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Editorial: SARS-CoV-2 Vaccine Responses and Breakthrough COVID-19

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Abstract In 2021, data from global disease monitoring and infection surveillance programs have shown that vaccination programs have reduced the incidence of SARS-CoV-2 infection and hospitalization and mortality rates. Currently, the US Centers for Disease Control and Prevention (CDC) identifies a fully vaccinated individual as being ≥14 days after the completion of all the recommended doses of a COVID-19 vaccine that has been authorized by the US Food and Drug Administration (FDA). A partially vaccinated individual is <14 days following primary vaccination or has not completed the vaccination program. Clinical studies and data on the vaccine status of populations have identified breakthrough COVID-19 cases in fully vaccinated individuals at 14 or more days after completing the recommended dose of an authorized SARS-CoV-2 vaccine. This Editorial presents an update on what has been learned in the past year on SARS-CoV-2 vaccine responses and breakthrough COVID-19.

Keywords: SARS-CoV-2 • COVID-19 • Vaccines • Breakthrough Infection • Editorial

In 2021, data from global disease monitoring and infection surveillance programs have shown that vaccination programs have reduced the incidence of SARS-CoV-2 infection and the rates of hospitalization and mortality [1]. There have been increasing concerns that variants of concern, such as the SARS-CoV-2 B.1.617.2 (delta) variant, may evade the immune protection offered by current vaccines [1,2]. However, a recent report from the Morbidity and Mortality Weekly Report (MMWR) from the US Centers for Disease Control and Prevention (CDC) showed that in 13 US jurisdictions, the incidence of hospital admissions and mortality for COVID-19 were unchanged when the SARS-CoV-2 B.1.617.2 (Delta) variant became predominant [1]. Analysis of vaccine status in this US population aged ≥18 years, between April 4 to July 17, 2021, included analysis by vaccination status [1]. Although protection from infection declined after vaccination, vaccination continued to reduce hospitalization and mortality rates from COVID-19 [1].

Data on the vaccine status of populations have also identified breakthrough COVID-19 cases. Currently, the CDC identifies a fully vaccinated individual as being ≥14 days after the completion of all the recommended doses of a COVID-19 vaccine that has been authorized by the US Food and Drug Administration (FDA) [3.4]. A partially vaccinated individual is <14 days following primary vaccination or has not completed the vaccination program [3,4]. Two main surveillance indicators are used to describe vaccine breakthrough COVID-19 cases and outcomes from SARS-CoV-2 infection [1,3,4]. These indicators are the incidence rate ratios (IRRs) between unvaccinated and vaccinated individuals and the percentage of vaccinated persons (PVC) in cases of COVID-19 [1]. Monitoring the incidence of COVID-19 by vaccination status has begun to provide signs of changes in vaccine effectiveness over time.

The CDC has also analyzed data from the Hospitalization Surveillance Network, COVID-NET, a population surveillance system that includes hospitalized patients with laboratory confirmation of SARS-CoV-2 infection [5]. The COVID-NET data on vaccination status according to age has shown that for all adults 18 years and older, the cumulative hospitalization rate for unvaccinated patients with COVID-19 was nine times greater than for vaccinated patients [5]. Also, for children and adolescents between 12 and 17 years of age, the cumulative hospitalization rate for unvaccinated patients with COVID-19 was ten times greater than for vaccinated patients [5]. These data also confirm that breakthrough infections occur and can lead to hospital admission [5].

The rationale for current vaccination programs is to re-vaccinate (or boost) vaccine status at between four and six months. This rationale has been supported by studies showing reduced immune response to the SARS-CoV-2 spike protein during this short time. In July 2021, the UK Virus Watch Collaborative members reported the findings from a longitudinal study in England and Wales that included 605 individuals of ≥18 years [6]. The immune response was measured by antibody serology, following a second dose of the BNT162b2 (Pfizer-BioNTech) vaccine and the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) vaccine, which are two vaccines with strong immunogenicity [6]. In this study population, 31% (n=186) were categorized as clinically

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vulnerable, 9% (n=117) were clinically extremely vulnerable, and 50% (n=302) were not clinically vulnerable and had no comorbidities [6]. The median interval between the first and second vaccine doses was 77 days [6]. Antibody levels to the spike protein significantly declined between days 21-41 and at 70 days or more after the second dose of the ChAdOx1 vaccine ($p<0.001$) and the BNT162b2 vaccine ($p<0.001$) [6]. Antibody levels were reduced by up to five-fold for the ChAdOx1 vaccine and up to two-fold for the BNT162b2 vaccine, between days 21-41 and at 70 days or more after the second dose [6]. The decline in the antibody response was consistent when the results were stratified by gender, age, and clinical vulnerability [6]. The UK Joint Committee on Vaccination and Immunisation (JCVI) has advised that booster vaccinations should be given with heterologous vaccine regimens to produce stronger antibody and T-cell immune responses [7,8].

In September 2021, Agrawal and colleagues reported the findings from a prospective cohort study, EAVE II, of hospital admissions and patient deaths in Scotland following 2·57 million vaccinations with the BNT162b2 and ChAdOx1 vaccines [9]. From December 2020, in Scotland, the ChAdOx1 vaccine and the BNT162b2 vaccine were approved and administered to healthcare workers and the most vulnerable members of the population, and breakthrough infections were rare [9]. Later in the year, breakthrough infections became increasingly reported and were believed to be due to either the increasing prevalence of the delta variant of SARS-CoV-2, waning immunity, and a decline in vaccine effectiveness, also known as 'immune escape' [9]. The findings from EAVE II showed that between December 2020 and April 2021, 2,572,008 individuals received a first vaccine dose, with 32.7% receiving the BNT162b2 vaccine and 67.3% receiving the ChAdOx1 vaccine [9]. Significantly reduced hospital admission rates with COVID-19 and mortality were reported in vaccinated individuals compared with unvaccinated individuals [9]. Severe clinical outcomes at 14 days or more after the first dose of vaccine occurred in <0.1% of vaccinated individuals [9]. They were associated with older age, lower socioeconomic status, comorbidities, care home residents, male gender, and smoking history [9]. However, the findings from EAVE II showed that a history of COVID-19 before vaccination was protective against severe clinical outcomes from breakthrough infections [9].

Israel continues to provide epidemiological and real-world data on the outcomes and prevention of COVID-19 [10,11]. From December 20, 2020, Israel began a national COVID-19 vaccination program to administer the BNT162b2 vaccine [10,11]. The vaccine program began with individuals older than 60 years, healthcare workers, residents of nursing homes, and individuals with severe comorbidities [10,11]. Vaccinations rapidly expanded to all age groups by February 2021 [10,11]. The national vaccination program has resulted in Israel having one of the highest vaccination rates per capita [10,11]. By the end of February 2021, 48.8% of the population had received the first vaccine dose, 34% received the second vaccine dose, and 7.5% had recovered from COVID-19 [10,11]

In July 2021, Bergwerk and colleagues reported the findings from a study of COVID-19 breakthrough infections in healthcare workers from the largest medical center in Israel [12]. Between December 19, 2020, to April 28, 2021, 91% of the healthcare workers at this center had received two doses of the BNT162b2 vaccine [12]. Breakthrough infections were identified by presenting symptoms, clinical investigations, repeat reverse transcriptase-polymerase chain reaction (RT-PCR) testing, antigen-detection rapid diagnostic testing (Ag-RDT), serological testing, and genomic sequencing [12]. Out of 1,497 fully vaccinated healthcare workers who had RT-PCR data, 39 SARS-CoV-2 breakthrough infections were identified [12]. Most breakthrough cases were mild or asymptomatic, but 19% of breakthrough cases had persistent symptoms lasting more than six weeks [12]. The B.1.1.7 (alpha) variant of SARS-CoV-2 was present in 85% of cases [12]. This well-conducted study showed that Among fully vaccinated health care workers, breakthrough infections with SARS-CoV-2 could be identified by the presence of neutralizing antibody titers during the period of infection [12]. Most breakthrough infections were associated with the B.1.1.7 (alpha) variant of SARS-CoV-2 and were mild or asymptomatic, with some experiencing persistent symptoms [12]. However, it does seem that the clinical course of breakthrough infections may differ between the variants of SARS-CoV-2.

More recently, in November 2021, Juthani and colleagues reported the findings for hospitalization for patients with breakthrough SARS-CoV-2 infections referred to the Yale-New Haven Health System [13]. This study evaluated patient admissions between March and July 2021, and SARS-CoV-2 infection was confirmed by RT- PCR testing [13]. Vaccine status and vaccination dates were recorded for three main vaccines, the mRNA-1273 Moderna vaccine, the BNT162b2 vaccine, and the Janssen Ad.26.COV2.S vaccine [13]. The study identified 969 patients with confirmed SARS-CoV-2 infection with a history of vaccination, of which 54 had been fully vaccinated and were identified as breakthrough cases [13]. This study used current guidelines to classify the severity of illness from SARS-CoV-2 infection [14]. Of the 54 breakthrough cases, 46% (n=25) were asymptomatic and had been admitted to hospital with a non-COVID-19-related diagnosis, 7% (n=4) had mild COVID-19, 20% (n=11) had moderate COVID-19, and 26% (n=14) had severe COVID-19 that required ventilatory support [13,14]. Of the 14 patients with severe breakthrough COVID-19, the median age was 80 years, four patients required intensive care, one patient required mechanical ventilation, and three died [13]. The 14 patients with severe breakthrough COVID-19 had pre-existing

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comorbidities, including a body mass index (BMI) >25 kg/m^2 (n=9), cardiovascular disease (n=12), lung disease (n=7), malignancy (n=4), type 2 diabetes (n=7), and immunosuppressive treatment (n=4) [13]. Up to 20% of patients admitted to hospital with a positive SARS-CoV-2 RT-PCR test had received at least one vaccine dose, but most patients had not completed the full vaccine course [13]. In this US population, more than 25% of fully vaccinated patients admitted to hospital with SARS-CoV-2 were severely or critically ill [13]. The authors suggested that this finding could have been due to the emergence of new viral variants or reduced immunity associated with comorbidities [13]. In the fully vaccinated, the incidence of severe or critical COVID-19 was low [13]. However, in this study, there were more severe breakthrough infections in patients who had received the BNT162b2 vaccine [13]. This recent study has raised further questions regarding the factors associated with breakthrough cases of COVID-19.

Conclusions

There have been reports and clinical studies on the prevalence of breakthrough infections with SARS-CoV-2 following vaccination. It is clear that factors associated with inadequate vaccine responses in patients with breakthrough infections are still not fully understood and remain to be investigated. However, it does seem that the clinical course of breakthrough infections may differ between the variants of SARS-CoV-2. Given the global inequalities in SARS-CoV-2 vaccine administration, surveillance of immune responses in populations post-vaccination may inform equitable and targeted booster vaccination programs in the future.

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