

EDITORIAL

Understanding Breakthrough Infections Following mRNA SARS-CoV-2 Vaccination

Michael Klompas, MD, MPH

The current surge in infections with the SARS-CoV-2 Delta variant has made it clear to health care workers and the public alike that fully vaccinated people remain at risk for SARS-CoV-2 infections. It is also apparent that breakthrough infections in fully



Related article

vaccinated people can sometimes be serious. As of October 21, 2021, for example, 35% of the 519 patients hospitalized with COVID-19 in Massachusetts had been fully vaccinated.¹ Furthermore, multiple reports have documented that if fully vaccinated individuals do become infected, their viral loads may be as high as the levels seen in unvaccinated individuals.² In July 2021, these observations led the US Centers for Disease Control and Prevention to modify its guidance for fully vaccinated people, advising that those in communities with substantial or high SARS-CoV-2 transmission rates should wear masks indoors regardless of their vaccination status.^{3,4} A wealth of new data has since emerged that is helping to deepen understanding of the frequency, severity, and importance of breakthrough infections in fully vaccinated individuals.

New evidence shows that even though fully vaccinated people remain at risk for SARS-CoV-2 infection, they are substantially less prone to carry SARS-CoV-2 compared with unvaccinated people. A point-prevalence survey of almost 100 000 people conducted in England in June-July 2021 during the height of that country's spring Delta variant surge found that fully vaccinated people ($n = 55\,962$) were two-thirds less likely to harbor SARS-CoV-2 compared with unvaccinated people ($n = 15\,135$), with absolute rates of 0.40% vs 1.21%, respectively.⁵ Likewise, in a randomized trial of the mRNA-1273 vaccine (Moderna) vs placebo, vaccinated participants ($n = 14\,287$) were two-thirds less likely to be asymptomatic carriers than unvaccinated participants ($n = 14\,164$), with absolute rates of 1.5% vs 3.5%, respectively (estimated vaccine effectiveness against asymptomatic infection, 63.0% [95% CI, 56.6%-68.5%]).⁶

Studies of viral dynamics further suggest that while viral loads in breakthrough infections may be as high in vaccinated individuals as they are in unvaccinated individuals, viral loads in those who are vaccinated decline more rapidly, and the virus that they shed is less likely to be culture-positive than virus shed by unvaccinated individuals.^{7,8} This suggests that people who are fully vaccinated are less likely to become infected and if infected, will be contagious for shorter periods than unvaccinated people. This is supported by transmission studies that confirm that vaccinated people are less likely to transmit SARS-CoV-2 to close contacts compared with unvaccinated people, including the

Delta variant.⁹ In a study of 7771 household contacts of 4921 index cases in the Netherlands, the rate of transmission from fully vaccinated household members was 13% vs 22% from unvaccinated household members (estimated vaccine effectiveness against transmission, 63% [95% CI, 46%-75%]).¹⁰ Similarly, in an English study of 151 821 contacts of 99 567 index patients, the rate of transmission from people fully vaccinated with BNT162b2 (Pfizer-BioNTech) was 23% vs 49% for transmission from unvaccinated people (adjusted odds ratio [aOR], 0.35 [95% CI, 0.26-0.48] for transmission of Delta to unvaccinated contacts; aOR, 0.10 [95% CI, 0.08-0.13] for transmission of Delta to fully vaccinated contacts).¹¹

Vaccines not only decrease transmission rates, but also decrease disease severity among individuals who do acquire infection. Vaccinated people with breakthrough infections, including infection with the Delta variant, are less likely to develop symptoms, less likely to develop severe symptoms, more likely to recover from their illness quickly, and much less likely to require hospitalization compared with unvaccinated people.^{8,12} As of August 28, 2021, the age-adjusted rate of hospitalization among US adults aged 18 years or older was 83.6 per 100 000 for unvaccinated persons compared with 4.5 per 100 000 for fully vaccinated persons.¹³

Nonetheless, the fact that vaccinated individuals can still become ill enough with COVID-19 to be hospitalized is understandably concerning. A valuable new study in this issue of *JAMA* by Tenforde and colleagues¹⁴ affirms the strong protection of mRNA vaccines against hospitalization overall and extends current understanding by delineating differences in protection against hospitalization depending on patients' immune status, age, vaccine preparation, time since vaccination, and infection with the Alpha vs Delta variants. The study further deepens understanding by demonstrating that vaccines are not only associated with a lower likelihood of hospitalization but are also associated with attenuation of the seriousness of illness during hospitalization among those who do require hospitalization.

Tenforde and colleagues performed a test-negative case-control study among 4513 adults hospitalized from March 11 to August 15, 2021 in 18 US states and compared vaccination rates among 1983 hospitalized case patients diagnosed with symptomatic, test-positive COVID-19 vs 2530 hospitalized control patients who tested negative for SARS-CoV-2.¹⁴ The investigators found that 15.8% of case patients with COVID-19 had been fully vaccinated vs 54.8% of control patients, an overall aOR for vaccination among patients hospitalized with COVID-19 of 0.15 (95% CI, 0.13-0.18), corresponding to estimated vaccine effectiveness of 85% to

prevent COVID-19 hospitalization (with vaccine effectiveness estimated as $[(1 - aOR) \times 100\%]$, whereby a lower aOR implies a higher vaccine effectiveness).

The strength of the association between hospitalization with COVID-19 and likelihood of vaccination varied considerably, however, depending on patients' immune function. Among immunocompetent hospitalized patients, 11.2% of COVID-19 cases were vaccinated vs 53.5% among controls (aOR for vaccination, 0.10 [95% CI, 0.09-0.13]) whereas 40.1% of immunocompromised patients hospitalized with COVID-19 were vaccinated vs 58.8% of immunocompromised controls (aOR for vaccination, 0.49 [95% CI, 0.35-0.69]). Protection against hospitalization was similar for the Alpha and Delta variants (aOR, 0.10 [95% CI, 0.06-0.16] for Alpha; aOR, 0.14 [95% CI, 0.10-0.21] for Delta). Likewise, the strength of the association between COVID hospitalization and likelihood of vaccination was similar across age groups.

There were important differences, however, between the mRNA-1273 and BNT162b2 vaccines, particularly among patients who had been vaccinated more than 120 days before hospitalization. The mRNA-1273 vaccine was somewhat more protective overall (aOR, 0.11 [95% CI, 0.08-0.14]) compared with the BNT162b2 vaccine (aOR, 0.19 [95% CI, 0.16-0.23]) ($P < .001$), but more marked differences became apparent when taking into consideration time since vaccination. The protective association against hospitalization for the BNT162b2 vaccine more than 120 days following vaccination declined notably (aOR, 0.36 [95% CI, 0.27-0.49]; median, 143 days from vaccine dose 2 to illness onset), whereas the effectiveness of the mRNA-1273 vaccine more than 120 days postvaccination was largely preserved (aOR, 0.15 [95% CI, 0.09-0.23]; median, 141 days from vaccine dose 2 to illness onset) ($P < .001$).

The investigators further quantified the association of vaccination with severity of illness during hospitalization among 1197 patients hospitalized with symptomatic COVID-19. Even though vaccinated individuals ($n = 142$ breakthrough cases) tended to be older and to have more comorbidities than unvaccinated individuals ($n = 1055$), vaccinated patients with COVID-19 were less likely to require intensive care (25% vs 40%), less likely to require invasive mechanical ventilation (7.7% vs 23%), and less likely to die (6.3% vs 8.6%). These differences persisted after risk adjustment: the odds of invasive mechanical ventilation or death by day 28 among vaccinated patients was significantly lower than among unvaccinated patients (12.0% vs 24.7%; aOR, 0.33 [95% CI, 0.19-0.58]).

A major limitation of the study is that the median interval from the second vaccine dose until onset of symptoms was only 111 days. This is important because multiple studies have reported substantial and progressive decreases in mRNA vaccine effectiveness over time, particularly for the BNT162b2 vaccine.¹⁵ Observational studies suggest that the effectiveness of the BNT162b2 vaccine more than 6 months

after inoculation may decrease by 50% or greater and that this has more to do with time since vaccination than the arrival of the Delta variant, except insofar as the high community incidence rates of SARS-CoV-2 infection associated with the Delta variant's arrival may be lowering vaccine effectiveness estimates because high community incidence rates lead to more opportunities for breakthrough cases and hence lower estimates of effectiveness.^{12,16,17} The observed decline in vaccine effectiveness has been most pronounced for milder infections, but the current study and parallel investigations in Qatar, Puerto Rico, and the US Veterans Health Administration suggest that there may be a parallel decrease in vaccine effectiveness against hospitalizations with the passage of more time.¹⁷⁻¹⁹

The current investigation by Tenforde et al¹⁴ highlights several factors that future studies of vaccine effectiveness will need to consider to provide as much clarity as possible. It is not sufficient to report vaccine effectiveness overall or against hospitalization as uniform monolithic values. This study and others demonstrate that it is crucial to differentiate between vaccine preparations and to tailor estimates to time since vaccination, participants' immune function, and community incidence rates.¹⁷⁻¹⁹ It is also important to differentiate between vaccine effectiveness against asymptomatic vs mildly symptomatic vs severely symptomatic infections because vaccines are least effective in preventing asymptomatic infections and most effective in preventing severe infections.^{6,12,17,18}

If, however, more observation time and additional studies confirm a substantial waning in the effectiveness of one or both mRNA vaccine preparations against hospitalizations, this would further increase the onus to use booster vaccinations. Data from Israel are consistent with many of the key observations in this study, namely, a significant increase in infections as well as hospitalizations starting about 6 months after vaccine rollout in a population that was mostly vaccinated with the BNT162b2 preparation.^{14,15} The good news is that the data from Israel also show that boosters appear capable of restoring protection against infections, hospitalizations, and deaths in all age groups.²⁰⁻²²

On balance, the study by Tenforde and colleagues offers equal measures of reassurance and concern. The reassurance is that mRNA vaccines are highly effective against hospitalizations, that this benefit is preserved against the Delta variant, and that when breakthrough infections lead to hospitalization, the clinical course is milder and less likely to require intubation or culminate in death. The concerns are that mRNA vaccines are much less effective in preventing hospitalizations for immunocompromised individuals compared with immunocompetent individuals and that protection against hospitalizations for all people may wane over time, particularly for the mRNA BNT162b2 vaccine. Fortunately, emerging data suggest boosters may mitigate these risks.

ARTICLE INFORMATION

Author Affiliations: Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston,

Massachusetts; Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts.

Corresponding Author: Michael Klompas MD, MPH, Department of Population Medicine, Harvard

Medical School and Harvard Pilgrim Health Care Institute, 401 Park Dr, Ste 401 E, Boston, MA 02215 (mklompas@bwh.harvard.edu).

Published Online: November 4, 2021.
doi:10.1001/jama.2021.19063

Conflict of Interest Disclosures: Dr Klompas reported receiving royalties from UpToDate and grant funding from the CDC, AHRQ, and Massachusetts Department of Public Health for research unrelated to the content of this article.

REFERENCES

1. Massachusetts Department of Public Health. COVID-19 Interactive Data Dashboard. Accessed October 24, 2021. <https://www.mass.gov/info-details/covid-19-response-reporting#covid-19-interactive-data-dashboard>
2. 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(31):1059-1062. doi:10.15585/mmwr.mm7031e2
3. Mandavilli A. As infections rise, CDC urges some vaccinated Americans to wear masks again. *New York Times*. July 27, 2021.
4. Centers for Disease Control and Prevention. Use masks to slow the spread of COVID-19. Updated August 12, 2021. Accessed October 24, 2021. <https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/diy-cloth-face-coverings.html>
5. Elliott P, Haw D, Wang H, et al; COVID-19 Genomics UK (COG-UK) Consortium11. Exponential growth, high prevalence of SARS-CoV-2, and vaccine effectiveness associated with the Delta variant. *Science*. 2021;eab19551. Published online November 2, 2021. doi:10.1126/science.abl9551
6. El Sahly HM, Baden LR, Essink B, et al; COVE Study Group. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. *N Engl J Med*. Published online September 22, 2021. doi:10.1056/NEJMoa2113017
7. Ke R, Martinez PP, Smith RL, et al. Longitudinal analysis of SARS-CoV-2 vaccine breakthrough infections reveal limited infectious virus shedding and restricted tissue distribution. *medRxiv*. Preprint posted online September 2, 2021. doi:10.1101/2021.08.30.21262701
8. Chia PY, Xiang Ong SW, Chiew CJ, et al. Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-breakthrough infections: a multi-center cohort study. *medRxiv*. Preprint posted online July 31, 2021. doi:10.1101/2021.07.28.21261295
9. Shah ASV, Gribben C, Bishop J, et al. Effect of vaccination on transmission of SARS-CoV-2. *N Engl J Med*. Published online October 28, 2021. doi:10.1056/NEJMc2106757
10. de Gier B, Andeweg S, Backer JA, et al. Vaccine effectiveness against SARS-CoV-2 transmission to household contacts during dominance of Delta variant (B.1.617.2), August-September 2021, the Netherlands. *medRxiv*. Preprint posted online October 14, 2021. doi:10.1101/2021.10.14.21264959
11. Eyre DW, Taylor D, Purver M, et al. The impact of SARS-CoV-2 vaccination on Alpha & Delta variant transmission. *medRxiv*. Preprint posted online October 15, 2021. doi:10.1101/2021.09.28.21264260
12. Tartof SY, Slezak JM, Fischer H, 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*. 2021;398(10309):1407-1416. doi:10.1016/S0140-6736(21)02183-8
13. Centers for Disease Control and Prevention. COVID Data Tracker. Rates of laboratory-confirmed COVID-19 hospitalizations by vaccination status. Accessed October 24, 2021. <https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination>
14. Tenforde MW, Self WH, Adams K, et al; Influenza and Other Viruses in the Acutely Ill (IVY) Network. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. *JAMA*. Published online November 4, 2021. doi:10.1001/jama.2021.19499
15. Thomas SJ, Moreira ED Jr, Kitchin N, et al; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. *N Engl J Med*. Published online September 15, 2021. doi:10.1056/NEJMoa2110345
16. Thompson MG, Burgess JL, Naleway AL, et al. Prevention and attenuation of Covid-19 with the BNT162b2 and mRNA-1273 vaccines. *N Engl J Med*. 2021;385(4):320-329. doi:10.1056/NEJMoa2107058
17. Chemaitelly H, Tang P, Hasan MR, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. *N Engl J Med*. Published online October 6, 2021. doi:10.1056/NEJMoa2114114
18. Robles Fontán MM, Nieves EG, Gerena IC, Irizarry RA. Time-varying effectiveness of three Covid-19 vaccines in Puerto Rico. *medRxiv*. Preprint posted online October 20, 2021. doi:10.1101/2021.10.17.21265101
19. Cohn BA, Cirillo PM, Murphy CC, Krigbaum NY, Wallace AW. Breakthrough SARS-CoV-2 infections in 620,000 U.S. veterans, February 1, 2021 to August 13, 2021. *medRxiv*. Preprint posted online October 14, 2021. doi:10.1101/2021.10.13.21264966
20. Bar-On YM, Goldberg Y, Mandel M, et al. Protection of BNT162b2 vaccine booster against Covid-19 in Israel. *N Engl J Med*. 2021;385(15):1393-1400. doi:10.1056/NEJMoa2114255
21. Bar-On YM, Goldberg Y, Mandel M, et al. Protection across age groups of BNT162b2 vaccine booster against Covid-19. *medRxiv*. Preprint posted online October 7, 2021. doi:10.1101/2021.10.07.21264626
22. Barda N, Dagan N, Cohen C, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *Lancet*. Published online October 29, 2021. doi:10.1016/S0140-6736(21)02249-2