A year in our understanding of COVID-19

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The COVID-19 pandemic, caused by SARS-CoV-2, has resulted in more than a million deaths and tens of millions of infections globally. As we approach the first anniversary of its characterization, it is timely to consider the developments, and persistent limitations, in our understanding of this pathogen. In this special edition of *Clinical and Experimental Immunology,* we present five reviews and research papers on crucial aspects of COVID-19.

The causes of COVID-19 severity, and possible routes to limit severity, are a major topic of immunological research. It is becoming increasingly apparent that while disease is initiated by viral infection, the immune response itself may become pathogenic in later phases of disease. The presence of autoantibodies against type-I interferons (IFNs) has recently been associated with COVID-19 severity [1], demonstrating the importance of this arm of antiviral immunity in limiting disease. Type-I IFNs are induced by the signalling of innate immune pattern recognition receptors (PRRs), and many viruses have evolved mechanisms to suppress PRR signalling. This virally mediated suppression of innate immunity has also been documented for SARS-CoV-2, as reviewed in this edition by Amor *et al.* [2]. Robust early innate immune responses probably contribute to early viral clearance, or the restriction of disease to asymptomatic or paucisymptomatic manifestations. By contrast, Amor *et al.* also discuss how elements of the innate immune system such as the activation of coagulation and complement may contribute to disease progression. Given the strong association between COVID-19 severity and age [3], 'inflammaging', may also contribute to disease through the dysfunction of early innate immune viral recognition and the propensity to initiate pathological inflammatory responses [2].

COVID-19 severity can be attenuated through the use of dexamethasone in patients with severe disease, demonstrating the role of steroid-sensitive inflammation in COVID-19 severity [4]. Numerous other therapeutics are being tested for their ability to attenuate COVID-19, including the COVACTA trial of the anti-interleukin (IL)-6 receptor monoclonal antibody tocilizumab [5] and granulocyte–macrophage colony-stimulating factor (GM-CSF) neutralizing monoclonal antibodies [6]. In addition to these immunomodulatory therapeutic agents, prophylactic immunomodulation may offer some benefit in limiting COVID-19 severity. Vaccination against *Mycobacterium tuberculosis* using the bacillus Calmette–Guérin (BCG) vaccine has been studied in many settings as a possible trigger of 'off-target' effects that protect against non-mycobacterial pathogens, and has been considered for its possible role in combating COVID-19 [7]. In this edition, Aksu *et al.* retrospectively studied the records of patients hospitalized with COVID-19 to determine their disease severity and BCG vaccine history [8]. Using multivariate analysis, age and socio-economic status were determined to be independent risk factors for severe disease, in line with other studies [3,9]. By contrast, BCG vaccine history was not associated with disease severity in this analysis. While this may indicate that BCG vaccine history is not a major determinant of COVID-19 severity, the relatively small size of this data set ($n = 123$ hospitalized patients) may require confirmation in larger-scale population studies.

The humoral immune response to SARS-CoV-2 may be a crucial determinant of viral clearance and could act as a correlate of protection following natural infection or vaccine-mediated immune responses. Additionally, antibody testing

is essential for understanding the rate of infection in the population through the use of public health serosurveillance, and therefore accurately determining populations at risk of severe disease and the absolute case fatality rate. As such, studies of the nature, scale and longevity of the antibody response to SARS-CoV-2 are essential. In this issue, Huang *et al.* monitored the immunoglobulin (Ig)G, IgM and IgA responses in longitudinal serum samples from 43 COVID-19 patients using a recombinant Spike-protein-based capture immunoassay [10]. This demonstrated that the scale of these antibody responses increased with disease severity, in agreement with other reports, and were largely well correlated between immunoglobulin isotypes. Furthermore, Huang *et al.* demonstrate that IgA, which has been relatively understudied thus far, may be detectable relatively early in the process of COVID-19, potentially offering a better serological marker of infection than other isotypes. This work highlights the urgent need for improved understanding of the serological response to SARS-CoV-2, for both diagnostic testing and public health serosurveillance studies.

It is widely considered that an effective vaccine against SARS-CoV-2 will be required to enable the lifting of social and workplace restriction imposed due to COVID-19. Here, Tregoning *et al.* provide a timely and thorough summary of vaccine approaches in development and in clinical trials for SARS-CoV-2 [11]. There are currently > 200 vaccines in development and 39 clinical trials ongoing globally, after less than 1 year since the first identification of SARS-CoV-2. This rate of global vaccine development is unprecedented, reflecting the urgency of this task. It is humbling to consider how much slower this response might have been without the global co-ordination of vaccine efforts and the early implementation of key technologies such as whole viral genome sequencing, which greatly expedited these efforts [12]. Some SARS-CoV-2 vaccine candidates utilize platform technologies common with many other vaccines, including inactivated virions, viral protein or peptide vaccines or attenuated viruses. Other approaches, such as vectored vaccines (e.g. the Oxford/AstraZeneca candidate ChAdOx1 nCoV-19 [13]) and self-amplifying RNA vaccines (e.g. self-amplifying RNA encoding pre-fusion stabilized Spike protein [14]), are more novel approaches to human vaccination. In addition to the immunogenicity, safety and efficacy of these vaccines, a crucial consideration is the ability to produce each vaccine candidate at the scale required for global immunization. As discussed by Tregoning *et al.*, this potential bottleneck in vaccine manufacture and deployment are important considerations for the probable global success of each candidate, as safety and efficacy data become available. These considerations are also crucial for preparedness against future pandemics. COVID-19 has highlighted the pressing need for vaccine platforms that can rapidly adapt to novel pathogens and be produced on a scale suitable for global immunization. Support for such basic

scientific work in the future could greatly expedite vaccine delivery in the face of novel pathogens.

Vaccines against SARS-CoV-2 may need to be selectively given to at-risk populations, including older adults and patients with diabetes [9], especially if the availability of vaccine doses is limited. Our understanding of which comorbidities might be associated with greater COVID-19 severity has developed substantially. One early consideration was the risk presented by the use of immunomodulatory therapies for autoimmune diseases and cancer. As presented in this issue by Baker *et al.*, depletion of B cells using anti-CD20 antibodies has been regarded as a potential aggravating factor that could enhance COVID-19 severity [15]. While data do not currently support this increase in severity, the possible impact upon antibody responses to infection, and the immunity generated by natural infection or vaccination, has yet to be determined. Baker *et al.* usefully extract information on the role of one anti-CD20 therapy, ocrelizumab, in inhibiting vaccine responses, measured by generation of specific antibodies. This provides further evidence that anti-CD20 therapies, and possibly other therapies that inhibit the adaptive immune system, might limit vaccine immunogenicity. This issue is likely to become an important consideration if natural or vaccine-induced immunity is dependent upon an antibody response, or may be of lesser significance if immunity is largely mediated by cytotoxic cells. The risks and benefits in temporarily pausing immunomodulatory therapies on the response to SARS-CoV-2 vaccines will require careful consideration as these vaccines emerge, and our understanding of COVID-19 severity in these patient populations evolves.

After nearly a year of research on SARS-CoV-2, great strides have been made in our understanding and ability to combat this pathogen. However, with many vaccine efficacy studies and therapeutic trials still under way, it is as important as ever that we continue to develop our understanding of this disease. Rationally designed therapeutic and prophylactic interventions, benefiting from the wealth of basic and translational research now available, may yet make major impacts on this pandemic.

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Disclosures

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