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SARS-CoV-2 Omicron: Light at the End of the Long Pandemic Tunnel or Another False Dawn for Immunodeficient Patients?

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COVID-19 has had a disastrous impact on the world. Apart from at least 6 million deaths, countless COVID-19 survivors are suffering long-term physical and psychiatric morbidity. Hundreds of millions have been plunged into poverty caused by economic misery, particularly in developing nations. Early in the pandemic, it became apparent certain groups of individuals such as the elderly and those with comorbidities were more likely to suffer severe disease. In addition, patients with some forms of immunodeficiency, including those with T-cell and innate immune defects, were at risk of poor outcomes. Patients with immunodeficiencies are also disadvantaged as they may not respond optimally to COVID-19 vaccines and often have pre-existing lung damage. SARS-CoV-2 Omicron (B.1.529) and its subvariants (BA.1, BA.2, etc) have emerged recently and are dominating COVID-19 infections globally. Omicron is associated with a reduced risk of hospitalization and appears to have a lower case fatality rate compared with previous SARS-CoV-2 variants. Omicron has offered hope the pandemic may finally be coming to an end, particularly for vaccinated, healthy individuals. The situation is less clear for individuals with vulnerabilities, particularly immunodeficient patients. This perspective offers insight into potential implications of the SARS-CoV-2 Omicron variant for patients with immunodeficiencies. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:2267-73)

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SARS-CoV-2, the agent responsible for COVID-19, has caused havoc around the globe. The true death toll is likely to far exceed the official number of over 6 million. COVID-19 has caused a pandemic of physical and psychiatric morbidity, which will last for generations. Large numbers of children have been orphaned, and the emotional scars will remain for the rest of their lives. Hundreds of millions of individuals have been plunged into abject poverty caused by economic misery in developing countries.[1] The economic gains of the last decade or longer have been reversed by the pandemic in some nations. The origin of SARS-CoV-2 is the subject of ongoing scrutiny.[2-4]

The virus appears to infect individuals in 3 overlapping clinical stages (Figure 1).[5] In the initial nasal phase, the virus engages cell-surface angiotensin-converting enzyme 2 (ACE2) receptors. Host proteases including transmembrane serine protease 2 (TMPRSS-2) and furin cleave the viral spike (S) glycoprotein.[6] The S2 subunit of the S glycoprotein is then able to fuse with the cell membrane allowing the viral genome to enter and hijack intracellular organelles, leading to the generation of viral progeny.

In the second pulmonary phase, the virus infects the lungs, most likely by aspiration from the nose and stomach.[7] Patients progressing to this stage experience increasing dyspnea, lethargy, and myalgia. Computerized tomography scans of the thorax may display ground-glass appearance. Laboratory parameters in the second stage show an increase in inflammatory markers including C-reactive protein.

A small number of patients enter the third systemic phase where they rapidly deteriorate and suffer multiple organ dysfunction, including acute respiratory distress syndrome (ARDS). These patients often require intensive care unit admission, but mortality remains high in spite of invasive ventilation or extracorporeal membrane oxygenation. Complement activation and endothelial damage lead to activation of the coagulation cascade.[8] An increase in D-dimers signifies a risk of arterial and venous thromboembolic disease.

Early in the pandemic, it became apparent that there was a steep age-related mortality gradient with poor outcomes in patients over 80 years of age.[9] Children are frequently infected but are often asymptomatic. In addition, patients with comorbidities

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Abbreviations used

ACE2- Angiotensin-converting enzyme 2
ARDS- Acute respiratory distress syndrome
CVID- Common variable immunodeficiency disorders
RATs- Rapid antigen tests
RBD- Receptor binding domain
RT-qPCR- quantitative reverse transcriptase polymerase chain reaction
S- Spike
TMPRSS-2- Transmembrane serine protease 2
XLA- X-linked agammaglobulinemia

including obesity, diabetes mellitus, coronary artery disease, hypertension, malignancy, renal, and pulmonary disease are at increased risk of severe outcomes.[9-11] The basis for these host susceptibilities is incompletely understood.

Current data also indicate racial and ethnic differences in adverse outcomes from COVID-19.[12] Patients of Black, Hispanic, Māori, Pacifika, and South Asian origin are at risk of severe outcomes. The reasons for these ethnic susceptibilities are not fully understood. Inequitable access to health care and an increased burden of comorbidities may partly underlie these disparities.[13]

THE IMMUNE RESPONSE TO COVID-19

The immune response to COVID-19 is now better appreciated. In the initial nasal phase, the innate immune response is muted.[14] SARS-CoV-2 is able to silence cytoplasmic viral sensors by a variety of mechanisms including coating double-stranded viral RNA in a membrane. Viral RNA is also capped impeding the response of molecules such as melanoma differentiation—associated protein 5. Retinoic acid-inducible gene-I-like receptors are ubiquitinated leading to degradation. Consequently, the incubation period is asymptomatic, and infected individuals can unwittingly infect others. Recent data suggest that wearing masks reduces transmission within households.[15]

Later in the pulmonary and systemic phases, the innate immune system aggravates the disease.[16] There is neutrophilia, and recruitment of neutrophils and macrophages (via monocytes) to the lungs can lead to a cytokine storm with the production of high concentrations of IL-6 and tumor necrosis factor. Activation of the inflammasome can lead to pyroptosis. Uncontrolled activation of the innate immune system underlies ARDS and multiple organ dysfunction. Neutralizing anti-interferon antibodies play an important role in amplifying disease severity.[17] These antibodies are present in higher titers in many patients who are severely affected by COVID-19.

The adaptive immune system is also subverted by the virus. The role of antibodies in the outcome of COVID-19 is uncertain.[18] There is evidence for both protection and aggravation of disease by antibodies.[18] In severe cases, there is a risk of antibody disease enhancement.[19]

In contrast, there is increasing evidence that cellular immune responses play a crucial role in both the outcome of COVID-19 and long-term protection after infection or vaccination.[20-22] A low avidity or delayed T-cell response is associated with severe outcomes in COVID-19.[20] An efficient early T-cell response can protect against SARS-CoV-2 and even abort the infection before quantitative reverse transcriptase polymerase chain reaction (RT-qPCR) tests become positive.[23]

SARS-CoV-2 AND IMMUNODEFICIENCY DISORDERS

Patients with primary immunodeficiency disorders have provided valuable insights into the role of various components of the immune system in the protective response to SARS-CoV-2.[24] Current data indicate that patients with innate immune system or T-cell defects have worse outcomes, attesting to the importance of these components of the immune response.[25] In contrast, most patients with X-linked agammaglobulinemia (XLA), without comorbidities, appear to be protected from severe disease.[26-29] This is evidence that antibodies in some circumstances can be harmful. The specific implications of the SARS-CoV-2 Omicron infection for immunodeficient patients are discussed in more detail below.

VIRAL EVOLUTION

There has been a poorly coordinated global response to COVID-19. Although effective vaccines and therapeutics have been developed, there have been political, financial, and logistical barriers hindering vaccine uptake, resulting in vaccine inequity. A substantial proportion of the African population remains unvaccinated and vulnerable to COVID-19. Vaccine hesitancy in developed countries has also left large numbers of patients unvaccinated. Consequently, the virus has been able to circulate widely resulting in the selection, emergence, and dominance of increasingly infectious variants. These SARS-CoV-2 variants have presented as successive waves of infection.

THE OMICRON VARIANT OF SARS-CoV-2

Omicron (B.1.529) and its subvariants (BA.1, BA.2 etc) are the latest highly infectious SARS-CoV-2 strains to emerge in November 2021.[30] Within a few weeks of its first discovery in Southern Africa, Omicron has displaced the previous incumbent, Delta (B.1.617.2), and now dominates global COVID-19 infections.[31] Omicron reaches very high viral loads during the nasal incubation period, which may underlie its infectiousness.[32,33] Omicron is also able to infect vaccinated individuals as well as those previously infected with other SARS-CoV-2 variants.[34,35] These observations underlie its high reproduction number (R0).

Apart from being highly transmissible, Omicron appears to fundamentally differ from previous SARS-CoV-2 strains. From a clinical perspective, the disease seems to be less severe with a lower rate of ARDS, hospitalization, and death.[36] Anosmia, which was a characteristic feature of previous SARS-CoV-2 variants, appears to be much less common with Omicron. In contrast, gastrointestinal symptoms including vomiting and diarrhea are more prominent features of Omicron infection (Figure 1).

SARS-CoV-2 Omicron infections have implications for the treatment of COVID-19. Immunosuppressive drugs such as dexamethasone, tocilizumab, and baricitinib are effective in patients suffering from ARDS from previous SARS-CoV-2 variants. Given that Omicron is less prone to cause ARDS, this may alter the risk ratio for administering dexamethasone, given the increased risk of mucormycosis in diabetic patients.

Omicron may also be less prone to cause inappropriate complement activation and endothelial damage, leading to

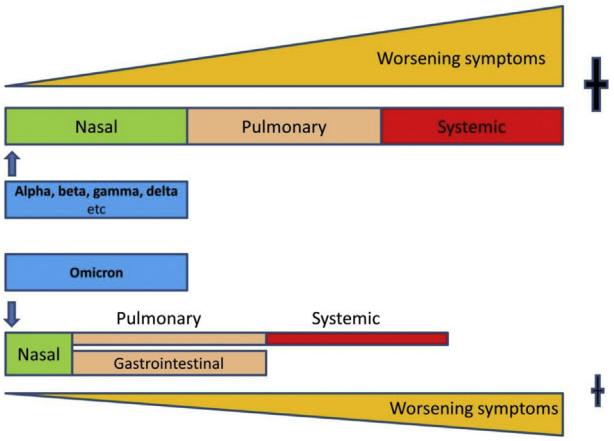

FIGURE 1. Illustration of the differences between Omicron and infection with previous SARS-CoV-2 variants. The nasal phase is shorter in Omicron infection. In the second phase, gastrointestinal symptoms are more prominent and fewer patients reach the systemic phase. The mortality rate is also lower for Omicron compared with other variants.

activation of the clotting cascade. Arterial and venous thromboembolic events may be less likely. Trials of anticoagulants may need to revisited, as the risk of adverse effects from these medicines may exceed the risks of thromboembolic disease caused by Omicron.

At the time of writing, it is unknown if Omicron will cause sequelae of COVID-19 including long COVID. Long COVID is a disabling syndrome where patients experience lethargy, chest pain, and neurological symptoms including autonomic instability and loss of clarity of thought (brain fog).[37] If long COVID is due to a dysfunctional immune response, this syndrome might be less likely to occur with SARS-CoV-2 Omicron infection. SARS-CoV-2 could also cause long COVID by invading the brain through the olfactory nerves.[38] Given the lower rate of anosmia with Omicron, this might suggest a lower risk of long COVID. A third nonmutually exclusive possibility is that long COVID is the result of microthrombi causing organ ischemia.[39] If the thromboembolic risk is lower with Omicron, it might indicate a lower incidence of long COVID. It also remains to be determined if Omicron is associated with the same risk of severe autoimmunity or other rare syndromes such as multisystem inflammatory syndrome of children, seen with previous SARS-CoV-2 variants.[40]

MOLECULAR DIFFERENCES BETWEEN OMICRON AND OTHER SARS-CoV-2 VARIANTS

There have been recent insights into the molecular biology of SARS-CoV-2 Omicron, which may underlie some of these clinical and epidemiological observations. The S glycoprotein of Omicron has over 30 mutations, and the nucleocapsid protein has 2 mutations compared with previous variants. This changes its conformation and allows the virus to bind with high affinity to ACE2, but it seems to be less susceptible to the action of proteases such as TMPRSS-2.[41-44] This impedes cellular fusion, and Omicron appears to infect pulmonary alveoli at a much lower frequency compared with previous SARS-CoV-2 variants. This is seen *in vitro*, where Omicron is less infectious for lung alveoli than other SARS-CoV-2 variants.[45] The lower tropism for alveolar and other cells is presumably why ARDS and multiple organ dysfunction are less severe with Omicron.

The disease outcome of COVID-19 is primarily determined by the dysregulated immune response to SARS-CoV-2.[46] Its milder nature suggests that Omicron is less prone to provoke a severe cytokine storm leading to ARDS and multiple organ dysfunction. It also suggests that Omicron is less likely to cause severe T-cell dysregulation compared with previous SARS-CoV-2 variants.[46] Dysregulated T-cell immunity is one of the key correlates of severe COVID-19.[18]

IMPLICATIONS FOR DIAGNOSIS, PREVENTION, AND TREATMENT OF SARS-CoV-2 OMICRON INFECTIONS

SARS-CoV-2 Omicron infection has implications for diagnostic testing. Because the receptor binding domain (RBD) of Omicron has multiple mutations, the current testing strategy may need to be revised. Rapid antigen tests (RATs) may not detect Omicron with the same accuracy as previous SARS-CoV-2 variants.[47,48] The BA.2 variant of Omicron may not be identified by some current RT-qPCR tests and has been described as a "stealth virus" in the popular press.[49] Retrospective sero-epidemiological antibody tests may also be negative in unvaccinated, Omicron infected individuals when measured by older assays. The antigenic target may have to be altered to the Omicron RBD. It will be important for such antibody assays to be carefully evaluated in external quality assurance programs to determine their sensitivity and specificity for different SARS-CoV-2 variants.

Of even more concern, current data suggest that Omicron is able to evade vaccine-induced antibodies.[50-53] A booster vaccine however mitigates some of this loss of vaccine efficacy in healthy persons.[54-57] Fortunately, T-cell responses to Omicron are mostly preserved in healthy vaccinated individuals.[58-61] As noted, T cells play a crucial role in the outcome of COVID-19 as well as long-term protection after either infection or vaccination. This indicates that the apparent loss of vaccine efficacy against Omicron is overestimated by antibody neutralization assays alone.

Because of the antigenic shift caused by multiple RBD mutations, Omicron appears to evade several previously effective monoclonal antibodies.[62] Most monoclonal antibodies have been derived from COVID-19 survivors of the ancestral Wuhan variant or mice immunized with early SARS-CoV-2 variants. The E484A and N501Y mutations of the Omicron RBD underlie much of the monoclonal and vaccine antibody evasion.[63-65] Some monoclonal antibodies, which bind outside the RBD, such as sotrovimab, have retained efficacy for early subvariants of Omicron.[66]

On the positive side, Omicron appears to be at least as susceptible to remdesivir and molnupiravir, compared with previous SARS-CoV-2 variants.[67] Paxlovid has also retained its efficacy to Omicron. Given that the nasal phase is much shorter, these drugs will have to be administered early in the infection. This will require access to accurate diagnostic testing with a rapid turnaround time. Alternatively, these drugs could be used as prophylaxis in high-risk situations.

DISCUSSION: IMPLICATIONS OF SARS-CoV-2 OMICRON INFECTION FOR IMMUNODEFICIENT PATIENTS

The emergence and global dominance of the Omicron (and its subvariants) of SARS-CoV-2 has far-reaching implications for the pandemic in general and immunodeficient patients, in particular. SARS-CoV-2 Omicron will lead to revision of the current understanding of the immunopathology of COVID-19. Omicron may need to be considered a new infection with some overlapping features of previous SARS-CoV-2 variants.[18]

SARS-CoV-2 Omicron infection is likely to impact the disease severity and prognosis of immunodeficient patients.[68] Immunodeficient patients often have pre-existing chronic lung disease including bronchiectasis.[69] Older immunodeficient patients with chronic lung disease and other comorbidities may be less susceptible to severe outcomes from Omicron infection compared with previous SARS-CoV-2 variants.[70] As with the general population, the case fatality rate in immunodeficient patients may be lower with Omicron. Future data will confirm the accuracy of this prediction. The increased susceptibility of patients with impaired innate immunity or T-cell defects, noted with previous variants, will need to be determined for Omicron. Future case series or registries should specify the SARS-CoV-2 variant infecting each immunodeficient patient, either by viral genotyping or epidemiological information on the variant(s) circulating in the community at the time.

Apart from the potential inaccuracy of RATs, RT-qPCR, and antibody tests, there are specific implications for the diagnosis of Omicron in immunodeficient patients. Patients with XLA, for example, are unable to generate antibodies but have preserved cellular immune responses to COVID-19 vaccines.[71] Furthermore, subcutaneous and intravenous immunoglobulin preparations now have high titers of SARS-CoV-2 antibodies.[72] There is thus an urgent need for diagnostic T-cell assays for SARS-CoV-2, for immunodeficient patients.[73] T-cell assays using the Omicron RBD and other antigens including the Nucleocapsid protein may identify breakthrough infections. Commercial T-cell assays to SARS-CoV-2 are likely to become obsolete given the rapid viral evolution noted to date. Diagnostic laboratories with the relevant experience should develop these assays urgently.[74,75] The RBD can be rapidly altered by these laboratories in the event a new SARS-CoV-2 variant emerges. In the future, these assays may indicate the efficacy of vaccines in immunodeficient patients and provide valuable information on the need for other treatments such as prophylactic drugs or monoclonal antibodies. SARS-CoV-2 T-cell assays will enable personalized medicine for COVID-19 in immunodeficient patients.

As noted, remdesivir and molnupiravir may be more effective for Omicron than previous SARS-CoV-2 variants. This is likely to disproportionately benefit immunodeficient patients infected with SARS-CoV-2 Omicron. It is possible that combinations of such drugs will prove very effective in mitigating severe outcomes in immunodeficient patients and others with comorbidities. Currently, there is a global shortage of these newer more effective drugs.

Early variants of Omicron have fortunately retained sensitivity to Evusheld (tixagevimab and cilgavimab), sotrovimab and bebtelovimab.[76] These can be used as prophylaxis or in the early stages of Omicron infection to reduce the risk progression to the pulmonary and systemic phases. It is likely to be of disproportionate benefit to immunodeficient patients as well as others at high risk of adverse outcomes. Currently available monoclonal antibodies will need to be re-evaluated for efficacy against Omicron and each of its subvariants.[77] It is likely that new monoclonal antibodies will need to be developed from Omicron convalescent individuals.

In contrast to many monoclonal antibodies, the NZACE2-Pātari project may prove to be very effective against SARS-CoV-2 Omicron as it is based on modified ACE2 receptors.[7,78] The project aims to intercept SARS-CoV-2 in the nose and reduce the burden of virus infecting the lungs. Viral evolution leading to reduced ACE2 binding is unlikely to be tolerated and will lead to loss of pathogenicity. If successful in future trials, this drug could be used in combination with other antiviral drugs. If proved to be effective, it could be used as prophylaxis particularly in patients with suboptimal responses to vaccines.

Immunodeficient patients are at risk of chronic COVID-19.[79,80] In chronic COVID-19, there is a stalemate between SARS-CoV-2 and a suboptimal immune response. Patients with chronic COVID-19 shed virus for weeks or months and are at risk of intrahost viral evolution leading to the emergence of dangerous vaccine and antibody evasion mutants. It is a public health emergency and must be prevented at all costs. It is currently too early to determine the risk of chronic COVID-19 with Omicron and its newer subvariants. If immunodeficient patients are vaccinated and have early access to effective antiviral therapeutics, chronic COVID-19 may be less likely.

Omicron will lead to reassessment of previously ineffective COVID-19 therapies.[81] Treatments such as convalescent plasma infusions might be more effective for SARS-CoV-2 Omicron than for previous variants. In immunodeficient patients suffering from chronic COVID-19 from previous SARS-CoV-2 variants, convalescent plasma infusions resulted in the emergence of vaccine and monoclonal antibody resistant clades.[82] Although chronic COVID-19 may be less likely with Omicron, in the event of such cases, convalescent plasma infusions from Omicron survivors may be more efficacious compared with previous SARS-CoV-2 variants. It would be sensible to recruit younger Omicron survivors as plasma donors, who are less likely to have neutralizing anti-interferon antibodies. Given that there may be less perturbations of cellular immunity, perhaps protection against Omicron is more dependent on antibodies compared with previous SARS-CoV-2 variants. Future studies will need to test this hypothesis. The protective role of subcutaneous immunoglobulin/intravenous immunoglobulin preparations containing high titres of anti-Omicron antibodies will also need to be studied.

Preventing COVID-19 by vaccination is problematic in immunodeficient patients, as by definition many have suboptimal responses to vaccines.[83,84] Two recent studies of common variable immunodeficiency disorders (CVID) however have shown that at least some of these patients are able to respond to vaccine challenges.[85] The majority of patients had excellent responses to tetanus toxoid and *Haemophilus influenzae* type B vaccine in the NZ hypogammaglobulinemia and CVID studies.[86] Two studies have shown that patients with CVID are able to respond partially to COVID-19 vaccines.[87,88] It is possible that this partial response to COVID-19 vaccines confers disproportionate protection for immunodeficient patients. Three

or 4 primary COVID-19 vaccine doses may provide adequate protection against severe outcomes in such patients.[89,90] Heterologous vaccination with an mRNA vaccine followed by an adenovirus-based or subunit vaccine provides robust immunity in healthy persons.[91] Such a strategy should be considered in immunodeficient patients. The risk of SARS-CoV-2 infection far exceeds the very small risk of COVID-19 vaccines in healthy and immunodeficient patients.[92]

Hybrid immunity, in patients who have had COVID-19 followed by vaccination, provides robust long-term protection in healthy[93] and immunodeficient patients.[94] If Omicron has a low case-fatality rate, it could serve as a highly effective "live attenuated virus vaccine" in both vaccinated healthy persons and many vaccinated immunodeficient patients. Omicron may boost those with pre-existing immunity and could "immunize" others who are unvaccinated. Omicron may therefore protect against future more virulent strains of SARS-CoV-2 and herald the end of the current pandemic. If this optimistic prediction proves accurate, Omicron may be the light at the end of the very long pandemic tunnel rather than another false dawn for immunodeficient patients.

REFERENCES

1. Mobarak AM, Miguel E, Abaluck J, Ahuja A, Alsan M, Banerjee A, et al. End COVID-19 in low- and middle-income countries. Science 2022;375:1105-10.
2. Tiwari R, Dhama K, Sharun K, Iqbal Yatoo M, Malik YS, Singh R, et al. COVID-19: animals, veterinary and zoonotic links. Vet Q 2020;40:169-82.
3. Segreto R, Deigin Y. The genetic structure of SARS-CoV-2 does not rule out a laboratory origin: SARS-COV-2 chimeric structure and furin cleavage site might be the result of genetic manipulation. Bioessays 2021;43:e2000240.
4. Holmes EC, Goldstein SA, Rasmussen AL, Robertson DL, Crits-Christoph A, Wertheim JO, et al. The origins of SARS-CoV-2: a critical review. Cell 2021;184:2848-56.
5. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
6. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271-80.e8.
7. Ameratunga R, Woon ST, Steele R, Snell R, Medlicott N, Mears E, et al. Perspective: the nose and the stomach play a critical role in the NZACE2-Patari* (modified ACE2) drug treatment project of SARS-CoV-2 infection. Expert Rev Clin Immunol 2021;17:553-60.
8. Chouaki Benmansour N, Carvelli J, Vivier E. Complement cascade in severe forms of COVID-19: recent advances in therapy. Eur J Immunol 2021;51:1652-9.
9. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
10. Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. Lancet 2020;395:1014-5.
11. Gao Y, Chen Y, Liu M, Shi S, Tian J. Impacts of immunosuppression and immunodeficiency on COVID-19: a systematic review and meta-analysis. J Infect 2020;81:e93-5.
12. Wan YI, Apea VJ, Dhairyawan R, Puthucheary ZA, Pearse RM, Orkin CM, et al. Ethnic disparities in hospitalisation and hospital-outcomes during the second wave of COVID-19 infection in east London. Sci Rep 2022;12:3721.
13. Abedi V, Olulana O, Avula V, Chaudhary D, Khan A, Shahjouei S, et al. Racial, economic, and health inequality and COVID-19 infection in the United States. J Racial Ethn Health Disparities 2021;8:732-42.
14. Baek WK, Sohn SY, Mahgoub A, Hage R. A comprehensive review of severe acute respiratory syndrome coronavirus 2. Cureus 2020;12:e7943.
15. Baker JM, Nakayama JY, O'Hegarty M, McGowan A, Teran RA, Bart SM, et al. SARS-CoV-2 B.1.1.529 (Omicron) variant transmission within households—four U.S. jurisdictions, November 2021–February 2022. MMWR Morb Mortal Wkly Rep 2022;71:341-6.
16. Wong LR, Perlman S. Immune dysregulation and immunopathology induced by SARS-CoV-2 and related coronaviruses—are we our own worst enemy? Nat Rev Immunol 2022;22:47-56.
17. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. Science 2020;370:eabd4585.
18. Ameratunga R, Woon ST, Lea E, Steele R, Lehnert K, Leung E, et al. The (apparent) antibody paradox in COVID-19. Expert Rev Clin Immunol 2022;18:335-45.
19. Negro F. Is antibody-dependent enhancement playing a role in COVID-19 pathogenesis? Swiss Med Wkly 2020;150:w20249.
20. Tan AT, Linster M, Tan CW, Le Bert N, Chia WN, Kunasegaran K, et al. Early induction of functional SARS-CoV-2-specific T cells associates with rapid viral clearance and mild disease in COVID-19 patients. Cell Rep 2021;34:108728.
21. Rydyznski Moderbacher C, Ramirez SI, Dan JM, Grifoni A, Hastie KM, Weiskopf D, et al. Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity. Cell 2020;183:996-1012.e19.
22. Casado JL, Häemmerle J, Vizcarra P, Velasco H, Velasco T, Fernandez-Escribano M, et al. SARS CoV-2 infections in health care workers with pre-existing T cell response: a prospective cohort study. Clin Microbiol Infect 2021;27:916.e1-4.
23. Swadling L, Diniz MO, Schmidt NM, Amin OE, Chandran A, Shaw E, et al. Pre-existing polymerase-specific T cells expand in abortive seronegative SARS-CoV-2. Nature 2022;601:110-7.
24. Ameratunga R, Longhurst H, Lehnert K, Steele R, Edwards ESJ, Woon ST. Are all primary immunodeficiency disorders inborn errors of immunity? Front Immunol 2021;12:706796.
25. Esenboga S, Ocak M, Akarsu A, Bildik HN, Cagdas D, Iskit AT, et al. COVID-19 in patients with primary immunodeficiency. J Clin Immunol 2021;41:1515-22.
26. Quinti I, Lougaris V, Milito C, Cinetto F, Pecoraro A, Mezzaroma I, et al. A possible role for B cells in COVID-19? Lesson from patients with agammaglobulinemia. J Allergy Clin Immunol 2020;146:211-3.e4.
27. Jin H, Reed JC, Liu STH, Ho HE, Lopes JP, Ramsey NB, et al. Three patients with X-linked agammaglobulinemia hospitalized for COVID-19 improved with convalescent plasma. J Allergy Clin Immunol Pract 2020;8:3594-6.e3.
28. Mira E, Yarce OA, Ortega C, Fernandez S, Pascual NM, Gomez C, et al. Rapid recovery of a SARS-CoV-2-infected X-linked agammaglobulinemia patient after infusion of COVID-19 convalescent plasma. J Allergy Clin Immunol Pract 2020;8:2793-5.
29. Van Damme KFA, Tavernier S, Van Roy N, De Leeuw E, Declercq J, Bosteels C, et al. Case report: convalescent plasma, a targeted therapy for patients with CVID and severe COVID-19. Front Immunol 2020;11:596761.
30. Viana R, Moyo S, Amoako DG, Tegally H, Scheepers C, Althaus CL, et al. Rapid epidemic expansion of the SARS-CoV-2 Omicron variant in southern Africa. Nature 2022;603:679-86.
31. Liu Y, Rocklöv J. The effective reproductive number of the Omicron variant of SARS-CoV-2 is several times relative to Delta. J Travel Med 2022;29:taac037.
32. Salvagno GL, Henry BM, Pighi L, De Nitto S, Montagnana M, Lippi G. SARS-CoV-2 Omicron infection is associated with high nasopharyngeal viral load. J Infect 2022;84:834-72.
33. Riediker M, Briceno-Ayala L, Ichihara G, Albani D, Poffet D, Tsai DH, et al. Higher viral load and infectivity increase risk of aerosol transmission for Delta and Omicron variants of SARS-CoV-2. Swiss Med Wkly 2022;152:w30133.
34. Zou J, Xia H, Xie X, Kurhade C, Machado RRG, Weaver SC, et al. Neutralization against Omicron SARS-CoV-2 from previous non-Omicron infection. Nat Commun 2022;13:852.
35. Helmsdal G, Hansen OK, Møller LF, Christiansen DH, Petersen MS, Kristiansen MF. Omicron outbreak at a private gathering in the Faroe Islands, infecting 21 of 33 triple-vaccinated healthcare workers. Clin Infect Dis. Published online February 3, 2022. https://doi.org/10.1093/cid/ciac089
36. Hussey H, Davies MA, Heekes A, Williamson C, Valley-Omar Z, Hardie D, et al. Assessing the clinical severity of the Omicron variant in the Western Cape Province, South Africa, using the diagnostic PCR proxy marker of RdRp target delay to distinguish between Omicron and Delta infections—a survival analysis. Int J Infect Dis 2022;118:150-4.
37. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature 2021;594:259-64.
38. Tian T, Wu J, Chen T, Li J, Yan S, Zhou Y, et al. Long-term follow-up of dynamic brain changes in patients recovered from COVID-19 without neurological manifestations. JCI Insight 2022;7:e155827.

39. Kell DB, Laubscher GJ, Pretorius E. A central role for amyloid fibrin microclots in long COVID/PASC: origins and therapeutic implications. Biochem J 2022; 479:537-59.
40. Rothan HA, Byrareddy SN. The potential threat of multisystem inflammatory syndrome in children during the COVID-19 pandemic. Pediatr Allergy Immunol 2021;32:17-22.
41. Hong Q, Han W, Li J, Xu S, Wang Y, Xu C, et al. Molecular basis of receptor binding and antibody neutralization of Omicron. Nature 2022;604:546-52.
42. Shah M, Woo HG. Omicron: a heavily mutated SARS-CoV-2 variant exhibits stronger binding to ACE2 and potently escapes approved COVID-19 therapeutic antibodies. Front Immunol 2021;12:830527.
43. Cui Z, Liu P, Wang N, Wang L, Fan K, Zhu Q, et al. Structural and functional characterizations of infectivity and immune evasion of SARS-CoV-2 Omicron. Cell 2022;185:860-71.e13.
44. Meng B, Abdullahi A, Ferreira I, Goonawardane N, Saito A, Kimura I, et al. Altered TMPRSS2 usage by SARS-CoV-2 Omicron impacts tropism and fusogenicity. Nature 2022;603:706-14.
45. Hui KPY, Ho JCW, Cheung MC, Ng KC, Ching RHH, Lai KL, et al. SARS-CoV-2 Omicron variant replication in human bronchus and lung ex vivo. Nature 2022;603:715-20.
46. Ameratunga R, Woon ST, Steele R, Lehnert K, Leung E, Brooks AES. Severe COVID-19 is a T cell immune dysregulatory disorder triggered by SARS-CoV-2. Expert Rev Clin Immunol 2022:18:557-65.
47. Osterman A, Badell I, Basara E, Stern M, Kriesel F, Eletreby M, et al. Impaired detection of omicron by SARS-CoV-2 rapid antigen tests. Med Microbiol Immunol 2022:211:105-17.
48. Navero-Castillejos J, Casals-Pascual C, Narváez S, Cuesta G, Hurtado JC, Fernandez M, et al. Diagnostic performance of six rapid antigen tests for SARS-CoV-2. Microbiol Spectr 2022;10:e0235121.
49. Vitiello A, Ferrara F, Auti AM, Di Domenico M, Boccellino M. Advances in the Omicron variant development. J Intern Med 2022;292:81-90.
50. Schubert M, Bertoglio F, Steinke S, Heine PA, Ynga-Durand MA, Maass H, et al. Human serum from SARS-CoV-2-vaccinated and COVID-19 patients shows reduced binding to the RBD of SARS-CoV-2 Omicron variant. BMC Med 2022;20:102.
51. Edara VV, Manning KE, Ellis M, Lai L, Moore KM, Foster SL, et al. mRNA-1273 and BNT162b2 mRNA vaccines have reduced neutralizing activity against the SARS-CoV-2 omicron variant. Cell Rep Med 2022;3:100529.
52. Chatterjee D, Tauzin A, Marchitto L, Gong SY, Boutin M, Bourassa C, et al. SARS-CoV-2 Omicron Spike recognition by plasma from individuals receiving BNT162b2 mRNA vaccination with a 16-week interval between doses. Cell Rep 2022;38:110429.
53. Zhou W, He P, Li J, Liu H, Shi M, Yu J, et al. Steep decline in binding capability of SARS-CoV-2 Omicron variant (B.1.1.529) RBD to the antibodies in early COVID-19 convalescent sera and inactivated vaccine sera. Viruses 2022;14:335.
54. Lauring AS, Tenforde MW, Chappell JD, Gaglani M, Ginde AA, McNeal T, et al. Clinical severity of, and effectiveness of mRNA vaccines against, covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. BMJ 2022;376:e069761.
55. Ariën KK, Heyndrickx L, Michiels J, Vereecken K, Van Lent K, Coppens S, et al. Three doses of BNT162b2 vaccine confer neutralising antibody capacity against the SARS-CoV-2 Omicron variant. NPJ Vaccines 2022;7:35.
56. Tseng HF, Ackerson BK, Luo Y, Sy LS, Talarico CA, Tian Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants. Nat Med 2022;28:1063-71.
57. Elliott P, Bodinier B, Eales O, Wang H, Haw D, Elliott J, et al. Rapid increase in Omicron infections in England during December 2021: REACT-1 study. Science 2022;375:1406-11.
58. Cohen H, Rotem S, Elia U, Bilinsky G, Levy I, Chitlaru T, et al. T cell response following anti-COVID-19 BNT162b2 vaccination is maintained against the SARS-CoV-2 Omicron B.1.1.529 variant of concern. Viruses 2022;14:347.
59. Naranbhai V, Nathan A, Kaseke C, Berrios C, Khatri A, Choi S, et al. T cell reactivity to the SARS-CoV-2 Omicron variant is preserved in most but not all individuals. Cell 2022;185:1041-51.e6.
60. GeurtsvanKessel CH, Geers D, Schmitz KS, Mykytyn AZ, Lamers MM, Bogers S, et al. Divergent SARS CoV-2 Omicron-reactive T- and B cell responses in COVID-19 vaccine recipients. Sci Immunol 2022;7:eabo2202.
61. Liu J, Chandrashekar A, Sellers D, Barrett J, Jacob-Dolan C, Lifton M, et al. Vaccines elicit highly conserved cellular immunity to SARS-CoV-2 Omicron. Nature 2022;603:493-6.
62. VanBlargan LA, Errico JM, Halfmann PJ, Zost SJ, Crowe JE Jr, Purcell LA, et al. An infectious SARS-CoV-2 B.1.1.529 Omicron virus escapes neutralization by therapeutic monoclonal antibodies. Nat Med 2022;28:490-5.
63. Liu Z, VanBlargan LA, Bloyet LM, Rothlauf PW, Chen RE, Stumpf S, et al. Identification of SARS-CoV-2 spike mutations that attenuate monoclonal and serum antibody neutralization. Cell Host Microbe 2021; 29:477-88.e4.
64. Yuan M, Huang D, Lee CD, Wu NC, Jackson AM, Zhu X, et al. Structural and functional ramifications of antigenic drift in recent SARS-CoV-2 variants. Science 2021;373:818-23.
65. Chen RE, Winkler ES, Case JB, Aziati ID, Bricker TL, Joshi A, et al. In vivo monoclonal antibody efficacy against SARS-CoV-2 variant strains. Nature 2021;596:103-8.
66. Corti D, Purcell LA, Snell G, Veesler D. Tackling COVID-19 with neutralizing monoclonal antibodies. Cell 2021;184:3086-108.
67. Li P, Wang Y, Lavrijsen M, Lamers MM, de Vries AC, Rottier RJ, et al. SARS-CoV-2 Omicron variant is highly sensitive to molnupiravir, nirmatrelvir, and the combination. Cell Res 2022;32:322-4.
68. Ameratunga R, Woon ST, Steele R, Lehnert K, Leung E, Edwards ESJ, et al. Common variable immunodeficiency disorders as a model for assessing COVID-19 vaccine responses in immunocompromised patients. Front Immunol 2021;12:798389.
69. Ameratunga R, Jordan A, Cavadino A, Ameratunga S, Hills T, Steele R, et al. Bronchiectasis is associated with delayed diagnosis and adverse outcomes in the New Zealand Common Variable Immunodeficiency Disorders cohort study. Clin Exp Immunol 2021;204:352-60.
70. Ameratunga R. Assessing disease severity in common variable immunodeficiency disorders (CVID) and CVID-like disorders. Front Immunol 2018;9:2130.
71. Gupta S, Agrawal S, Sandoval A, Su H, Tran M, Demirdag Y. SARS-CoV-2-specific and functional cytotoxic CD8 cells in primary antibody deficiency: natural infection and response to vaccine. J Clin Immunol. Published online April 2, 2022. https://doi.org/10.1007/s10875-022-01256-y
72. Romero C, Díez J-M, Gajardo R. Anti-SARS-CoV-2 antibodies in healthy donor plasma pools and IVIG products—an update. Lancet Infect Dis 2022;22: 19.
73. Ameratunga R, Woon ST, Jordan A, Longhurst H, Leung E, Steele R, et al. Response to letter to the editor: the clinical utility of diagnostic T cell assays for COVID-19. Expert Rev Clin Immunol 2021;17:1159-61.
74. Ameratunga R, Lederman HM, Sullivan KE, Ochs HD, Seyama K, French JK, et al. Defective antigen-induced lymphocyte proliferation in the X-linked hyper-IgM syndrome. J Pediatr 1997;131:147-50.
75. Ameratunga R, Woon ST, Koopmans W, French J. Cellular and molecular characterisation of the hyper immunoglobulin M syndrome associated with congenital rubella infection. J Clin Immunol 2009;29:99-106.
76. Hoffmann M, Krüger N, Schulz S, Cossmann A, Rocha C, Kempf A, et al. The Omicron variant is highly resistant against antibody-mediated neutralization: implications for control of the COVID-19 pandemic. Cell 2022;185: 447-56.e11.
77. Cameroni E, Bowen JE, Rosen LE, Saliba C, Zepeda SK, Culap K, et al. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. Nature 2022;602:664-70.
78. Ameratunga R, Lehnert K, Leung E, Comoletti D, Snell R, Woon ST, et al. Inhaled modified angiotensin converting enzyme 2 (ACE2) as a decoy to mitigate SARS-CoV-2 infection. N Z Med J 2020;133:112-8.
79. Ameratunga R, Longhurst H, Steele R, Lehnert K, Leung E, Brooks AES, et al. Common variable immunodeficiency disorders, T-cell responses to SARS-CoV-2 vaccines, and the risk of chronic COVID-19. J Allergy Clin Immunol Pract 2021;9:3575-83.
80. Brown LK, Moran E, Goodman A, Baxendale H, Bermingham W, Buckland M, et al. Treatment of chronic or relapsing COVID-19 in immunodeficiency. J Allergy Clin Immunol 2022;149:557-61.e1.
81. Valk SJ, Piechotta V, Chai KL, Doree C, Monsef I, Wood EM, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review. Cochrane Database Syst Rev 2020;5:CD013600.
82. Chen L, Zody MC, Di Germanio C, Martinelli R, Mediavilla JR, Cunningham MH, et al. Emergence of multiple SARS-CoV-2 antibody escape variants in an immunocompromised host undergoing convalescent plasma treatment. mSphere 2021;6:e0048021.
83. Ameratunga R, Woon ST. Perspective: evolving concepts in the diagnosis and understanding of common variable immunodeficiency disorders (CVID). Clin Rev Allergy Immunol 2020;59:109-21.
84. Ameratunga R, Allan C, Woon ST. Defining common variable immunodeficiency disorders in 2020. Immunol Allergy Clin North Am 2020;40:403-20.
85. Ameratunga R, Allan C, Lehnert K, Woon ST. Perspective: application of the American College of Medical Genetics variant interpretation criteria to common variable immunodeficiency disorders. Clin Rev Allergy Immunol 2021;61: 226-35.

86. Ameratunga R, Ahn Y, Steele R, Woon ST. The natural history of untreated primary hypogammaglobulinemia in adults: implications for the diagnosis and treatment of common variable immunodeficiency disorders (CVID). Front Immunol 2019;10:1541.
87. Amodio D, Ruggiero A, Sgrulletti M, Pighi C, Cotugno N, Medri C, et al. Humoral and cellular response following vaccination with the BNT162b2 mRNA COVID-19 vaccine in patients affected by primary immunodeficiencies. Front Immunol 2021;12:727850.
88. Salinas AF, Mortari EP, Terreri S, Quintarelli C, Pulvirenti F, Di Cecca S, et al. SARS-CoV-2 vaccine induced atypical immune responses in antibody defects: everybody does their best. J Clin Immunol 2021;41:1709-22.
89. Gernez Y, Murugesan K, Cortales CR, Banaei N, Hoyte L, Pinsky BA, et al. Immunogenicity of a third COVID-19 mRNA vaccine dose in PID patients with functional B-cell defects. J Allergy Clin Immunol Pract 2022;10:1385-8.e2.
90. Barmettler S, DiGiacomo DV, Yang NJ, Lam T, Naranbhai V, Dighe AS, et al. Response to severe acute respiratory syndrome coronavirus 2 initial series and additional dose vaccine in patients with predominant antibody deficiency. J Allergy Clin Immunol Pract 2022;10:1622-34.e4.
91. Khong KW, Liu D, Leung KY, Lu L, Lam HY, Chen L, et al. Antibody response of combination of BNT162b2 and CoronaVac platforms of COVID-19 vaccines against Omicron variant. Vaccines (Basel) 2022;10:160.
92. Ameratunga R, Woon ST, Sheppard MN, Garland J, Ondruschka B, Wong CX, et al. First identified case of fatal fulminant necrotizing eosinophilic myocarditis following the initial dose of the Pfizer-BioNTech mRNA COVID-19 vaccine (BNT162b2, Comirnaty): an extremely rare idiosyncratic hypersensitivity reaction. J Clin Immunol 2022;42:441-7.
93. Pilz S, Theiler-Schwetz V, Trummer C, Krause R, Ioannidis JPA. SARS-CoV-2 reinfections: overview of efficacy and duration of natural and hybrid immunity. Environ Res 2022;209:112911.
94. Quinti I, Locatelli F, Carsetti R. The immune response to SARS-CoV-2 vaccination: insights learned from adult patients with common variable immune deficiency. Front Immunol 2021;12:815404.