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REVIEW

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# COVID-19 vaccines: Immune correlates and clinical outcomes

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**ABSTRACT**

Severe disease due to COVID-19 has declined dramatically as a result of widespread vaccination and natural immunity in the population. With the emergence of SARS-CoV-2 variants that largely escape vaccine-elicited neutralizing antibody responses, the efficacy of the original vaccines has waned and has required vaccine updating and boosting. Nevertheless, hospitalizations and deaths due to COVID-19 have remained low. In this review, we summarize current knowledge of immune responses that contribute to population immunity and the mechanisms how vaccines attenuate COVID-19 disease severity.

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## Introduction

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to significant global morbidity and mortality since its emergence in late December of 2019. Initial cases reporting the natural course of SARS-CoV-2 infection described a viral pneumonia presenting as fever and progressively worsening cough.[1,2] However, a proportion of patients subsequently developed acute respiratory distress syndrome (ARDS) requiring intensive care and ventilator support.[3] In the absence of effective treatment strategies during the early stages of the COVID-19 pandemic, there were concerns that hospitals would be overwhelmed by a surge in critically ill patients.[4] A multistate regional assessment carried out in the United States during the first peak of COVID-19 cases showed that daily intensive care unit (ICU) censuses exceeded pre-pandemic ICU capacity by up to 250% in some areas.[5] Shortages in ICU beds were compounded with the imminent shortages in ventilators, yielding excessive mortality in affected hospitals.[6] Accordingly, rapid advancement of a worldwide vaccine development effort was undertaken with the goal of curbing transmission, and more importantly, protecting vulnerable patient populations from severe disease and death.

Initial phase 3 clinical trials of COVID-19 vaccines began enrolling patients between the summer and fall of 2020, with interim efficacy readouts occurring by December of 2020 and February of 2021. Several vaccine candidates demonstrated remarkable protection ranging from 67% to 95% against symptomatic COVID-19.[7–10] Since the initial readouts occurred, several SARS-CoV-2 variants of concern with the capacity to escape vaccine-elicited neutralizing antibodies (NAb) have emerged, including the Alpha (B.1.1.7), Beta (B.1.351), and Gamma (P.1) variants in late 2020, the Delta (B.1.617.2) variant in mid 2021, the Omicron (B.1.1.529) variant in late 2021, along with its subvariants BA.1, BA.2, BA.3, BA.4, BA.5, XBB.1.5 in mid to late 2022, and more recently, XBB.1.5, EG.5.1, HV.1, and JN.1 in 2023.[11] The estimated protection from symptomatic infection afforded by COVID-19 vaccines, assessed based on follow-up studies completed in late 2021, significantly dropped within 6 months post-immunization, which likely reflects both waning immunity and the emergence of variants.[12–14] Reassuringly, more recent trends show that COVID-19 infections have largely decoupled from COVID-19-related hospitalizations and deaths. In the United States, the ratio of hospitalizations to infections was 1:37 during the Omicron peak of cases in early 2022 compared to 1:15 during the highest peak of cases in winter of 2020.[15] Moreover, the BNT162b2 and Ad26.COV2.S vaccines conferred 70% and 82% protection against ICU admission 1 to 2 months post-immunization, respectively, during a wave of Omicron cases in South Africa, despite marked reductions in protection from symptomatic infection.[16] Taken together, these observations suggest that vaccines continue to provide robust protection against severe disease despite the emergence of progressively more antibody-evasive and increasingly transmissible variants.

The field has largely focused on quantification of NAbs, which have emerged as a potential correlate of protection from SARS-CoV-2 infection in pre-clinical models[17–19] and clinical trials.[20] However, despite low cross-reactive NAbs to new variants, which may predict poor protection, clinical outcomes among vaccinees who experience breakthrough infection remain favorable. Accordingly, investigating other key features of the vaccine-elicited immune response influencing disease outcome could inform the design of next-generation vaccines or modify the approach to patient risk stratification. In this review, we summarize our current understanding of what drives COVID-19 severity, the role of vaccines in the era of

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emerging variants, and the possible mechanisms through which vaccines continue to protect against severe disease.

## Clinical COVID-19 disease

SARS-CoV-2 is a predominantly respiratory pathogen that initially establishes infection via introduction to mucosal surfaces in the upper pharynx.[21] While approximately 15% of cases may resolve asymptomatically,[22] the vast majority present with mild to moderate symptoms.[23] Progression to severe COVID-19 in unvaccinated and previously naïve individuals typically occurs one week after the onset of symptoms and is characterized by a reduction in the blood oxygen saturation[24] secondary to impaired gas-exchange at the alveolar-capillary interface. Patients who develop hypoxemia and dyspnea often succumb to respiratory failure and meet criteria for ARDS,[25] defined as radiographic evidence of bilateral lung infiltrates of non-cardiac origin appearing within 1 week of a known predisposing exposure.[26] In the early stage of the pandemic prior to the development of vaccines and a revised standard of care for managing severe COVID-19, in-hospital mortality among those who developed ARDS was estimated to be around 40% and increased to a range of 65%–94% if mechanical ventilation was indicated.[27]

The pathophysiology of progression to ARDS in the setting of COVID-19 is likely multifactorial but can be broadly categorized as virus mediated injury to alveolar pneumocytes followed by a dysregulated systemic inflammatory response.[28] In the absence of preexisting adaptive immunity to SARS-CoV-2, viral replication with damage to cells along the respiratory tract may occur unimpeded for several hours before host detection by pathogen recognition receptors, such as Toll-like receptors, which initiate an innate immune response.[29] The subsequent release of cytokines, including interleukins, interferons, and chemokines, coordinates trafficking of neutrophils, monocytes, and macrophages to the affected respiratory tissue.[30] Dissemination of SARS-CoV-2 to the lower lung may occur with inadequate type I or type III interferon responses that stimulate antiviral cellular immunity,[31,32] allowing for viral spread distally along the tracheobronchial tree. Upon reaching the lower respiratory tract, SARS-CoV-2 predominantly infects type 2 alveolar cells, which produce pulmonary surfactant and serve as progenitor cells for the alveolar epithelium.[33] Loss of epithelial integrity at the alveolar surface leads to hypoxia, and together with the parallel release of cytokines, namely interleukin-6 (IL-6), serves as a systemic stimulus that increases vascular endothelial permeability, activates coagulation factors, and drives formation of fibrin-rich hyaline membranes,[34] a pathognomonic finding in ARDS. Indeed, postmortem evaluation of lung tissue from patients with severe COVID-19-associated ARDS demonstrated a pattern of injury known as diffuse alveolar damage, characterized by interstitial and intra-alveolar edema, dying pneumocytes, hyaline membranes, and microvascular thrombosis.[35] Interestingly, single-cell sequencing of fatal COVID-19 lung tissue showed an increase in infiltrating macrophages and natural killer cells, but not T cells,[36] suggesting that impaired T cell responses may contribute to lethal outcomes.

The simultaneous activation and recruitment of innate immune cells via cytokine release, while initially intended to protect the host from further viral spread, can devolve into a positive feedback loop of dysregulated systemic inflammation, known as cytokine storm.[37] Serum levels of pro-inflammatory cytokines such as IL-6 and TNFα have been shown to significantly rise within 3 d of symptom onset among patients who subsequently required ICU admission,[38] suggesting that dysregulation can begin early in the disease course. Furthermore, previously immunologically naïve COVID-19 patients displayed a broad increase in inflammatory cytokines with a concurrent reduction in absolute numbers of CD4+ and CD8+ T cells.[39] Accordingly, an early uncoordinated innate immune response may predispose to dysfunctional adaptive immunity, permitting progression of disease and continued nonspecific inflammation.

Patients with COVID-19 induced ARDS demonstrate laboratory evidence of systemic inflammation, including elevated serum concentrations of C-reactive protein, ferritin, and D-dimer.[40] Moreover, levels of IL-6, IL-8, and TNFα, are known independent predictors of patient survival.[41] Mitigating the acute inflammatory response to SARS-CoV-2 infection with monoclonal anti-cytokine antibodies or systemic glucocorticoids has shown mortality benefit in randomized controlled trials.[42,43] Fortunately, the rapid development and deployment of effective COVID-19 vaccines worldwide has proven a critical intervention in controlling the rates of severe cases, hospitalizations, and deaths. With the implementation of vaccination and antiviral drugs, the age-adjusted mortality associated with COVID-19 dropped by 47% in 2022 compared to 2021[44] and further dropped by 71% in 2023 compared to 2022.[45]

## COVID-19 vaccines in the era of SARS-CoV-2 variants

### *Development of COVID-19 vaccines and initial protective efficacy*

Within weeks of the first reported cases of COVID-19 in Wuhan, China, the SARS-CoV-2 virus was isolated, sequenced, and made publicly available for the global scientific community by the Chinese Center for Disease Control.[46] In large part informed by prior research on SARS-CoV, a similar coronavirus from the sarbecovirus subgenus, the spike (S) protein was identified as the optimal SARS-CoV-2 immunogen given its role in facilitating viral entry into host cells.[47] Over the last decade, several platforms including nucleic acid, protein subunit, and viral vectored vaccines have been developed for rapid adaptability to emerging pathogens and therefore have become a fundamental component of the COVID-19 vaccine response.[48] The WHO has approved 12 COVID-19 vaccines to date, of which two are nucleic acid, three are protein subunit, four are viral vectored, and three are inactivated virus.[49]

Initial phase 3 clinical trials of COVID-19 vaccines in the United States demonstrated protective efficacy from symptomatic infection of 94% to 95% with two-shot mRNA vaccines (mRNA-1273, BNT162b2)[7,8] and a two-shot Ad26.COV2.S vaccine,[50] 90% with a two-shot protein

subunit vaccine (NVX-CoV2373),[51] and 72% with a one-shot Ad26.COV2.S vaccine.[10] Even more impressively, all vaccines provided nearly 100% protection from hospitalizations and death. Based on data from animal models[17,18] and post-hoc analyses of clinical trial participants,[20] NAb titer has been established as a key correlate of protection. The mRNA and protein subunit vaccines are known to elicit high NAb titers within weeks of completing the series, although they rapidly wane over time.[52] Conversely, viral vectored vaccines elicit initially lower NAb titers, but maintain greater durability over time.[53] NAb breadth has been shown to expand over time following both Ad26.COV2.S vaccination[54,55] and mRNA vaccination,[56,57] which may be related to expansion and persistence of germinal center B-cells and the seeding of long-lived antibody-secreting cells in the bone marrow.

## SARS-CoV-2 variants and booster immunizations

Despite the impressive initial vaccine efficacy reported in 2020, a rise in breakthrough COVID-19 cases was reported in the setting of waning NAb titers.[58] Moreover, several waves of SARS-CoV-2 variants that escape vaccine-elicited NAbs have emerged since the data from the phase 3 clinical trials were reported.[59] Serologic testing among vaccinees has demonstrated NAb escape by the Alpha, Beta, Delta, and Omicron variants along with its subvariants BA.1, BA.1.1, BA.2, BA.2.12.1, BA.4, BA.5,[60–63] and more recently, XBB.1.5, EG.5.1, HV.1, and JN.1.[64–66] Accordingly, vaccine efficacy against symptomatic COVID-19 has significantly diminished. Interestingly, the rate of hospitalizations and deaths continues to remain stable among the vaccinated population, indicating that current COVID-19 vaccines continue to provide excellent protection from severe disease despite low NAb titers.

To address NAb escape displayed by the Omicron variant, a bivalent mRNA vaccine containing the ancestral spike and the Omicron subvariant BA.5 was approved for clinical use in the fall of 2022.[67] However, boosting with the bivalent vaccine did not demonstrate substantially better induction of NAb titers against BA.5 compared with boosting with the original monovalent vaccine.[68,69] This observation may relate to immune imprinting, by which preferential activation of memory B-cells generated by primary immunization results in antibody responses predominantly against the ancestral strain.[70] Nevertheless, boosting with the bivalent vaccine improved protection against severe disease.[71]

More recently, an updated mRNA Omicron XBB.1.5 monovalent booster was approved for use in fall of 2023.[72] Infection with the XBB.1.5 variant has been shown to increase NAbs to XBB.1.5 as well as other emerging variants, including EG.5.1 and FL.1.5.1.[65] Moreover, boosting with an mRNA Omicron XBB.1.5 monovalent vaccine elicited a significant increase in NAb titer to not only XBB.1.5, but also to EG.5.1, HV.1, HK.3, JD.1.1, and JN.1,[73] suggesting it could provide enhanced protection to these emerging variants. Areas of current interest include the role of mucosal immunity as a strategy to block infection and curb transmission[74,75] and the immunologic mechanisms that provide clinical protection conferred by current vaccines.

## Harnessing mucosal immunity

Given that SARS-CoV-2 typically gains entry at the nasopharynx and oral mucosa, eliciting a robust memory immune response in the upper respiratory tract could prevent acquisition of virus altogether. For example, it was recently shown that increased wild-type SARS-CoV-2 S-specific mucosal IgA titer, but not mucosal IgG titer, reduced the risk of breakthrough infection with the Omicron variant in a population of vaccinated healthcare workers.[76] Mucosal IgA titers were significantly higher in those with a history of COVID-19 infection, suggesting that the current intramuscular (IM) vaccines do not elicit mucosal responses that fully recapitulate natural infection.

Although some evidence suggests that IM immunization may elicit some mucosal immunity at the upper and lower respiratory tract,[77,78] current vaccines do not appear to protect against acquisition of SARS-CoV-2 infection. It is believed that the weak mucosal immunity induced by IM immunization may result from a small amount of vaccine antigen uptake at the local draining lymph node, with migration to the pulmonary and nasopharynx lymphoid tissue occurring thereafter.[79,80] Serum IgA responses elicited by IM immunization decline more rapidly than serum IgG.[81] Conversely, direct antigenic stimulation of respiratory mucosal tissue-resident memory T-cells primes for a rapid CD4+ and CD8+ mediated adaptive immune response upon antigen re-exposure in a mouse model,[82] which has shown to confer robust protection from respiratory pathogens like influenza virus.[83]

Indeed, pre-clinical studies evaluating mucosal administration of COVID-19 vaccines exhibit induction of SARS-CoV-2 S binding IgA and IgG antibodies and increased NAbs in bronchioalveolar lavage (BAL) samples.[84–86] In a non-human primate animal model, rhesus macaques previously immunized and boosted with an IM Ad26.COV2.S or Ad26.COV2.S Beta variant-adapted vaccine were randomized into five groups.[87] Macaques were subsequently boosted with a bivalent Ad26.COV2.S/Omicron variant-adapted vaccine via the IM (Ad26 IM), intranasal (Ad26 IN), or intratracheal routes (Ad26 IT), or with a bivalent mRNA (Pfizer-BioNTech) vaccine by the intranasal route (mRNA IN), or not boosted. Evaluation of BAL and nasal swab samples demonstrated that mucosal NAbs, IgG, and IgA binding antibody responses, as well as CD4+ and CD8+ T-cell responses appeared to be highest in the Ad26 IT group, exceeding those induced by both IN and IM boosting. Upon SARS-CoV-2 BQ.1.1 challenge at 16 weeks post-boost, macaques in the Ad26 IT group displayed near complete protection from acquisition of infection. Moreover, mucosal humoral and cellular immune responses in BAL samples were the strongest correlates of protection against SARS-CoV-2 challenge. The data suggest that IT immunization, compared to IM or IN immunization, induces a more potent mucosal immune response that robustly protects from subsequent SARS-CoV-2 challenge. In a separate study in mice, IN immunization of a viral vectored COVID-19 vaccine generated multifunctional respiratory mucosal tissue-resident memory T-cells and provided potent B- and T-cell dependent protection from both ancestral and variant SARS-CoV-2 challenge, whereas IM immunization did not.[88]

The clinical applicability of mucosal vaccines remains promising, as an Ad5 vaccine from CanSino delivered by the IT route[89] has already been approved for clinical use in China and a ChAd vaccine from Bharat Biotech delivered by the IN route[90] has already been approved for clinical use in India. Overall, it is evident that the induction of upper respiratory tract immune responses by mucosal vaccines could significantly enhance protection from transmission and improve durability against emerging variants.

## Durable protection against severe COVID-19 disease

### *Clinical protection and hybrid immunity*

Since the emergency use authorization of several COVID-19 vaccines between late 2020 and early 2021, approximately 13 billion doses have been administered worldwide, with around 70% of the global population having received at least one dose.[49] The subsequent emergence of NAb-evasive, highly transmissible SARS-CoV-2 variants has led to multiple waves of COVID-19 cases even after the worldwide deployment of vaccines. During the Delta wave in the United States, which peaked in August of 2021, the 7-day moving average reached over 150,000 cases, of which approximately 12,000 were being admitted to the hospital.[15] During the Omicron BA.1 wave in the United States, which peaked in January of 2022, the 7-day moving average reached 800,000 cases, of which approximately 20,000 were being admitted to the hospital.[15] A near 5-fold increase in cases from the Delta variant to the Omicron variant yielded less than a 2-fold increase in hospitalizations.

One theory behind this observation is that SARS-CoV-2 has evolved to become more transmissible but less virulent, optimizing its fitness at a population level. More likely, vaccine immunity and natural immunity continue to provide excellent protection from severe COVID-19 despite waning immunity and declining efficacy against mild symptomatic infection. A systematic review and meta-analysis of 78 vaccine-specific efficacy evaluations including 4 distinct vaccine platforms (BNT162b, mRNA-1273, Ad26.COV2.S, ChAdOx1-S) showed that despite an average 20% to 30% drop in protection from symptomatic COVID-19, protection from severe disease remained greater than 70% across vaccine platforms.[12] More recently, results from a randomized controlled trial showed the two-shot BNT162b2 and the two-shot Ad26.COV2.S vaccines conferred 70% and 72% protection against hospitalization and 70% and 82% protection against intensive care unit admission during the Omicron surge in South Africa despite largely undetectable NAb titers.[16] These data demonstrate that the original vaccines continue to provide robust clinical protection and suggest that immunologic mechanisms other than NAbs contribute substantially to protection against severe disease.

It should be noted that with impaired vaccine efficacy against SARS-CoV-2 acquisition and transmission, a large proportion of vaccinees experience breakthrough infections and subsequently develop hybrid immunity.[91,92] Accordingly, it is likely that continued protection from hospitalization and death among vaccinees is partly driven by both B-cell and T-cell responses induced by both vaccination and infection, including responses to SARS-CoV-2 viral proteins other than spike.[91,93] In fact, it has been shown that NAb responses are greater in breadth and durability among those who have hybrid immunity compared to immunization or natural infection alone.[94] Clinical protection from severe disease in the setting of diminished NAb titers is likely also mediated by cellular immunity, further supported by observations that vaccine-induced memory T-cells maintain their robust cross reactivity with SARS-CoV-2 variants.[95–98]

### *T-cells and disease severity*

The adaptive immune response to SARS-CoV-2 infection involves humoral immunity, which includes antibodies produced by B-cells, and cellular immunity, which includes CD4+ or CD8+ T-cells. Successful bridging of the innate immune response to the adaptive immune response is critical for resolution of SARS-CoV-2 infection.[31,32] Circulating antibodies largely prevent viral entry into host cells, and antigen-specific CD8 + T-cells mediate clearance of virally infected cells.[99] T-cell responses may be particularly important for protection against severe disease with viral variants, as they show greater durability and cross-reactivity compared with serum NAbs.[95–98,100]

During infection with antibody-evasive variants, T-cells with antigen specificity for conserved SARS-CoV-2 epitopes can control viral replication to prevent progression to more severe disease. Indeed, CD4+ and CD8+ T-cells have both been associated with improved COVID-19 outcomes.[101] Serologic analysis in convalescent individuals has reproducibly demonstrated that infection-elicited antibodies at the time of recovery are not proportional to disease severity,[102,103] indicating that disease resolution is mediated independent of antibody response. Moreover, increased T-cell responses in a cohort of vaccinated individuals yielded lower odds of severe disease among those with breakthrough infections.[104] A prospective cohort study comparing vaccinated and unvaccinated individuals who acquired SARS-CoV-2 infection showed that serum concentrations of 7 distinct pro-inflammatory cytokines, including IL-8 and TNFα, were significantly lower in vaccinees both at 14- and 90-d post-infection even after adjusting for confounders, suggesting that vaccination imparts both a short- and long-term reduction in inflammation during infection as well.[105]

Pre-clinical data has mechanistically shown that CD8+ T-cells contribute to protection against SARS-CoV-2 challenge. In a non-human primate animal model, rhesus macaques were immunized with the Ad26.COV2.S vaccine or a sham injection and randomized to receive either an anti-CD8α, anti-CD8β, or isotype matched sham monoclonal antibody (mAb) at 5 weeks post-immunization.[106] Macaques then underwent high-dose SARS-CoV-2 Delta variant challenge and were evaluated for viral load in BAL and nasal swab samples. CD8-depletion of vaccine-elicited T-cells using the anti-CD8α mAb, which yielded undetectable CD8+ T-cell counts in the peripheral blood, led to significantly higher peak viral loads in both upper and lower respiratory tracts compared to sham controls, suggesting that CD8+ T-cells directly contribute to virologic control even in the setting of antibody-evasive variants. In a separate study, rhesus macaques were challenged with SARS-CoV-2, allowed to recover,

then randomized into two groups with similar NAb titers.[18] One group was administered a CD8-depleting antibody while the other group served as a control. Upon re-challenge with SARS-CoV-2, the control group displayed nearly full protection whereas the CD8-depleted group displayed significantly higher peak viral loads in BAL and nasal swab samples. The impaired protection occurring among CD8-depleted rhesus macaques despite similar levels of NAb titers suggests that virologic control was partially mediated by CD8+ T-cells induced by prior infection.

Data on the role of cellular immunity in humans is technically challenging and more correlative than mechanistic. A study that profiled the cellular immune responses in COVID-19 infected, recovered, and vaccinated individuals showed a significantly lower ratio of activated T-cells to total lymphocytes among patients who died from COVID-19 compared to those who were hospitalized and recovered.[107] Moreover, vaccinated individuals who experienced breakthrough infection and recovered with mild to moderate symptoms demonstrated enhanced T-cell responses when compared to those who required hospitalization. Possessing a large repertoire of T-cells is understandably a key determinant of the response to a viral infection. Old age has been established as the strongest predictor for COVID-19 disease severity,[27] likely in part secondary to the well-characterized decline in the abundance of naïve T-cells during the aging process.[108,109] In fact, immune profiling among patients ≥65 y old during acute COVID-19 infection showed uncoordinated CD4+ and CD8+ T-cell responses on a background of a significantly reduced naïve T-cell pool compared to younger counterparts.[101] Furthermore, there were strong correlations between age, magnitude of CD8+ naïve T-cell pool, and COVID-19 disease severity. Interestingly, patients experiencing critical COVID-19, defined as requiring intensive care or mechanical ventilation, displayed nearly undetectable levels of CD8+ interferon gamma secreting T-cells.

Clinical evidence in those with immunologic impairments seems to also support the role of T-cells modifying COVID-19 disease outcome. A case series of 10 patients with combined variable immunodeficiency, of which 3 displayed low CD19+ cell counts and 7 received intravenous immunoglobulin infusions for hypogammaglobulinemia, demonstrated full COVID-19 resolution without developing pneumonia or requiring mechanical ventilation.[110] Total CD3+ T-cell counts were largely preserved across all individuals. While the study had a small group size composed of patients with a rare disease, the data suggest that in this population, T-cells are partly responsible for disease resolution despite impaired humoral immunity. In a separate study carried out on a cohort of patients with hematologic cancer and superimposed SARS-CoV-2 infection, those with a greater number of CD8+ T-cells demonstrated improved survival, even in the setting of B-cell depletion with anti-CD20 therapy,[111] indicating that T-cells may be modifying clinical outcome independent of B-cell function. A cluster of patients with depleted T-cells but preserved B-cells demonstrated the lowest survival probability and highest disease severity despite the presence of SARS-CoV-2-specific IgG antibodies, suggesting that humoral immunity, without functional T-cells, may not be sufficient to protect from disease progression. Furthermore, in those who had an absolute CD8+ T-cell count <55.9/mm$^3$, survival probability was 0% by 150 d post-infection compared to around 60% in those with a CD8+ T-cell count ≥55.9/mm$^3$. Although again observed in a relatively small group of patients in a unique disease context, these data provide evidence for cellular immunity as a key contributor to clinical outcome during SARS-CoV-2 infection.[111]

## Conclusion

The rapid development and deployment of effective COVID-19 vaccines has been a triumph of biomedical research and has dramatically reduced the overall clinical severity of SARS-CoV-2 infection among vaccinees. Mechanisms by which vaccines provide clinical protection are multifactorial, including antibodies that wane quickly following immunization and T-cells that are more durable and more cross-reactive against SARS-CoV-2 variants. The emergence of new SARS-CoV-2 variants continues to threaten vaccine efficacy, requiring constant reevaluation on how to optimize next-generation COVID-19 vaccines. Developing vaccine platforms that provide greater durability and that induce better mucosal immunity will be important for next-generation COVID-19 vaccines to protect against infection as well as severe disease.

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