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PERSPECTIVE

The (apparent) antibody paradox in COVID-19

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ABSTRACT

Introduction: The immunological response to COVID-19 is only partly understood. It is increasingly clear that the virus triggers an inappropriate host inflammatory reaction in patients experiencing severe disease.
Areas covered: The role of antibodies in COVID-19 remains to be fully defined. There is evidence for both protection and harm in different clinical syndromes triggered by SARS-CoV-2. Many patients dying from COVID-19 had both high titers of antibodies to SARS-CoV-2 and elevated viral loads. The uncertain protective role of humoral immunity is mirrored by the lack of benefit of therapeutic convalescent plasma infusions in COVID-19. In contrast, there is increasing evidence that a vigorous T-cell response is protective. Delayed or low avidity T cell reactions were seen in patients suffering severe COVID-19.
Expert opinion: These observations suggest T cell responses to SARS-CoV-2 are the dominant long-term protective mechanism following either infection or vaccination. The magnitude and quality of the antibody response is likely to reflect underlying T cell immunity to SARS-CoV-2. Much of what has been learned about COVID-19 will need to be revised following the recent rapid emergence and dominance of the omicron variant of SARS-CoV-2.

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1. Introduction

Following its origin from Wuhan city in China, SARS-CoV-2 has spread to almost all continents on earth with calamitous health, economic and societal consequences. The origin of the virus is the subject of intense scrutiny [1–3]. Apart from a death toll exceeding 6 million, hundreds of millions of people have been infected with SARS-CoV-2, resulting in ongoing medical and psychiatric sequelae. A much larger number have been plunged into poverty, triggered by economic misery faced by many developing nations.

The infection appears to evolve in three overlapping clinical stages (Figure 1). In the first asymptomatic nasal phase, the virus targets cells bearing membrane ACE2 in the upper respiratory tract. Host proteases including TMPRSS-2 cleave the spike (S) glycoprotein [4]. The S2 subunit is then able to fuse with the cell, releasing the viral genome, which hijacks cellular machinery to produce daughter virus.

Following the nasal phase, some patients progress to the second pulmonary stage, probably by microaspiration from the nose and stomach [5]. Patients in this phase experience increasing breathlessness, lethargy and myalgia. High-resolution CT scans of the thorax may show ground glass appearance.

Patients progressing to the third systemic stage suffer multiple organ dysfunction including acute respiratory distress syndrome (ARDS) and activation of the coagulation cascade [6]. A cytokine storm is triggered by inappropriate activation of macrophages and neutrophils. In spite of invasive ventilation and extracorporeal membrane oxygenation, mortality is very high.

There is a steep age-related mortality rate, approaching 30% in those over 80 years [7]. In addition, comorbidities such as obesity, diabetes, malignancy, coronary artery disease, hypertension, renal and pulmonary disease are added risk factors for severe outcomes (Figure 1) [6–8]. Black, Hispanic and South Asian patients are at increased risk [9]. The immunological basis for these adverse outcomes is poorly understood. Part of this ethnic susceptibility may be due to sociodemographic factors, increased burden of comorbidities and inequitable access to healthcare [10].

In spite of intense study, the protective immunological correlates of COVID-19 remain uncertain [11,12]. The role of antibodies, in particular, during COVID-19 infection and following vaccination is incompletely understood. Since the beginning of the pandemic, several apparently contradictory observations have been made on the protective vs harmful roles of antibodies in COVID-19 syndromes/clinical scenarios. Some of these apparent paradoxes are reviewed and emerging explanations are discussed in this essay.

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Article highlights

- SARS-CoV-2 the agent responsible for COVID-19 has caused calamitous social, economic and health consequences globally
- The virus is able to evade the innate immune system and is also able to subvert the adaptive immune system in those who are severely affected
- The role of antibodies in protection against the infection is incompletely understood. In some circumstances, the humoral immune response appears to be protective, while in other situations it may be aggravating the inflammatory response
- At this time, it is not possible to predict specific protective antibody levels that prevent breakthrough infections in patients who have been vaccinated
- The antibody response may be best viewed as a biomarker of either infection or vaccination.
- It is becoming increasingly clear that cellular immunity is the most critical part of the response to either the virus or immunization, which allows long-term protection.
- In the future, it is possible measurement of T cell responses will predict protective responses to vaccines in vulnerable individuals
- This article seeks to provide an overview of the current status of knowledge on the role of antibodies in COVID-19
- What is currently understood about COVID-19 may need to be revised with the rapid emergence and dominance of the omicron variant of SARS-CoV-2.
- Omicron appears to be fundamentally different to previous SARS-CoV-2 variants and may need to be considered a new infection

2. SARS-CoV-2 antibodies in the diagnosis of COVID-19

2.1. Variable antibody responses in COVID-19

Patients typically develop antibodies to the virus in the second week of infection. The magnitude of the antibody response may reflect the severity of the infection in some studies [13,14], but not in others [15]. Patients with more severe disease also appear to have longer-lasting antibody responses [13]. Antibodies are present for over 1 year in infected Health Care Workers (HCW) [16] and memory B cells are present for at least 6 or 8 months [17–19]. Memory B cells may be present long after antibodies wane. COVID-19 survivors generate long-lasting mucosal antibodies [20]. Their role in preventing reinfection remains to be defined.

Unexpectedly, many persons with documented infection have poor antibody responses to the virus and yet had only mild symptoms [21–23]. Mildly symptomatic HCWs had short-lived antibody responses [24] and asymptomatic infected persons frequently had low antibody responses or did not seroconvert [25–28]. Children also had lower antibody levels compared to adults and yet are less severely affected [29,30].

Lower viral loads as judged by the RT-qPCR cycle threshold (Ct) were associated with failure to seroconvert [31]. Self-prescribed ivermectin was associated with lower antibody titers but there was no difference in disease severity [32]. Ivermectin does not appear to be effective in the treatment of COVID-19 [33]. Overall, approximately 10% of infected patients with confirmed COVID-19 do not seroconvert [34–37]. It is uncertain if these individuals are susceptible to reinfection.

2.2. Variable sensitivity of diagnostic serology tests for COVID-19

Currently, there are a large number of commercial and in-house assays for SARS-CoV-2 antibodies. Potential targets include the nucleocapsid (N), envelope (E), membrane (M) proteins or the S glycoprotein. The reader should seek up-to-date information as many vendors offer tests to several target antigens.

The S glycoprotein is post-translationally modified by carbohydrates, which may reduce its immunogenicity and antibodies may not be durable [27]. Yet it appears antibodies to the S glycoprotein are longer lasting than those to other proteins. Anti N antibodies decline more rapidly than anti S antibodies [38–42]. IgA and IgM antibodies to SARS-CoV-2 also rapidly wane. Antibodies to the M, E and N proteins have an important role in distinguishing COVID-19 survivors from those who have been vaccinated. First-generation COVID-19 vaccines comprise the S glycoprotein presented in different formats.

Recent studies have shown considerable variability in sensitivity in head-to-head comparisons of COVID-19 antibody assays [43,44]. While most of the antibody tests are specific for SARS-CoV-2, there is variable sensitivity. The sensitivity of the assay is determined by the antigen used and the relevant detection system. Currently, there are many laboratories offering in-house SARS-CoV-2 assays and it will be important for these assays to be verified and validated to ISO 9001 and 17,025 standards. External quality assurance (EQA) programs will improve the performance of these assays.

2.3. Inconsistent neutralising antibody titers in the protection against COVID-19

Measuring neutralizing antibodies by preventing in vitro infection of Vero cells requires access to Physical Containment Class 3 (PC3) laboratories. PC3 facilities are typically found in regional government laboratories or in academic institutions [45]. A surrogate virus neutralization assay has been created by a competitive ELISA, blocking antibody binding to soluble ACE2 [46,47]. A similar assay could be configured with pseudovirus [48].

Neutralizing antibodies can persist up to 9 months in mildly affected young adults [49] and were present 13 months after disease in another study [50]. The mechanism of action of neutralizing antibodies has not been completely defined. Very recent data suggest that both linear and conformation epitopes are important in neutralizing activity [51]. This indicates immunization strategies with linear peptides alone, may not be successful in conferring protective immunity.

There have been paradoxical observations on the role of neutralizing antibodies following infection. Some data indicate neutralizing antibodies predict protection [35] and patients who developed delayed neutralizing antibody responses had more severe disease [52]. Specific neutralizing antibody titers however do not reliably predict protection from breakthrough SARS-CoV-2 infection [53,54]. As

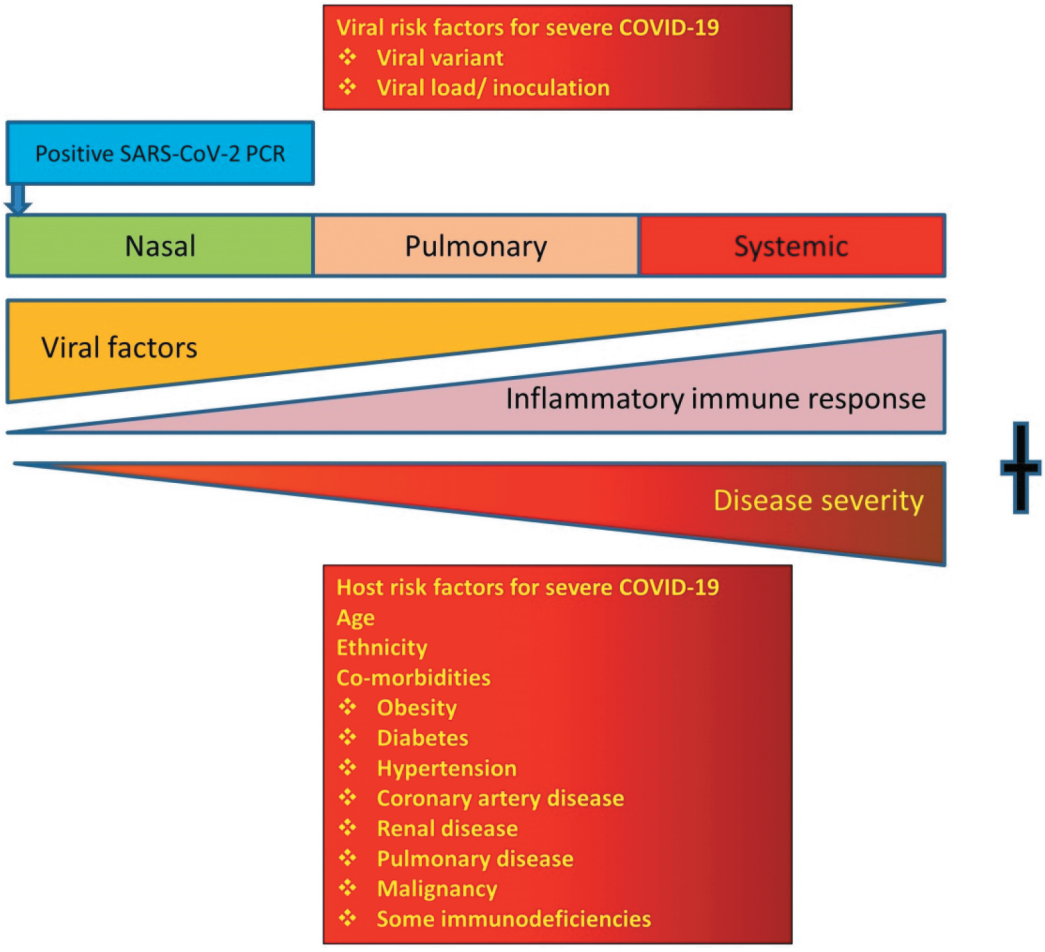

Figure 1. Factors determining the outcome of COVID-19. Both viral and host risk factors are important in progression from the nasal to the pulmonary and systemic phases. The omicron variant appears to produce milder pulmonary disease and may have a shorter nasal phase. New antiviral drugs such as molnupiravir (Merck) or paxlovid (Pfizer) are only likely to be effective early in disease. Later in disease, immunomodulatory drugs are more effective. Vaccines reduce the risk of aberrant immune responses, making the pulmonary and systemic phases less likely.

discussed below, there is no consistent, predetermined protective antibody level following infection or vaccination. As outlined below, many of these apparently contradictory observations may be explained by the underappreciated critical protective role of T cell responses to SARS-CoV-2 [55,56].

3. The role of antibodies in the pathogenesis of various COVID-19 syndromes

3.1. The risk of Antibody Dependent Enhancement (ADE)

Early in the pandemic it was realized antibody responses did not necessarily confer protection. Many patients dying from COVID-19 had both high viral loads as well as high antibody titers [57,58]. The antibody response was not protective in these individuals [59] and there was concern this was evidence of antibody-dependent enhancement (ADE).

Recent studies have explored possible mechanisms for ADE in vitro [57]. One study identified four regions within the viral receptor-binding domain (RBD) of SARS-CoV-2 [57]. Antibodies to specific epitopes resulted in either neutralization or enhancement by allowing the virus to infect Raji cells. What may be neutralizing antibodies in vitro may be enhancing in vivo. Another recent study implicated inappropriate antibody-dependent phagocytosis of SARS-CoV-2 into macrophages, triggering inflammasome activation leading to pyroptosis and a cytokine storm [60]. As discussed below, these inconsistent observations underscore the importance of T cell responses to SARS-CoV-2.

3.2. Multisystem Inflammatory Syndrome in Children (MISC)

ADE may be occurring in the multisystem inflammatory syndrome in children (MISC) and adults. Here, a severe inflammatory response occurs 4–6 weeks after infection with SARS-CoV-2. These patients have high titers of antibodies, particularly IgA to the virus. In vitro studies have shown these antibodies are proinflammatory and trigger neutrophil and macrophage responses. The latter cells may be the source of multiple cytokines, which could be the basis of this rare but severe syndrome. Whether MISC is an example of ADE is the subject of ongoing study [61].

3.3. Passive transfer of SARS-CoV-2 antibodies through the placenta and breast milk

Antibodies can be transferred through the placenta or via breast milk to protect the infant. Antibodies to SARS-CoV-2 have also been noted in breast milk of mothers after vaccination [62] or infection [63,64]. The role of these passively acquired antibodies in protecting infants is the subject of ongoing investigation. To date, there is no evidence these antibodies cause ADE/MISC in infants [65].

3.4. Antibody response in long COVID

Long COVID is a recently recognized syndrome following COVID-19 where patients experience a range of disabling symptoms including severe fatigue, chest pain, breathlessness and neurological symptoms including autonomic instability, loss of memory and clarity of thought (brain fog) [66,67]. There is ongoing debate about the case-definition of Long-COVID. It seems likely this is a heterogeneous disorder with disparate symptoms of variable duration [68]. Current data indicate vaccines reduce the risk of long-COVID, suggesting the disorder may be a consequence of either a suboptimal immune response to the infection or ongoing immune dysregulation. Some data indicate endothelial dysfunction and microthrombi may be contributing to ongoing organ dysfunction [69,70]. It remains to be determined if the new omicron variant will cause a similar syndrome in COVID-19 survivors.

Many of these patients were infected early in the pandemic, did not have access to reliable RT-qPCR tests and their antibodies may have waned [71]. Some patients are in a diagnostic vacuum, without an explanation for their disorder [72]. There is an urgent need for diagnostic SARS-CoV-2 T cell assays for these patients [73,74].

3.5. The antibody response in chronic COVID-19

Chronic COVID-19 is a dangerous stalemate between SARS-CoV-2 and a suboptimal cellular immune response [75]. Patients may shed the virus for months before either succumbing or recovering. Chronic COVID-19 can lead to intra-host viral evolution with the emergence of dangerous mutants evading vaccines and monoclonal antibodies [76].

Some patients with Chronic COVID-19 have received passive immunotherapy with convalescent plasma. Intra-host viral evolution caused the emergence of new resistant variants, indicating passive immunotherapy was not protective [77]. There is a risk of variants of high consequence evolving. Chronic COVID-19, although rare, is a public health emergency within a global crisis and must be prevented at any cost.

3.6. Antibody responses in immunodeficient patients

Many patients with primary and secondary immunodeficiencies are unable to generate antibodies. Some of these patients respond poorly to vaccines and are susceptible to breakthrough infections [78,79]. Patients with Common Variable Immunodeficiency Disorders (CVID) often have poor responses to vaccines, although this can be inconsistent [80–82]. Recent studies indicate such patients will derive at least partial protection from COVID-19 vaccines [83,84].

The severity of COVID-19 may depend on the nature of the immune defect [74]. Patients with innate immune defects and those with T cell defects are at increased risk [85–87]. Paradoxically, patients with X-linked agammaglobulinemia (XLA) without co-morbidities, may be at lower risk of severe disease [88–91]. This indicates antibodies can be harmful in some circumstances and it infers T cell responses, which are intact in XLA, are protective. Patients with secondary immunodeficiency may also have suboptimal T cell responses to vaccines and infection.

Immunodeficient patients are frequently treated with subcutaneous or intravenous immunoglobulin (SCIG/IVIG). With increasing rates of COVID-19 infection and immunization, most plasma donors are likely to have SARS-CoV-2 antibodies [92]. It will be impossible to judge humoral responses to vaccines or infections in these patients. It will also not be possible to use SARS-CoV-2 antibody responses as a neoantigen for patients on SCIG/IVIG. At this time, it is uncertain if passively acquired SARS-CoV-2 antibodies will influence the severity of SARS-CoV-2 infections or if they will modulate responses to COVID-19 vaccines. Again, a T cell assay for SARS-CoV-2 may be very helpful in identifying infection in immunodeficient patients including those on SCIG/IVIG.

4. Limited therapeutic and protective role of SARS-CoV-2 antibodies following vaccination or infection

4.1. Limited role of passive immunotherapy

Early in the pandemic, there was enthusiasm for passive immunotherapy with convalescent plasma [93]. It was hoped that high titers of neutralizing antibodies would provide effective antiviral activity in the absence of proven therapeutics for COVID-19. Some studies have shown that convalescent plasma from patients infected with the original Wuhan virus are able to neutralize the alpha (B.1.1.7) variant in vitro [94]. In other studies, convalescent plasma from the Wuhan variant was less effective against newer variants including delta (B.1.617.2) [95,96], but may still be protective [97].

ADE may be a risk with passive immunotherapy [98]. ADE could amplify the inflammatory response to the virus and precipitate multiple-organ failure [58]. Anti-interferon antibodies in convalescent plasma could aggravate COVID-19. Ongoing studies aim to identify the risk of ADE with various therapeutic antibody preparations.

Meta-analysis of the results of randomized studies was disappointing, and the therapeutic role of such infusions is uncertain [99]. Any benefit seen in some trials may have been obscured by the variability in the quality and quantity of neutralizing antibodies. Recently, other components of plasma have been stated to have either beneficial or detrimental effects, increasing the complexity of assessing this form of treatment [100].

There has been interest in using post-vaccination serum for passive immunotherapy. As noted above, there was concern, however, that some of the new variants may be less susceptible to viral neutralization in vivo [101].

Newer biological products such as nanobodies may prove to be useful, but like many therapeutics, their role will need to

investigated in patients suffering from the omicron variant. Detailed discussion of nanobodies [102] is beyond the scope of this article, which aims to provide an overview of the current status of human antibodies in COVID-19.

4.2. The role of monoclonal antibodies remains to be determined

Monoclonal antibodies (mabs) have revolutionized the treatment of several disorders including malignancy, autoimmunity and more recently infectious diseases. These antibodies are derived from immunized mice or convalescent humans. In the case of mice, murine complementarity determining regions can be grafted to human immunoglobulins to minimize anti-mab responses.

The FDA has recently granted emergency use authorization to several monoclonal antibodies directed to SARS-CoV-2. Therapeutic monoclonal antibodies include imdevimab, casirivimab, etesivimab sotrovimab, regdanivimab and bamlanivimab. These can be used individually (bamlanivimab) or as combinations (casirivimab and imdevimab or bamlanivimab and etesivimab) to prevent viral resistance [103].

Their main role appears to be in high-risk patients early in disease or as prophylaxis. Most current mabs are directed to the RBD. These antibodies block the attachment of the S glycoprotein to ACE2. There are multiple mechanisms of action including complement activation and opsonophagocytosis. Some can prematurely trigger or lock the S glycoprotein conformation, leading to viral inactivation. The role of the Fc fragment in mabs is uncertain. Some therapeutic mabs have inactivated Fc components. Fc function may be needed for therapy but not prophylaxis. In mice, neutralizing antibodies appear to require Fc function [104].

Mutations at the E484 and N501 position of the RBD confer resistance to several mabs [105–107]. The E484K mutation is present in the highly infectious delta variant [95]. Emergence of E484K mutants were identified in patients treated with the bamlanivimab [108]. A recent meta-analysis of published studies showed there was insufficient evidence for the efficacy of mabs in terms of hospital admissions or mortality [109]. The results of future trials will determine their efficacy [109]. A newly described mab, VIR-7831 (sotrovimab) appears to have broad neutralizing activity across the subgenus of beta coronaviridae [103]. Such antibodies may be resistant to viral evolution [103]. Other long-acting mabs such as AZD442 are undergoing phase 3 trials for prophylaxis. These trials may have to be repeated as the new omicron SARS-CoV-2 variant appears to be resistant to many of these monoclonal antibodies [110–112]. Monoclonal antibodies are not representative of a physiological polyclonal antibody response to SARS-CoV-2 and cannot be construed as evidence for the protective role of antibodies in COVID-19.

4.3. Vaccines and inconsistent protective antibody titers in breakthrough infections

Vaccines against SARS-CoV-2 have proved effective. Vaccines can boost immunological responses in COVID-19 survivors [113]. However, there are increasing reports of breakthrough infections in fully immunized persons. Antibodies wane after 3-4 months and boosters may be needed [114] Some countries are now advocating a third booster injection after 4 months or less [115]. A booster dose may improve cross-protection to other variants of concern. It appears heterologous vaccination with Astra Zeneca and mRNA vaccines lead to a robust antibody response [116]. There may be a move to include the N protein in future vaccines, which may confer acute protection for the brain and lung in infected persons [117].

In spite of declining antibody titers [118], vaccines do however provide partial protection beyond 6 months and shift the severity of the disease to the milder end of the spectrum. Hospitalizations and deaths are much less common in vaccinated persons than those who are unvaccinated.

Several factors appear to predispose to these breakthrough infections; age, comorbidities, waning immunity and the emergence and dominance of the delta and omicron variants [119–121]. Breakthrough infections in vaccinated individuals were more common with SARS-CoV-2 strains bearing mutations at the E484 and N501 positions, including the delta (E484K/N501Y) and omicron (E484A/N501Y) variants [122]. As noted, vaccines using the founder (Wuhan) strain may not induce optimal cross-protective antibodies (and therefore T cell responses) to other variants [123].

Although some articles suggest levels of neutralizing antibodies are relevant to breakthrough infections [54], there is no predefined protective level, as noted above. Deaths are age-related and not dependent on the titer of neutralizing antibodies [53]. As discussed below, it seems likely age, ethnicity and the well-known comorbidities are more important than antibody titers in breakthrough infections leading to death.

4.4. The NZACE2-Pātari project (Pātari – Māori verb for decoy, which will lead to interception)

Given the propensity for rapid viral evolution, one option has been to intercept and block SARS-CoV-2 in the nasal phase of the infection [124,125]. The NZACE2-Pātari project proposes using modified ACE2 molecules (N90D/R273A) to bind the virus early in the nasal phase to mitigate the pulmonary and systemic phases. Because the project uses ACE2 molecules, it is resistant to viral evolution, unlike most monoclonal antibodies or polyclonal antibodies. SARS-CoV-2 cannot evade therapeutics based on ACE2. The molecules would be administered as soon as the patient receives a positive RT-qPCR or rapid antigen test. The lower burden of SARS-CoV-2 in the nose would in turn mitigate the severity of the pulmonary and systemic phases. This treatment is likely to be well suited for the newer viral variants including omicron and delta. Clinical trials will confirm the efficacy of this type of treatment in the future.

5. Emerging explanations for the (apparent) antibody paradox in COVID-19

5.1. The role of age, ethnicity and comorbidities in COVID-19

The role of age, ethnicity and comorbidities in the outcome of COVID-19 is poorly understood. Recently, a study suggested

that a higher prevalence of anti-interferon autoantibodies in patients with severe outcomes, particularly in older persons [126]. This may aggravate the inflammatory response.

It has been noted in multiple studies that patients prescribed proton pump inhibitors (PPIs) are at increased risk of severe disease [127]. The stomach may serve as a reservoir for intact SARS-CoV-2 and be aspirated to the lungs [125]. Data from China showed exposure to a higher viral inoculum was associated with a risk of death even in younger HCWs, before the use of personal protective equipment.

Similarly, inappropriate macrophage activation has been noted in patients with type 2 diabetes [128]. This could contribute to the cytokine storm and multiple-organ dysfunction seen in the systemic phase of the infection. Such observations might also be relevant to worse outcomes in persons of Black, Hispanic and South Asian ethnicity, who have increased rates of comorbidities including obesity, gastroesophageal reflux and diabetes.

Apart from biological factors, sociodemographic determinants including inequitable access to healthcare are likely to be major factors responsible for adverse outcomes in some disadvantaged ethnic groups [9].

5.2. The critical role of T cells in COVID-19

The role of T cells is being defined in the acute phase of COVID-19. Current data indicate uncoordinated over or under activation of acute T cell responses lead to severe disease [129,130]. Patients with severe disease were noted to have low avidity T cell responses [131]. Unbalanced T cell subsets in acute disease may be responsible for an ineffective, non-protective antibody response [132]. In contrast, patients who were either asymptomatic or mildly symptomatic had robust T-cell responses to the virus [28,133,134]. Data suggest patients exposed to the virus, who do not develop symptoms may be protected [135]. Such patients with borderline RT qPCR and negative antibodies may have a robust T cell response [27]. Pre-existing high avidity T cells aborted COVID-19 in exposed healthcare workers (HCWs) before these patients developed positive RT-qPCR tests to the virus. These individuals remained seronegative [136].

In individuals who succumbed to COVID-19, a recent study showed poor T cell responses in spite of a high antibody titer and viral loads [134]. This may explain early paradoxical observations from China, where individuals died from COVID-19 in spite of having high titers of antibodies to the virus. It is possible the difference between neutralizing function in vitro and ADE in vivo is an early and vigorous protective T cell response to vaccination or infection.

A robust memory T cell response following infection, confers long-term protection [19,27,133]. There are excellent T cell responses to the virus 6 months later [135,137] and T cell responses persist in spite of waning antibody responses [138–140]. A recent community-based survey from Sweden showed 17% of patients with T cell responses to SARS-CoV-2 were seronegative [141]. This highlights the importance of diagnostic T cell assays for SARS-CoV-2.

Vaccination provides protection against an unbalanced, uncoordinated cellular immune response causing severe disease and death [135]. Vaccination does not prevent infection but does alter the prognostic trajectory of COVID-19 in most patients. Robust T cell responses are likely to be the critical outcome of vaccination, which prevents severe disease [135]. Similarly, an effective T cell response to vaccines may protect against long-term sequelae of COVID-19 including Long COVID, Chronic COVID-19 and MISC [142]. It seems likely the T cell response to vaccines also protects against ADE.

Passive immunotherapy with convalescent plasma and monoclonal antibodies does not confer T cell immunity. This might explain why convalescent plasma has not been as successful as hoped. Given the critical role of cellular immunity, current data suggests antibodies to SARS-CoV-2 are arguably at best, epiphenomena and at worst, bad actors.

6. Expert opinion

Science will ultimately prevail against SARS-CoV-2. In spite of the havoc caused by the virus, there have been major advances including the development, testing and deployment of effective vaccines and therapeutics. Currently, there is a race between global vaccination and emergence of escape mutants. The ultimate death toll will be determined by the outcome of this race. The uncoordinated global response to the pandemic has allowed the virus to continue evolving, resulting in the selection and emergence of vaccine and antibody resistant SARS-CoV-2 variants.

This was seen with the emergence and dominance of the new SARS-CoV-2 omicron variant. This variant has multiple nucleotide substitutions in the S glycoprotein and N protein. The new omicron variant has far-reaching implications for the diagnosis, treatment and prevention of COVID-19 [143]. This essay has explored the current role of antibodies in the diagnosis and treatment of previous SARS-CoV-2 variants. Much of what has been written here may need to be revised with the emergence of the omicron variant. From preliminary data, omicron may need to be considered an entirely new viral infection and many aspects of what has been learned about previous SARS-CoV-2 variants will need to be amended.

Antibody-based assays will need to be reviewed for their sensitivity for this variant. New antibody assays may need to be developed with the specific mutations in the omicron RBD as the antigenic target. Assays will need to be compared in EQA programs and it is possible different antibody tests will be needed to determine the specific variant causing infection. This is particularly important if RT-qPCR tests were not undertaken at the time of viral shedding.

Evidence has been presented here that antibodies do not play a critical role in protecting against COVID-19. This again will have to be reviewed. It is possible antibodies will have a greater role in protecting against omicron than previous variants. Serum from omicron convalescent donors may be more effective than against previous SARS-CoV-2 variants. New trials of convalescent and post-vaccine plasma will be needed in the future.

It is becoming apparent omicron will evade many monoclonal antibodies currently in use. Current monoclonal antibodies in development will need to be tested against the RBD

of omicron. It is hoped that at least some will be effective. New monoclonal antibodies generated from patients recovering from omicron infection will need to be developed.

In spite of the many mutations in the RBD, NZACE2-Pātari project is likely to prevail against omicron. Omicron requires binding to ACE2 for cellular entry and NZACE2-Pātari is likely to remain effective. Viral evolution of the RBD will not be tolerated without loss of infectivity. It appears the omicron variant has a shorter nasal phase than other SARS-CoV-2 variants, so treatment with NZACE2-Pātari will need to commence very early to alter the prognostic trajectory of patients.

The response of immunodeficient patients to omicron remains to be determined. Given omicron appears to be less prone to cause ARDS, the case fatality rate in immunodeficient patients may be less. Partial responses to three or four primary doses of current COVID-19 vaccines may suffice in protecting immunodeficient patients from severe outcomes. If omicron is less virulent, it may be less prone to causing Chronic COVID-19 in immunocompromised persons. Unlike previous variants, therapeutic plasma infusions may be more effective in immunocompromised persons infected with omicron.

The role of omicron in the outcomes in patients with comorbidities and the elderly will need to be revisited. Patients with pre-existing pulmonary disease may have milder disease given omicron is less likely to cause ARDS. All of this remains to be confirmed by future studies.

Drugs, such as remdesivir or favipiravir, which were previously shown to be ineffective against other SARS-CoV-2 variants, will need to be reassessed in new randomized trials of omicron infected patients. Similarly, the role of drugs such as dexamethasone will also need to be re-evaluated, as ARDS is less of a problem with omicron. Dexamethasone may increase the risk of secondary bacterial and fungal infections such as mucormycosis, which may alter the therapeutic index. It is possible machine learning and artificial intelligence may provide helpful information determining the optimal treatment strategies, based on the viral variant and detailed immunological parameters.

The role of T cells in protection against omicron will have to be revisited. Evidence has been presented here that cellular immunity is critical for recovery from COVID-19 caused by previous SARS-CoV-2 variants. It is possible existing vaccines confer effective cellular immunity to omicron and this may be enhanced by heterologous primary or booster vaccinations. Entirely new vaccines may need to be produced, but there is always the risk yet newer variants will emerge in the interim.

The final chapter on COVID-19 has not been written. If omicron has a low case fatality rate, it may serve as an efficient 'live attenuated viral vaccine'. Omicron infection may confer protection against more virulent variants of concern. Inadvertent infection of immunized persons by omicron could confer a 'booster' effect, with robust long-term immune protection. Omicron may signal the beginning of end rather than the end of the beginning of the COVID-19 pandemic. This optimistic perspective must be tempered against hospitals being overwhelmed by COVID-19 infections in predominantly unvaccinated individuals.

Declaration of interest

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