The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) mRNA Vaccine-Breakthrough Infection Phenotype Includes Significant Symptoms, Live Virus Shedding, and Viral Genetic Diversity

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Little is known about severe acute respiratory syndrome coronavirus 2 “vaccine-breakthrough” infections (VBIs). Here we characterize 24 VBIs in predominantly young healthy persons. While none required hospitalization, a proportion endorsed severe symptoms and shed live virus as high as $4.13 \times 10^3$ plaque-forming units/mL. Infecting genotypes included both variant-of-concern (VOC) and non-VOC strains.

Keywords. SARS-CoV-2; vaccine breakthrough; symptoms; patient-reported outcomes; live virus.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines have been administered in the United States and elsewhere in the world since late 2020. Several of these vaccines demonstrated high efficacy in phase III clinical trials [1, 2]. A number of vaccine-effectiveness studies have recapitated protection against virologically proven SARS-CoV-2 infection [3–6]. In the United States, over 100 million persons have received a SARS-CoV-2 vaccine dose, including many US Military Health System (MHS) beneficiaries [7, 8].

Our understanding of the clinical and virological phenotype and functional impact of SARS-CoV-2 vaccine-breakthrough infections (VBIs) remains very limited. The mRNA-1273 and BNT162b2 mRNA phase III clinical trials demonstrated no severe coronavirus disease 2019 (COVID-19) cases after the second dose of vaccine [1, 2]. These trials measured the severity of COVID-19 in the context of clinical outcomes such as hospitalization, critical illness, and death [1, 2]. These studies did not focus on patient-reported outcomes such as symptom severity. Similarly, post–phase III observational studies have focused on endpoints such as infection frequency and hospitalization requirements, rather than subjective outcomes [6, 9]. Such patient-reported outcomes represent an extensive additional burden of the SARS-CoV-2 pandemic, yet it remains unclear whether SARS-CoV-2 VBI is associated with symptoms severe enough to interfere with daily activities or employment.

The virological phenotype of SARS-CoV-2 VBI is also unclear. While data show a reduction in quantitative polymerase chain reaction (qPCR)–estimated viral load in VBI [10], it is unclear if live virus shedding occurs in VBI, thereby representing an ongoing transmission risk. Further, it is unclear whether VBI occurs with non–variant-of-concern (VOC) genotypes [11]. We therefore present an extensive clinical, serological, and virological characterization of SARS-CoV-2 VBI among subjects enrolled in a cohort of US MHS beneficiaries. We particularly focus on the functional impact and detection of infectious virus in SARS-CoV-2 infections among vaccinated individuals.

METHODS

US Military Health System beneficiaries presenting with a positive SARS-CoV-2 test, a COVID-19–like illness, or a high-risk SARS-CoV-2 exposure were eligible for enrollment into the ongoing Epidemiology, Immunology and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EPICC) study, a SARS-CoV-2 natural history study enrolling at 9 US Military Treatment Facilities since March 2020 (see Supplementary Material).

We evaluated EPICC-enrolled subjects with a history of PCR-confirmed SARS-CoV-2 infection a minimum of 14 days post–final dose of SARS-CoV-2 vaccination. Structured interview and medical record review were used to determine demographics, comorbidities, medications, SARS-CoV-2 vaccine type, and vaccine dose timing. Clinical outcomes, including hospitalization, were abstracted from clinical records. Symptom severity and functional outcomes in VBI were assessed by
questionnaires, which included subjective symptom severity, ability to perform daily activities, duration of illness, and days-to-recovery. We also measured personal and household infection risk factors. Nasal, nasopharyngeal, and/or oropharyngeal swabs were collected and sent for qPCR, viral culture, and SARS-CoV-2 whole-genome sequencing (see Supplementary Materials). Venous sera were collected and sent for anti-spike (S) immunoglobulin G (IgG) and anti-nucleoprotein (NP) IgG binding antibodies (see Supplementary Materials).

RESULTS

From March 2020 through 3 May 2021, the EPICC study enrolled 1547 subjects (1229 outpatients, 318 inpatients) with confirmed SARS-CoV-2 infection. We observed a total of 24 infections that occurred 14 or more days after the final dose of a SARS-CoV-2 vaccine, with a median illness onset of 50.5 days (interquartile range [IQR], 31.5–73.5 days; range, 15–95 days) from final vaccination dose (Table 1). Infections that occurred 7–14 days after the final dose of vaccine are characterized in Supplementary Table 1. The other EPICC subjects were not vaccinated before infection. The mean age was 37.8 years (SD, 13.4 years; range, 20.9–77.7 years), and 71% were male. Most infections (67%) were observed in those without comorbidities. Hypertension, obstructive airway disease, diabetes, and chronic kidney disease were the most common comorbidities noted (Table 1). One subject reported receiving immunosuppressant medication (mycophenolate and prednisone) for a renal transplant.

Most cases were active-duty military service members (19/24, 79%). Fifteen of 24 (63%) were healthcare workers, and 13 of 23 (57%) reported close contact with a COVID-19 case in the last month. In the prior month, 19 of 23 (83%) reported staying 6 feet away from people in public more than half the time. The majority lived with children and/or another adult (Table 1).

No VBI resulted in hospitalization. Three of 21 (14%) reported severe symptoms (based on the question “Overall, how would you rate your symptoms at their worst up until this point in time?”). Illness duration was up to 2 weeks in those study participants who reported feeling back to a usual state of health (“back to normal”) at the time of assessment (Table 1). The assessment occurred a median of 6 (IQR, 4–12) days after illness onset.

Quantitative PCR was performed on upper respiratory tract specimens from 22 cases collected a median of 6 days post–symptom onset (IQR, 4–10 days; range, 0–18 days). Thirteen were positive by qPCR, with a median RNA abundance of 1.08 × 10^6 GE/reaction (IQR, 21.52–10.59 × 10^6 genome equivalents (GE)/reaction; range, 2.60–1.42 × 10^6 GE/reaction). Ten of these 13 qPCR-positive specimens were successfully genotyped and included the VOCs B.1.1.7 (n = 2), P.1 (n = 1), and B.1.429 (n = 2), in addition to non-VOC strains B.1.1 (n = 1), B.1.1.519 (n = 1), B.1.2 (n = 2), and B.1.243 (n = 1) strains. Quantitative PCR–positive specimens in which no genotype was determined were associated with low sequencing coverage and high cycle threshold (CT) values (N1 CT >33). Respiratory tract specimens from 6 qPCR-positive cases were analyzed by viral culture, 3 of which had viral loads of 113, 200, and 4130 plaque-forming units (PFU)/mL on specimens collected between day 6 and 7 post–symptom onset.

Anti-S IgG serology results were available in 19 of 24 of subjects, with the first sera collected a median of 12 days (IQR, 7–16 days; range, 4–25 days) after illness onset. All participants were anti-S IgG positive by their first sera collection, with the first sera collected a median of 12 days (IQR, 7–16 days; range, 4–25 days) after illness onset. All participants were anti-S IgG positive by their first sera collection, with the first sera collected a median of 12 days (IQR, 7–16 days; range, 4–25 days) after illness onset. All participants were anti-S IgG positive by their first sera collection, with the first sera collected a median of 12 days (IQR, 7–16 days; range, 4–25 days) after illness onset.

Anti-NP IgG serology results were available in 6 of 24 subjects, 4 of whom were anti-NP IgG positive by day 15–22 after symptom onset. The remaining 2 subjects were anti-NP seronegative at day 6 and day 29 after illness onset (latest available time points), respectively.

DISCUSSION

We have observed SARS-CoV-2 postvaccine infections across a range of ages in this cohort, predominantly in those with no comorbidities and no immunosuppression. The number of VBIs in our study population remain low to date.

We note a proportion of VBIs were associated with functional impact and symptoms self-reported as severe. No SARS-CoV-2 VBI led to hospitalization, correlating with results from mRNA-1273 and BNT162b2 clinical trials. However, the typical duration of illness was significant, with symptoms documented for as long as 2 weeks in those who had recovered (n = 6). Many infections occurred in subjects at higher risk for SARS-CoV-2—with 55% of cases in healthcare workers—as well as risks for secondary household transmission. In this case series, the frequency of VBI by occupation, and vaccine product received, needs to be interpreted carefully in the context of vaccine prioritization and implementation strategy in the US MHS [8]. The high frequency of Pfizer vaccine receipt in this case series reflects the product being most used at EPICC sites.

While our study did not compare viral loads or genotypes between vaccinated and unvaccinated subjects, we note VBI in genotypes not previously associated with significant vaccine immune escape in vitro, including B.1.1, B.1.1.519, B.1.2, and B.1.243 genotypes. Our results also underscore the emerging vaccine escape risk of the P.1 and B.1.429 variants. Sieve analyses from larger sample sizes are required to definitively confirm specific genotypes with a higher risk of vaccine breakthrough. We observed live virus shedding in VBI as high as 4130 PFU/mL at day 7 post–symptom onset; although relatively
### Table 1. Characteristics and Outcomes of 24 Vaccine-Breakthrough Infections

| Demographic characteristics | Valuesb |
|-----------------------------|---------|
| Age, mean (SD), range, years | 37.8 (13.4), 20.9–77.7 |
| Male, n (%)                 | 17 (71) |
| Race/ethnicity, n (%)       |         |
| Asian                       | 2 (8)   |
| Black                       | 1 (4)   |
| Hispanic                    | 3 (13)  |
| Native Hawaiian             | 1 (4)   |
| White                       | 17 (71) |
| Occupational characteristics and military status, n (%) | |
| Active duty                 | 19 (79) |
| Dependent                   | 4 (17)  |
| Retired                     | 1 (4)   |
| Healthcare worker           | 15 (63) |
| Risk behaviors, n (%)       |         |
| Lives with another adult    | 15 (71) |
| Lives with children         | 7 (30)  |
| Close contact with person with COVID-19 in past monthc | 13 (57) |
| Stayed 6 feet away from people in public more than half the time in past month | 19 (83) |
| Increased frequency of handwashing in the past month | 15 (65) |
| Wore mask all the time in the past month | 19 (83) |
| Comorbidities, n (%)        |         |
| Any comorbidity             | 8 (33)  |
| Multiple comorbidities      | 3 (13)  |
| Hypertension                | 4 (17)  |
| Asthma or chronic obstructive pulmonary disease | 3 (13) |
| Obesity                     | 2 (8)   |
| Diabetes                    | 2 (8)   |
| Chronic kidney disease      | 2 (8)   |
| Renal transplant            | 1 (4)   |
| History of venous thromboembolism | 1 (5) |
| Immunosuppressant medication, n (%) | 1 (4) |
| None                        | 16 (67) |
| Vaccine product received, n (%) |       |
| BNT162b2 (Pfizer-BioNTech)  | 22 (92) |
| mRNA-1273 (Moderna)         | 2 (8)   |
| Illness onset from time of final dose,d median (IQR, range), days | 50.5 (31.5–73.5, 15–95) |
| Symptom severity, n (%)     |         |
| Never had symptoms          | 5 (24)  |
| Mild                        | 7 (33)  |
| Moderate                    | 6 (29)  |
| Severe                      | 3 (14)  |
| Critical                    | 0 (0)   |
| Illness outcomes and other characteristics, n (%) | |
| Prior SARS-CoV-2 infection  | 0 (0)   |
| Hospitalized                | 0 (0)   |
| Feeling back to normale     | 6 (35)  |
| Days to recovery,f median (range) | 5 (0–14) |

*None* refers to no comorbidities.

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

aRestricted to those with illness onset ≥14 days after final dose of vaccination.

bDenominator varies based on response rate.

cBased on the question: “In the month before you were ill, tested for, or exposed to COVID-19, did you have close contact (eg, caring for or living with) a person who tested positive for COVID-19 or had symptoms of COVID-19 such as fever and/or acute respiratory illness?”

dDerived from time to earliest SARS-CoV-2 test positivity in those without symptoms.

*eAt time of interview.*

fIn those recovered by time of interview (n = 6).
low magnitude, the presence of infectious virus may indicate a transmission risk of VBI [12].

While we did not have sera collected before infection in these subjects, our finding of a lack of anti-S IgG seroconversion 36 days after the final vaccine dose in an immunosuppressed renal transplant participant suggests a failure to develop an appropriate humoral response to the vaccine, as has been noted in a small study of BNT162b2 in renal transplant recipients. We further observed that anti-NP seroconversions did not occur in all PCR-positive VBI cases who were tested, with 1 case not seroconverting to anti-NP IgG by 29 days after symptom onset.

Our findings are descriptive, preliminary, and can inform further study, including comparison of risk factors, viral load, and subjective outcomes with unvaccinated SARS-CoV-2 infections. Such comparisons require larger sample sizes of VBI, particularly to adjust for confounding. However, these findings offer several early insights into the clinical and viral phenotype of VBI, including data not typically collected in clinical trials or vaccine effectiveness studies [1–4, 6, 9].

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. S. D. P., M. P. S., T. H. B., and D. T. report that the Uniformed Services University (USU) Infectious Diseases Clinical Research Program (IDCRP), a US Department of Defense institution, and the Henry M. Jackson Foundation (HJF) were funded under a Cooperative Research and Development Agreement to conduct an unrelated phase III COVID-19 monoclonal antibody immunophrophylaxis trial sponsored by AstraZeneca. The HJF, in support of the USU IDCRP, was funded by the Department of Defense Joint Program Executive Office for Chemical, Biological, Radiological, and Nuclear Defense to augment the conduct of an unrelated phase III vaccine trial sponsored by AstraZeneca. Both of these trials were part of the US Government COVID-19 response. Neither is related to the work presented here. T. H. B., and M. P. S., report that they are US military service members. This research was funded by US Department of Defense, Defense Health Program. A. G. reports support from the National Institute of Allergy and Infectious Diseases, Defense Medical Research and Development Program, outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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