

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

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Abstract

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

Conflict of interest disclosure

All authors declare no conflict of interest.

Author contributions

Zeinab Mohseni Afshar: Conceptualization, Writing - Original Draft; **Mohammad Barary:** Investigation, Writing - Original Draft, Writing - Review & Editing; **Feizollah Mansouri:** Investigation, Writing - Original Draft; **Soheil Ebrahimpour:** Investigation, Writing - Original Draft; **Kosar Nazary:** Investigation, Writing - Original Draft; **Terence T. Sio:** Writing - Review & Editing; **Mark J. M. Sullman:** Writing - Review & Editing; **Kristin Carson-Chahhoud:** Writing - Review & Editing; **Arefeh Babazadeh:** Conceptualization, Writing - Original Draft, Supervision.

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.

Keywords: SARS-CoV-2, Breakthrough, Vaccination, COVID-19

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 in people previously infected with SARS-CoV-2 (4). 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 (5). Since the SARS-CoV-2 vaccination program started, several breakthroughs of COVID-19 infection have been identified in individuals who had been vaccinated (6). In this article, we review the literature on breakthrough SARS-CoV-2 infections following vaccination.

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 (7), while others report post-infection antibody persistence for up to five months (8). 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 (9, 10). 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 (11).

Definition of breakthrough infections

Breakthrough infections can be defined as the reinfection with a pathogen after being fully vaccinated for the same disease. This phenomenon has been well documented following many viral and bacterial vaccines, and SARS-CoV-2 infection has not been an exception (12-14). However, another related phenomenon is vaccine-associated enhanced diseases (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 (15).

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 (16-18). 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 (19-21). 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 (22). 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 (23, 24). 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 (25). Therefore, vaccinated people may develop an infection before the booster shot takes full effect.

Furthermore, the effectiveness of anti-SARS-CoV-2 vaccinations in preventing infection from the new variants is still unclear. 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) (26). The evolution of mutations in the genes of SARS-CoV-2 can affect the efficacy of vaccine- or natural-induced immunity (27). 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 (27, 28). Thus, these variants could be the reason why vaccine breakthrough infections occur two weeks post-vaccination, even with high titers of vaccine-induced antibodies (29). However, some new variants are less likely to escape vaccine-induced immunity and, therefore, less problematic (30). Although most cases of post-vaccination infections are because of VOCs (31), it does not appear that these cases are due to remarkable genetic diversity or spike protein mutations in VOCs (32).

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, $C_t < 30$) (27, 33). However, breakthrough infections with lower viral loads can further reduce onward transmission (34). 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 (35). 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 (36). However, it is thought that those vaccinated against COVID-19 would have less severe and shorter breakthrough infections with lower viral loads (37). Studies have shown that post-vaccination COVID-19 infections less commonly require hospitalization and admission to an intensive care unit (ICU) than infections occurring in non-vaccinated individuals (38). The risk factors of SARS-CoV-2 infection after COVID-19 vaccination have been reported to include younger age, adverse health determinants, such as ex-

tended social isolation, obesity, unhealthy lifestyle, less adherence to preventive measures, and the presence of concomitant comorbidities, including renal disease, and receiving immunosuppressant medication (39).

Prediction of antibody response to vaccination

A clinical response to a vaccine booster can be predicted by developing symptoms, such as those generally associated with the flu shortly after vaccination. This can also be confirmed through the identification of high titers of neutralizing antibodies (40). Following vaccination and same-day testing, active daily symptoms can help evaluate or predict protective immune response following SARS-CoV-2 vaccination (41).

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 (42), 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 (43). Another beneficial tool to differentiate post-vaccination breakthrough infections from infections acquired just before vaccination can be evaluating the Ct, so patients with a Ct < 30 are more likely to have been infected after vaccination than those with higher values (44).

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 (45).

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 (46). 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 (47) or it is an exacerbation of a pre-existing 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.

Strategies to prevent and decrease post-vaccination breakthrough infections

Due to the documented waning immunity following the complete vaccine dosing schedule, booster doses may be necessary at periodic intervals after the second vaccine dose to maintain adequate immunity (48). Perhaps, vaccines being administered via the mucosal route would be an advantageous option to be studied and produced since they may induce higher levels of local protective immunity and lead to the settlement of T and B cells in the nasopharyngeal tissue (49). From a public policy perspective, further public education around the need for vaccination is required. People remain hesitant to vaccinate, with some media outlets reporting nihilism following the latest delta strain and breakthrough infections with anecdotal stories rapidly spreading unhelpful messages against vaccination (50). Hesitancy even remains among highly educated and high-risk

individuals such as medical students (51), healthcare workers (52), and people with autoimmune disorders (53). Understanding why this is the case and addressing these factors needs to be a public health priority supported through dedicated resources and rapid information sharing to disseminate recommendations across countries. Some research and evaluation are already underway for the broad topic of vaccination hesitancy (54, 55). However, the impact of breakthrough infections and how this relates to the uptake of vaccinations is unknown.

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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