

Breakthrough SARS-CoV-2 infections after COVID-19 immunization

Joshua Hirsh, Thwe Htay, Shubhang Bhalla, Victoria Nguyen, Jorge Cervantes 

Medical Education, Texas Tech University Health Sciences Center El Paso Paul L Foster School of Medicine, El Paso, Texas, USA

Correspondence to
Dr Jorge Cervantes, Texas Tech University Health Sciences Center El Paso Paul L Foster School of Medicine, El Paso, TX 79905, USA; jorge.cervantes@ttuhsc.edu

Accepted 13 April 2022
Published Online First
29 June 2022

ABSTRACT

As no vaccines are 100% effective at preventing illness, COVID-19 vaccine breakthrough cases are expected. We here aim to review the most recent literature on COVID-19 vaccine breakthrough infections. SARS-CoV-2 breakthrough infections are, in general, rare. Age may still be a factor in SARS-CoV-2 infections in immunized individuals.

THE EFFICACY OF COVID-19 VACCINES

Current evidence strongly suggests that COVID-19 vaccines offer protection against SARS-CoV-2 and its variants.¹ Vaccines to prevent severe forms of the COVID-19 are effective and are a critical tool to bring the pandemic under control.² There is no vaccine that provides absolute protection against any infection, and COVID-19 is no exception. Therefore, some individuals who have been vaccinated will still get COVID-19 breakthrough infection.

As currently used, COVID-19 vaccines aim to prevent the development of severe symptomatology, rather than preventing infection by SARS-CoV-2. Asymptomatic or mild infections among vaccinated people will still occur. Nevertheless, real-world data after the initial clinical trials showed that the BNT162b2 (Pfizer-BioNTech COVID-19 vaccine) reduced asymptomatic infections greatly.^{3,4}

The two mRNA COVID-19 vaccines authorized for use in the USA showed a 94.1% (mRNA-1273, Moderna COVID-19 vaccine) and 95% efficacy (BNT162b2 Pfizer COVID-19 vaccine) for the prevention of symptomatic SARS-CoV-2 infection at 14 and 7 days after the second dose, respectively.⁵ The third approved vaccine in the USA based on an adenovirus vector, Ad26.COV2.S (Janssen/Johnson & Johnson COVID-19 vaccine), showed a global efficacy of 66% and 100% against hospitalizations and death, respectively.^{6–8} The Centers for Disease Control and Prevention (CDC)-collected data from participating health programs report breakthrough infection rates with vaccine products: 125.77, 86.63, and 150.39 events per 100,000 population in BNT162b2, mRNA-1273, and Ad26.COV2.S, respectively.⁹

The COVID-19 vaccine targets the envelope spike protein S of the virus. This is a major structural protein exposed at the virus surface

whose receptor-binding domain (RBD) region mediates host cell receptor binding after undergoing conformational change.¹⁰

SARS-COV-2 VARIANTS

RNA viruses, in general, have high mutation rates that correlate with enhanced virulence considered beneficial for the virus.¹¹ However, not all mutations lead to significant advantageous features for the virus. From 65,776 variants, 5775 were distinct variants, with most of them being missense or synonymous mutations in the non-coding regions, followed by non-coding deletions, in-frame deletions, non-coding insertions, stop codon variants, frame-shift deletions, and in-frame insertions. One mutation, D614 G interferes with the binding affinity of SARS-CoV-2 to the human host cell receptor ACE2. This mutation is associated with an increased transmissibility of the virus.¹⁰

There are currently two variants of concern (VOCs) in the USA, Delta strain (B.1.617.2 and AY lineages) and Omicron (B.1.1.529 and BA lineages).¹² From November 20, 2021 to December 12, 2021, the Delta B.1.617.2 lineage was responsible for over 90% of COVID-19 cases in the USA. Since then, a sharp decline in the incidence of Delta infections was observed. From January 1, 2022 to the most recent data collection on February 19, 2022, Omicron lineages B.1.1.529 and BA 1.1 have been responsible for over 95% of new COVID-19 cases.¹² Throughout the last week of February up to March 5, 2022, the Omicron variants were responsible for 100% of new cases.¹³

The RBD region appears to remain conserved in SARS-CoV-2 isolates. However, some mutations in the S protein could impact the pathogenicity of the virus. SARS-CoV-2 genetic variability can impact vaccine protection as mutations may lead to escape from immune recognition,¹⁴ thus affecting the efficacy of vaccines in certain geographic locations.

BREAKTHROUGH INFECTIONS AND PROTECTION AGAINST VARIANTS

A COVID-19 vaccine breakthrough infection is defined as the detection of SARS-CoV-2 RNA or antigen in a respiratory specimen collected from a person ≥ 14 days after receipt of all recommended doses of a Food and Drug Administration-authorized COVID-19



► <http://dx.doi.org/10.1136/jim-2022-002520>



© American Federation for Medical Research 2022. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Hirsh J, Htay T, Bhalla S, et al. *J Invest Med* 2022;**70**:1429–1432.

Table 1 Reports of SARS-CoV-2 breakthrough infections in COVID-19 vaccinated populations

Study	Location	Vaccine	Population	Breakthrough percentage (%)	Breakthrough counts
Dyer ¹⁶	USA	BNT162b2 and mRNA-1273	Entire population	0.01	5800/77 million
Hall ³	England	None (prevaccine) PCR/Antibody+	Public hospital workers	0.67	44/6614
Keehner ⁵	California, USA	BNT162b2 and mRNA-1273	UCSD and UCLA healthcare workers	0.05	7/14,990
Pollett ¹⁸	USA	BNT162b2 and mRNA-1273	Military health system	1.55	24/1547
		BNT162b2		1.42	22/1547
		mRNA-1273		0.13	2/1547
Ramirez ⁴³	USA	BNT162b2, mRNA-1273 and Ad26.COV2.S	University students and employees	0.55	14/2551
		BNT162b2		0.24	6/2551
		mRNA-1273		0.20	5/2551
		Ad26.COV2.S		0.12	3/2551
Hacisuleyman ⁴⁴	USA	BNT162b2 and mRNA-1273	University students	4.79	2/417
Teran ⁴⁵	Chicago, USA	Unspecified	Skilled nursing facility staff and residents	0.15	22/14,765
Tenforde ²⁹	US hospitals	BNT162b2 and mRNA-1273	Hospital patients	43.9	1983/4513
Tenforde ⁴²	US hospitals	BNT162b2 and mRNA-1273×2 doses	Hospital patients	31	212/679
		BNT162b2 and mRNA-1273×3 doses		8	10/131

UCLA, University of California Los Angeles; UCSD, University of California San Diego.

vaccine.¹⁵ SARS-CoV-2 breakthrough infections are, in general, rare¹⁶ (table 1).

RNA viruses have remarkable higher mutation rates compared with their hosts.¹¹ Vaccines appear to preferentially block viruses that are the most genetically in common with the vaccine insert.¹⁴ This would lead to breakthrough infections in vaccinated individuals from viruses more genetically distant from the vaccine insert.

A few cohort studies done in healthcare workers reported a risk of testing positive for SARS-CoV-2 after vaccination to be higher than the risks reported in the initial vaccine clinical trials.⁵ It is possible that the higher infection rate could be due to breakthrough infections by variants, as in India, B.1.1.7 variants appear to be important in breakthrough infections among healthcare workers.¹⁷ A recent study in US military population vaccinated with BNT162b2 or mRNA-1273 vaccine showed that breakthrough infections included VOC B.1.1.7, P.1, and B.1.429,¹⁸ underscoring the emerging vaccine escape risk of the P.1 and B.1.429 variants.

By July 2021, 46,312 SARS-CoV-2 breakthrough infections within 13 Jurisdiction in the USA had been reported. Eight per cent (2976) of hospitalizations were from fully vaccinated individuals, and 9% (616) of deaths occurred in fully vaccinated individuals.¹⁹ The surge of the Delta (B.1.617.2) variant emphasized a persistent risk and danger of infection by new COVID-19 variants. Estimates from 16 US jurisdictions indicate that unvaccinated individuals have a 6.1 increased risk of testing positive and 11.3 higher risk of mortality associated with COVID-19 when compared with vaccinated individuals.¹⁹ Meta-analytical data of reports by early September 2021 showed an incidence of 113.66 per 100,000 population of COVID-19 diagnosis in vaccinated individuals.²⁰ An age-adjusted comparison of vaccination status revealed an approximately equal incidence and mortality ratio. However, within the vaccinated cohort,

ages 30–49 years had the highest incidence of breakthrough infection (129.10 per 100,000), followed by ages 18–29, 50–64, and 12–17, respectively.^{20–21} Vaccinated individuals aged 80 years and above had the highest mortality associated with COVID-19 infection.²⁰ It is important to note that not all hospitalizations and deaths of those fully vaccinated and diagnosed with COVID-19 are due to COVID-19. CDC reports from July 2021 indicate that of 5601 hospitalized breakthrough cases, 27% were asymptomatic, and that of 1.141 fatal cases, 26% were asymptomatic or not related to COVID-19.¹⁹

Region and population-specific data help identify and project the trajectory of breakthrough infections with SARS-CoV-2-associated variants.^{22–23} Vermont, Rhode Island, and Massachusetts are states with high vaccination rates, which provide comprehensive population data regarding breakthrough infections.²⁴ Fully vaccinated population in Vermont is 71.81%, and 1% of this population (4881 cases) account for breakthrough infections. The Vermont Department of Health reports 134 hospitalizations and 59 deaths associated with breakthrough cases between January and September 2021.²⁵ Rhode Island has approximately 71.47% of the state's population fully vaccinated, and this population of fully vaccinated individuals account for only one-sixth of total COVID-19 diagnoses, 4.9% of hospitalization rates and 2.7% total deaths compared with the unvaccinated cohort.^{26–27} Data from Massachusetts in October 2021 suggest that breakthrough cases, hospitalizations, and deaths are significantly lower among the vaccinated cohort (1.02%, 0.03%, and 0.008%, respectively).²⁸

The most recent longitudinal study in the USA correlated the association of BNT162b2 vaccine and hospitalization among vaccinated versus unvaccinated cohorts in 18 US states.²⁹ The investigators found that 54.8% of unvaccinated individuals required hospitalization compared with only 15.8% of vaccinated individuals. Notably, vaccinated

patients were less likely to require invasive treatment and intensive care.²⁹ It is possible that breakthrough infections may occur predominantly in individuals with comorbidities, but this association requires further exploration.

Current vaccine data also suggest that full vaccination status correlates with decreased COVID-19 severity among cases of active infection, including Delta variant infections.²⁹ COVID-19 vaccination seems to reduce the viral load in breakthrough infections.³⁰ While there is evidence that viral loads in breakthrough infections can be as high in vaccinated individuals as in unvaccinated individuals, the rate of viral load decrease is more rapid in vaccinated individuals.^{29,31} This may translate clinically as less severe illness after vaccination. Patients who have recovered from COVID-19 can still be re-infected³² but without developing clinical symptoms. The phenomenon of antibody-dependent enhancement, postulated for sequential infections with different dengue virus genotype, is unlikely to occur with SARS-CoV-2 breakthrough infections.³³ A point-prevalence study (n=100,000) in England during the peak of the country's B.1.617.2 surge found that fully vaccinated people (n=55,962) were 2/3 less likely to act as carriers for SARS-CoV-2 compared with unvaccinated people.³⁴ A randomized controlled trial comparing mRNA-1273 vaccine with placebo reported comparable results.^{35,36}

Full vaccination status may also affect transmission as it provides a shorter period of contagiousness. Transmission studies have suggested that vaccinated individuals are less likely to transmit SARS-CoV-2, including the Delta variant.³¹ A study in England on COVID-19 contact positive individuals reported that the rate of transmissions from individuals fully vaccinated with BNT162b2 vaccine was 23% compared with the 49% transmission rate from unvaccinated individuals.³⁷ A report from the Netherlands showed a similar reduction in transmission between the vaccination cohorts.³⁸

OMICRON VARIANT

It is important to note that data obtained on Omicron breakthrough rates are relatively sparse. All information provided to the CDC is voluntary and therefore may not give an accurate picture of breakthrough rates. However, a study conducted between November and December 2021 showed that a group of seven Germans visiting Cape Town, South Africa all developed symptomatic infections with the Omicron variant despite full vaccination and a booster dose. Of this group, 5/7 had homologous vaccination course with BNT162b2 (Pfizer) and 2/7 had a heterologous vaccination course, using three full doses CX-024414 (Moderna), not recommended at the time, and a combination of ChAdOx1-S (AstraZeneca) and BNT162b2. None of these individuals required hospitalization and symptoms were rated as 3–4 on the National Institutes of Health COVID-19 Treatment Guidelines.³⁹ Asymptomatic breakthroughs, as with the other variants, can go completely undetected and can only be gauged by estimates. Data estimating the protection conferred by two vaccine doses show ~40% a few months after the second dose and increases to ~60%–70% within a couple weeks of receiving the booster.⁴⁰ In the first WHO International Standard, there was a predicted ± 40 -fold reduction of antibody neutralization for Omicron strains.

A serum study of 17 medical providers from a Stockholm University were analyzed and showed a 1-fold to 23-fold reduction in neutralization ability. All 17 of these individuals had COVID-19 and were fully vaccinated thereafter.⁴¹ Based off of evidence of decreased efficacy of the variant it can be inferred that breakthrough infections will be more common than with other variants. The CDC compiled data from 21 hospitals across 18 US States documenting vaccine breakthrough rates from August to December 2021. Although the variants of concern are not specified, the Omicron variant grew in predominance in November and December. Of the 679 patients that received 2 doses of an mRNA vaccine, 212 tested positive for COVID-19. In patients that received 3 doses of an mRNA vaccine, 10/131 tested positive.⁴² While the data are not specific for the omicron variant, it shows 31% and 8% breakthrough (table 1), respectively, when Omicron was first being detected.

CONCLUSION

In conclusion, there will be a very small percentage of people who, despite being fully vaccinated, will still present symptomatology, face hospitalization, or die from COVID-19. Thus, identification and detailed characterization of the effects of a particular mutation for the pathogenesis of SARS-CoV-2 is crucial. We should continue our efforts for sequencing and tracking SARS-CoV-2 evolution as the pandemic continues and adjust immunization strategies accordingly.

Contributors TH and JC conceptualized the study. JH and SB acquired the data. JH, TH, SB, VN, and JC wrote the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iD

Jorge Cervantes <http://orcid.org/0000-0002-4359-5951>

REFERENCES

- 1 Tavilani A, Abbasi E, Kian Ara F, et al. COVID-19 vaccines: current evidence and considerations. *Metabol Open* 2021;12:100124.
- 2 Hotez PJ, Nuzhath T, Callaghan T, et al. COVID-19 vaccine decisions: considering the choices and opportunities. *Microbes Infect* 2021;23:104811.
- 3 Hall VJ, Foulkes S, Charlett A, et al. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (siren). *Lancet* 2021;397:1459–69.
- 4 Tande AJ, Pollock BD, Shah ND, et al. Impact of the coronavirus disease 2019 (COVID-19) vaccine on asymptomatic infection among patients undergoing Preprocedural COVID-19 molecular screening. *Clin Infect Dis* 2022;74:59–65.
- 5 Keehner J, Horton LE, Pfeffer MA, et al. SARS-CoV-2 infection after vaccination in health care workers in California. *N Engl J Med* 2021;384:1774–5.
- 6 Inc. JB. FDA Briefing document. Janssen Ad26.COV2.S vaccine for the prevention of COVID-19, 2021.
- 7 El Chaar M, King K, Galvez Lima A. Are black and Hispanic persons disproportionately affected by COVID-19 because of higher obesity rates? *Surg Obes Relat Dis* 2020;16:1096–9.
- 8 Tirupathi R, Muradova V, Shekhar R, et al. COVID-19 disparity among racial and ethnic minorities in the US: a cross sectional analysis. *Travel Med Infect Dis* 2020;38:101904.
- 9 Self WH, Tenforde MW, Rhoads JP, et al. Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing

- COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions - United States, March-August 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1337–43.
- 10 Dos Santos WG. Impact of virus genetic variability and host immunity for the success of COVID-19 vaccines. *Biomed Pharmacother* 2021;136:111272.
 - 11 Duffy S. Why are RNA virus mutation rates so damn high? *PLoS Biol* 2018;16:e3000003.
 - 12 Prevention CfDca.. About variants of the virus that causes COVID-19, 2021. Available: <https://www.cdc.gov/coronavirus/2019-ncov/transmission/variant.html>
 - 13 Control CfD. Variant proportions 2021, 2021. Available: <https://covid.cdc.gov/covid-data-tracker/#variant-proportions>
 - 14 Rolland M, Gilbert PB. Sieve analysis to understand how SARS-CoV-2 diversity can impact vaccine protection. *PLoS Pathog* 2021;17:e1009406.
 - 15 CDC. COVID-19 breakthrough case investigations and reporting, 2021. Available: <https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html>
 - 16 Dyer O. Covid-19: US reports low rate of new infections in people already vaccinated. *BMJ* 2021;373:n1000.
 - 17 Philomina J B, Jolly B, John N, et al. Genomic survey of SARS-CoV-2 vaccine breakthrough infections in healthcare workers from Kerala, India. *J Infect* 2021;83:237–79.
 - 18 Pollett SD, Richard SA, Fries AC. The SARS-CoV-2 mRNA vaccine breakthrough infection phenotype includes significant symptoms, live virus shedding, and viral genetic diversity. *Clin Infect Dis* 2022;74:897–900.
 - 19 Prevention CfDca. Monitoring incidence of COVID-19 cases, hospitalizations, and deaths, by vaccination status - 13 U.S. jurisdictions, April 4–July 17, 2021, 2021. Available: https://www.cdc.gov/mmwr/volumes/70/wr/mm7037e1.htm?s_cid=mm7037e1_w#T1_down
 - 20 Prevention CfDca. CDC COVID data Tracker, 2021. Available: https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total%0Ahttps://covid.cdc.gov/covid-data-tracker/#vaccinations-pregnant-women%0Ahttps://covid.cdc.gov/covid-data-tracker/#datatracker-home%0Ahttps://covid.cdc.gov/covid-data-trac
 - 21 Oran DP, Topol EJ. The proportion of SARS-CoV-2 infections that are asymptomatic. *Ann Intern Med* 2021;174:1344–5.
 - 22 Klompas M. Understanding breakthrough infections following mRNA SARS-CoV-2 vaccination. *JAMA* 2021;326:2018–20.
 - 23 Center JHCR. State breakthrough case data inconsistencies, 2021. Available: <https://coronavirus.jhu.edu/pandemic-data-initiative/data-outlook/the-state-of-state-level-breakthrough-case-reporting>
 - 24 Times TNY. Covid-19 vaccinations: County and state Tracker, 2021. Available: <https://www.nytimes.com/interactive/2020/us/covid-19-vaccine-doses.html>
 - 25 Health VDo. Testing 2021. Available: <https://www.healthvermont.gov/covid-19/testing>
 - 26 Bozio CH, Grannis SJ, Naleway AL, et al. Laboratory-Confirmed COVID-19 Among Adults Hospitalized with COVID-19-Like Illness with Infection-Induced or mRNA Vaccine-Induced SARS-CoV-2 Immunity - Nine States, January–September 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1539–44.
 - 27 Health RiDo.. Ri department of health COVID-19 response, 2021. Available: <https://ri-department-of-health-covid-19-response-vaccine-data-rihealth.hub.arcgis.com/>
 - 28 Massachusetts Co. Massachusetts COVID-19 vaccination data and updates, 2021. Available: <https://www.mass.gov/info-details/massachusetts-covid-19-vaccination-data-and-updates>
 - 29 Tenforde MW, Self WH, Adams K, et al. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. *JAMA* 2021;326:2043–54.
 - 30 Petter E, Mor O, Zuckerman N. Initial real world evidence for lower viral load of individuals who have been vaccinated by BNT162b2. *medRxiv* 2021.
 - 31 Chia PY, Ong SWX, Chiew CJ, et al. Virological and serological kinetics of SARS-CoV-2 delta variant vaccine breakthrough infections: a multicentre cohort study. *Clin Microbiol Infect* 2022;28:612.e1–612.e7.
 - 32 Nainu F, Abidin RS, Bahar MA, et al. SARS-CoV-2 reinfection and implications for vaccine development. *Hum Vaccin Immunother* 2020;16:3061–73.
 - 33 Halstead SB, Katzelnick L. COVID-19 vaccines: should we fear ade? *J Infect Dis* 2020;222:1946–50.
 - 34 Elliott P, Haw D, Wang H, et al. Exponential growth, high prevalence of SARS-CoV-2, and vaccine effectiveness associated with the delta variant. *Science* 2021;374:eabl9551.
 - 35 El Sahly HM, Baden LR, Essink B, et al. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. *N Engl J Med* 2021;385:1774–85.
 - 36 Thomas SJ, Moreira ED, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. *N Engl J Med* 2021;385:1761–73.
 - 37 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;398:1407–16.
 - 38 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), the Netherlands, August to September 2021. *Euro Surveill* 2021;26.
 - 39 Kuhlmann C, Mayer CK, Claassen M, et al. Breakthrough infections with SARS-CoV-2 omicron despite mRNA vaccine booster dose. *Lancet* 2022;399:625–6.
 - 40 Willyard C. What the omicron wave is revealing about human immunity. *Nature* 2022;602:22–5.
 - 41 Callaway E. Omicron likely to weaken COVID vaccine protection. *Nature* 2021;600:367–8.
 - 42 Tenforde MW, Patel MM, Gaglani M, et al. Effectiveness of a Third Dose of Pfizer-BioNTech and Moderna Vaccines in Preventing COVID-19 Hospitalization Among Immunocompetent and Immunocompromised Adults - United States, August–December 2021. *MMWR Morb Mortal Wkly Rep* 2022;71:118–24.
 - 43 Ramirez E, Wilkes RP, Carpi G. . SARS-CoV-2 breakthrough infections in fully vaccinated individuals. *MedRxiv* 2021.
 - 44 Hacisuleyman E, Hale C, Saito Y, et al. Vaccine breakthrough infections with SARS-CoV-2 variants. *N Engl J Med* 2021;384:2212–8.
 - 45 Teran RA, Walblay KA, Shane EL, et al. Postvaccination SARS-CoV-2 Infections Among Skilled Nursing Facility Residents and Staff Members - Chicago, Illinois, December 2020–March 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:632–8.