

## Review Article



Received: Nov 23, 2021

Accepted: Dec 19, 2021

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### Funding

None.

### Conflict of Interest

No conflicts of interest.

### Author Contributions

Conceptualization: EL. Data curation: EL.  
Formal analysis: EL. Investigation: EL.  
Methodology: EL. Project administration: EL.  
Resources: EL. Software: EL. Supervision:  
EL. Validation: EL. Visualization: EL. Writing - original draft: EL. Writing - review & editing: EL.

# Should Breakthrough SARS-CoV-2 Infection Affect Our Confidence in the COVID-19 Vaccines?

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## ABSTRACT

Coronavirus disease 2019 (COVID-19) vaccines have shown excellent clinical efficacy and effectiveness in real-world data. Although they are regarded as a means of ending the global pandemic, some individuals become infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) after immunization. This growing evidence or lack of effectiveness has led to vaccine refusal. This paper sought to help the public gain a deeper understanding of breakthrough events creating the positive perception that vaccines remain effective in ending the pandemic. Discussions vital for the general public's active participation in vaccination are expressed to create confidence or provide a potential solution to the challenge of vaccine hesitancy.

**Keywords:** COVID-19 breakthroughs infections; Vaccines; Confidence; Hesitancy

## INTRODUCTION

Since coronavirus disease 2019 (COVID-19) emerged at Wuhan City of China in early December 2019, the infection has spread rapidly worldwide, and people contract the virus each day. The infection occurs in three stages, with different clinical manifestations and can cause death in some individuals [1, 2].

Stage I is the incubation period in which affected individuals are asymptomatic and hidden carriers unknowingly spread the virus [3]. In stage II, symptoms become detectable ranging from mild to moderate, whereas there is a sharp increase in viral load and severe acute respiratory illness at Stage III [3]. These clinical features are likely to be experienced by 15% of individuals who contract severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4]. Severe forms occur in patients with various underlying conditions and the aged [1, 3]. Currently, there are at least 80 distinct SAR-CoV-2 variants classified as either a Variant of Concern (VOC) or a Variant of Interest (VOI) [5]. A variant of concern is the one for which there is evidence of an increase in transmissibility, more severe disease, and a significant reduction in neutralization by antibodies during vaccination or previous infection, and also reduced effectiveness of treatments [6]. While a variant with specific genetic markers that affect characteristics of the virus such as disease severity, immune and diagnostic escape and transmissibility is known as a variant of interest [7]. The Alpha, Beta, Gamma, Delta are variants of concern, whereas the Eta, Iota, Kappa and Lambda fall under a variant of interest [7].

With this diverse heterogeneity of the virus, the World Health Organization (WHO) has expressed concerns about the possibility of reinfection or a breakthrough infection [8]. Given the probability that an individual can acquire two of these distinct strains [9], fully vaccinated people become infected with COVID-19 and may spread to others.

This is known as breakthrough infection, in which the SARS-CoV-2 RNA is detected in a respiratory specimen collected after 14 days of completing all recommended doses [10]. Fully vaccinated people with breakthrough infections appear to be infectious for a short period which is a concern undermining the effectiveness of developed vaccines and their ability to protect against circulating variants. As of September 13, 2021, more than 178 million people have been fully vaccinated in the United States, of which 15,790 had breakthrough infections with some hospitalizations and deaths [10].

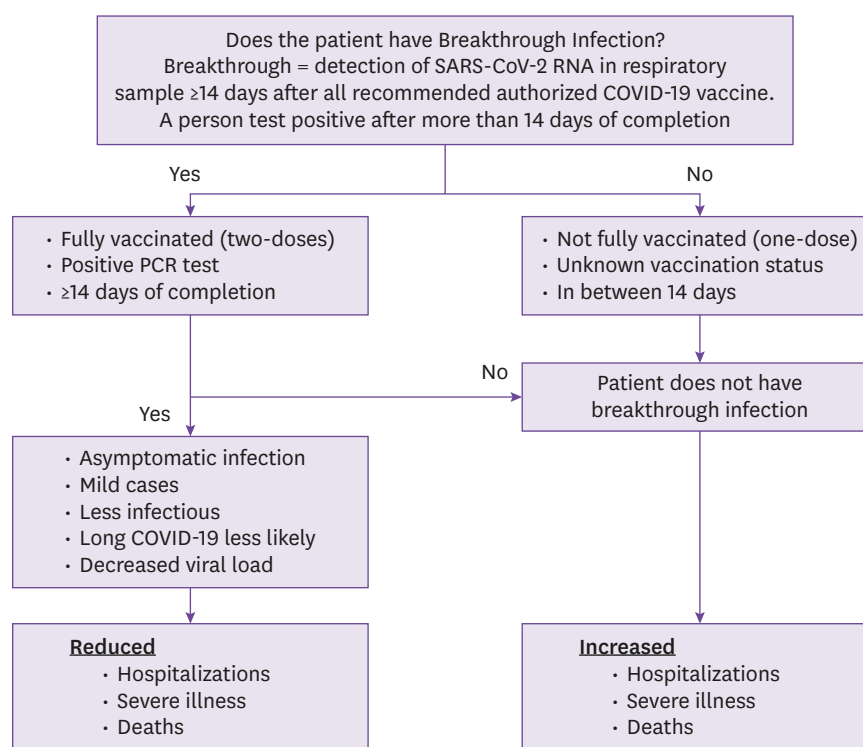
The emergence of these breakthrough infections has resulted in pervasive anxiety, miscommunication, and unrealistic expectations about the role of vaccines among the general population [11] which is a reminder that the pandemic is far from over. People tend to think we are back to square when we are in a much better position [11]. As developed vaccines remain effective in protecting people against the deadly virus and its complications, they do not form a gold shield [12]. Breakthrough events are expected, and some people who are fully vaccinated have COVID-19 [12].

The previous vaccines showed a similar trend. The measles vaccine failed to protect about 3% of vaccinated individuals who were exposed to the virus [13, 14]. Consequently, breakthrough infections of flu were common with the effectiveness of the vaccine ranging from 40 - 60% [13, 15]. A better understanding of the phenomenon promotes the confidence that the game is not yet over and vaccines still matter [16]. This helps to monitor the effectiveness of ongoing vaccines, determine whether the virus is evading available vaccines and inform decisions among the public. While this paper does not assess for the efficacy of vaccination campaigns or vaccines in preventing the pandemic. The present paper describes breakthrough infection, and discuss a pathway that is critical for building high confidence in the efficacy and safety of the COVID-19 vaccines.

## OVERVIEW OF BREAKTHROUGH INFECTIONS

Breakthrough infections are being reported globally, and this occurs after two weeks of taking COVID-19 jabs when protective effects are at their highest [17]. A person testing positive for the virus between the first and second doses of the vaccine or between the two weeks of their final dose is not considered a breakthrough infection (**Fig. 1**) [18].

The symptoms when analyzed are similar to those in the unvaccinated population except for a small difference. They include runny nose, headache, sneezing, sore throat and loss of smell [19]. Unvaccinated people have fever and persistent cough which is minimal in breakthrough cases. Fever is 58% less likely to occur in vaccinated individuals who develop breakthroughs and the feeling is described as cold for many [20]. Similarly, hospitalization and long COVID are less likely in vaccinated individuals [21]. The milder manifestations of breakthrough events could be that the vaccines block the infection or help contain fewer viral particles in the body [21].



**Figure 1.** Simplified algorithm of COVID-19 breakthrough infection.

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction.

A related study in Los Angeles County reported that unvaccinated individuals were 29 times more prone to hospitalization and four times more susceptible to SARS-CoV-2 infection than the vaccinated [22]. Data from reliable sources in the United States revealed that the risk of breakthroughs for most vaccinated people is approximately 1 in 5000 cases and 1 in 10,000 cases in areas of low contagiousness [23]. The period of contagiousness is shorter in those immunized, and the viral load decreases after five days [24].

Sources from the study of the COVID-19 symptoms in the United Kingdom documented that of the 971,504 people fully vaccinated with the BNT162b2 (Pfizer-BioNTech, Kalamazoo, MI, USA), mRNA-1273 (Moderna Tx, Inc., Norwood, MA, USA), ChAdOx1 (Astra Zeneca, Oxford, Oxfordshire, United Kingdom), only 0.2% had breakthrough infections between December 2020 and July 2021 [25]. These findings are among the first large scale, real-world data showing the importance of vaccines in breakthrough infections. Thus, vaccination cuts the odds of experiencing long-term effects even if there are breakthrough events [26].

Although data on how people catch COVID-19 after vaccination are limited and unclear. Breakthrough events are still evolving because the virus is constantly changing through mutation, and there is always a new variant expected [24]. The variant of concern now is the B.1.617.2 (Delta) variant which is more infectious and easily transmissible when compared to other variants in vaccinated people [24]. In America, 99% of all new cases are caused by this variant [27]. According to the WHO, the Delta lineage is among the four variants of concern, resistant to vaccines, and causes more breakthrough events. Irrespective of the type of vaccine, the Delta variant accounts for most cases of breakthrough events and how each

vaccine protects against SARS-CoV-2 and its variants measures differently. Breakthrough events sometimes can be influenced by the type of vaccine and its effectiveness. Some vaccines may or may not be suitable for other people [28]. A considerable number of studies have suggested that certain vaccines have varied effectiveness to offer protection against newer variants that cause breakthrough incidences [29].

Nonetheless, these findings are not conclusive as one vaccine is more effective than the other [30] and some studies have reported otherwise [31]. Data on breakthrough infections are not easily categorized by vaccine brands and cases occur with all vaccines [30]. Individual factors such as the immune system, underlying conditions, and the population receiving the vaccine play a major role [30]. Individuals with co-morbidities, even if they are fully vaccinated, can develop breakthroughs [32]. Also as age advances, the immune system diminishes, which may also impair the response to the vaccine [33]. In a nutshell, how well an individual responds to the COVID-19 vaccine depends on these factors [34].

Granted that breakthroughs are common with the above mentioned factor, the risk of contracting COVID-19 after vaccination is highly associated with deprived conditions and can affect all people in a cramped environment [26]. Transmission of the SARS-CoV-2 is likely, and chances of spreading are high when spaces are cramped and poorly ventilated. Dropped health precautions (not taking the vaccine, poor physical distancing and masking up) spill over the infection and which causes or increases the likelihood of breakthrough cases among the vaccinated [35].

In addition, gender plays a role in breakthroughs. Emerging research demonstrates that vaccines are less effective for women than men [36]. The BNT162b2 (Pfizer, Kalamazoo, MI, USA) was found to have a 96.4% efficacy rate in men and 93.7% in women [37]. The Centers for Disease Control and Prevention also reported that women account for 63% of breakthrough infections [38]. Nevertheless, vaccines perform the basic function of creating memory cells in both sexes which trains the immune system to be asymptomatic upon subsequent infections [36, 39].

Above all, some data sources suggest there is a possibility of declining antibodies in vaccinated people leading to the risk of breakthrough infection with time [40]. Antibodies that prevent Angiotensin-converting enzyme 2 (ACE2) receptors from binding to the five SARS-CoV-2 spike variants of concern also decreased at three months [41]. Despite the impact of these factors may increase the likelihood of breakthrough events, it does not imply vaccines are not working. The public should not feel frustrated because vaccination still provides robust immune response and protection which natural immunity would not have been sufficient to prevent fatalities associated with the pandemic.

## DISCUSSIONS TO PROMOTE VACCINE CONFIDENCE

Vaccination is the key strategy to eradicating the COVID-19 pandemic globally. The COVID-19 vaccines remain potent in preventing the infection, stopping people from catching or spreading the virus [42], and confidence is the trust patients have in the recommended vaccines. It is associated with behavior, and a decline in effectiveness can cause persistent loss of trust making it difficult to improve vaccination coverage [43].

COVID-19 vaccines have held their grounds to reduce severe illness, hospitalization and deaths [44]. As of June 30, 2021, approximately 279,000 lives were saved and 1.25 million hospitalizations prevented in the United States alone [45]. In Europe, England averted 46,300 hospitalizations, 30,300 deaths and 8.15 million infections whereas the incidence of cases and hospitalizations reduced by 77% and 68% respectively within the same timeline [46, 47]. Mapping changes in death rates, these countries managed to give at least 50 vaccine doses for every 100 of their citizens, reached the target zone of high vaccination rate, and a steady decline was seen [48]. More than 20 countries have eased lockdown restrictions they had in place during the rise in cases last year [48]. COVID-19 vaccination has reduced COVID anxiety, protected the vulnerable, offered a way to transition out of the pandemic and restored the society to its normal status [49, 50]. Global economies which were affected by the pandemic have achieved recovery through vaccination [51]. This is a huge step towards recovery, ending the pandemic, saving lives which is an extraordinary achievement. These overwhelming pieces of evidence justify vaccinating the mass population, and everyone is encouraged to take the jabs.

Breakthrough infections after vaccination have raised several questions about whether vaccine effectiveness is practically reassuring and has a larger benefit to the general population. There is also skepticism as to whether vaccines can hold ongoing mutations of the virus and the emergence of a new variant. Responding to these concerns builds public engagement that sustains confidence in the vaccine and immunization [48]. Educational and evidence-based scientific messages must address the what, when, how and why of breakthrough events for the benefit of communication and public perception of vaccines [52]. Thus, a more rigorous explanation of the situation is necessary to avoid people from concluding that the vaccine is not a perfect shield from the virus as this leads to hesitancy which in turns fuels breakthrough events. Unavailable information over these concerns presents another challenge or limitation undermining sustainable vaccination campaigns.

These low immunogenicity findings are not associated with worse outcomes [53]. When people undermine the vaccine due to breakthroughs, the virus continues to have the opportunity to evolve in a wave that dodges the aims of vaccination [54]. Breakthrough infections and the emergency of the delta variant although changed the landscape of the pandemic does not mean vaccines are not effective at preventing COVID-19 illness [55]. Vaccines are not impregnable or 100% perfect [56]. When there is an increase in the frequency of breakthrough cases, vaccines are working to prevent hospitalization and deaths [56]. Transmissions are reduced in all cases, and if they happen there is less severity (less severe symptom, fewer hospitalization and deaths) [56].

To date, vaccination remains effective against all known or existing variants because the rate of hospitalization, deaths and critical care treatment associated with breakthroughs are low [57]. Vaccines have fairly done their job, and they are better than nothing as they are saving lives [57].

Irrespective of the variant or vaccine type, efficacy wanes over time naturally [58] but vaccines still afford protection against severe COVID-19 disease and deaths.

Rather than low effectiveness against the pandemic, breakthrough events might be partly because many people are not taking the vaccines as required. Persistent hesitancy takes us back in an unexpected direction [59] and put everyone in a dangerous position [60]. It is about how much virus is out there trying to get in and the vaccination rate in the community.

The more that the virus is out there circulating the higher the chances that the pathogen can mutate to cause breakthrough infections. The best way to slow the emergence of a new variant or breakthroughs is to reduce the spread by protecting ourselves and getting vaccinated [32]. Direct protection of the vulnerable population can also be best achieved by vaccination [32].

Vaccinating the general population makes it extremely unlikely but not impossible to transmit the infection to others [61]. Vaccinated individuals have a low viral load in the nasal pharynx to cause severe symptoms or spread to others even if they test positive [61]. The risk of getting the COVID-19 disease amid the circulating delta variant is reduced [31]. The unvaccinated incubate new variant to evolve, which could even be more deadly than the delta variant [36].

The vaccines' ability to reduce severe illness and break the link between infection and death in most cases remain the judgement of the general population, and this makes getting vaccinated extremely important [62]. It reminds the general public to get vaccinated as soon as possible and urge the unvaccinated to do the same [63, 64]. Knowing and characterizing these risk factors can promote public confidence in the vaccines, improve vaccination rates and prevent breakthrough infections [57].

The public must also critically analyze the outcomes of persons with breakthrough events. Thus the difference between testing positive and getting the severe form of the disease [65]. Testing positive means there is a tiny amount of the virus in the body but not enough to make anyone ill. Those with asymptomatic breakthrough infection could alternatively be viewed as being successfully protected from the severe illness of SARS-CoV-2 by the vaccine [66]. Immunity induced by the COVID-19 vaccine is strong and reliable than natural immunity. It can sustain or raise protection for much longer than natural immunity [67]. These differences in results show assurance even if breakthrough infections occur [68].

It is not valid to argue that the unfavorable effects of the vaccine caused breakthrough infection or it is not worth taking the jabs. Even though widespread vaccination is unlikely to prevent all infections, the risk of breakthrough events should not deter from taking the vaccines. Vaccination is the same tool the world used to eradicate measles, came close to doing the same with polio, and COVID-19 vaccines could be done with this [30]. Healthy vaccination behaviors such full dosing schedule are viable to ending the pandemic. Two dose schedule is strongly encouraged to achieve firm control of the pandemic [69]. Vaccine effectiveness may be higher when two doses are fully completed than when a single [69]. The above discussion highlights the opportunity to increase our confidence in the COVID-19 vaccines, slow down the circulating virus and minimize breakthrough cases because there is exposure to the coronavirus for everyone [70].

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