Review

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Reinfection and Breakthrough Infection of SARS-CoV-2: An Emerging Challenge That Is Threatening Our World

Lin Gao[1,2,3], Xiuying Mu[1,2], Yan-Mei Jiao[1], Fu-Sheng Wang[1,2,*]

[1] Department of Infectious Diseases, The Fifth Medical Center of Chinese PLA General Hospital, National Clinical Research Center for Infectious Diseases, Beijing 100039, China;
[2] Peking University 302 Clinical Medical School, Beijing 100039, China;
[3] Department of Microbiology & Infectious Disease Center, School of Basic Medical Science, Peking University Health Science Center, Beijing 100191, China.

Abstract

The pandemic of coronavirus disease 2019 has threatened humans for more than one and a half years. In particular, viral mutation like delta strain has led to third- or fourth-wave transmission among the countries in Asia, Europe, and North America. Although large-scale vaccination has been carried out in many countries, the incidence of reinfection and vaccine-past breakthrough infection is becoming an emerging challenge to humans worldwide. The related mechanisms underlying the reinfection and breakthrough infection remain unknown. In this review, we summarized the challenge and related reasons for severe acute respiratory syndrome coronavirus 2 reinfection and breakthrough infection. Simultaneously, we addressed some critical contents of the study in future.

Keywords: Breakthrough infections; Reinfection; SARS-CoV-2; Vaccine

Coronavirus disease 2019 (COVID-19) is an acute self-limited infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection. Approximately 70% to 80% of infected individuals are asymptomatic and the rest have clinically different manifestations and symptoms included four kinds of clinical types: mild, common, severe, and critical.[1] The severe and critical cases are complicated diseases with severe pneumonia and multiple organ malfunctions. Most recovered patients developed protective immunity, including virus-specific humoral immunity and cellular immunity responsible for virus clearance.

As of September 2, 2021, 218 million cases of COVID-19 have been confirmed, with 4.54 million deaths.[2] More importantly, sporadic outbreaks and the local spread of SARS-CoV-2 in China have become a tricky issue due to reinfection and breakthrough infection, although approximately 969 million people have been vaccinated.[3] SARS-CoV-2 reinfection is defined by the reappearance of COVID-19 clinical symptoms with viral nucleotide re-positivity in convalescent patients within 90 days exposed to hazardous environments or closing contact with infections,[4] or the virus sequence data show that reinfection is different from the sequence of the first infected virus strain.[5] Furthermore, the vaccine breakthrough infection is referred to as the antigen or SARS-CoV-2 RNA positivity of respiratory specimens more than 14 days since receiving all recommended doses of COVID-19 vaccine.[6] In theory, there are many similarities in the mechanism between the vaccine breakthrough infection and reinfection. Herein, we summarize the progress and challenges for both reinfection and vaccine breakthrough infection.

Reasons for both reinfection and breakthrough infection

The reasons for reinfection and vaccine breakthrough infection are unclear, but they may be related to the anatomical features of virus infection, insufficient protective immune response, short duration of adaptive immunity, and virus mutation. First, as summarized in Figure 1, since SARS-CoV-2 at first infects those cells that expressing angiotensin-converting enzyme 2 (ACE2) receptors in the mucosal epithelium of the nose, mouth, and upper respiratory tract where there is an immunological anatomical "exemption" site, specific immunity, including cellular and humoral immunity, hardly reach to these anatomical sites. IgG antibodies produced by vaccine or infection exist mainly in serum or lymph nodes, making it difficult to reach the mucous membranes of the nose, mouth, and upper respiratory tract to prevent virus infection and effectively against the virus.[7] Since the virus entering the blood can be cleared by neutralizing antibodies and viral-specific T cells, there is almost no systemic infection by the SARS-CoV-2. Even if recovered COVID-19 patients have generated an adaptive protective immunity against SARS-CoV-2, they are likely to be reinfected by variant strains, as anatomical features in mucosal epithelial cells of the mouth, nose,

Lin Gao, Xiuying Mu, and Yan-Mei Jiao contributed equally to this work.

* **Corresponding author:** Fu-Sheng Wang, E-mail: fswang302@163.com

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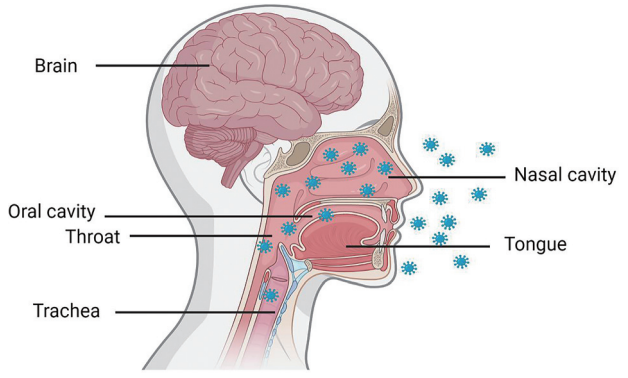

Figure 1: Severe acute respiratory syndrome coronavirus 2 enters and then firstly infects the mucosa ACE2$^+$ cells in the oral cavity, nasopharynx cavity, and upper respiratory tract and replicates in these cells, where viruses cannot be cleared by neutralizing antibodies and specific cellular immunity that fail to reach the anatomical exemptive site in mucosal epithelial cells in the mouth, nose, and upper respiratory tract. ACE2: Angiotensin-converting enzyme 2.

and upper respiratory tract are hardly protected by host innate and adaptive immunities. In addition, neutralizing antibodies and vaccines do not seem to eliminate SARS-CoV-2 in the nose of hamsters[7] and SARS-CoV-2 can easily enter target cells and replicate quickly, and then become a new source of infection through release.

Second, protective antibodies can be produced after initial infection or vaccination, but some people have very low antibody levels and cannot obtain immune protection, suggesting that they only induce an ineffective immune response that cannot protect against virus reinfection. Memory B-lymphocytes in humoral immunity and circulating neutralizing antibodies are crucial for preventing reinfection in SARS-CoV-2.[8] Studies have shown that virus-specific memory T cells can help clear the virus with SARS-CoV-2 reinfection quickly, and long-lived SARS-CoV-2 specific T cells can support the feasibility of vaccination to control the COVID-19 epidemic.[9–11] However, it is still doubtful whether sufficient and sustained immune memory responses exist in most infected people. Immune protection acquired after natural infection with SARS-CoV-2 is weaker than that induced by vaccination, but neither is completely avoids the occurrence of virus "reinfection" and "vaccine breakthrough infection".[12] The protective antibodies produced by natural infection with SARS-CoV-2 have a protective effect of 95.2% against reinfection for at least 7 months during the follow-up period.[13] Vaccines have a certain effect on preventing reinfection and spreading; a previous clinical study found that the reinfection rate among antibody-negative people is 27-fold that of neutralizing antibody-positive people.[13]

Although age, sex, autoimmunity, type and route of vaccination, and viral mutations affect the immune protective effect of the vaccination, the incidence of severity is significantly reduced after vaccination. It has been proved that the inhaled recombinant novel coronavirus vaccine (adenovirus vector)-Ad5-nCoV can provide the first line of defense when SARS-CoV-2 enters the human body and induces a large number of IgG and neutralized antibody responses.[14] However, the data of phase III clinical trial have not been published, and the effectiveness still needs to be further verified. The protective immune response of the upper respiratory tract may be a significant direction for vaccine development. Since antibody levels are greatly associated with the timing after exposure, it is necessary to determine the strength of response to spinous process proteins in the event of reinfection.[15] In addition, some recovered patients with RNA re-positive suggested that the virus remain exists in the body. Whether the virus is reactivated or reinfected is worthy of further in-depth study. Current research shows that vaccination can reduce the transmission rate of SARS-CoV-2 and the severity of COVID-19 disease, it is the most effective means of epidemic prevention and control,[16] and it is beneficial to receive a third dose of the COVID-19 vaccine.

More importantly, the rapid mutation rate of SARS-CoV-2 strains with rapid replication ability and increased transmissibility is one of the major reasons for reinfection and vaccine breakthrough infection. The binding ability to ACE2 receptors and replication of mutant strains were significantly improved.[17,18] Several studies have reported that the infectivity of the SARS-CoV-2 variants was generally higher than that of wild strains.[19,20] The protection rates of vaccines against the mutant virus were reduced, such as the Pfizer/Biontech BNT162B2 mRNA vaccine was significantly less effective against B.1.315 variants (Beta) than non-B.1.351 variants and the AstraZeneca Chadox1 vaccine showed only 10% protection against the B.1.351 variants.[21,22] Both B.1.351 and P.1 variants (Gamma) were significantly less sensitive to vaccine-induced and convalescent serum antibodies.[23] B.1.617 variants have been identified as the main mutant strain responsible for the outbreak of infection in India, and vaccines and convalescent plasma showed reduced neutralization in B.1.617.1 and B.1.617.2 variants.[18,24] All of the above suggest that SARS-CoV-2 may escape from neutralizing antibodies through different SARS-CoV-2 spike protein variants[25]; looking for the relatively conservative sequences of mutant strains for vaccine development may be another effective path for vaccine development.

B.1.617.2 is one of the three sub-strains of B.1.617 first reported in India in October 2020; it has the dual effects of enhancing the affinity of the S protein and ACE2 receptor and reducing antibody recognition, then the WHO named the B.1.617.2 variant as Delta, avoiding the stigmatization and discrimination caused by regional naming. Delta has spread to more than 130 countries and regions worldwide in about half a year, and the proportion of variant strain cases has increased from <5% at the end of April to approximately 90% at the beginning of August, and has become the main virus strain in the current world pandemic of the new crown epidemic. As the Delta variant has a certain immune evasion property, the clinical symptoms may be atypical, even beyond the scope of our current understanding of SARS-CoV-2 infection.

Clinical characteristics and epidemiology of reinfection and breakthrough infection

To date, there have been no reports based on a large population with SARS-CoV-2 reinfection. Approximately 10,262 cases with vaccine breakthrough infections were reported in the United States until April 30, 2021. Moreover, 6446 (63%) cases were females, 2725 (27%) cases were asymptomatic, 995 (10%) were hospitalized, and a total of 160 (2%) patients died. Approximately 555 (5%) cases completed the virus sequencing and 356 (64%) of them were infected with SARS-CoV-2 variants of concern, such as B.1.1.7 (199; 56%), B.1.429 (88; 25%), B.1.427 (28; 8%), P.1 (28; 8%), and B.1.351 (13; 4%).[6] These data showed that the decreased protective effect of plasma from recovered and vaccinated individuals on variant strains and

reinfection may occur in recovered patients and vaccinated individuals.

SARS-Cov-2 infection cases can self-heal during acute infection without antiviral treatment. Moreover, the cases of reinfection and vaccine breakthrough infections were mostly asymptomatic; it has been proved that neutralizing antibodies are involved in controlling SARS-CoV-2 infection *in vivo* and *in vitro*.[9] Recently, some studies have shown that most re-positive patients were young people; computed tomography (CT) images showed that the lesions were further absorbed compared with the first hospitalization period with limited infectivity.[26] Meanwhile, older patients (>60 years old) experienced at least one of the main clinical symptoms, including fever or chills, febrile influenza-like syndrome, such as fever, cough, fatigue, and dyspnea during reinfection, while CT scans showed signs of acute viral pneumonia and virus culture suggests infectivity generally.[27] The median time of virus shedding in the symptomatic group was significantly shorter than that of the asymptomatic group (14 days vs. 19 days), and the virus-specific IgG level was significantly higher in the acute phase.[28] Defining reinfection has crucial implications for treatment and infection control measures; therefore, it is necessary for clinicians to improve the ability of differential diagnosis between reinfection, recurrence of positive (re-positive) nucleic acid detection, and relapsed infection.

Comparison of viruses with and without reinfection and vaccine breakthrough infection

With the increasing number of SARS-CoV-2 infections, two kinds of increasing infections-reinfection and vaccine breakthrough infection begin to challenge the past cognition of clinicians and disease control experts. As described in Figure 2, general viral infectious diseases (blue word) (ie, hepatitis B, Japanese encephalitis) can effectively avoid reinfection and vaccine breakthrough infection after the first infection with the same virus completely cured or vaccination according to the procedure. However, some viruses cannot prevent reinfection and vaccine breakthrough infections, such as influenza virus and SARS-CoV-2. First, most of these reinfected viruses are RNA viruses with high variability during the nucleic acid repair process. For example, reinfection of respiratory viruses may be caused by a modest initial immune response (ie, human respiratory syncytial virus), reinfection with other genotypes (ie, rhinovirus), or high variability of the virus (ie, influenza virus). The reinfection frequently occurs 12-month later after the initial infection, suggesting that only short-term protective immunity is induced after the initial infection.[29,30] However, no systematic research report on the related mechanisms of respiratory virus reinfection and vaccine breakthrough infection. In addition, vaccines without permanent immune protection are all respiratory viruses, and the reinfected site of the virus is in the respiratory tract.

Recommendations for the third dose of vaccination and enhanced immune protection

The available data show that after the first dose of vaccine, the percentage of people who produce antibodies is low; meanwhile, the level of antibodies increases significantly after the second dose.[31] Since the first two doses of vaccine have already produced decent immune memory, a powerful immune response can be rapidly induced after the third dose of vaccine, and antibody levels will increase further. Recent studies have

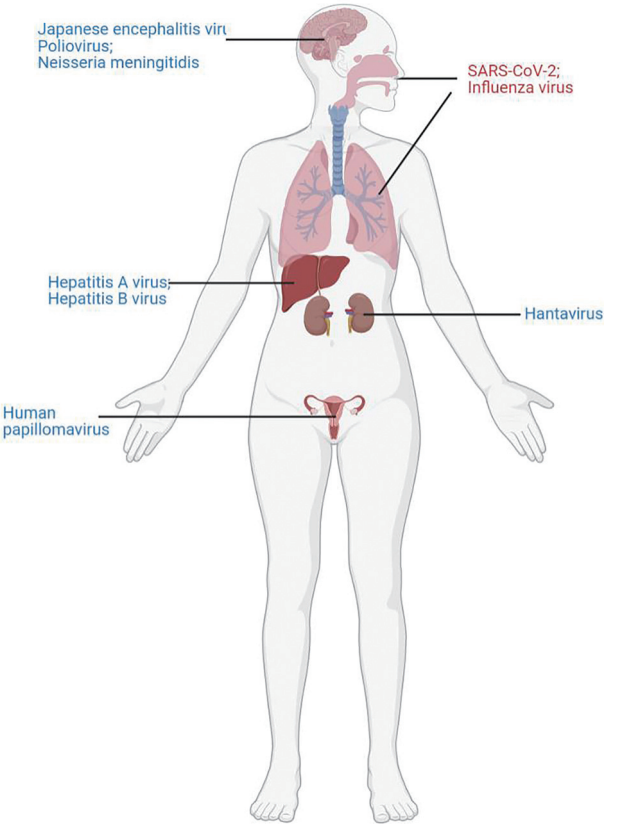

Figure 2: A schematic diagram of immune protection of vaccines. In general, there is no breakthrough infection for the vaccines to hepatitis B virus, Japanese encephalitis virus, and hantavirus. However, the vaccines to highly variable RNA viruses including SARS-CoV-2 (red) and influenza virus (red) that are all respiratory viruses, cannot avoid the vaccination breakthrough infection, due to the immunological anatomical "exemption" sites such as in the upper respiratory tract and the oral-nasal mucosa. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

reported significant increases in antibody levels in immunocompromised populations, such as patients receiving organ transplants after a third dose of the vaccine, and no cases of breakthrough infection in these populations.[31–33] Israel has recently begun to offer a third dose of the SARS-CoV-2 vaccine to all individuals over 60 years of age, and the United States, Germany, Indonesia, and Thailand have already offered a third dose of vaccine to populations of priority concern. Although the occurrence of reinfection and local outbreaks and spread due to vaccine breakthrough infection cannot be completely prevented after the third dose of vaccine, it is of great practical importance to reduce symptomatic, critical patients with COVID-19 and deaths and to control the pandemic of Delta variant strains.

Should the third dose of the SARS-CoV-2 vaccine administered with the same type of vaccine as before or other types, such as inhaled mucosal vaccine? To date, there was no official consensus on which type of vaccine should be given for the third dose. The FDA recommends a third dose of the same type of vaccine 28 days after the second dose. However, some studies have shown that different types of a third vaccine induce higher levels of antibodies and better immune response than the same type.[34,35] Some research teams are developing a respiratory inhalation vaccine that can induce the production of IgA antibodies in the mucosa of

the oral and nasal cavities and upper respiratory tracts that improve mucosal immunity and theoretically inhibit viral replication in the early stages of viral infection,[22] which could also be administered as a third dose after successful clinical trials of the mucosal vaccine.

Who needs the third dose of vaccine? Considering the differences in population size, geographic characteristics, and the risk of infection of different countries, along with the problems of insufficient vaccine supply and high cost for universal third-dose vaccination, it is preferable at this stage to prioritize the third dose among higher-risk populations, such as medical and disease prevention and control workers, relevant scientific researchers, cold-chain and transportation stations personnel, overseas workers, and immunocompromised populations. Therefore, we recommend that the third dose of vaccination be scheduled around 3 to 6 months after completing two doses of vaccination for the above-mentioned population. Contemporaneously, relevant departments of state authorities should consider the epidemic control situation and the progress of vaccine development to better define how to promote the third dose of vaccination for the whole population with the three-dose vaccine policy.

Summary

Reinfection and breakthrough infection with SARS-CoV-2 indicate that we still face a great challenge to fully control the COVID-19 pandemic. It appears that there have been many cases of asymptomatic reinfection or breakthrough infection. However, how long can they release the infectious viruses? How long does viral clearance take? To date, there are not sufficient medical data to highlight whether they need medical treatment? Which regimens are the best for patients? All these questions require further in-depth study. Immunization protection still requires safe and effective vaccinations, and the same type or different types of third shot vaccination should also be implemented for key populations as soon as possible. In addition, mutated strains should be monitored continuously, and the epitopes targeted by the vaccine need to be updated continuously. Current evidence suggests that existing vaccines still offer some protection against variants; thus, timely vaccination remains the primary means of protection against (primary and secondary) infection. It is necessary to understand the characteristics of mutant strains from many dimensions, such as epidemiology, clinical medicine, virology, and immunology, and pay attention to research on SARS-CoV-2 variant strains.

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Authors' Contributions

All the authors conceived the manuscript. Lin Gao and Xiuying Mu acquired data. Lin Gao, Xiuying Mu, and Yan-Mei Jiao drafted the manuscript. Fu-Sheng Wang revised the manuscript. All the authors approved the manuscript.

Conflicts of Interest

None.

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