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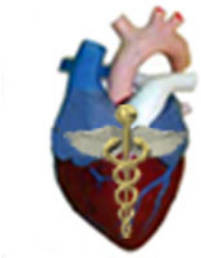

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EDITORIAL

COVID-19 Breakthrough Infections in Vaccinated Individuals

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Abstract

Vaccine breakthrough COVID-19 infections are increasingly occurring in fully vaccinated individuals, who may also spread COVID-19 to others. Hence, one is better protected if one wears a mask and maintaining distancing when in indoor public places. Mild infections pose little risk to vaccinated individuals and their contacts, while they may boost the individual immune responses and thus necessitate only monitoring as a precautionary measure. However, higher infectiousness and transmissibility of viral variants remain worrisome. Variants of concern are overrepresented among post-vaccination breakthrough COVID-19 infections. Identifying subgroups at a high risk for severe breakthrough infections is important in prioritizing early preventive treatment or prophylaxis. Despite a strong protection afforded by vaccination against severe disease, breakthrough infections may still advance to severe or critical illness at not-insignificant rates. The age distribution of patients with severe breakthrough infections is skewed towards older age groups and individuals with underlying comorbidities. All these issues and factors modulating the probability of a breakthrough COVID-19 infection in vaccinated people are herein discussed, and a tabulated list of the recommendations of the World Health Organization on COVID-19 infection prevention and control is also presented. ***Rhythmos 2022;17(1): 92-99***.

Key Words: COVID-19; SARS-CoV-2; COVID-19 vaccines; breakthrough infections; COVID-19 variants

Abbreviations: COVID-19 = corona virus disease 2019; NAATs = nucleic acid amplification tests; RT-PCR = reverse transcription polymerase chain reaction; VOC = variants of concern; WHO = World Health Organization

Introduction

According to the Centers for Disease Control and Prevention (CDC) of the USA, COVID-19 vaccines protect individuals aged ≥5 years from getting infected and severely ill, and significantly reduce the likelihood of hospitalization and death (www.cdc.gov/coronavirus/2019-ncov/vaccines/effectiveness/why-measure-effectiveness/breakthrough-cases.html).[1] A vaccine breakthrough COVID-19 infection can occur in a fully vaccinated person and fully vaccinated individuals with vaccine breakthrough infections may spread COVID-19 to others. Hence, one is better protected if one wears a mask when in indoor public places. People who are immunocompromised may not always build adequate levels of protection after an initial 2-dose primary mRNA COVID-19 vaccine series. They should continue to take all precautions recommended for unvaccinated people. Further, CDC recommends that

moderately or severely immunocompromised people receive an additional (booster) primary dose of vaccine. Since vaccines are not 100% effective, as the number of fully vaccinated persons rises, the number of vaccine breakthrough infections will also rise, even in non-immunosuppressed hosts.[2] However, vaccines attenuate the viral RNA load and mitigate risk of febrile symptoms, and duration of illness among those who have breakthrough infection despite vaccination.[3] Importantly, the risk of COVID-19 infection remains much higher for unvaccinated than vaccinated individuals.

According to statistics from the New York State Department of Health based on data accumulated through December 20, 2021, there have been **291,880** laboratory-confirmed breakthrough cases of COVID-19 among fully-vaccinated people (≥2 weeks after completing their vaccine series) in New York State, corresponding to **2.2%** of the population of fully-vaccinated people 12-years or older (COVID-19 Breakthrough Data Department of Health (ny.gov)).[4] Furthermore, there were recorded **14,383** hospitalizations with COVID-19 infection among fully-vaccinated people in New York State, corresponding to **0.11%** of the population of fully-vaccinated people 12-years or older.

Adaptive Immunity to COVID-19 Infection

CD4(+) T cells, CD8(+) T cells, and B cells (the source of neutralizing antibodies) all contribute to control of COVID-19 infection in both non-hospitalized and hospitalized patients.[5] Immunity is conferred by natural infection or by vaccination. However, vaccine efficacy, side effects, and seroconversion differ among the various types of vaccines. [6]

Breakthrough Infections in Fully Vaccinated Individuals

The infection rate ≥7 days after the second vaccine dose has been reported at 0.7 per 1000 person-days of follow up.[7] Increasing age may increase the risk (**Table 1**). However, even young healthy persons may have breakthrough infections, and some may develop severe symptoms.[8]

Among 1497 fully vaccinated health care workers, 39 COVID-19 breakthrough infections were detected.[9] Neutralizing antibody titers in case patients during the peri-infection period were lower than those in matched uninfected controls (case-to-control ratio, 0.361). Higher peri-infection neutralizing antibody titers were associated with lower infectivity. Most breakthrough cases were mild or asymptomatic, although 19% had persistent symptoms (>6 weeks). The B.1.1.7 (alpha) variant was found in 85% of samples tested. A total of 74% of case patients had a high viral load at some point during their infection; however, of these patients, only 17 (59%) had a positive result on concurrent antigen-detecting rapid diagnostic testing. No secondary infections were documented.

Data on breakthrough infections in a cohort of health care workers in a tertiary care hospital in India who received the AstraZeneca ChAdOx1 nCoV-19 (recombinant) vaccine, indicated that a total of 184 of 7170 health care workers (2.6%) tested positive after receiving at least one dose of vaccine; the median time between receipt of the first dose and the positive test was 44 days.[10] A total of 72 of 3650 health care workers (2%) tested positive after the second dose; the median time from receipt of the second dose to the positive test was 20 days. Among the health care workers who received both doses and completed at least 14 days of follow-up after the second dose, the incidence of breakthrough infection was 1.6% (48 of 3000); the median time from receipt of the second dose to breakthrough infection was 29.5 days.

Table 1. Factors Modulating the Probability of a Breakthrough COVID-19 Infection in Vaccinated People

Time since vaccination
High viral load
Lack of proper masking and/or distancing
Type of COVID-19 vaccine
Individuals with obesity
Various immunocompromising conditions
Other underlying comorbidities (e.g., cardiovascular and lung disease, diabetes, history of malignancy, use of immunosuppressive medications)
Older age
Frailty
Delta and Omicron variants
Lack of a booster dose of vaccine
Living in deprived areas

Variants

Vaccine safety and effectiveness is actively monitored by CDC and other health authorities against new and emerging variants for all approved COVID-19 vaccines. Vaccine failure due to variants poses potential risk of illness after successful vaccination and subsequent infection with variant virus.[11-13] Some studies indicate that variants of concern (VOC) are overrepresented among post-vaccination breakthrough COVID-19 infections. [14, 15]

The Delta variant is more contagious than previous variants of the virus that causes COVID-19.[1] However, studies so far indicate that the currently available vaccines work well against the Delta variant, particularly in preventing severe disease and hospitalization.

A meta-analysis of 24 studies indicated that the neutralizing activity against the ancestral SARS-CoV-2 was highly predictive of neutralization of VOC.[16] Decreases in neutralization titer to the alpha (1·6-fold), beta (8·8-fold), gamma (3·5-fold), and delta (3·9-fold) variants, compared to the ancestral virus, were not

significantly different among different vaccines. Neutralization was strongly correlated with protection from symptomatic infection with SARS-CoV-2 variants of concern. Booster vaccine doses are predicted to provide a higher degree of protection from infection with VOC than primary vaccination schedules alone.

Regarding the *Omicron variant*, designated as a VOC like the Delta variant, it is likely that this variant will spread more easily than the original SARS-CoV-2 virus and will thus be more transmissible. CDC expects that anyone with Omicron infection can spread the virus to others, even if they are vaccinated or remain asymptomatic.[17] Current vaccines are expected to protect against severe illness, hospitalizations, and deaths due to infection with the Omicron variant.

An artificial intelligence (AI) model indicates that Omicron may be >10-fold more contagious than the original virus or ~3 times as infectious as the Delta variant.[18] Furthermore, Omicron may have a high likelihood to escape current vaccines, may variably diminish the efficacy of current monoclonal antibodies, calling for new strategies to develop the next generation mutation-proof COVID-19 vaccines and antibodies.

The majority of post-vaccine COVID-19 cases occur prior to the expected onset of full, vaccine-derived immunity.[19] However, they appear to be asymptomatic or mildly symptomatic, although severe disease may also occur.[2] Hence, continued infection control measures in the workplace and in the community including social distancing and masking, particularly in the early days post-vaccination, and continued variant surveillance is necessary in order to avoid surges of infection.

Booster vaccines

Efficacy of primary vaccination with one or two doses against COVID-19 infection has been shown to decrease over time; such waning of vaccine-induced immunity, coupled with the emergence of COVID-19 variants has led to rising breakthrough infections, prompting consideration for vaccine booster doses.[20] A study showed that the vaccine effectiveness of two-dose mRNA vaccine series against COVID-19 decreased from 82% at 14-90 days after vaccination to 53% after 6 months.[21] Other studies showed similar results of declining antibody levels after 4-6 months among recipients of COVID-19 vaccines.[22] Thus, a booster dose after the 5- or 6-month period following the second dose has been advocated and implemented to ensure maximal protection against COVID-19.[23]

Of course, there are also sceptics about the need of a booster dose pointing to a paucity of data clarifying the clinical importance of triple-dosing of SARS-CoV-2 vaccines, at least for the young, where this requires further investigation.[24] It is also felt that determining the interval between the second and third dose will require clinical trials in different populations. Oxford–AstraZeneca, Pfizer–BioNTech and Moderna have already started clinical trials to assess the validity of the third booster vaccination by using different combinations.

Importantly, vaccine-elicited T cells respond strongly to emerging viral variants. Booster mRNA vaccination can boost T-cell responses and potentially reduce the chance of breakthrough infection through the generation of cross-protective T-cell immunity.[25]

CDC recommends that everyone aged 18 years and older should get a booster shot at least 2 months after their initial J&J/Janssen vaccine or 6 months after completing their primary COVID-19 vaccination series of Pfizer-BioNTech or Moderna.

Although the benefits of initial COVID-19 vaccination clearly outweigh the incurred risks, there could be risks if boosters are widely administered too soon, or too often, particularly with vaccines that can have immune-mediated adverse effects, including *myocarditis*, which is more common after the second dose of some mRNA vaccines, or *Guillain-Barre syndrome*, which has been associated with adenovirus-vectored COVID-19 vaccines.[26] Thus, widespread boosting should be undertaken only if there is clear evidence that it is useful.

In addition to the durability of vaccine-induced immunity, further challenges of booster doses include temporary shortages in vaccine supplies, significant vaccine inequity, and the emergence of viral variants, characterized by enhanced transmissibility and ability to at least partially evade neutralizing antibodies.[27] With serum antibody levels starting to wane within a few months after vaccination, the risk of breakthrough infections may increase.

However, even if humoral immunity appears to wane over time, reductions in neutralizing antibody titers do not necessarily predict reductions in vaccine efficacy over time. Even if reductions in vaccine efficacy do occur, they may lead to mild disease and not necessarily severe disease. Protection against severe disease is mediated not only by antibody responses, which might be relatively short lasting for some vaccines, but also by memory responses and cell-mediated immunity, which are generally longer lasting.

A US study assessing the frequency of and risk factors for developing a severe COVID-19 outcome (defined as hospitalization with a diagnosis of acute respiratory failure, need for noninvasive or invasive ventilation, admission to an intensive care unit, or succumbing to the disease) after completing a primary COVID-19 vaccination series, among 1,228,664 persons who completed primary vaccination reported that a total of 2,246 (18 per 10,000 vaccinated persons) developed COVID-19 and 189 (1.5 per 10,000) had a severe outcome, including 36 who died (0.3 deaths per 10,000).[28] Risk for

severe outcomes was higher in older (≥65 years) or immunosuppressed persons, or those with comorbidities. The authors suggested that these persons should receive targeted interventions including chronic disease management, precautions to reduce exposure, additional primary and booster vaccine doses, and effective pharmaceutical therapy as indicated to reduce risk for severe COVID-19 outcomes.

An Israeli study assessing the efficacy of a booster dose among 843,208 persons, of whom 758,118 (90%) received a booster at least 5 months after a second dose of the BNT162b2 vaccine (Pfizer-BioNTech) indicated that these individuals had 90% lower mortality due to COVID-19 compared with those who did not receive a booster.[29] Similarly, another study showed that rates of confirmed COVID-19 and severe illness were significantly lower among participants (aged ≥16 years) who received a booster dose of the BNT162b2 vaccine than among those who did not.[30] In keeping with these reports, another Israeli study matched the third dose and control groups, each including 728,321 individuals (median age 52 years, 51% female, median follow-up 13 days) and evaluated vaccine efficacy at least 7 days after receipt of the third dose.[31] Compared with receiving only two doses at least 5 months previously, efficacy of the third dose was estimated to be 93% (231 events for two doses vs 29 events for three doses) for admission to hospital, 92% (157 vs 17 events) for severe disease, and 81% (44 vs 7 events) for COVID-19-related death.

A study examining data on the comparative safety and immunogenicity of 7 different COVID-19 vaccines given as a booster dose (after 2 doses of ChAdOx1 nCov-19/Oxford-AstraZeneca or BNT162b2/Pfizer-BioNtech) indicated that all study vaccines boosted antibody and neutralizing responses after ChAd/ChAd initial course and all except one after BNT/BNT, with no safety concerns.[32]

Masks / Distancing

Masks and distancing offer protection against all variants. CDC continues to recommend wearing a mask in public indoor settings in areas of substantial or high community transmission, regardless of vaccination status.[1] Similarly, the World Health Organization (WHO) is urging the public to practice COVID mitigation tactics – including masking and distancing – regardless of vaccination status as cases surge across countries (***Table 2***). [33]

Table 2. WHO Guideline on COVID-19 Infection Prevention and Control [33]

● In settings where there is community or cluster transmission of SARS-CoV-2, ***irrespective of vaccination status or history of prior infection***, wearing a **well-fitting mask** that covers the nose and mouth is recommended for the general public when interacting with individuals who are not members of their household

● **Physical distance** should be increased *beyond 1 m* whenever feasible

● In settings where there is community or cluster transmission of SARS-CoV-2, policies should be developed, strengthened and implemented to encourage appropriate adherence to a comprehensive package of preventive measures to reduce transmission (*ventilation, physical distance, hand hygiene, and respiratory etiquette*) including in particular, *mask adherence* by the general public

● In any transmission scenario, persons with any symptoms suggestive of COVID-19 should wear a medical mask and additionally:

• self-isolate and seek medical advice as soon as they start to feel unwell with potential symptoms of COVID-19 (even if symptoms are mild);

• follow instructions on how to put on, take off and dispose of medical masks and wash hands thoroughly;

• follow all additional measures, in particular, respiratory hygiene, frequent hand washing and maintaining a physical distance of at least 1 m from other persons

• If a medical mask is not available for individuals with suspected or confirmed COVID-19, a fabric mask with fit, filtration and breathability assessed to meet WHO's essential parameters for non-medical masks should be worn by patients as a source control measure, pending access to a medical mask. The use of a non-medical mask can minimize the projection of respiratory particles from the user

● Asymptomatic persons who test positive for SARS-CoV-2 should wear a *medical mask* when with others for a period of 10 days after testing positive

● Individuals with a higher risk* of severe complications from COVID-19 should wear a *medical mask* where physical distancing of at least 1 m cannot be maintained

● Persons with suspected COVID-19 or mild COVID-19 symptoms should wear a *medical mask* as much as possible, especially when there is no alternative to being in the same room with other people

● Caregivers of or those sharing living space with people with suspected COVID-19 or with mild COVID-19 symptoms should wear a *medical mask* when in the same room as the affected person

● WHO advises that people should not wear masks *during vigorous-intensity physical activity* because masks may reduce the ability to breathe comfortably. The most important preventive measure is to maintain *physical distancing of at least 1 m* and to ensure good ventilation when exercising.

● At present, ***face shields*** *are considered to provide a level of eye protection only*, and *should not be considered as an equivalent to masks* with respect to respiratory protection and/or source control. Current laboratory testing standards only assess face shields for their ability to provide eye protection from chemical splashes

● WHO and UNICEF advise decision-makers to apply the following criteria for use of masks in **children** when developing national policies, in countries or areas where there is known or suspected community transmission of SARS-CoV-2 and in settings where physical distancing cannot be achieved

• Based on the expert opinion gathered through online meetings and consultative processes, *children aged up to 5 years should not wear masks* for source control

● WHO and UNICEF advise decision-makers to apply the following criteria for use of masks in children when developing national policies, in countries or areas where there is known or suspected community transmission of SARS-CoV-2 and in settings where physical distancing cannot be achieved

• For children between 6 and 11 years of age, a risk-based approach should be applied to the decision to use a mask

● Advice on mask use in children and adolescents 12 years or older should follow the WHO guidance for mask use in adults and/or the national mask guidelines for adults †

● Children with severe cognitive or respiratory impairments who have difficulties tolerating a mask should, under no circumstances, be required to wear a mask

● Children with developmental disorders or disabilities may face additional barriers, limitations and risks, and should therefore be given alternative options to mask wearing, such as *face shields*

● The use of a medical mask for immunocompromised children or for pediatric patients with cystic fibrosis or certain other diseases (e.g., cancer) is usually recommended but should be assessed in consultation with the child's medical provider

● WHO and UNICEF advise that when physical distancing cannot be maintained, and in situations where it is not practical to wear a mask (e.g., among children with hearing loss or other disabilities, or health conditions that limit compliance with wearing fabric or medical masks and consequently their utility), face shields may be used while taking the following considerations into account:

• The face shield is an incomplete physical barrier and does not provide the filtration layers of a mask

• The face shield should cover the entire face, be wrapped around the sides of the face and extend to below the chin

• Reusable face shields must be properly cleaned (with soap or a detergent and water), disinfected (with 70–90% alcohol) and stored correctly after each use. Face shields that can withstand the use of disinfectants without damaging their optical properties should be selected

• Maintaining a physical distance of at least 1 m should be maintained where feasible, with the ongoing promotion of frequent hand hygiene and respiratory etiquette

• Caution should be taken to avoid injury when children don, wear and doff face shields

● To facilitate the operationalization of this guidance in school settings, it is advised that the age categories be adapted to the national/local education level structure

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**High-risk populations* are defined as: people aged ≥ 60 years; or people with underlying comorbidities, such as cardiovascular disease or diabetes mellitus, chronic lung disease, cancer, cerebrovascular disease, immunosuppression, obesity or asthma

† For children of any age with developmental disorders, disabilities or other specific health conditions that might interfere with mask wearing, the use of masks should not be mandatory and should be assessed on a case-by-case basis by the child's educator and/or medical provider

Testing

Testing can determine if one is currently infected with COVID-19. Two types of tests are used to test for current infection: nucleic acid amplification tests (NAATs) and antigen tests. A Nucleic Acid Amplification Test, or NAAT, is a type of viral diagnostic test for SARS-CoV-2. NAATs detect genetic material (nucleic acids). NAATs for SARS-CoV-2 specifically identify the RNA sequences that comprise the genetic material of the virus.

Antigen tests are immunoassays that detect the presence of a specific viral antigen, which implies current viral infection. Antigen tests are currently authorized to be performed on nasopharyngeal or nasal swab specimens placed directly into the assay's extraction buffer or reagent. The currently authorized antigen tests include point-of-care, laboratory-based, and self-tests, and they are applicable to people of any age.

Antigen tests are relatively inexpensive, and most can be used at the point-of-care. Most of the currently authorized tests return results in approximately 15–30 minutes. Antigen tests for SARS-CoV-2 are generally less sensitive than real-time reverse transcription polymerase chain reaction (RT-PCR) and other NAATs for detecting the presence of viral nucleic acid. However, NAATs can remain positive for weeks to months after initial infection and can detect levels of viral nucleic acid even when virus cannot be cultured, suggesting that the presence of viral nucleic acid may not always indicate contagiousness.

Additional tests would be needed to determine if the infection is caused by Omicron. Self-tests can be used at home or anywhere, are easy to use, and produce rapid results. If the self-test has a positive result, one should stay home or isolate oneself for 10 days, wear a mask if one has contact with others, and inform the healthcare provider.

Neutralizing Antibody Testing

Neutralizing antibody titers during the first months after vaccination appear to be well correlated with vaccine effectiveness and are predictive of the risk of breakthrough infection in individuals.[9, 34, 35] However, no specific antibody or neutralizing threshold titer has yet been determined that can predict the degree of protection as it varies over time with waning post infection or vaccination, or waxing with boosting. Nevertheless, neutralizing antibodies do not necessarily protect against infection.[36] Individuals can have neutralizing antibodies and still get infected. Thus, protection against SARS-CoV-2 infection

cannot currently be presaged exclusively using *in vitro* antibody assays against wild-type SARS-CoV-2 spike protein.[37] Generating higher neutralizing antibody levels is better, but there is no defined threshold of protection. Furthermore, most tests are not standardized and calibrated. Importantly, all antibodies bind but only some of them neutralize the virus, and almost none of the authorized clinical tests can distinguish between them.

Circulating antibodies against the virus peak 2-3 months after natural infection or vaccination and then begin to decrease. However, the immune system's ability to mount a defense lasts longer due to immunological memory. Memory T cells and memory B cells persist for at least 6 to 8 months and continue to evolve and mature. None of this information is relayed by an antibody test.

Reinfection with the COVID-19 virus activates memory B cells to differentiate into antibody-secreting cells. However, this process can take 3-5 days, it does not prevent COVID-19 infections from occurring, but it does help to mitigate severe COVID-19 illness, which is actually the goal of the vaccine, i.e., to provide protection against severe illness, hospitalization and death.

Sequelae of Breakthrough Infections

Mild infections pose little risk to vaccinated individuals and their contacts, while they may boost the individual immune responses and thus necessitate only monitoring as a precautionary measure. However, higher infectiousness and transmissibility of the variants remain worrisome. Therefore, planning and measures to prevent additional surges are mandatory.

COVID-19 infection has been associated with several short- and long-term sequelae on patient health including long COVID. [38] These late sequelae of COVID-19 infection have been observed in both severe and mild or even in asymptomatic cases, albeit they are significantly reduced in breakthrough infections.[39]

Despite a robust protection afforded by vaccination against severe disease, breakthrough infections may still advance to severe or critical illness at not-insignificant rates.[40] The age distribution of patients with severe breakthrough infections is skewed towards older age groups and individuals with underlying comorbidities compared with those who are unvaccinated (Table 1). Despite these differences, a shorter mean duration of hospitalization, lower risk of advanced oxygen or ventilatory support, and lower in-hospital mortality have been reported among patients with breakthrough COVID-19 than among those who are unvaccinated. [40]

In children, breakthrough infections that occur in vaccinated children are expected to have a reduced likelihood of leading to multisystem inflammatory syndrome (MIS-C) [41] compared with COVID-19 infections in unvaccinated children. Currently, no data have been available regarding this issue.

Identifying subgroups at a high risk for severe breakthrough infections is important in prioritizing early preventive treatment or prophylaxis (Table 1).

Factors Modulating Vaccine Effectiveness and thus the Probability of Breakthrough Infection

Time since vaccination is a key factor that modulates vaccine efficacy (Table 1).[42] The amount of protection offered by a vaccine against infection might decline over time, allowing more breakthrough infections as the immune response wanes over months or years. Also, different COVID-19 vaccines provide different levels of immunity following immunization and thus have varying effectiveness. COVID-19 vaccination is less immunogenic in persons with various immunocompromising conditions, e.g., hematological neoplasms. Importantly, COVID-19 variants can affect the degree of protection conferred by vaccines. It seems that that the probability of breakthrough infection is higher with the Omicron and Delta variants than with the Alpha variant.

Exposure to higher viral loads can reduce vaccine effectiveness and increase the probability of breakthrough infection. This indicates that proper masking and distancing may be helpful in this context. [39]

As immunity wanes to certain degree, the most noticeable declines of vaccine efficacy seem to relate to asymptomatic infections, milder infection outcomes, older individuals, those vaccinated earliest, and likely in the presence of the Delta and Omicron variants. Importantly, in vaccinated people, it takes longer time from initial COVID-19 infection to develop severe disease; this time delay is sufficient for the memory immune response to take effect. The longer time available for the virus, including the variants, to incite an effective immune response may explain the vaccine effectiveness against severe disease observed even as time since vaccination elapses.

Considering these modulating factors, it may be plausible to explain the efficacy of a booster dose of the COVID-19 vaccine against the variants, even though the third dose encodes the original COVID-19 spike protein rather than a variant-specific spike protein. [42]

Finally, there is an argument that rather than trying to discern the contributions of factors such as age, viral variants and time since vaccination, the rates of breakthrough infection are best seen as a consequence of the level of immunity at any moment in a person, the variant to which that person is exposed and the severity of disease being considered. [42]

Perspectives

Completing a primary COVID-19 vaccination defined as receipt of 2 doses of an mRNA vaccine of Pfizer-

BioNTech or Moderna, or a single dose of Janssen ≥14 days before illness onset, does not seem to offer adequate protection. Protective immunity conferred by vaccines continues to decline substantially after the first 6 months, and this is coupled with the emergence of COVID-19 variants, hence the argument for booster doses. However, significant waning has not been noted for all types of vaccines and in all age groups. There is also evidence of higher immunogenicity for two-dose regimens with a longer interval between doses which should be further investigated in future trials. Thus, not all intricacies have been worked out regarding booster vaccination.[42] It has been reported that boosters administered to ≥18 year-olds may reduce the hospitalization peak by 25-43%, with a delay of 5 months between second and third dose. [43] A recent Italian study indicated that primary COVID-19 vaccination efficacy was 76-92% and decreased to 34-80% after 6 months; administration of vaccine booster doses decreased COVID-19 infections by 65%, hospitalizations and by 69% and deaths by 97% compared to vaccine efficacy after 6 months. [44] With the emergence and rise of variants that can elude vaccines and immunity, breakthrough infections would likely increase. Versatile tools will be needed to monitor duration of vaccine-conferred protection, impact of variants on vaccine effectiveness, and a strategy allowing facilitating adaptation of vaccine antigens and dosing intervals.[42] Finally, it has been stated by some country officials that they are preparing to offer an annual COVID-19 booster vaccine program if one is required. [45]

References

1. CDC: The Possibility of COVID-19 after Vaccination: Breakthrough Infections. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/ effectiveness/why-measure-effectiveness/breakthrough-cases.html. 2021.
2. Teran RA, Walblay KA, Shane EL, et al. Postvaccination SARS-CoV-2 Infections Among Skilled Nursing Facility Residents and Staff Members - Chicago, Illinois, December 2020-March 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:632-38.
3. Thompson MG, Burgess JL, Naleway AL, et al. Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines. *N Engl J Med* 2021;385:320-29.
4. New York State: COVID-19 Breakthrough Data. https://coronavirus.health.ny.gov/covid-19-breakthrough-data. 2021.
5. Sette A, Crotty S. Adaptive immunity to SARS-CoV-2 and COVID-19. *Cell* 2021;184:861-80.
6. Khandker SS, Godman B, Jawad MI, et al. A Systematic Review on COVID-19 Vaccine Strategies, Their Effectiveness, and Issues. *Vaccines (Basel)* 2021;9.
7. Butt AA, Khan T, Yan P, et al. Rate and risk factors for breakthrough SARS-CoV-2 infection after vaccination. *J Infect* 2021;83:237-79.
8. Pollett SD, Richard SA, Fries AC, et al. The SARS-CoV-2 mRNA vaccine breakthrough infection phenotype includes significant symptoms, live virus shedding, and viral genetic diversity. *Clin Infect Dis* 2021 Jun 12; ciab543. doi: 10.1093/cid/ciab543. Online ahead of print.
9. Bergwerk M, Gonen T, Lustig Y, et al. Covid-19 Breakthrough Infections in Vaccinated Health Care Workers. *N Engl J Med* 2021;385:1474-84.
10. Rana K, Mohindra R, Pinnaka L. Vaccine Breakthrough Infections with SARS-CoV-2 Variants. *N Engl J Med* 2021;385:e7.
11. Hacisuleyman E, Hale C, Saito Y, et al. Vaccine Breakthrough Infections with SARS-CoV-2 Variants. *N Engl J Med* 2021;384:2212-18.
12. Krause PR, Fleming TR, Longini IM, et al. SARS-CoV-2 Variants and Vaccines. *N Engl J Med* 2021.
13. Kustin T, Harel N, Finkel U, et al. Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2-mRNA-vaccinated individuals. *Nat Med* 2021;27:1379-84.
14. McEwen AE, Cohen S, Bryson-Cahn C, et al. Variants of concern are overrepresented among post-vaccination breakthrough infections of SARS-CoV-2 in Washington State. *Clin Infect Dis* 2021 Jun 24;ciab581. doi: 10.1093/cid/ciab581. Online ahead of print.
15. Ioannou P, Karakonstantis S, Astrinaki E, et al. Transmission of SARS-CoV-2 variant B.1.1.7 among vaccinated health care workers. *Infect Dis (Lond)* 2021;53:876-79.
16. Cromer D, Steain M, Reynaldi A, et al. Neutralising antibody titres as predictors of protection against SARS-CoV-2 variants and the impact of boosting: a meta-analysis. *Lancet Microbe* 2022;3:e52-e61.
17. CDC. Science Brief: Omicron (B.1.1.529) Variant. https://www.cdc.gov/coronavirus/2019-ncov/science/ science-briefs/scientific-brief-omicron-variant.html. 2021.
18. Chen J, Wang R, Gilby NB, Wei GW. Omicron Variant (B.1.1.529): Infectivity, Vaccine Breakthrough, and Antibody Resistance. *J Chem Inf Model* 2022 Jan 6. doi: 10.1021/acs.jcim.1c01451. Online ahead of print.
19. Jacobson KB, Pinsky BA, Montez Rath ME, et al. Post-vaccination SARS-CoV-2 infections and incidence of presumptive B.1.427/B.1.429 variant among healthcare personnel at a northern California academic medical center. *Clin Infect Dis* 2021 Jun 17;ciab554. doi: 10.1093/cid/ciab554. Online ahead of print.
20. Burckhardt RM, Dennehy JJ, Poon LLM, Saif LJ, Enquist LW. Are COVID-19 Vaccine Boosters Needed? The Science behind Boosters. *J Virol* 2021 Nov 24; JVI0197321. doi: 10.1128/JVI.01973-21. Online ahead of print.

21. Poukka E, Baum U, Palmu AA, et al. Cohort study of Covid-19 vaccine effectiveness among healthcare workers in Finland, December 2020 - October 2021. *Vaccine* 2021 Dec 18;S0264-410X(21)01640-6. doi: 10.1016/j.vaccine.2021.12.032. Online ahead of print.
22. Bajema KL, Dahl RM, Evener SL, et al. Comparative Effectiveness and Antibody Responses to Moderna and Pfizer-BioNTech COVID-19 Vaccines among Hospitalized Veterans - Five Veterans Affairs Medical Centers, United States, February 1-September 30, 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1700-05.
23. Fast HE, Zell E, Murthy BP, et al. Booster and Additional Primary Dose COVID-19 Vaccinations Among Adults Aged ≥65 Years - United States, August 13, 2021-November 19, 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1735-39.
24. Rahimi F, Bezmin Abadi AT. The third booster vaccination dose against COVID-19: indication for circulating SARS-CoV-2 variants. *Future Virol* 2021 Oct;10.2217/fvl-2021-0240. doi: 10.2217/fvl-2021-0240. Epub 2021 Nov 4.
25. Nixon DF, Ndhlovu LC. Vaccine Breakthrough Infections with SARS-CoV-2 Variants. *N Engl J Med* 2021;385:e7.
26. Krause PR, Fleming TR, Peto R, et al. Considerations in boosting COVID-19 vaccine immune responses. *Lancet* 2021;398:1377-80.
27. Rzymski P, Camargo CA, Jr., Fal A, et al. COVID-19 Vaccine Boosters: The Good, the Bad, and the Ugly. *Vaccines (Basel)* 2021;9.
28. Yek C, Warner S, Wiltz JL, et al. Risk Factors for Severe COVID-19 Outcomes Among Persons Aged ≥18 Years Who Completed a Primary COVID-19 Vaccination Series - 465 Health Care Facilities, United States, December 2020-October 2021. *MMWR Morb Mortal Wkly Rep* 2022;71:19-25.
29. Arbel R, Hammerman A, Sergienko R, et al. BNT162b2 Vaccine Booster and Mortality Due to Covid-19. *N Engl J Med* 2021;385:2413-20.
30. Bar-On YM, Goldberg Y, Mandel M, et al. Protection against Covid-19 by BNT162b2 Booster across Age Groups. *N Engl J Med* 2021;385:2421-30.
31. Barda N, Dagan N, Cohen C, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *Lancet* 2021;398:2093-100.
32. Munro APS, Janani L, Cornelius V, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. *Lancet* 2021;398:2258-76.
33. WHO. COVID-19 Infection Prevention and Control. file:///C:/Users/ASM/Downloads/WHO-2019-nCoV-IPC_masks-2021.1-eng.pdf. 2021.
34. Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021;27:1205-11.
35. Earle KA, Ambrosino DM, Fiore-Gartland A, et al. Evidence for antibody as a protective correlate for COVID-19 vaccines. *Vaccine* 2021;39:4423-28.
36. Abbasi J. The Flawed Science of Antibody Testing for SARS-CoV-2 Immunity. *Jama* 2021;326:1781-82.
37. Bradley BT, Bryan A, Fink SL, et al. Anti-SARS-CoV-2 Antibody Levels Measured by the AdviseDx SARS-CoV-2 Assay Are Concordant with Previously Available Serologic Assays but Are Not Fully Predictive of Sterilizing Immunity. *J Clin Microbiol* 2021;59:e0098921.
38. Manolis AS, Manolis TA. Long COVID: An Emerging Puzzle. *Rhythmos* 2021;16:89-94.
39. Antonelli M, Penfold RS, Merino J, et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. *Lancet Infect Dis* 2022;22:43-55.
40. Wang SY, Juthani PV, Borges KA, et al. Severe breakthrough COVID-19 cases in the SARS-CoV-2 delta (B.1.617.2) variant era. *Lancet Microbe* 2022;3:e4-e5.
41. Manolis AS, Manolis TA. Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-Cov-2 Infection (PIMS-TS): Kawasaki-Like Multisystem Inflammatory Syndrome in Children (MIS-C) During the COVID-19 Pandemic with Predominant Myocarditis. *Rhythmos* 2020;15:42-46.
42. Lipsitch M, Krammer F, Regev-Yochay G, Lustig Y, Balicer RD. SARS-CoV-2 breakthrough infections in vaccinated individuals: measurement, causes and impact. *Nat Rev Immunol* 2022;22:57-65.
43. Bosetti P, Tran Kiem C, Andronico A, et al. Impact of booster vaccination on the control of COVID-19 Delta wave in the context of waning immunity: application to France in the winter 2021/22. *Euro Surveill* 2022;27.
44. Mattiuzzi C, Lippi G. Primary COVID-19 vaccine cycle and booster doses efficacy: analysis of Italian nationwide vaccination campaign. *Eur J Public Health* 2022 Jan 3; ckab220. doi: 10.1093/eurpub/ckab220. Online ahead of print.
45. Iacobucci G. Covid-19: England is preparing to offer annual booster vaccination, says NHS boss. *Bmj* 2021;375:n2824.