

Public health investigations of COVID-19 vaccine breakthrough cases

Case investigation protocol

Background

As of the end of March 2021, >30 million coronavirus disease 2019 (COVID-19) cases and >546,000 COVID-related deaths had been reported in the United States.¹ Safe and effective COVID-19 vaccines are an important tool in controlling the pandemic. The U.S. Food and Drug Administration (FDA) has issued Emergency Use Authorization (EUA) for three COVID-19 vaccines.² In large, randomized controlled trials, each vaccine was safe and efficacious for preventing symptomatic, laboratory-confirmed COVID-19 disease.³⁻⁵ There were no statistically significant differences in efficacy by age, gender, race, or comorbidities. Despite the high level of efficacy, a small number of breakthrough cases occurred. The phase 3 studies have not yet identified risk factors for vaccine breakthrough cases; however, approximately 44,000 people received the FDA-authorized vaccines during the clinical trials and follow-up is ongoing. In addition, several other COVID-19 vaccines are in late-stage development.⁶

As FDA-authorized COVID-19 vaccines are administered more broadly, it will be important to monitor breakthrough cases to identify unexpected trends or clustering in the patients (i.e., demographics, geography, underlying medical conditions, time since vaccine receipt, and clinical severity), the administered vaccine (i.e., type, dosing, lot, storage, and handling), or infecting virus (i.e., variant strains and mutations). While some studies have found that neutralizing antibodies persist for months following natural infection with SARS-CoV-2, others have detected some waning immunity over time.⁷⁻⁹ Some of the FDA-authorized COVID-19 vaccines require strict temperature control.¹⁰⁻¹² Vaccine failures could result from partial vaccine degradation due to inadequate cold chain or other issues during shipping, storage, or administration. The current FDA-authorized vaccines, and the majority COVID-19 vaccines in late-stage development, target the SARS-CoV2 spike glycoprotein.^{6,13} In recent months, five SARS-CoV-2 variants of concern have emerged that contain mutations in the spike glycoprotein (i.e., B.1.1.7, B.1.351, P.1, B.1.427, and B.1.429).¹⁴⁻¹⁶ The B.1.1.7 lineage was first detected in the United Kingdom, the B.1.351 lineage was first identified in South Africa, the P.1 lineage was identified in travelers from Brazil, and the B.1.427, and B.1.429 lineages emerged in California. Preliminary data suggest these variant strains may be more transmissible or cause increased severity of disease.¹⁴⁻¹⁷ At least one *in vitro* study suggests the B.1.351 variant might be neutralized less effectively by convalescent plasma from patients infected with other strains of SARS-CoV-2.^{17,18} There is mixed evidence regarding whether these variant strains are less susceptible to vaccine-induced immunity.¹⁹⁻²⁵ However, it will be important to detect vaccine breakthrough cases that may result from shifts in the susceptibility of circulating viral strains.

This protocol can be used to guide public health investigations of COVID-19 vaccine breakthrough cases. We aim to capture both symptomatic and asymptomatic infections. Characterization of vaccine breakthrough cases could provide the first indication that a vaccine is less effective in certain demographic groups or that vaccine-induced immunity is waning and booster doses may be needed. Clustering of cases among vaccinated persons by time, geographic area, or lot could help identify an issue in manufacturing, shipping, handling, or administration. Evaluating SARS-CoV-2 strains that cause vaccine breakthrough cases provides one way to monitor for variant strains that could result in lower vaccine efficacy.

Objective

Investigate SARS-CoV-2 infections among people who received COVID-19 vaccine to identify trends or clustering in patient characteristics, the administered vaccine, or the infecting virus.

Case definition

For the purpose of this investigation, a vaccine breakthrough case will be defined as a U.S. resident who has SARS-CoV-2 RNA or antigen detected on a respiratory specimen collected ≥ 14 days after completing the primary series of an FDA-authorized SARS-CoV-2 vaccine. An acceptable respiratory specimen includes a nasal swab, nasal wash, nasopharyngeal swab, oropharyngeal swab, saliva, sputum, bronchoalveolar lavage fluid, pleural fluid, or lung tissue.

A case will be excluded from further investigation if: 1) they received a COVID-19 vaccine that is not authorized or approved by FDA; 2) the respiratory specimen that was positive for SARS-CoV-2 RNA or antigen was collected < 14 days after completing the primary series; or 3) the person was recently positive for COVID-19, defined as a positive test < 45 days prior to the positive test currently under investigation.

Case finding and investigation

Cases will be reported to CDC through state or territorial health departments. These health departments will enter, store, and manage data for cases in their jurisdiction directly in the national COVID-19 vaccine breakthrough REDCap database. Local health departments, laboratories, or healthcare providers who identify a possible case will be directed to their state health department for further investigation and reporting to the national system.

CDC will monitor the National Notifiable Diseases Surveillance System (NNDSS) and Vaccine Adverse Event Reporting System (VAERS) for additional cases. For cases that meet the criteria, CDC will upload available data reported to those systems into the national vaccine breakthrough REDCap database. Health department staff will review and confirm the available information from previously completed case investigations. If needed, the health department staff will complete the investigation by reviewing the patient's medical record, contacting the patient's healthcare provider, or interviewing the case-patient. If a case-patient is contacted, they should be provided with a basic information sheet regarding the evaluation (**Appendix A**).

Data collection

The case investigation will include case-patient demographics, laboratory confirmation, COVID-19 vaccination history, underlying medical conditions, clinical signs and symptoms, COVID-19-related medical care, hospitalization, ICU care, outcome, and available specimens (**Appendix B**). To ensure complete capture of COVID-19 vaccination history, health department staff should query various sources of information, including a COVID-19 vaccination record card, the participant medical record, and the state immunization information system. Clinical outcome data should be updated when clinical status changes are known after initial data entry. For vaccine breakthrough cases with an outcome of death, health departments will be asked to upload a copy of the death certificate in the REDCap database linked to the case so that a determination could be made if COVID-19 contributed to the cause of death.

Specimen collection and testing

Respiratory specimen that tested positive for SARS-CoV-2 RNA or antigen

The investigating health department should contact the laboratory that performed the diagnostic test confirming the case-patient was positive for SARS-CoV-2 RNA or antigen. If available, RNA sequence data will be collected to characterize the infecting strain, sequence, or mutations (**Appendix C**). The laboratory is requested to send any residual primary respiratory specimen for additional testing at CDC. If a sample is available and sequencing was not already completed, CDC will perform RT-PCR and whole genome sequencing on the remaining primary specimen.

New respiratory specimen for SARS-CoV-2 RNA

In selected cases of public health importance, if the original specimen is not available, an additional respiratory sample may be collected if this can occur ≤ 10 days after respiratory specimen that tested positive for SARS-CoV-2 RNA or antigen (**Appendix C**). The nasal or nasopharyngeal swab will be sent to CDC for SARS-CoV-2 RT-PCR to extract and amplify RNA. If successful, sequencing will be performed on the viral RNA to characterize the infecting strain, sequence, or mutations. Additional analyses evaluating viral binding and neutralization also may be performed if viable virus is isolated.

Shipping specimens to CDC

Samples will be shipped to CDC labeled only with the project ID, the state case ID, and the case's study ID that is generated at the initiation of the REDCap data entry for each case. Samples will be processed through the CDC Sample Triage and Tracking (STAT) lab and moved to appropriate laboratories for testing (**Appendix C**).

Data entry and management

CDC has developed a national COVID-19 vaccine breakthrough REDCap database with data access groups so designated state health department investigators can enter, store, and manage data for cases in their jurisdiction. The health department investigator will have full access to data for cases reported from their jurisdiction. Case data and laboratory specimen information will be identified using the study ID assigned by REDCap. If a state health department chooses not to enter case information directly into the national database, CDC can provide a REDCap survey or help the state establish a database that can be synched with the national database.

Data analysis

Data will be aggregated across all reported cases and analyzed at CDC using SAS version 9.4 (SAS Institute, Cary, NC). Ongoing monitoring will be performed to identify possible clusters by time, geographic location, or vaccine type or lot number. Characteristics of cases will be compared using chi-square tests or Fisher's exact tests for categorical variables or median or Wilcoxon rank-sum tests for continuous variables. The analysis will be stratified by the type of laboratory confirmation (i.e., SARS-CoV-2 RNA or antigen) and whether the patient meets the national surveillance case definition clinical criteria for symptomatic COVID-19 disease.²⁶

The SARS-CoV-2 sequence results will be reported to the state health department, state public health laboratory, and submitting laboratory. The sequence results will not be shared with the provider nor individual because non-CLIA-approved tests will be used. All data will

be shared in aggregate form with state and local partners. In addition, information may be summarized on the CDC website or in publications.

Human subjects' determination

CDC has determined the project is non-research public health case investigation. The objective is to evaluate cases of COVID-19 vaccine breakthrough reported to CDC. It is not intended to be a systematic investigation of all persons in the United States with SARS-CoV-2 infection following vaccination and, therefore, will not be generalizable to a larger population.

References

1. Centers for Disease Control and Prevention. CDC COVID data tracker, 2020. https://covid.cdc.gov/covid-data-tracker/#cases_casesper100klast7days. Access date, March 2021.
2. Food and Drug Administration. COVID-19 vaccines. <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines>. Access date, March 2021.
3. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Eng J Med* 2021;383:2603–2615.
4. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;384:403–416.
5. Oliver SE, Gargano JW, Scobie H, et al. The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Janssen COVID-19 Vaccine — United States, February 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:329–332.
6. Centers for Disease Control and Prevention. Different COVID-19 vaccines, 2020. <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines.html>. Access date, March 2021.
7. Wajnberg A, Amanat F, Firpo A, et al. SARS-CoV-2 infection induces robust, neutralizing antibody responses that are stable for at least three months. *Science* 2020;370:1227–30.
8. Choe PG, Kim KH, Kang CK, et al. Antibody responses 8 months after asymptomatic or mild SARS-CoV-2 infection. *Emerg Infect Dis* 2020;27.
9. Seow J, Graham C, Merrick B, et al. Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection. *Nature Microbiol* 2020;5:1598–1607.
10. Pfizer. COVID-19 vaccine U.S. distribution fact sheet, 2020. <https://www.pfizer.com/news/hot-topics/covid-19-vaccine-u-s-distribution-fact-sheet>. Access date, March 2021.
11. Food and Drug Administration. Emergency use authorization (EUA) of the Pfizer-BioNTech COVID-19 vaccine to prevent coronavirus disease 2019 (COVID-19), 2020. <https://www.fda.gov/media/144413/download>. Access date, March 2021.
12. Food and Drug Administration. Emergency use authorization (EUA) of the Moderna COVID-19 vaccine to prevent coronavirus disease 2019 (COVID-19), 2020. <https://www.fda.gov/media/144637/download>. Access date, March 2021.
13. Dai L, Gao GF. Viral targets for vaccines against COVID-19. *Nature Rev Immunol* 2021;21:73–82.

14. Centers for Disease Control and Prevention. SARS-CoV-2 variants. <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html>. Access date, March 2021.
15. Galloway SE, Paul P, MacCannell DR, et al. Emergence of SARS-CoV-2 B.1.1.7 Lineage — United States, December 29, 2020–January 12, 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:95–99.
16. Zhang W, Davis BD, Chen SS, Sincuir Martinez JM, Plummer JT, Vail E. Emergence of a novel SARS-CoV-2 variant in Southern California. *JAMA* 2021. doi:10.1001/jama.2021.1612.
17. Fontanet A, Autran B, Lina B, et al. SARS-CoV-2 variants and ending the COVID-19 pandemic. *Lancet* 2021;doi.org/10.1016/S0140-6736(21)00370-6.
18. Wibmer CK, Ayres F, Hernamus T, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. Pre-print at <https://www.biorxiv.org/content/10.1101/2021.01.18.427166v1.full>.
19. Wu K, Werner AP, Moliva JI, et al. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. Pre-print at <https://www.biorxiv.org/content/10.1101/2021.01.25.427948v1>.
20. Collier DA, De Marco A, Ferreira IATM, et al. SARS-CoV-2 B.1.1.7 escape from mRNA vaccine-elicited neutralizing 1 antibodies. Pre-print at <https://www.medrxiv.org/content/10.1101/2021.01.19.21249840v4>.
21. Edara VV, Floyd K, Lai L, et al. Infection and mRNA-1273 vaccine antibodies neutralize SARS-CoV-2 UK variant. Pre-print at <https://www.medrxiv.org/content/10.1101/2021.02.02.21250799v1>.
22. Wang P, Liu L, Iketani S, et al. Increased resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7 to antibody neutralization. Pre-print at <https://www.biorxiv.org/content/10.1101/2021.01.25.428137v1>.
23. Shen X, Tang H, McDanal C, et al. SARS-CoV-2 variant B.1.1.7 is susceptible to neutralizing antibodies elicited by ancestral Spike vaccines. Pre-print at <https://www.biorxiv.org/content/10.1101/2021.01.27.428516v2>.
24. Tarke A, Sidney J, Methot N, et al. Negligible impact of SARS-CoV-2 variants on CD4+ and CD8+ T cell reactivity in COVID-19 exposed donors and vaccinees. Pre-print at <https://www.biorxiv.org/content/10.1101/2021.02.27.433180v1>.
25. Deng X, Garcia-Knight MA, Khalid MM, et al. Transmission, infectivity, and antibody neutralization of an emerging SARS-CoV-2 variant in California carrying a L452R spike protein mutation. Pre-print at: <https://doi.org/10.1101/2021.03.07.21252647>
26. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19): 2020 Interim Case Definition, Approved August 5, 2020. <https://www.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/08/05/>. Access date, January 2021.

Appendix A. Information sheet for participants

COVID-19 vaccine breakthrough evaluation

Information sheet for participants

Vaccines can help stop people from getting sick with COVID-19. COVID-19 vaccines are very good at keeping people from getting sick, but we know that some people will still get COVID-19 even though they were vaccinated. When this happens, we call it a “vaccine breakthrough.”

Your health department is working with the Centers for Disease Control and Prevention (CDC) to identify people who have a COVID-19 vaccine breakthrough. This will help us learn if some people are more likely to have a vaccine breakthrough than others. It can also tell us if the virus is changing in a way that makes the vaccine not work as well. If we find a pattern, we may be able to find ways to prevent more breakthroughs in the future.

We have contacted you because you got COVID-19 after you were vaccinated. We want to ask you a few questions about you and your health. These questions will be about your age, sex, race, medical conditions, and symptoms. We also will collect information about your COVID-19 vaccination and diagnosis by reviewing your medical and vaccination records.

We would like to study the virus that causes COVID-19—the virus that infected you. We want to check if there are changes in the virus that made the vaccine not work as well. We will contact the lab that tested your sample to see if they still have any of the sample left. If they do not, we may ask you to have another nose swab for testing. You will not get the results of the additional virus testing we do for this investigation.

We will keep all of your information private. We will store it in a secure location so that other people cannot look at it. No specific information about you will be shared or reported. Your information will be combined with the information we collect from other people. We will look to see if there are any patterns for the whole group. For example, we will make sure that breakthrough infections do not occur more often in people who are older or have immune problems. Our goal is to use this information to help keep people safe and help stop the COVID-19 pandemic.

Appendix B. Data collection elements

- Health department contact
 - Name
 - Organization/affiliation
 - Title
 - Email address
 - Phone number
- Healthcare provider contact
 - Name
 - Organization/affiliation
 - Title
 - Email address
 - Phone number
- Case-patient identification and demographics
 - Name
 - Date of birth
 - Sex [Select one: male, female, unknown]
 - Race [Select all that apply: American Indian/Alaska Native, Asian, Black or African American, Native Hawaiian/Other Pacific, White, unknown]
 - Ethnicity [Select one: Hispanic or Latino, not Hispanic or Latino, unknown]
 - County of residence
 - State of residence
 - CDC case identification number
 - State/local case identification number
 - Email address
 - Phone number
- COVID laboratory confirmation
 - Specimen type [Select one: upper respiratory sample (nasopharyngeal swab, nasal swab, nasal wash, oropharyngeal swab), saliva, sputum, bronchoalveolar lavage fluid, pleural fluid, or lung tissue]
 - Date specimen was collected
 - Location where testing performed [Select one: lab testing, home test only]
 - Test type [Select one: RT-PCR, other NAAT, antigen]
 - Test result [Select one: positive, negative, indeterminate]
 - Ct value if PCR
 - Laboratory where testing was performed
 - Laboratory contact
 - Laboratory phone
 - Sample available [Select one: yes, no, unknown]
- COVID vaccination information
 - Dose # 1
 - Vaccine manufacturer and type
 - Date received
 - Vaccine lot number
 - Name of facility where vaccine was received

- City and state where vaccine was received
 - Dose # 2, if applicable
 - Vaccine manufacturer and type
 - Date received
 - Vaccine lot number
 - Name of facility where vaccine was received
 - City and state where vaccine was received
- Symptoms during the course of illness [Select one: yes, no, unknown]
- Clinical symptoms from 2 days before to 2 weeks after the positive test [Select any present]:
 - Fever
 - Chills
 - Rigors
 - Myalgia
 - Headache
 - Sore throat
 - Nausea or vomiting
 - Diarrhea
 - Fatigue
 - Congestion or runny nose
 - Cough
 - Shortness of breath
 - Difficulty breathing
 - New olfactory disorder
 - New taste disorder
 - No COVID-like symptoms
- Clinical course
 - Presented for outpatient medical care (e.g., telemedicine, clinic, urgent care, or emergency room) from 2 days before to 2 weeks after the positive test [Select one: yes, no, unknown]
 - Hospitalized for ≥ 1 night in an inpatient facility within 2 weeks after the positive test [Select one: yes, no, unknown]
 - Admitted to an intensive care unit during the hospitalization [Select one: yes, no, unknown]
 - Required mechanical ventilation during the hospitalization [Select one: yes, no, unknown]
 - Died [Select one: yes, no, unknown]
 - Date died
- Type of residence [Select one: house, apartment, hotel, long-term care facility, correctional facility, mobile home, group home, shelter, other, unknown]
- Underlying medical conditions [Select all that apply]:
 - Pregnancy
 - Diabetes mellitus
 - Chronic kidney disease
 - Chronic liver disease
 - Autoimmune disease

- Immunocompromised
 - HIV infection
 - Active cancer
 - Solid organ transplant
 - Hematopoietic stem cell transplant
 - Other immunosuppressive condition: specify
- Systemic immunosuppressive therapy or medications (i.e., chemotherapy, corticosteroids, monoclonal antibodies, excludes topical agents and inhaled steroids) [Select one: yes, no, unknown]
 - Specify therapy or medication
- Available specimens from initial COVID laboratory confirmation [Select all that apply]:
 - SARS-CoV-2 sequence data
 - Primary respiratory specimen
 - None
- Additional nasal swab (collected after diagnostic positive COVID test)
 - Date collected
 - Facility name where collected
 - Facility phone number
 - City and state where collected

Appendix C. Specimens for investigating COVID-19 vaccine breakthrough cases

Original specimen that tested positive for SARS-CoV-2 RNA or antigen

- Objective
 - Characterize SARS-CoV-2 infecting strain, sequence, or mutations.
- Specimen types
 - SARS-CoV-2 sequence data from respiratory specimen RNA or isolate
 - Primary respiratory specimen (i.e., nasopharyngeal swab, nasal swab, nasal wash, oropharyngeal swab, saliva, sputum, bronchoalveolar lavage fluid, pleural fluid, or lung tissue)
- Laboratory testing to be performed
 - RT-PCR and whole genome sequencing of viral RNA
 - Viral isolation
- Laboratory where testing will be performed
 - Specimens will be directed to the CDC Sample Triage and Tracking (STAT) Team for distribution.
 - Clinical respiratory specimens will be directed to the Triage and Reporting Laboratory for RNA extraction and RT-PCR.
 - Tissue specimens will be directed to the Infectious Diseases Pathology Branch, DHCPP, NCEZID.
 - SARS-CoV-2 isolates will be directed to the Respiratory Viruses Branch, DVD, NCIRD.
 - RNA sequence data will be sent to the GSL, BCFB, DSR, NCEZID or GDT, RVB, DVD, NCIRD for analysis.

New respiratory specimen for SARS-CoV-2 RNA or antigen

- Objective
 - Characterize SARS-CoV-2 infecting strain, sequence or mutations, if that information cannot be obtained from the initial respiratory specimen that tested positive for SARS-CoV-2 RNA or antigen.
- Specimen types
 - Nasal swab collected ≤ 10 days after initial respiratory specimen that tested positive for SARS-CoV-2 RNA or antigen
- Laboratory testing to be performed
 - SARS-CoV-2 RT-PCR to extract and amplify RNA
 - Whole genome sequencing of viral RNA or isolate
- Laboratory where testing will be performed
 - Specimens will be directed to the CDC Sample Triage and Tracking (STAT) Team for distribution to the Triage and Reporting Laboratory for RNA extraction and RT-PCR.