant or vaccination status. However, we estimated that peak viral load increases with age (*pp*=0·96 that the slope of peak viral load with log[age] was >0), with an estimated slope of 0·24 (95% CrI –0·02 to 0·49) log_{10} copies per mL per unit change in log(age). This estimate translates to a difference of 0·39 (–0·03 to 0·79) in mean peak log_{10} copies per mL between those aged 10 years and 50 years.

Within-group individual participant estimates of viral load growth rate were positively correlated with peak viral load, with a correlation coefficient estimate of 0·42 (95% CrI 0·13 to 0·65; appendix p 8). Hence, individuals with faster viral load growth tend to have higher peak viral load. The decline rate of viral load was also negatively correlated with viral load growth rate, with a correlation coefficient estimate of –0·44 (95% CrI –0·67 to –0·18), illustrating that individuals with faster viral load growth tend to experience slower viral load decline.

Discussion

Households are the site of most SARS-CoV-2 transmission globally.[19] In our cohort of densely sampled household contacts exposed to the delta variant, SAR was 38% in unvaccinated contacts and 25% in fully vaccinated contacts. This finding is consistent with the known protective effect of COVID-19 vaccination against infection.[8,9] Notwithstanding, these findings indicate continued risk of infection in household contacts despite vaccination. Our estimate of SAR is higher than that reported in fully vaccinated household contacts exposed before the emergence of the delta variant.[1,20,21] The time interval between vaccination and study recruitment was significantly higher in fully vaccinated PCR-positive contacts than fully vaccinated PCR-negative contacts, suggesting that susceptibility to infection increases with time as soon as 2–3 months after vaccination—consistent with waning protective immunity. This potentially important observation is consistent with recent large-scale data and requires further investigation.[17] Household SAR for delta infection, regardless of vaccination status, was 26% (95% CI 20–32), which is higher than estimates of UK national surveillance data (10·8% [10·7–10·9]).[10] However, we sampled contacts daily, regardless of symptomatology, to actively identify infection with high sensitivity. By contrast, symptom-based, single-timepoint surveillance testing probably underestimates the true SAR, and potentially also overestimates vaccine effectiveness against infection.

We identified similar SAR (25%) in household contacts exposed to fully vaccinated index cases as in those exposed to unvaccinated index cases (23%). This finding indicates that breakthrough infections in fully vaccinated people can efficiently transmit infection in the household setting. We identified 12 household transmission events between fully vaccinated index case–contact pairs; for three of these, genomic sequencing confirmed that the index case and

contact were infected by the same delta variant sub-lineage, thus substantiating epidemiological data and temporal relationships of viral load kinetics to provide definitive evidence for secondary transmission. To our knowledge, one other study has reported that transmission of the delta variant between fully vaccinated people was a point-source nosocomial outbreak—a single health-care worker with a particular delta variant sub-lineage in Vietnam.[22]

Daily longitudinal sampling of cases from early (median 4 days) after exposure for up to 20 days allowed us to generate high-resolution trajectories of URT viral load over the course of infection. To date, two studies have sequentially sampled community cases of mild SARS-CoV-2 infection, and these were from highly specific population groups identified through asymptomatic screening programmes (eg, for university staff and students[23] and for professional athletes[24]).

Our most predictive model of viral load kinetics estimated mean peak $\log_{10}$ viral load per mL of 8·14 (95% CrI 7·95–8·32) for adults aged 50 years, which is very similar to the estimate from a 2021 study using routine surveillance data.[25] We found no evidence of variation in peak viral load by variant or vaccination status, but we report some evidence of modest but significant (pp=0·95) increases in peak viral load with age. Previous studies of viral load in children and adults[4,25,26] have not used such dense sequential sampling of viral load and have, therefore, been restricted in their power to resolve age-related differences; the largest such study[25] reported a similar difference between children and adults to the one we estimated. We found the rate of viral load decline was faster for vaccinated individuals with delta infection than all other groups, and was faster for individuals in the alpha and unvaccinated delta groups than those with pre-alpha infection.

For all variant vaccination groups, the variation between participants seen in viral load kinetic parameter estimates was substantially larger than the variation in mean parameters estimated between groups. The modest scale of differences in viral kinetics between fully vaccinated and unvaccinated individuals with delta infection might explain the relatively high rates of transmission seen from vaccinated delta index cases in our study. We found no evidence of lower SARs from fully vaccinated delta index cases than from unvaccinated ones. However, given that index cases were identified through routine symptomatic surveillance, there might have been a selection bias towards identifying untypically symptomatic vaccine breakthrough index cases.

The differences in viral kinetics we found between the pre-alpha, alpha, and delta variant groups suggest some incremental, but potentially adaptive, changes in viral dynamics associated with the evolution of SARS-CoV-2 towards more rapid viral clearance. Our study provides the first evidence that, within each variant or vaccination group, viral growth rate is positively correlated with peak viral load, but is negatively correlated with viral decline rate. This finding suggests that individual infections during which viral replication is initially fastest generate the highest peak viral load and see the slowest viral clearance, with the latter not just being due to the higher peak. Mechanistically, these data suggest that the host and viral factors determining the initial growth rate of SARS-CoV-2 have a fundamental effect on the trajectory throughout infection, with faster replication being more difficult (in terms of both peak viral load and the subsequent decline of viral load) for the immune response to control. Analysis of sequentially sampled immune markers during infection might give insight into the immune correlates of these early differences in infection kinetics. It is also possible that individuals with the fastest viral load growth and highest peaks contribute disproportionately to community transmission, a hypothesis that should be tested in future studies.

Several population-level, single-timepoint sampling studies using routinely available data have found no major differences in cycle threshold values between vaccinated and unvaccinated individuals with delta variant infection.[10,27,28] However, as the timepoint of sampling in the viral trajectory is unknown, this restricts the interpretation of such results. Two other studies longitudinally sampled vaccinated and unvaccinated individuals with delta variant infection.[23,29] A retrospective cohort of hospitalised patients in Singapore[29] also described a faster rate of viral decline in vaccinated versus unvaccinated individuals with delta variant, reporting somewhat larger differences in decline rates than we estimated here. However, this disparity might be accounted for by the higher severity of illness in unvaccinated individuals in the Singaporean study (almost two-thirds having pneumonia, one-third requiring COVID-19 treatment, and a fifth needing oxygen) than in our study, given that longer viral shedding has been reported in patients with more severe illness.[30] A longitudinal sampling study in the USA reported that pre-alpha, alpha, and delta variant infections had similar viral trajectories.[24] The study also compared trajectories in vaccinated and unvaccinated individuals, reporting similar proliferation phases and peak cycle threshold values, but more rapid clearance of virus in vaccinated individuals. However, this study in the USA stratified by vaccination status and variant separately, rather than jointly, meaning vaccinated individuals with delta infection were being compared with, predominantly, unvaccinated individuals with pre-alpha and alpha infection. Moreover, sampling was done as part of a professional sports player occupational health screening programme, making the results not necessarily representative of typical community infections.

Our study has limitations. First, we recruited only contacts of symptomatic index cases as our study recruitment is derived from routine contact-tracing notifications. Second, index cases were defined as the first household member to have a PCR-positive swab, but we cannot exclude the possibility that another household member might already have been infected and transmitted

to the index case. Third, recording of viral load trajectories is subject to left censoring, where the growth phase in prevalent contacts (already PCR-positive at enrolment) was missed for a proportion of participants. However, we captured 29 incident cases and 15 additional cases on the upslope of the viral trajectory, providing valuable, informative data on viral growth rates and peak viral load in a subset of participants. Fourth, owing to the age-stratified rollout of the UK vaccination programme, the age of the unvaccinated, delta variant-infected participants was lower than that of vaccinated participants. Thus, age might be a confounding factor in our results and, as discussed, peak viral load was associated with age. However, it is unlikely that the higher SAR observed in the unvaccinated contacts would have been driven by younger age rather than the absence of vaccination and, to our knowledge, there is no published evidence showing increased susceptibility to SARS-CoV-2 infection with decreasing age.[31] Finally, although we did not perform viral culture here—which is a better proxy for infectiousness than RT-PCR—two other studies[27,32] have shown cultivable virus from around two-thirds of vaccinated individuals infected with the delta variant, consistent with our conclusions that vaccinated individuals still have the potential to infect others, particularly early after infection when viral loads are high and most transmission is thought to occur.[30]

Our findings help to explain how and why the delta variant is being transmitted so effectively in populations with high vaccine coverage. Although current vaccines remain effective at preventing severe disease and deaths from COVID-19, our findings suggest that vaccination alone is not sufficient to prevent all transmission of the delta variant in the household setting, where exposure is close and prolonged. Increasing population immunity via booster programmes and vaccination of teenagers will help to increase the currently limited effect of vaccination on transmission, but our analysis suggests that direct protection of individuals at risk of severe outcomes, via vaccination and non-pharmacological interventions, will remain central to containing the burden of disease caused by the delta variant.

Contributors

AS, JD, MZ, NMF, WB, and ALal conceptualised the study. AS, SH, JD, KJM, AK, JLB, MGW, ND-F, RV, RK, JF, CT, AVK, JC, VQ, EC, JSN, SH, EM, TP, HH, CL, JS, SB, JP, CA, SA, and NMF were responsible for data curation and investigation. AS, SH, KJM, JLB, AC, NMF, and ALal did the formal data analysis. MAC, AB, DJ, SM, JE, PSF, SD, and ALac did the laboratory work. RV, RK, JF, CT, AVK, JC, VQ, EC, JSN, SH, EM, and SE oversaw the project. AS, SH, JD, KJM, JLB, NMF, and ALal accessed and verified the data. JD, MZ, and ALal acquired funding. NMF sourced and oversaw the software. AS and ALal wrote the initial draft of the manuscript. AS, JD, GPT, MZ, NMF, SH, and ALal reviewed and edited the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

The ATACCC Study Investigators

Anjna Badhan, Simon Dustan, Chitra Tejpal, Anjeli V Ketkar, Janakan Sam Narean, Sarah Hammett, Eimear McDermott, Timesh Pillay, Hamish Houston, Constanta Luca, Jada Samuel, Samuel Bremang, Samuel Evetts, John Poh, Charlotte Anderson, David Jackson, Shahjahan Miah, Joanna Ellis, and Angie Lackenby.

Declaration of interests

NMF reports grants from UK Medical Research Council, UK National Institute of Health Research, UK Research and Innovation, Community Jameel, Janssen Pharmaceuticals, the Bill & Melinda Gates Foundation, and Gavi, the Vaccine Alliance; consulting fees from the World Bank; payment or honoraria from the Wellcome Trust; travel expenses from WHO; advisory board participation for Takeda; and is a senior editor of the *eLife* journal. All other authors declare no competing interests.

Data sharing

An anonymised, de-identified version of the dataset can be made available upon request to allow all results to be reproduced. Modelling code will also be made publicly available on the GitHub repository.

Acknowledgments

This work is supported by the National Institute for Health Research (NIHR200927), a Department of Health and Social Care COVID-19 Fighting Fund award, and the NIHR Health Protection Research Units (HPRUs) in Respiratory Infections and in Modelling and Health Economics. NMF acknowledges funding from the MRC Centre for Global Infectious Disease Analysis and the Jameel Institute. PSF and MAC are supported by the UK Dementia Research Institute. JD is supported by the NIHR HPRU in Emerging and Zoonotic Infections. MGW is supported by the NIHR HPRU in Healthcare Associated Infections and Antimicrobial Resistance. GPT is supported by the Imperial NIHR Biomedical Research Centre. We thank all the participants who were involved in the study, Public Health England staff for facilitating recruitment into the study, the staff of the Virus Reference Department for performing PCR and sequencing assays, and the Immunisations Department for assisting with analysis of vaccination data. We also thank Kristel Timcang, Mohammed Essoussi, Holly Grey, Guilia Miserocchi, Harriet Catchpole, Charlotte Williams, Niamh Nichols, Jessica Russell, Sean Nevin, Lulu Wang, Berenice Di Biase, Alice Panes, Esther Barrow, and Lauren Edmunds for their involvement in logistics, conducting data entry, or quality control; and the Molecular Diagnostics Unit at Imperial College London, in particular Lucy Mosscrop, Carolina Rosadas de Oliveira, and Patricia Watber, for performing RNA extraction, quantitative RT-PCR, and preparing samples for sequencing.

References

1 Harris RJ, Hall JA, Zaidi A, Andrews NJ, Dunbar JK, Dabrera G. Effect of vaccination on household transmission of SARS-CoV-2 in England. *N Engl J Med* 2021; **385:** 759–60.

2 Levine-Tiefenbrun M, Yelin I, Katz R, et al. Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine. *Nat Med* 2021; **27:** 790–92.

3 Singanayagam A, Patel M, Charlett A, et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. *Euro Surveill* 2020; **25:** 2001483.

4 Lyngse FP, Mølbak K, Træholt Franck K, et al. Association between SARS-CoV-2 transmissibility, viral load, and age in households. *medRxiv* 2021; published online June 4. https://doi.org/10.1101/2021.02.28.21252608 (preprint).

5 Liu Y, Rocklöv J. The reproductive number of the delta variant of SARS-CoV-2 is far higher compared to the ancestral SARS-CoV-2 virus. *J Travel Med* 2021; published online Aug 9. https://doi.org/10.1093/jtm/taab124.

6 Challen R, Dyson L, Overton CE, et al. Early epidemiological signatures of novel SARS-CoV-2 variants: establishment of B.1.617.2 in England. *medRxiv* 2021; published online June 7. https://doi.org/10.1101/2021.06.05.21258365 (preprint).

7 Sheikh A, McMenamin J, Taylor B, Robertson C. SARS-CoV-2 delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. *Lancet* 2021; **397:** 2461–62.

8 Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 (delta) variant. *N Engl J Med* 2021; **385:** 585–94.

9 Seppälä E, Veneti L, Starrfelt J, et al. Vaccine effectiveness against infection with the delta (B.1.617.2) variant, Norway, April to August 2021. *Euro Surveill* 2021; **26:** 2100793.

10 Public Health England. SARS-CoV-2 variants of concern and variants under investigation in England Technical briefing 20. Aug 6, 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1009243/Technical_Briefing_20.pdf (accessed Oct 21, 2021).

11 Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA COVID-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med* 2021; **384:** 1412–23.

12 Chung H, He S, Nasreen S, et al. Effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines against symptomatic SARS-CoV-2 infection and severe COVID-19 outcomes in Ontario, Canada: test negative design study. *BMJ* 2021; **374:** n1943.

13 Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med* 2020; **383:** 2603–15.

14 WHO. WHO COVID-19 case definition. 2020. https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2 (accessed Aug 19, 2021).

15 Ferguson NM, Kien DT, Clapham H, et al. Modeling the impact on virus transmission of wolbachia-mediated blocking of dengue virus infection of *Aedes aegypti*. *Sci Transl Med* 2015; **7:** 279ra37.

16 Elliott P, Haw D, Wang H, et al. REACT-1 round 13 final report: exponential growth, high prevalence of SARS-CoV-2 and vaccine effectiveness associated with delta variant in England during May to July 2021. https://spiral.imperial.ac.uk/bitstream/10044/1/90800/2/react1_r13_final_preprint_final.pdf (accessed Oct 21, 2021).

17 Pouwels K, Pritchard E, Matthews P, et al. Impact of delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. https://www.ndm.ox.ac.uk/files/coronavirus/covid-19-infection-survey/finalfinalcombinedve20210816.pdf (accessed Oct 21, 2021).

18 O'Toole Á, Hill V, Pybus OG, et al. Tracking the international spread of SARS-CoV-2 lineages B.1.1.7 and B.1.351/501Y-V2 with grinch. *Wellcome Open Res* 2021; **6:** 121.

19 Thompson HA, Mousa A, Dighe A, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) setting-specific transmission rates: a systematic review and meta-analysis. *Clin Infect Dis* 2021; **73:** e754–64.

20 House T, Pellis L, Pritchard E, McLean AR, Walker AS. Total effect analysis of vaccination on household transmission in the Office for National Statistics COVID-19 infection survey. *arXiv* 2021; published online July 14. http://arxiv.org/abs/2107.06545 (preprint).

21 de Gier B, Andeweg S, Joosten R, et al. Vaccine effectiveness against SARS-CoV-2 transmission and infections among household and other close contacts of confirmed cases, the Netherlands, February to May 2021. *Euro Surveill* 2021; **26:** 2100640.

22 Chau NVV, Ngoc NM, Nguyet LA, et al. An observational study of breakthrough SARS-CoV-2 Delta variant infections among vaccinated healthcare workers in Vietnam 2021. *E Clin Med* 2021; **41:** 101143

23 Ke R, Martinez PP, Smith RL, et al. Daily sampling of early SARS-CoV-2 infection reveals substantial heterogeneity in infectiousness. *medRxiv* 2021; published online July 12. https://doi.org/10.1101/2021.07.12.21260208 (preprint).

24 Kissler SM, Fauver JR, Mack C, et al. Densely sampled viral trajectories suggest longer duration of acute infection with B.1.1.7 variant relative to non-B.1.1.7 SARS-CoV-2. *medRxiv* 2021; published online Aug 25. https://doi.org/10.1101/2021.02.16.21251535 (preprint).

25 Jones TC, Biele G, Mühlemann B, et al. Estimating infectiousness throughout SARS-CoV-2 infection course. *Science* 2021; **373:** eabi5273.

26 Madera S, Crawford E, Langelier C, et al. Nasopharyngeal SARS-CoV-2 viral loads in young children do not differ significantly from those in older children and adults. *Sci Rep* 2021; **11:** 3044.

27 Riemersma KK, Grogan BE, Kita-Yarbro A, et al. Shedding of infectious SARS-CoV-2 despite vaccination when the delta variant is prevalent—Wisconsin, July 2021. Version 4. *medRxiv* 2021; published online Aug 24. https://doi.org/10.1101/2021.07.31.21261387 (preprint).

28 Brown CM, Vostok J, Johnson H, et al. Outbreak of SARS-CoV-2 infections, including COVID-19 vaccine breakthrough infections, associated with large public gatherings–Barnstable County, Massachusetts, July 2021. *MMWR Morb Mortal Wkly Rep* 2021; **70:** 1059–62.

29 Chia PY, Ong S, Chiew CJ, et al. Virological and serological kinetics of SARS-CoV-2 delta variant vaccine-breakthrough infections: a multi-center cohort study. *medRxiv* 2021; published online July 31. https://doi.org/10.1101/2021.07.28.21261295 (preprint).

30 Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. *Lancet Microbe* 2021; **2:** e13–22.

31 Viner RM, Mytton OT, Bonell C, et al. Susceptibility to SARS-CoV-2 infection among children and adolescents compared with adults: a systematic review and meta-analysis. *JAMA Pediatr* 2021; **175:** 143–56.

32 Shamier MC, Tostmann A, Bogers S, et al. Virological characteristics of SARS-CoV-2 vaccine breakthrough infections in health care workers. *medRxiv* 2021; published online Aug 21. https://doi.org/10.1101/2021.08.20.21262158 (preprint).