

COVID-19 vaccine breakthrough infections

Vaccine efficacy wanes over time but can be fully restored with a booster dose

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The pivotal phase 3 clinical trials of the two-dose messenger RNA (mRNA) vaccines, among the largest ever conducted, led to the notable finding of ~95% efficacy for prevention of symptomatic COVID-19 2 months after the second dose. Adenovirus vectored vaccines showed lower protection against infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) but achieved >90% protection against severe disease. No vaccines protect against all infections, and very few achieve such a high level of protection as that of the COVID-19 vaccines. In the early months after vaccinations at scale began, around January 2021, post-vaccination infections (or breakthrough infections) were rare, accounting for <1% of COVID-19 cases, and only ~0.1% resulted in hospitalization or death in high-income countries (1, 2). However, by 5 to 6 months after vaccinations began, this pattern changed. Even before vaccine introduction, it was anticipated that a third, booster dose would be necessary to preserve efficacy, but when that would be needed was uncertain.

Variants of SARS-CoV-2 with multiple immune-escape and infectivity-enhancing mutations (particularly in the spike protein, which facilitates infection of human cells) likely arise after chronic infection (3). Some, such as the Alpha variant, showed increased infectivity and transmissibility, whereas other variants, such as Beta, were less sensitive to neutralization by vaccine- and infection-induced antibodies. As Delta became prevalent in Israel, the United Kingdom, Qatar, and the United States, there were multiple reports of a substantial increase in breakthrough infections after mRNA and adenovirus vectored vaccination.

The Israel Ministry of Health reported vaccine effectiveness of 40% against symptomatic infections 4 to 6 months after the second dose, representing a substantial decline (see the figure). Although initially it was unclear whether this was due to waning immunity over time or the more transmissible Delta variant, it became apparent that time itself was a key driver, with attrition of efficacy seen in the participants of initial clinical trials (4). Waning immunity occurred, to a variable extent, after all vaccines studied to date, and loss of protection was likely amplified by increased prevalence of Delta.

The Delta variant contains mutations in the spike protein that are divergent from

surface. For optimal cellular infection of the produced virions, S1S2 also needs processing at the S2' site adjacent to the FCS; this processing is carried out by transmembrane protease serine 2 (TMPRSS2) in the plasma membrane. Spike is then able to interact with the host cell receptor, angiotensin-converting enzyme 2 (ACE2), through the receptor binding domain (RBD) (in S1) to drive efficient fusion of the viral membrane with the host cell membrane for entry of the virus.

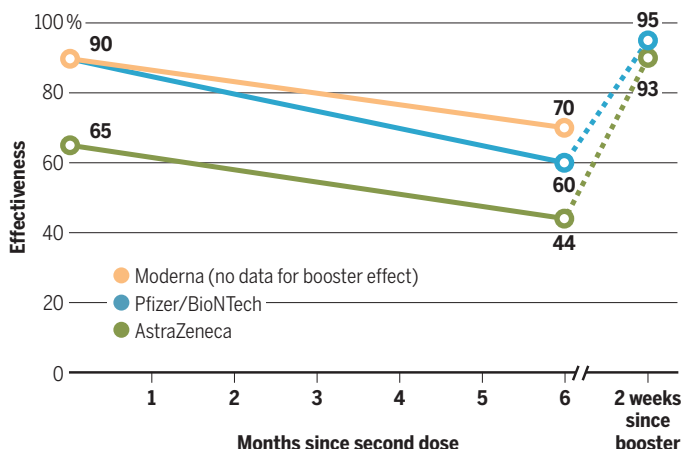
One mutation, P681R (Pro⁶⁸¹ → Arg), is located in the FCS and is specific to Delta. The mutation is associated with increased cleavage of spike into S1 and S2 fragments (5). The role of P681R might be related to other spike mutations—for example, in the amino-terminal domain (NTD) of S1, where Delta bears a deletion of amino acids 157–158—as well as T19R, G142D, and R156G mutations. These NTD mutations lead to substantial rearrangement of the NTD that may have allosteric effects on the RBD and/or promote binding with additional cellular receptors to increase infectivity. Spike mutations that increase infectivity could enable virus to rapidly attach and infect epithelial respiratory cells, avoiding the relatively sparse neutralizing antibodies in the mucosa. Furthermore, Delta's spike protein can achieve membrane fusion far more efficiently than can other variants (5). This ability to fuse cells to generate

syncytia (multinucleated cells) might enable virus to propagate from one cell to another without needing to exit the cell, avoiding exposure to neutralizing antibodies.

Delta has also demonstrated moderate evasion from neutralizing antibodies, which appears to be partly related to the RBD mutation L452R with a less clear contribution from T478R in the RBD. Mutations in the Delta NTD have also been shown to reduce recognition by NTD-specific neutralizing antibodies. Together, immune evasion and increased replication likely underpin Delta's ability to cause reinfection and vaccine breakthrough.

Vaccine effectiveness over time

Two doses of messenger RNA (mRNA) or adenovirus vectored COVID-19 vaccines elicit high levels of protection from symptomatic disease, but this wanes over time. Emerging studies show that a third dose (booster) of the same type can restore effectiveness to >90%. Data are averages for Delta variant from multiple studies.



the three prior variants of concern, Alpha (B.1.1.7), Beta (B.1.351), and Gamma (P.1). SARS-CoV-2 is an enveloped virus, taking lipid bilayer from infected cells. The infected cell produces the viral spike protein after translation from the viral RNA template, and spike is embedded in the lipid bilayer surrounding the virus core. The spike protein has two main regions, S1 and S2. During transport of spike to the plasma membrane, it is cleaved by cellular furin proteases at the furin cleavage site (FCS) between the S1 and S2 regions. The two cleaved pieces then associate with each other to form semimature spike at the cell

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A consistent finding across studies has been the high viral load associated with Delta infections, no matter whether they occur among unvaccinated or vaccinated individuals. Recent transmission studies of the Delta variant have also revealed some distinct features, particularly a faster onset of illness and clearance. Faster clearance of the virus and a shorter duration of infectivity was noted in a study of vaccinated compared with unvaccinated people (6). The magnitude of transmissibility by individuals with Delta breakthrough infections appears to be approximately half that compared with unvaccinated individuals (7), which is supported by reduced culture-positive virus in some vaccinated individuals with high viral loads [as assessed by <25 cycle threshold (Ct), the number of cycles required for a positive result in real-time polymerase chain reaction (RT-PCR) tests]. A recent report of nearly 140,000 people who were contacts of individuals with RT-PCR-confirmed COVID-19 showed that both the AstraZeneca and Pfizer/BioNTech vaccines suppressed transmission, but their capacity to do so was markedly lower for Delta compared with Alpha and lower in people vaccinated with AstraZeneca compared with the Pfizer/BioNTech vaccine (8).

Furthermore, two independent reports have confirmed that high amounts of viral RNA (Ct <25) occur in asymptomatic Delta breakthrough infections, and that these individuals could be transmitting SARS-CoV-2 to others (9). However, distinction should be made between infectious virus and Ct value, and the relationship between the two in vaccinated versus unvaccinated individuals needs further evaluation. Overall, transmission from vaccinated individuals is increased by the Delta variant, compared with previous strains, according to the setting and length of time elapsed from initial vaccination.

Time appears to be the key driver of the post-vaccination reduction in effectiveness, as demonstrated from a study of 3.4 million members of the Kaiser Permanente health care organization that found a similar pattern of decline in immunity against multiple variants from 2 months after the second dose (4). Although many studies have confirmed a reduction in serum concentrations of neutralizing antibodies from 4 to 6 weeks after vaccination (10, 11), the picture is less clear for CD4⁺ and CD8⁺ T cell responses, with studies showing small changes consistent with the development of immune memory. The clinical waning of immunity after the first 2 months is particularly notable in people over 60 years of age, in whom susceptibility increased for both symptomatic infections and hospitalizations, as first noted in Israel and later confirmed in mul-

iple US Centers for Disease Control and Prevention (CDC) reports. Circulating and tissue-neutralizing antibodies are expected to wane in a few months despite maintenance of specific memory B cell populations in the circulation. T cells, normally mobilized in response to infection, are thought to protect individuals from severe disease. That hospitalizations were increasingly noted in people of advanced age with breakthrough infections is consistent with poorer B cell and T cell responses to vaccination in older people, as shown in a study examining responses to the Pfizer/BioNTech mRNA vaccine (12). More studies exploring the trajectory of vaccine-induced cellular responses over time and according to age are needed.

Although the clinical trials of mRNA vaccines used a short time interval between two doses, 3 to 4 weeks for Pfizer/BioNTech and Moderna, shortage of the vaccines in many countries led to adoption of 8- to 16-week spacing. Scotland and Canada found that extended spacing of mRNA vaccines led to >80% effectiveness against symptomatic infection in the first few weeks after vaccination. Moreover, the most substantial drop-off in vaccine effectiveness (before the Delta variant became dominant) was observed using a 3- to 4-week dosing interval, such as in Israel, the United States, and Qatar. A direct comparison of short and long dose spacing for the Pfizer/BioNTech vaccine demonstrated that a 16-week spacing between doses resulted in optimal humoral immune responses (13). Administration of two mRNA vaccine doses, closely spaced by 3 to 4 weeks, may have acted as a primary immunization—maximally inducing neutralizing antibodies but compromising durable immunity. That compromise may take the form of both humoral and cellular immunity waning in high-risk individuals, such as the elderly or immunocompromised as early as 2 months after the second dose.

Immunologic studies of responses to boosters, given 6 months after the last vaccine dose, have uniformly shown the induction of very high amounts of neutralizing antibodies, which correlates with protection from breakthrough infection. In Israel, where more than 1.1 million people over 60 years of age received an mRNA vaccine booster dose 6 months after the second dose, restoration of more than 90% effectiveness against severe COVID-19 was achieved (14). The restoration of vaccine effectiveness against hospitalizations and deaths with a booster dose was subsequently demonstrated for adults aged 40 years and older. A large, placebo-controlled randomized trial of the Pfizer/BioNTech booster indicated 95% efficacy, with reduction of symptomatic

infections across all adults, age 18 and over (15). Data are lacking for other vaccines and the durability of this effect. With continued circulating virus over time, it is likely that improved efficacy of a booster dose will be further demonstrated, in addition to reduced transmission and fewer cases of Long Covid (which can probably occur after vaccine breakthrough infection).

The high transmission rates observed in North America and Europe, where vaccine coverage is greatest, portends selection of vaccine escape variants of SARS-CoV-2 that could overcome some of the protection against severe disease. These variants are likely to arise during chronic infections in those with suboptimal vaccine responses, such as people who are immune-compromised, or where vaccine waning has occurred. New variants may evolve from Delta or may be radically different and could even be recombinants of variants due to mixed infections within individual hosts. Recent identification of B.1.1.529 (Omicron) with multiple spike mutations in southern Africa is a reminder of the ongoing threat posed by SARS-CoV-2. Continued transmission in highly vaccinated populations underscores the need for expansion of vaccination across age groups while maintaining nonpharmacological interventions, such as mask wearing. Investigation of intranasal vaccine preparations as a means of preventing breakthrough infection, development of pan-sarbecovirus vaccines, and exploration of the potential for antiviral medications should also be explored to limit transmission. ■

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