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MINI-REVIEW

Breakthrough SARS-CoV-2 infections after vaccination: a critical review

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ABSTRACT

At the beginning of the current pandemic, it was believed that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection would induce lifelong immunity and that reinfections would be unlikely. However, after several cases of reinfection were documented in previously infected patients, this was understood to be a false assumption, and this waning humoral immunity has raised significant concerns. Accordingly, long-term and durable vaccine-induced antibody protection against infection have also become a challenge, as several breakthroughs of COVID-19 infection have been identified in individuals who were fully vaccinated. This review discusses the current evidence on breakthrough COVID-19 infections occurring after vaccination.

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1. Introduction

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in many individuals becoming infected, more than four million deaths, and has placed an unprecedented burden on public health services worldwide.[1–3] At the beginning of the coronavirus 2019 (COVID-19) pandemic, it was speculated that SARS-CoV-2 infection would result in lifelong immunity, and reinfections would be unlikely. However, there have been several documented cases of reinfection with SARS-CoV-2.[4] A cohort study reports reinfection rates among a large north Indian HCW (n = 4978) with SARS-CoV-2 infection in 15 months (including the second wave, which was closely linked to the delta variant). As the result of this study, 124 cases of reinfection (2.5%) were identified.[5] Another study from India from January 22 to 7 October 2020, reported that out of 1300 individuals, 58 (4.5%) were reinfected.[5] Therefore, waning humoral immunity is increasingly recognized as a significant concern. Accordingly, long-term and durable vaccine-induced antibody protection against infection is now a significant challenge facing scientists.[6] Since the SARS-CoV-2 vaccination program started, several breakthroughs of COVID-19 infection have been identified in individuals who had been vaccinated.[7] This article reviews the literature on breakthrough SARS-CoV-2 infections following vaccination.

2. Persistence of natural- or vaccine-induced antibodies

Miscellaneous reports are available about the duration of immunity persistence in COVID-19-infected patients. Several studies have concluded that anti-SARS-CoV-2 antibodies decline rapidly, lasting up to three months after the primary infection,[8] while others report post-infection antibody persistence for up to five months.[9] Some studies have shown that the mRNA vaccines, Moderna and Pfizer, have an efficacy of up to 95% for preventing symptomatic SARS-CoV-2 infection 7–14 days after the second dose.[10,11] However, it should be noted that mild antibody decreases, following natural- or vaccine-induced immunity does not necessarily indicate an absolute waning of immunity, as, in most people, a durable immunity against secondary COVID-19 disease would be possible up to 8-months following infection or vaccination through anti-S memory B cells.[12] Looking at the immunological background in SARS-CoV-2 infection, memory T and B cells certainly contribute to some degree of protection, but there is strong evidence supporting the protective role of serum neutralizing antibodies. For instance, passive transfer of neutralizing antibodies can prevent severe SARS-CoV-2 infection in multiple animal models,[13,14] and recent reports show similar data in humans.[15,16]

3. Definition of breakthrough infections

A breakthrough infection can be defined as a case of infection in which a vaccinated individual becomes infected with the same pathogen they were vaccinated against because the vaccine has failed to provide complete immunity against the pathogen. This phenomenon has been well documented following many viral and bacterial vaccines, and SARS-CoV-2 infection has not been an exception.[17–19] However, another related phenomenon is vaccine-associated enhanced diseases

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(VAED), which is not the focus of the present review. This term points to the situation in which an individual who received a vaccine develops a more severe or modified presentation of that infection when later exposed to that pathogen than when infection occurs with no prior vaccination history.[20]

4. Underlying causes and characteristics of SARS-CoV-2 infections, following vaccination

As previously mentioned, waning immunity after a de novo infection or vaccination can be the reason that some people get infected or reinfected following COVID-19 vaccines.[21–23] Moreover, some individuals with diminished capacity to produce protective antibodies, such as immunosuppressed patients, are also susceptible to being infected even after being naturally infected with this virus or receiving both vaccine doses.[24–26] Ineffective antibody production, due to relatively ineffective vaccines, an inadequate number of doses, and the time after the vaccination are also involved in the pathogenesis of post-vaccination infections.[27] It is not unusual to get infected in the first 14 days following the first dose of the vaccine since protective immunity cannot build within this period.[28,29] For example, it has been estimated that the Pfizer COVID-19 vaccine has efficacy in preventing COVID-19 infection of 52.4% before and 90.5% one week after the second dose, respectively.[30] Therefore, vaccinated people may develop an infection before the booster shot takes full effect.

There have been studies regarding the effectiveness of anti-SARS-CoV-2 vaccinations in preventing infection by the newly discovered SARS- CoV-2 variants.[31] For instance, one study was conducted to evaluate the effectiveness of the mRNA- 1273 vaccine against SARS-CoV-2 variants and assess its effectiveness by time against the delta variant since vaccination.[31] In this study, 8153 cases were studied, and the result is as follows: two-dose vaccine effectiveness was 86.7% against infection with the delta variant, 98.4% against alpha, 96–98% against other identified variants, and 79.9% against unidentified variants (specimens that failed sequencing).[31]

In general, vaccinated individuals are less likely to get infected than those who are unvaccinated, although the level of prevention strongly depends on the specific variant of concern (VOC).[32] The evolution of mutations in the genes of SARS-CoV-2 can affect the efficacy of vaccine- or natural-induced immunity.[33] The emergence of new SARS-CoV-2 variants, including the alpha (B.1.351) or delta (B.1.617.2) variants, with higher transmissibility and less susceptibility to the previously produced protective antibodies, is another reason why some individuals become infected even after being fully vaccinated.[33,34] Thus, these variants could be the reason why vaccine breakthrough infections occur two weeks post-vaccination, even with high titers of vaccine-induced antibodies.[35] However, some new variants are less likely to escape vaccine-induced immunity and, therefore, less problematic.[36] Although most cases of post-vaccination infections are because of VOCs,[37] it does not appear that these cases are due to remarkable genetic diversity or spike protein mutations in VOCs.[38]

Researchers have found that vaccination with the ChAdOx1 or BNT162b2 vaccines can significantly decrease new positive SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) from 21 days after the first dose onwards, with greater immunity following a second dose and significant reductions for symptomatic infections and infections with higher viral loads (cycle threshold, Ct < 30).[33,39] However, breakthrough infections with lower viral loads can further reduce onward transmission.[40] Nevertheless, there is some concern that the new variants which evade vaccine-induced immunity may also lead to asymptomatic infection, resulting in more viral spread.[41] Moreover, since the COVID-19 vaccine is administered by injection and designed to prevent viremia, they are thought to be unable to prevent nasal SARS-CoV-2 infection, resulting in more asymptomatic shedding and more viral spread through asymptomatic patients' upper airways.[42] However, it is thought that those vaccinated against COVID-19 would have less severe and shorter breakthrough infections with lower viral loads.[43] Studies have shown that post-vaccination COVID-19 infection less commonly requires hospitalization and admission to an intensive care unit (ICU) than infections in non-vaccinated individuals.[44] The risk factors of SARS-CoV-2 infection after COVID-19 vaccination have been reported to include younger age, adverse health determinants, such as extended social isolation, obesity, unhealthy lifestyle, less adherence to preventive measures, and the presence of concomitant comorbidities, including renal disease, and receiving immunosuppressant medication.[45]

5. Differentiate between pre-and post-vaccination infections

Another interesting issue is that many vaccinated individuals have received the vaccine within the SARS-CoV-2 incubation period and might have received their RT-PCR results after being vaccinated. Some individuals even had the prodromal manifestations of COVID-19, such as rhinorrhea or headache, which they neglected or misunderstood as a simple allergy or migraine. However, usually, vaccine recipients get infected after vaccination, in the first 14 days following vaccination, before the antibodies have had time to develop and produce effective protective immunity,[46] making it challenging to identify the exact date of infection as being pre- or post-vaccination. Nonetheless, the dates of symptom onset, in addition to the usual incubation period, can be used to estimate the time of exposure.[47] Another beneficial tool to differentiate post-vaccination breakthrough infections from infections acquired just before vaccination can be evaluating the Ct.

6. The difference between various vaccines in preventing breakthrough infections

At the time of writing, no studies have been published on the efficacy of various anti-SARS-CoV-2 vaccines and any differences in preventing breakthrough COVID-19 infections. However, it can be inferred that this phenomenon would be more likely after being vaccinated with vaccines that have lower efficacy and potency.[48]

7. Differentiating between COVID-19 infection symptoms and vaccine side effects

Several manifestations of SARS-CoV-2 infection are similar to vaccine-induced side effects. Symptoms, such as a sore throat, myalgia, headache, fever, chills, cough, rhinorrhea, diarrhea, and

nausea, can be presented both as an adverse reaction after vaccination and a result of breakthrough SARS-CoV-2 infection. Thus, these symptoms do not help to distinguish between these two conditions.[49] Nevertheless, shortness of breath and chest pain/tightness is less likely to occur following COVID-19 vaccination unless it results from vaccine-induced pulmonary thromboembolism[50]or it is an exacerbation of a preexisting condition. In addition, anosmia and persistent cough are specific manifestations of a COVID-19 infection, rather than being side effects of vaccination. Furthermore, vaccination side effects tend to last for a short period, usually disappearing within a few days. The persistence of symptoms several days after vaccination should prompt testing for SARS-CoV-2 infection. Moreover, a history of close contact with a confirmed or suspected case of COVID-19 can also be a useful criterion in considering a probable infection, which necessitates confirmation via diagnostic laboratory or imaging tools.

8. Conclusion

All the issues mentioned above reinforce the fact that vaccination does not entirely prevent SARS-CoV-2 infections but will lead to less morbidity and mortality, as demonstrated by less hospitalization and less need for ICU care. In addition, the reality that vaccinated individuals may develop asymptomatic breakthrough infections should be a concerning issue, as this increases the risk of viral transmission and spread in the community. Moreover, the relatively high rates of post-vaccination infection, either due to insufficient efficacy of the vaccines or through the evolution of new variants, highlight the importance of maintaining social distancing and other preventive measures, even when vaccinated.

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Disclosure statement

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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