

The first 12 months of COVID-19: a timeline of immunological insights

Thiago Carvalho, Florian Krammer¹ and Akiko Iwasaki²

Abstract | Since the initial reports of a cluster of pneumonia cases of unidentified origin in Wuhan, China, in December 2019, the novel coronavirus that causes this disease — severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) — has spread throughout the world, igniting the twenty-first century's deadliest pandemic. Over the past 12 months, a dizzying array of information has emerged from numerous laboratories, covering everything from the putative origin of SARS-CoV-2 to the development of numerous candidate vaccines. Many immunologists quickly pivoted from their existing research to focus on coronavirus disease 2019 (COVID-19) and, owing to this unprecedented convergence of efforts on one viral infection, a remarkable body of work has been produced and disseminated, through both preprint servers and peer-reviewed journals. Here, we take readers through the timeline of key discoveries during the first year of the pandemic, which showcases the extraordinary leaps in our understanding of the immune response to SARS-CoV-2 and highlights gaps in our knowledge as well as areas for future investigations.

At the beginning of the coronavirus disease 2019 (COVID-19) pandemic, the immunology of coronavirus infections was not at the forefront of research in most laboratories. However, over the past 12 months, we have gained incredible insights into the innate and adaptive immune responses against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and have brought to fruition the development of multiple vaccines against the virus. The COVID-19 pandemic has caused a seismic shift in the speed at which scientific research is conducted and shared. Many laboratories uploaded their yet-to-be peer-reviewed studies on preprint servers, enabling the public sharing of information in a matter of days, instead of the months that it often takes for peer-reviewed publication, and scientists often shared unpublished data on social media platforms. In addition, major media outlets began covering the preprint studies instead of waiting for the peer-reviewed publication.

As such, we have opted to use the preprint date, where available, instead of the official publication date for the chronology of the studies that we highlight in our timeline of key discoveries during

the first year of the pandemic (FIG. 1), noting however that the peer-reviewed publication details are given in the reference list. In order to keep the timeline coherent with respect to the topics covered, once we introduce a study on a particular topic, we also include the discussion of other relevant studies that came later. Thus, not all of the text follows a strict chronological order with respect to when studies were posted or published.

Finally, in an article of this length, it is not possible to include everything that we have learnt and some of the false turns that have been taken. Inevitably, we have been selective based on the common themes that we feel are the most important take-home messages from the past year; therefore, to some extent, this article represents a personal perspective of our highlights of what we have learnt so far about the immunology of COVID-19. We apologize to all colleagues whose work we could not discuss owing to space constraints.

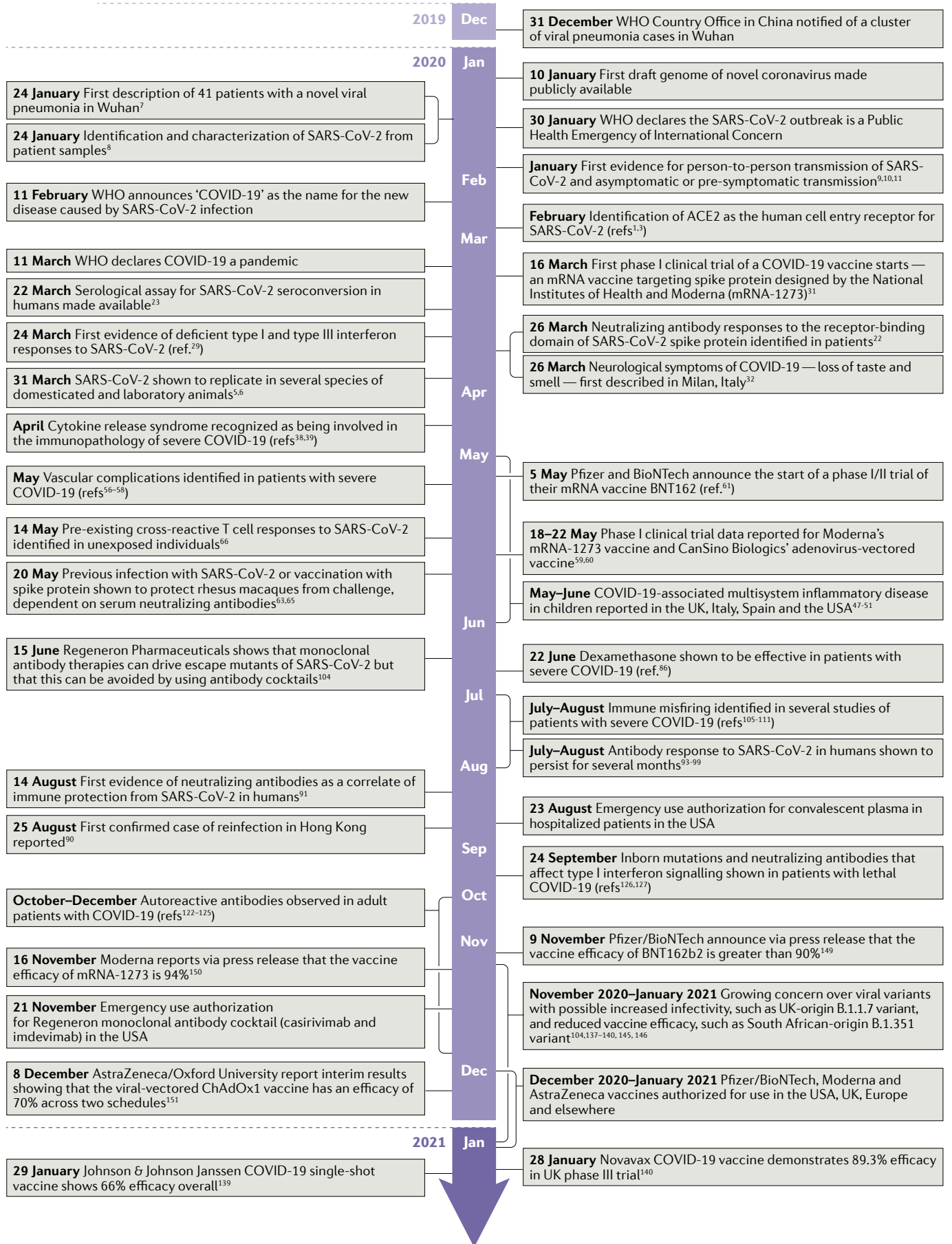
January–February 2020

Identification of SARS-CoV-2. On the last day of 2019, the WHO Country Office in China was notified of a cluster of cases of a

novel viral pneumonia of unknown cause in Wuhan City, Hubei province. Less than 2 weeks later, on 10 January 2020, the first draft genome of the new coronavirus thought to be responsible for these cases was made public via a blog post and then on GenBank (Accession number MN988668). The new coronavirus likely originated in bats, where its closest relative described to date, RaTG13, is found¹. The virus, later termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the third betacoronavirus to cause an outbreak in humans this century (BOX 1). The SARS-CoV outbreak in 2002–2003 that spread to 29 countries was controlled with less than 9,000 cases and approximately 800 deaths worldwide. The Middle East respiratory syndrome (MERS) outbreak that was first reported in Saudi Arabia in 2012 was caused by another coronavirus of zoonotic origin (MERS-CoV). MERS cases continue to be reported in the region but they number fewer than 3,000 in total.

Identification of the viral entry receptor

ACE2. An important early finding was that SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as a receptor to enter host cells. Zhou et al.¹ from the Wuhan Institute of Virology showed, in early February 2020, that the ability of SARS-CoV-2 to infect cells in vitro was dependent on the expression of ACE2, the cell-surface molecule that had previously been shown to be the receptor for SARS-CoV (REF.²). The interaction between SARS-CoV and ACE2 was known to be mediated by the receptor-binding domain (RBD) of the SARS-CoV spike protein. The use of ACE2 as the receptor for SARS-CoV-2 was confirmed soon after by Letko et al.³. The McLellan laboratory quickly followed with the structural analysis of the interaction, revealing the molecular interactions between the RBD of SARS-CoV-2 and human ACE2 (REF.⁴). We now know that many neutralizing antibodies elicited by SARS-CoV-2 infection bind to the RBD and prevent its interaction with ACE2 on host cells, effectively neutralizing the virus. ACE2 is also a determinant of host tropism and, in March 2020, it was shown that SARS-CoV-2 can replicate well in several domesticated animals, including cats and ferrets, as well as in certain laboratory animals^{5,6}.



◀ Fig. 1 | **Timeline of key discoveries in the immune response to SARS-CoV-2.** In the case of data that were posted as preprints before peer-reviewed publication, the timeline follows the date of the preprint but the reference list details the peer-reviewed journal publication. ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Early descriptions of COVID-19. The first description of 41 patients with what we now term COVID-19 (the name for the new disease being announced by the WHO on 11 February 2020) in Wuhan listed the most common symptoms at onset of disease as fever, cough, myalgia and fatigue⁷. All patients developed pneumonia, 13 required treatment in an intensive care unit (ICU) and 6 had died by the time the study was published on 24 January 2020 (REF.⁷). Huang et al.⁷ also reported that 26 of the 41 patients had lymphopenia and that those admitted to the ICU had increased plasma levels of cytokines and chemokines, specifically IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (GCSF; also known as CSF3), CC-chemokine ligand 2 (CCL2; also known as MCP1) and tumour necrosis factor (TNF). On the same day (24 January 2020), Zhu et al. reported the isolation of the novel coronavirus from the bronchoalveolar lavage fluid (BALF) of three patients (one of whom died) in Wuhan⁸.

Huang et al.⁷ had raised concerns about the potential for person-to-person transmission, and a study of a family cluster in Shenzhen, China, by Chan et al.⁹ showed that five infected individuals who had recently returned from Wuhan most likely infected a sixth family member who had not travelled to the affected region. A cluster of cases in which the first symptomatic patient was a German businessman who had previously had a meeting with a business partner from Shanghai, China, pointed to another disturbing characteristic of COVID-19: that individuals who were not yet showing symptoms (pre-symptomatic) could infect others¹⁰. The epidemiological analysis of 425 laboratory-confirmed cases in Wuhan estimated that the mean incubation period was just over 5 days. The authors estimated that human-to-human transmission of SARS-CoV-2 had been occurring since mid-December 2019 (REF.¹¹). Finally, epidemiological evidence from these early cases indicated that COVID-19 is more likely to affect older males with comorbidities such as chronic

diseases, including cardiovascular and cerebrovascular diseases, endocrine system diseases, digestive system diseases, respiratory system diseases, malignant tumours and nervous system diseases¹². On 30 January 2020, the WHO declared the SARS-CoV-2 outbreak a Public Health Emergency of International Concern.

Thus, by February 2020, less than 2 months after the first reports, the new disease had been named COVID-19 and three key features had been established that set it apart from the previous coronavirus outbreaks: an efficient person-to-person transmission; the strong signs that people could transmit the virus before, or even without ever, showing symptoms; and its longer incubation period of 5.7 days (pooled mean)¹³ than that of SARS-CoV (mean incubation time of 4.0 days)¹⁴ and MERS-CoV (range of incubation times from 4.5 to 5.2 days)¹⁵. By the end of February 2020, COVID-19 had already registered 83,652 cases globally¹⁶, roughly 10 times the global case count of the entire 2002–2003 SARS outbreak.

March 2020

On 11 March 2020, the WHO declared COVID-19 a pandemic.

Antibodies to SARS-CoV-2. One early assumption was that, as is the case for most acute respiratory virus infections, infection with SARS-CoV-2 would induce a neutralizing antibody response. The first data showing antibody responses to SARS-CoV-2 were included in the seminal paper by Zhou et al.¹ published in early February 2020 that characterized patient-derived virus isolates. Additional data, partially already suggesting that the virus could be neutralized by convalescent sera, were published shortly thereafter in March 2020 (REFS^{17–21}). These results

were also confirmed in March 2020 by the isolation of RBD-specific monoclonal antibodies derived from individuals infected with SARS-CoV-2 (REF.²²). Reagents and protocols to better characterize these antibody responses were rapidly created and shared globally²³. In addition, commercial tests for SARS-CoV-2-specific antibodies started to become available^{19,24–27}, leading to serological surveys to determine the spread of the virus and infection fatality rates. Unfortunately, the FDA guidelines for allowing commercial tests to be marketed in the USA were initially very flexible, with a similarly wide use of commercial tests in many countries around the world²⁸, leading to a flood of underperforming assays and confusion over seroprevalence estimates.

Transcriptional profiling of patients with COVID-19.

March 2020 also brought key insights into the pathogenesis of COVID-19. Blanco-Melo et al.²⁹ compared transcriptional responses to SARS-CoV-2 using cell lines, ferrets and samples from patients and found that, compared with other respiratory viruses, the host immune response to SARS-CoV-2 fails to launch a robust type I and type III interferon response while simultaneously inducing high levels of chemokines and pro-inflammatory cytokines. The authors predicted that this lack of interferon responses would enable sustained viral replication and lead to serious SARS-CoV-2 infection. This prediction was later confirmed by multiple groups using animal models and human samples (see July 2020 and September–October 2020).

Early vaccine development. The ability of the spike protein of SARS-CoV-2, particularly the RBD, to induce neutralizing antibody responses makes it the prime target for vaccine development³⁰. The first clinical study of a vaccine targeting

Box 1 | Human coronavirus OC43 and the 'Russian flu' pandemic

A pandemic of respiratory disease known as the 'Russian flu' occurred in 1889 and 1890 and caused approximately one million deaths globally. This pandemic has been speculated to be caused by an influenza A virus. However, a study from 2005 showed that OC43, which is a human betacoronavirus, diverged from the closely related bovine coronavirus during the time frame of the 'Russian flu'¹⁵⁹. This makes it plausible that OC43 — which is still circulating in humans, causing common colds — was the causative agent of this pandemic. Interestingly, it has been shown, at least in one case, that bovine coronaviruses can infect humans¹⁶⁰. The other three endemic coronaviruses in humans — NL63, 229E (both alphacoronaviruses) and HKU1 (betacoronavirus) — are speculated to also be of zoonotic origin¹⁶¹. NL63-like and 229E-like viruses have been found in bats^{162–164} and viruses related to HKU1 have been found in rats¹⁶⁵. This suggests that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is not the first coronavirus to cause a pandemic and, given the frequency of outbreaks (SARS-CoV in 2003 and MERS CoV since 2012), it is likely not the last one. Importantly, studying circulating human coronaviruses and their origin will likely inform us better about the future of SARS-CoV-2 in the human population as well as about future pandemics with other coronaviruses.

the spike protein (in this case an mRNA vaccine), designed by the Vaccine Research Center at the National Institutes of Health, USA, and by the US pharmaceutical and biotechnology company Moderna, started on 16 March 2020 in Seattle, barely more than 2 months after the genomic sequencing of SARS-CoV-2 (REF.³¹).

April 2020

Neurological symptoms associated with COVID-19. As COVID-19 symptoms and complications expanded beyond pneumonia, April 2020 saw a surge in reports of neurological symptoms. In late March 2020, physicians in Milan, Italy, described that 20 of 59 patients hospitalized with COVID-19 reported a loss of taste or smell³². A study published on 22 April 2020 including 202 patients, also in Northern Italy, found that 64% of outpatients with mild COVID-19 symptoms reported a loss of taste or smell³³. A later study, based on tracking via a smartphone app, found that 65% of those who tested positive for SARS-CoV-2 reported a loss of taste and/or smell compared with 22% of those who tested negative³⁴. Broader neurological complications were described in a retrospective study of 214 patients with COVID-19 in Wuhan, which found that 78 (36.4%) of these had neurological complications, with acute cerebrovascular disease, conscious disturbance and skeletal muscle injury being the most frequent complications in severe cases³⁵. Patients with COVID-19 who have acute respiratory distress syndrome also have high rates of delirium and encephalopathy³⁶. Although the precise mechanisms of these neurological symptoms are unknown, infection of the central nervous system by SARS-CoV-2 and inflammation are likely to have a role³⁷.

Immunopathology of COVID-19 and immunomodulatory therapy. The role of the immune system not only in host protection but also in the pathogenesis of severe COVID-19 was highlighted by similarities with the systemic inflammatory syndromes of haemophagocytic lymphohistiocytosis (HLH) and cytokine release syndrome (CRS)^{38,39}. IL-6 is central to the pathogenesis of both HLH and CRS and, by early April 2020, several studies had shown a correlation between IL-6 levels and adverse outcomes in patients with COVID-19 (REF.⁴⁰). In addition, Chen et al.³⁸ showed that patients who were critically ill had significantly higher IL-6 concentrations than patients with moderate disease.

These similarities between COVID-19 and both HLH and CRS made the IL-6 pathway an early target of both compassionate use therapeutic interventions and clinical trials in COVID-19, largely based on the success of monoclonal antibodies that target the IL-6 receptor (such as tocilizumab) in treating chimeric antigen receptor T cell-induced CRS in oncology⁴¹. However, by the end of April 2020, Sanofi and Regeneron had halted the phase II/III trial of their IL-6 receptor-targeting monoclonal antibody, sarilumab, in patients with severe COVID-19 (REF.⁴²), announcing that they would focus on trialling a higher dose for patients in critical condition. Although multiple compassionate use, observational and retrospective studies reported beneficial effects of tocilizumab in patients with COVID-19, randomized controlled trials have not shown major effects on survival⁴³. However, it should be noted that two recent clinical trials (reported in January 2021) have posted more positive results. In one study of 389 patients hospitalized with COVID-19-associated pneumonia but not yet undergoing mechanical ventilation, the tocilizumab group had a 12.0% rate of progression to mechanical ventilation or death versus 19.3% in the placebo group⁴⁴. A second study of patients with COVID-19 in intensive care found that mortality for 397 individuals in the placebo group was 35.8% compared with 28% in 350 patients treated with tocilizumab and 22% in 45 patients who received sarilumab⁴⁵. Based on these new data, the Medicines & Healthcare products Regulatory Agency (MHRA) in the UK issued an alert on 8 January 2021 encouraging organizations to consider prescribing either tocilizumab or sarilumab for the treatment of patients admitted to the ICU with COVID-19 pneumonia⁴⁶.

May–June 2020

Multisystem inflammatory syndrome in children. Until May 2020, children infected with SARS-CoV-2 were thought to have only mild or asymptomatic infections. However, studies began to emerge showing that a small subset of children who recovered from SARS-CoV-2 infection had, what were described at the time as, severe Kawasaki disease-like symptoms 4–6 weeks after recovery from the initial infection, with reports emerging from the UK^{47,48}, Italy⁴⁹, Spain⁵⁰ and the USA⁵¹. Kawasaki disease is a vasculitis of the medium-sized arteries, with highest incidence in children younger than 5 years of age. Despite decades of research, the cause of Kawasaki disease

is unknown⁵², although some evidence suggests that autoreactive antibodies induced by an acute viral infection could lead to inflammation and vascular damage. However, unlike Kawasaki disease, post COVID-19 hyperinflammatory responses in children affect an older age group (infants to teens) and there are distinct symptoms, including a more diffuse presentation involving intestine, myocardium and brain⁵³. The disease has been renamed several times during 2020 to now be called multisystem inflammatory syndrome in children (MIS-C). A comparison of MIS-C with acute COVID-19 and Kawasaki disease (first posted in preprint form in August 2020) noted important differences. IL-17A and its accompanying signalling pathway drive Kawasaki disease but not MIS-C⁵³. By contrast, patients with MIS-C develop a distinct set of autoantibodies to MAP2K2 and to three members of the casein kinase family (CSNK1A1, CSNK2A1 and CSNK1E1)⁵³. In addition, another study preprinted in July 2020 found that antibodies to La (the autoantigen of systemic lupus erythematosus (SLE) and Sjogren's disease) and to Jo-1 (the autoantigen of idiopathic inflammatory myopathies) were found in patients with MIS-C⁵⁴, suggesting the autoimmune nature of this syndrome. Consistently, patients with MIS-C have increased levels of IgG⁺ plasmablasts in circulation and increased levels of IgG capable of binding to human cardiac microvascular endothelial cells⁵⁵.

COVID-19 causes vascular damage in the lung. Within the respiratory tract, patients with severe COVID-19 have evidence of vascular damage according to autopsy findings first published in May 2020 (REF.⁵⁶). In addition, later studies showed that there was increased expression of the gene encoding bradykinin (an inflammatory vasodilator) by cells in BALF. A critical imbalance in the renin–angiotensin system, which regulates blood pressure, fluid and electrolyte balance and systemic vascular resistance, was observed, including the reduced expression of ACE and the increased expression of ACE2, renin, angiotensin, kinogen and bradykinin receptors⁵⁷. In addition, neutrophil infiltration and neutrophil extracellular traps were found inside the micro-vessels of autopsy samples from patients with COVID-19. The intravascular aggregation of neutrophil extracellular traps leads to rapid occlusion of the affected vessels, disturbed microcirculation and organ damage⁵⁸.

Phase I clinical trial results for COVID-19 vaccines. In May 2020, the Chinese vaccine company CanSino Biologics reported the first clinical trial results of a COVID-19 vaccine — an adenovirus type 5 (Ad5)-based vector expressing SARS-CoV-2 spike glycoprotein⁵⁹. The vaccine was shown to be safe, with no severe adverse reactions reported, and to induce specific antibody and T cell responses in most participants. However, a caveat was the frequency of pre-existing immunity to Ad5 (anti-vector immunity), which correlated with poorer T cell responses *in vitro*⁵⁹. Also in May 2020, Moderna announced via a press release that its own RNA-based vaccine, mRNA-1273, was both safe and immunogenic⁶⁰. At the beginning of the month, Pfizer and BioNTech had also announced via press release that they were launching human phase I/II trials of four RNA-based COVID-19 vaccines⁶¹. Importantly, several mRNA-based vaccines against infectious diseases had, by this point, advanced to phase I and II trials for cytomegalovirus, HIV-1, rabies, Zika virus and influenza virus. Although published results were scarce, the overall safety profile of these vaccines was already thought to be acceptable⁶².

Correlates of immune protection. The interpretation of the vaccine studies is complicated by a lack of clear correlates of protection against betacoronavirus infections in humans. In May 2020, Chandrashekar et al.⁶³ showed that previous infection with SARS-CoV-2 protected rhesus macaques challenged 35 days after the initial infection. The authors did not observe full sterilizing immunity, as four of nine animals had detectable levels of viral RNA in the upper respiratory tract after challenge, although the levels declined rapidly and viral RNA was detected in only two BALF samples very transiently; protection correlated with strong humoral responses⁶³. Deng et al.⁶⁴ showed that rhesus macaques were completely protected from SARS-CoV-2 rechallenge 28 days after primary infection. In another study also released in May 2020, a set of SARS-CoV-2 DNA vaccines encoding six different variants of the spike protein were tested in rhesus macaques. Animals were immunized intramuscularly (without adjuvant), boosted at week 3 and challenged with SARS-CoV-2 at week 6. Vaccinated animals showed a significant reduction in viral load in both nasal swabs and BALF and there was an inverse correlation between serum neutralizing antibody titres and viral load⁶⁵.

Cross-reactive immunity to SARS-CoV-2. A key area of public interest focused on whether there is pre-existing immunity to SARS-CoV-2 in human populations and whether such pre-existing responses would confer protective immunity. On 14 May 2020, Grifoni et al.⁶⁶ published a key study showing that around 30–50% of people have pre-existing CD4⁺ T cell-mediated immunity against SARS-CoV-2 antigens; cross-reactive CD4⁺ T cells were specific for the spike, nsp14, nsp4 and nsp6 proteins of SARS-CoV-2. This and other studies over the next couple of months^{66–70} showed that the magnitude of T cell responses to SARS-CoV-2 in unexposed individuals was in general lower than in those individuals who were exposed to the virus. It was proposed that these pre-existing T cells may have been generated in response to seasonal human coronaviruses (HCoVs). These studies were used by some media outlets in support of the message that many humans already have immunity to SARS-CoV-2 and, by extension, that herd immunity exists and protects against COVID-19. Scientists quickly responded by explaining the findings and implications of these studies to clarify confusion⁷¹.

A study by Ng et al.⁷², first posted as a preprint in May 2020, detected cross-reactive antibodies against SARS-CoV-2 in pre-pandemic sera from the UK, particularly in children and adolescents 6–16 years of age, having a high seroprevalence of 62%. Cross-reactive antibodies were found to target conserved regions of the spike protein within the S2 domain and had neutralizing activities *in vitro*⁷². However, another study that examined pre-pandemic sera from PCR-confirmed cases of HCoV-OC43, HCoV-NL63 or HCoV-229E infection in Scotland found no cross-neutralizing antibodies to SARS-CoV-2 (REF.⁷³). Furthermore, another study of pre-pandemic sera from children and adults in Pennsylvania, USA, found that ~23% of these individuals had non-neutralizing antibodies that cross-reacted with SARS-CoV-2 spike and nucleocapsid proteins. However, these antibodies were not associated with protection against SARS-CoV-2 infection or hospitalization⁷⁴. Further research is needed to understand whether pre-existing cross-reactive antibodies and T cells can confer protection in different age groups and/or geographical locations.

In addition to cross-reactive adaptive immunity, O'Neill and Netea⁷⁵ argued that innate immunity could be 'trained' to combat infectious diseases, including

COVID-19. Vaccination with bacillus Calmette–Guérin (BCG), a live attenuated vaccine against tuberculosis, reduces childhood mortality caused not only by tuberculosis but also owing to unrelated infections. This non-specific effect is mediated by metabolic and epigenetic rewiring in innate immune cells, which leads to increased transcription and improved host defence. Currently, there are 22 randomized clinical trials ongoing to test whether BCG vaccination can confer protection against SARS-CoV-2 infection.

Dexamethasone effective as COVID-19 therapy. Various antivirals such as remdesivir, convalescent plasma and anti-inflammatory agents, including tocilizumab, hydroxychloroquine and high-dose steroids, have been the subject of randomized clinical trials (RCTs) for COVID-19. Unfortunately, not all of these trials showed significant benefit in reducing disease severity, duration of hospitalization or death rate. Hydroxychloroquine, which was widely used early during the pandemic, was shown to have no significant benefits in RCTs as pre-exposure prophylaxis⁷⁶, as post-exposure prophylaxis^{77,78}, in patients with mild disease who were not hospitalized⁷⁹, in mild to moderate disease^{80,81}, or in patients hospitalized with moderate or severe disease^{82,83}. By contrast, a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection showed that mortality rates were 6.7% with remdesivir and 11.9% with placebo by day 15 after treatment and 11.4% with remdesivir and 15.2% with placebo by day 29 (REF.⁸⁴). It should be noted, however, that the WHO's Solidarity Trial failed to find significant changes in either mortality rate or hospitalization time in patients treated with remdesivir⁸⁵.

Encouraging news for therapy came from the effectiveness of dexamethasone in patients who were hospitalized. In the RECOVERY Collaborative Group trial, a total of 2,104 patients were randomly assigned to receive dexamethasone and 4,321 were assigned to receive usual care⁸⁶. The use of dexamethasone for up to 10 days resulted in lower mortality at 28 days than usual care in patients who were receiving invasive mechanical ventilation and in those who were receiving oxygen. However, there was no evidence that dexamethasone provided any benefit, and indeed may lead to possible harm, among patients who were

not receiving respiratory support. These results support the idea that hyperimmune stimulation is the basis of severe COVID-19 and that immunosuppressive therapy only benefits patients with severe disease. Furthermore, these results formalized the concept of stage-specific COVID-19 disease interventions⁸⁷.

Antibody quality, longevity and

protection. In June of 2020, Long et al.⁸⁸ published a report showing that 40% of asymptotically infected individuals lost their (mostly) anti-nucleoprotein antibody titres in a non-quantitative assay over an 8-week period. Although they also showed that neutralizing antibody titres were stable over that period, the study was hyped up by the media and caused panic in the population. In addition, a small number of reinfections were starting to be reported^{89,90}. Of course, this raised the question of whether infection could protect from reinfection and, if so, which type of immune response correlates with protection and how easily could this response be overcome by viral escape mutants. A preprint published in August 2020, showing that all individuals who had neutralizing antibodies to SARS-CoV-2 were protected from reinfection during a SARS-CoV-2 outbreak with a high attack rate on a fishing vessel, provided the first evidence for neutralizing antibodies as a correlate of protection in humans⁹¹. A recent study has confirmed that antibodies indeed correlate with protection from reinfection⁹². In addition, the question of durability of the antibody response to SARS-CoV-2 was addressed by several studies in late July and August 2020, which showed that the antibody response is indeed normal and long lasting^{93–99}.

Analysis of the B cells specific for SARS-CoV-2 spike protein in a single patient 21 days after the onset of clinical disease found only a small number of somatic mutations, even though the patient had high serum titres of anti-spike antibodies¹⁰⁰. Several other groups had reported a low frequency of somatic mutations in SARS-CoV-2 neutralizing antibodies^{101–103}, which suggests that germline-encoded B cell receptor sequences have a sufficiently high affinity for the spike protein to limit antigen access to the germinal centre.

June 2020 also brought important advances for antibody therapeutics. Baum et al.¹⁰⁴, from Regeneron Pharmaceuticals, published a very detailed paper about the therapeutic monoclonal antibodies that they had in development and the viral escape that these monoclonal antibodies could drive. It is well

known that, for most RNA viruses, escape mutants can be relatively quickly selected under pressure from a single monoclonal antibody but that using two monoclonal antibodies avoids this issue. This was confirmed in the Regeneron study, which also showed the detailed escape mutagenesis¹⁰⁴. The Regeneron study had two important implications. First, their monoclonal antibody cocktail received emergency use authorization from the FDA later in the year (21 November 2020). Second, the detailed mutagenesis that was carried out helped us to quickly understand the natural variants that were to emerge later — for example, with mutations at position 484 (present in the South African-origin variant lineage B.1.351) or the Y453F mutation in mink.

July 2020

Immunopathology of COVID-19 better

defined. A study that measured cytokine levels in 1,484 patients with COVID-19 in New York, USA, found that high serum levels of IL-6, IL-8 and TNF at the time of hospitalization were strong and independent predictors of patient mortality¹⁰⁵. Highly heterogeneous immunotypes were found in patients with COVID-19. Among these, patients who had very little activation of T cells or B cells had milder disease, whereas those who had a hyperactivation of CD4⁺ T cells and CD8⁺ T cells had worse disease severity¹⁰⁶. Severe disease was characterized by increased cytokine levels and activated CD4⁺ T cells and CD8⁺ T cells with an effector memory or exhausted phenotype¹⁰⁶. A single-cell RNA-sequencing analysis of immune cells in BALF showed that patients with moderate COVID-19 had increased numbers of clonally expanded CD8⁺ T cells compared with patients with severe disease¹⁰⁷. Cytokine analysis of patients with COVID-19 in several other studies also showed increased levels of pro-inflammatory cytokines and chemokines (such as CXCL10, IL-6 and IL-10), of the inflammasome-dependent cytokines (IL-18 and IL-1 β) and of interferons (IFN α , IFN γ and IFN λ) in severe disease^{29,80,108}. The top biomarkers for predicting mortality from a longitudinal analysis were IL-18 and IFN α ¹⁰⁹. In addition to these soluble factors, severe COVID-19 was characterized by dysregulated immune cell composition, with increased numbers of inflammatory monocytes, plasmablast-like neutrophils¹¹⁰ and eosinophils¹⁰⁹. Among all peripheral blood cell types, these granulocytes were most associated with mortality in patients with COVID-19 (REF.¹¹¹).

Impact of COVID-19 on germinal centres.

Kaneko et al.¹¹² examined thoracic lymph nodes from deceased patients with COVID-19 and compared them to those of patients who had succumbed to non-COVID-19-related causes. Lymph nodes and spleens from patients with COVID-19 had only one-third of the total T cell and B cell numbers when compared with controls and germinal centres were absent. Kaneko et al.¹¹² attributed the germinal centre defect to impaired differentiation of BCL-6⁺ T follicular helper (T_{FH}) cells, which were also greatly reduced in number, although other studies have not replicated any reduction in T_{FH} cells or germinal centre responses in patients with severe COVID-19. Consistent with Woodruff et al.¹¹³, Kaneko et al.¹¹² also reported increased levels of extrafollicular IgD⁺CD27⁻ B cells, which are also found in autoimmune diseases such as SLE, in their COVID-19 post-mortem lymph node and spleen samples. The authors speculate that the loss of germinal centres may be associated with increased TNF levels in patients with severe COVID-19. By contrast, Juno et al.¹¹⁴ had previously reported robust levels of circulating T_{FH} cells that recognize SARS-CoV-2 spike protein but much lower levels of circulating T_{FH} cells recognizing the RBD. A study of a lipid nanoparticle-mRNA vaccine encoding SARS-CoV-2 spike protein in mice showed very efficient induction of germinal centres and the generation of antigen-specific T_{FH} cells, suggesting that vaccination may outperform natural immunization in some cases¹¹⁵.

August 2020

Convalescent plasma therapy. Convalescent plasma, which was one of the first medications to be used for compassionate treatment of patients, received an emergency use authorization from the FDA on 23 August 2020. In March 2020, Shen et al.¹¹⁶ had reported that five patients with COVID-19 with acute respiratory distress syndrome showed clinical improvement after receiving convalescent plasma, with three being discharged. However, an open-label, RCT of convalescent plasma in 103 patients with severe or life-threatening COVID-19 failed to show significant benefits, as reported in June 2020 (REF.¹¹⁷). Furthermore, a multi-centre, open-label trial of convalescent plasma in India failed to show any benefits in terms of clinical improvement or 28-day mortality when compared with standard of care in a study of 464 patients with moderate COVID-19 disease. However, the study had several limitations, most prominent being that it did not measure anti-SARS-CoV-2

antibody titres in donor plasma¹¹⁸. In September 2020, a retrospective study of 39 patients with severe or life-threatening COVID-19 at Mount Sinai Hospital, New York, USA, showed a positive effect of convalescent plasma treatment when donor sera were screened for anti-SARS-CoV-2 spike IgG titres of $\geq 1:320$ (REF.¹¹⁹). In line with this, an RCT of convalescent plasma with high IgG titres against SARS-CoV-2 in older adult patients within 72 hours after the onset of mild COVID-19 symptoms was found to reduce severe respiratory disease¹²⁰.

The efficacy of most therapies for COVID-19 has been shown to vary greatly across disease stages. In addition to disease stage, convalescent plasma therapy is further complicated by the diverse antibody titres of donor sera, the lack of standardized methods for measuring neutralizing antibody titres, and onerous requirements for both collection and transfusion of plasma. On 15 January 2021, the RECOVERY trial in the UK closed recruitment of patients hospitalized with COVID-19 for convalescent plasma therapy based on preliminary data from 1,873 reported deaths among 10,406 randomized patients, which showed that convalescent plasma therapy showed no significant difference in terms of the primary end point of 28-day mortality¹²¹.

September–October 2020

Autoantibodies in adults with COVID-19.

In addition to children with MIS-C, autoreactive antibodies have also been observed in adult patients with COVID-19. For example, patients were shown to have increased levels of autoantibodies that are found in rheumatic diseases, including antinuclear antibodies and anti-rheumatoid factor antibodies¹²² as well as antibodies to annexin A2 (REF.¹²³). Circulating B cells in critically ill patients with COVID-19 are phenotypically similar to the extrafollicular B cells that were previously identified in patients with autoimmune diseases such as SLE. Interestingly, the frequency of extrafollicular B cells in patients with COVID-19 correlated with the early production of high titres of neutralizing antibodies as well as with inflammatory biomarkers (such as C-reactive protein) and organ damage¹¹³. Using a new tool called Rapid Extracellular Antigen Profiling (REAP), in December 2020, Wang et al.¹²⁴ identified a wide range of autoantigens targeted by antibodies in patients with severe COVID-19. These include antibodies to cytokines, interferons, chemokines and leukocytes, which could directly

affect the nature of antiviral immunity as well as antibodies to tissue-specific antigens expressed in the central nervous system, vasculature, connective tissues, cardiac tissue, hepatic tissue and intestinal tract, which could potentially cause antibody-mediated organ damage¹²⁴. Indeed, autoantibodies have been found in people with long-term symptoms of COVID-19 (long COVID) months after infection¹²⁵. Currently, it is unknown how long these autoantibodies persist and whether they can lead to autoimmune disease or whether autoantibodies have a pathogenic role in long COVID.

Importance of type I interferon in COVID-19.

While we were learning about the immunopathogenesis of severe COVID-19 over the summer months, the innate immune responses that protect against disease remained unclear. In particular, the role of key innate viral sensors and antiviral cytokines (type I and type III interferons) in controlling virus replication and disease was unknown. Two studies from Casanova and collaborators first published on 24 September 2020 showed, unequivocally, that type I interferon induction and signalling have key roles in preventing lethal COVID-19. They found that either inborn mutations in interferon induction and signalling¹²⁶ or neutralizing antibodies to type I interferons¹²⁷ predispose patients to life-threatening COVID-19.

Zhang et al.¹²⁶ found that 23 of 659 (3.5%) patients with severe COVID-19 had deleterious mutations in 8 loci that render them incapable of producing or responding to type I interferon. By contrast, only 1 of 534 patients with either asymptomatic or mild COVID-19 carried a heterozygous loss-of-function mutation at one of these loci (*IRF7*). Combined with a report of severe COVID-19 infection in four young male patients who have loss-of-function *TLR7* mutations¹²⁸, these two studies show that inborn errors in innate sensors or their downstream interferon signalling pathways are associated with severe COVID-19. Bastard et al.¹²⁷ found that 135 of 987 (13.7%) patients with severe COVID-19 had antibodies to IFN α , IFN ω or both, a finding that was later confirmed by another study¹²⁴. Notably, 94% of the patients were men. These autoantibodies had interferon-neutralizing activity in vitro. By contrast, none of the 663 patients with asymptomatic or mild COVID-19 and only 4 of the 1,227 (0.3%) healthy donors had auto-antibodies to type I interferon. Collectively, these studies show the

devastating consequences of lack of type I interferons in COVID-19.

How do these results fit with other reports showing protective versus pathogenic roles of type I and type III interferons in COVID-19 (FIG. 2)? Although interferons are highly potent at blocking SARS-CoV-2 replication, SARS-CoV-2 has an arsenal of evasion mechanisms to block the induction of endogenous interferons and interferon receptor signalling^{129,130}. This reduced early interferon response can lead to imbalanced host immune responses and to an inability to clear the virus²⁹. Ultimately, this leads to the prolonged increased levels of interferons and interferon-stimulated genes that have been observed in severe COVID-19 in many studies^{109,131–133} although not in others¹³⁴. Furthermore, an increased level of IFN α is a biomarker for mortality¹⁰⁹. These results suggest pathological roles of delayed and prolonged type I and type III interferon responses in COVID-19.

By contrast, a robust early interferon response is likely essential in controlling COVID-19. For example, a double-blind, placebo-controlled trial conducted in the UK evaluated inhaled IFN β 1a (once daily for up to 14 days) in non-ventilated patients hospitalized with COVID-19. Compared with the patients receiving placebo ($n = 50$), the patients receiving inhaled IFN β 1a ($n = 51$) had greater odds of improvement and recovered more rapidly from SARS-CoV-2 infection¹³⁵. Consistent with this, an open-label, phase II clinical trial that randomized 127 participants to receive either combination antiviral therapy (IFN β 1a injected subcutaneously every other day for 7 days plus lopinavir–ritonavir) or lopinavir–ritonavir alone showed that participants who received the combination therapy had more rapid clinical improvement and quicker time to viral control¹³⁶. The timing and route of the interferon therapy seem to be key, as an interim report from the WHO Solidarity Trial, an open label trial in which patients of all stages of disease who were hospitalized were randomly assigned to receive subcutaneous IFN β 1a or other repurposed antivirals, showed little or no effect of interferon therapy on overall mortality, initiation of ventilation or duration of hospital stay⁸⁵.

November–December 2020

Virus variants on the rise. November and December 2020 brought much activity regarding both positive and negative developments. In early November 2020, an outbreak of SARS-CoV-2 in Danish mink

farms with spill-over back into humans was reported¹³⁷. The virus seemed to have potentially adapted to mink by introducing a Y453F mutation into the spike protein RBD (in addition to other mutations). This led to the mass culling of mink in Denmark and, as a result, more attention started to be given to variant viruses, including Cluster 5 variants in Europe that carry the N439K mutation in the RBD. Both Y453F and N439K have been shown to affect neutralization by some SARS-CoV-2-specific monoclonal antibodies¹⁰⁴, although other antibodies are unaffected, which makes it unlikely that these two mutations alone would impair vaccine effectiveness.

Additional variants of concern were described in December 2020, such as the UK-origin variant (B.1.1.7), which seems to be more infectious than other variants and is spreading quickly in the UK and elsewhere. This variant carries several mutations, including N501Y in the RBD and a truncation of open reading frame 8 (ORF8)¹³⁸. Although the increase in transmissibility is highly concerning, evidence so far indicates that the current vaccines retain significant levels of

protection against B.1.1.7. Other variants of concern, especially the South African-origin variant B.1.351, which also carries a mutation at position 501 in the RBD (and other mutations at positions 417 and 484), is now shown to reduce the neutralization capacity and efficacy of certain vaccines^{139,140}. Thus, despite the number of neutralizing epitopes, the fact that affinity-matured antibody clonotypes have been shown to be able to cope with variant viruses¹⁴¹ and that it is likely that only low antibody titres are needed for protection from disease^{142–144}, some viral variants of concern are potentially rendering the vaccine candidates less effective in controlling infection and disease. This may be a result of marked changes in amino acids (for example, E484K) that significantly modify the neutralizing epitopes for antibody escape^{145,146} and are mainly focused around the RBD as well as in the N-terminal domain of the spike protein^{101–103,147,148}.

Phase III COVID-19 vaccine trial triumph. November 2020 also brought important updates regarding vaccines. First, on 9 November 2020, Pfizer and

BioNTech announced an interim vaccine efficacy of more than 90% for their mRNA vaccine candidate BNT162b2 (REF.¹⁴⁹). This was followed by an announcement from Moderna on 16 November 2020 stating a 94.5% efficacy for their mRNA vaccine candidate mRNA-1273 (REF.¹⁵⁰). On 10 December 2020, Pfizer then announced meeting all primary end points for BNT162b2 with an overall vaccine efficacy of 95% and of 94% in the high-risk group of 65–85 year olds¹⁴². On 30 November 2020, Moderna released its final efficacy data of 94.1%¹⁴³. Interim results from AstraZeneca of their viral-vectored ChAdOx1 vaccine followed suit on 8 December 2020, showing an overall vaccine efficacy of 70.4% across two cohorts¹⁵¹. Over the course of November and December 2020, further vaccine effectiveness data with viral-vectored and inactivated vaccine candidates were released, ranging in the 80–90% effectiveness range^{152–155}. Some of these vaccines (Sputnik V and CanSino) had already been used in Russia and China, respectively, even before phase III data were available^{156,157}. Both the Pfizer and Moderna vaccines were then authorized for emergency

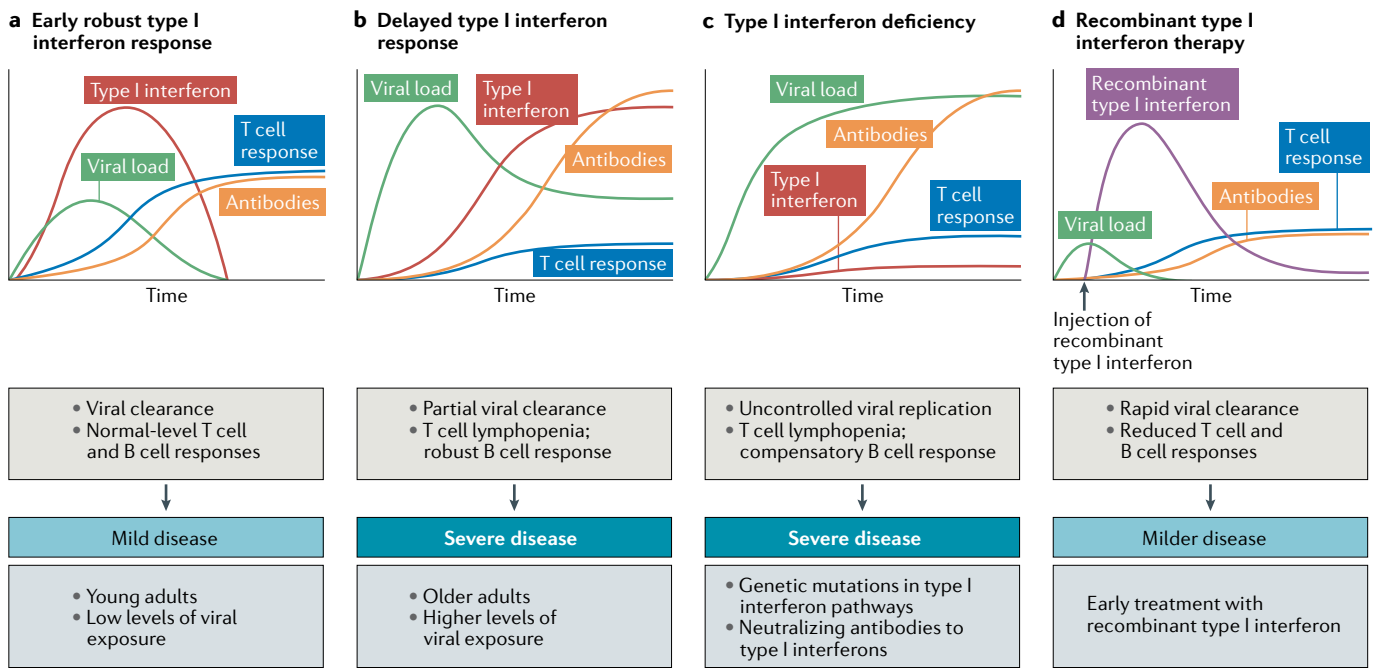


Fig. 2 | A hypothetical figure showing how the timing of interferon responses might control innate and adaptive immunity to SARS-CoV-2. **a** | When the type I interferon response to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is early and robust, the viral load is quickly controlled, resulting in mild disease. This is followed by normal-level T cell and B cell responses. This may occur in young people or after low-dose viral exposure. **b** | When the type I interferon response is delayed or reduced early during infection with SARS-CoV-2, viral replication and spread occur. Severe coronavirus disease 2019 (COVID-19) is accompanied by T cell lymphopenia. Despite this, strong antibody responses are induced. Type I interferon induced late during infection may be detrimental in driving pathological responses. This may occur in older adults or after high-dose viral exposure. **c** | In those individuals who are either genetically or serologically deficient in type I interferon, the replication of SARS-CoV-2 occurs unopposed, causing severe to life-threatening COVID-19. T cell lymphopenia is observed. Compensatory activation of antibody responses occurs but is insufficient to control disease. **d** | Early post-exposure prophylaxis with recombinant type I interferon can reduce the viral load of SARS-CoV-2 and hasten recovery. However, this leads to reduced antigen load and reduced adaptive immune responses.

Box 2 | The impact of the pandemic on scientific progress and disparity

In addition to the dramatic changes in all our lives, the pandemic has had a sizable impact on the way in which science is conducted. Immunologists and virologists who were previously working on basic science have reached out and collaborated with physicians, nurses, epidemiologists, biostatisticians and computer scientists. This 'team science' approach has propelled the rapid discovery of key aspects of the immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; FIG. 1). At the same time, young investigators, women and under-represented scientists were disproportionately affected by the pandemic. They had to take on more responsibilities at home, including childcare and eldercare. For example, a study that looked at submitted manuscripts for all Elsevier journals between February and May of 2020 compared with between February and May of 2018 and 2019, including data on ~6 million academics, showed that women submitted proportionally fewer manuscripts than men during the coronavirus disease 2019 (COVID-19) lockdown. This deficit was particularly pronounced among women at more advanced stages of their career¹⁶⁶. Among research papers on COVID-19 published in 2020, the percentage having a female first author was 19% lower than for papers published in the same journals in 2019 (REF.¹⁶⁷). A study in Brazil found that childless male academics were the least affected with respect to whether they were able to submit manuscripts as planned or meet deadlines, whereas female academics, especially Black women and mothers of younger children, were the most impacted by the pandemic¹⁶⁸. If we do nothing proactively to promote the careers of those affected by the pandemic, the disproportionate impact on gender and racial groups will end up reversing the clock on the progress made in the past few decades towards equal representation in academia.

disease mechanisms and immunology of long COVID and other post-viral diseases. Investment in the scientific research of infectious diseases, immunology and vaccines will be crucial in our ability to be better prepared for future pandemics.

Amidst all this, science was conducted at an unprecedented speed and vaccines were developed, tested and approved within 11 months. These are historical moments for science and immunology. However, women and under-represented scientists were also disproportionately impacted by the pandemic (BOX 2), setting the clock back on the progress made over the years on equity in science. As we begin to control the pandemic with a mass vaccination effort, we must also begin to close the gap created by the pandemic by supporting young and vulnerable scientists throughout the world.

Thiago Carvalho¹, Florian Krammer^{1,2} and Akiko Iwasaki^{1,3,4,5,6}

¹Champlimaud Center for the Unknown, Lisbon, Portugal.

²Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

³Department of Immunobiology, Yale University School of Medicine, New Haven, CT, USA.

⁴Department of Molecular, Cellular and Developmental Biology, Yale University, New Haven, CT, USA.

⁵Howard Hughes Medical Institute, Chevy Chase, MD, USA.

⁶e-mail: akiko.iwasaki@yale.edu

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use in the USA and the Pfizer, Moderna and AstraZeneca vaccines were approved for use in the UK. These vaccines were then approved in several other countries in December 2020 and January 2021. In late January 2021, phase III trial results for the Novavax vaccine were reported showing 89.3% efficacy in the UK¹⁴⁰ and for the Johnson & Johnson Janssen single-shot vaccine showing 66% efficacy¹³⁹.

Although no major safety issues were detected during phase III trials, anaphylactic reactions were observed during rollout for both the Pfizer and Moderna vaccines, first in the UK and later in other countries. These severe allergic reactions seem to occur at a rate of 11 per 1 million vaccinations (Pfizer) and 2.5 per 1 million vaccinations (Moderna) (as per the US Centers for Disease Control and Prevention) and are often associated with a known history of anaphylaxis. The mechanism behind this phenomenon is unknown.

The vaccine efficacy reported in most cases relates to the prevention of symptomatic SARS-CoV-2 infection but not to asymptomatic infections. Based on the results from non-human primate models, most of the vaccines in development, while protecting the lungs and preventing disease, will still allow for replication of the virus in the upper respiratory tract¹⁵⁸. Virus replication was usually lower and of shorter duration in vaccinated animals than in control animals but replication did still occur. The limited data available from Moderna's phase III trial shed first light on this aspect in humans, for which fewer asymptomatic cases were found in the vaccine group after the first vaccination

than in the placebo group, suggesting that the vaccine does confer some protection against infection. Another important point that came to light in both the Pfizer and Moderna studies is that the vaccines start to offer protection approximately 10 days after the first vaccination, when neutralizing antibody titres are still low or even undetectable in many recipients¹⁴², suggesting that high antibody titres might not be needed for protection from disease.

Concluding remarks

The COVID-19 pandemic has brought enormous challenges to humankind. Close to 100 million people have been infected and 2 million people have died worldwide from COVID-19 within the first 12 months of the pandemic according to official figures — with the true numbers likely to be significantly higher. COVID-19 has had a devastating economic impact. This virus has disproportionately affected Black and Latinx populations and has put the spotlight on the deep-rooted racial disparities in health care. There are many lessons to be learned from this pandemic, which will hopefully prepare us better for future pandemics. SARS-CoV-2 will likely not be the last coronavirus to cause a pandemic and it is likely that coronaviruses that are now endemic in humans first caused pandemics resulting in large numbers of deaths (BOX 1). In addition to acute disease, COVID-19 causes long-term symptoms collectively known as long COVID. As millions of people will suffer from long-term debilitating disease even after the pandemic is controlled by vaccination, we must continue to improve our understanding of the underlying

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

The Icahn School of Medicine at Mount Sinai has filed patent applications relating to SARS-CoV-2 serological assays and NDV-based SARS-CoV-2 vaccines, naming F.K. as co-inventor. The authors would also like to note the following, which could be perceived as a conflict of interest for F.K.: he has previously published work on influenza virus vaccines with S. Gilbert (University of Oxford), has consulted for Curevac, Merck and Pfizer (before 2020), is currently consulting for Avimex (Mexico) and Seqirus (Australia), his laboratory is collaborating with Pfizer on animal models of SARS-CoV-2, his laboratory is collaborating with N. Pardi at the University of Pennsylvania on mRNA vaccines against SARS-CoV-2, his laboratory was working in the past with GlaxoSmithKline on the development of influenza virus vaccines, and two of his mentees have recently joined Moderna. A.I. served as a consultant for Adaptive Biotechnologies. T.C. declares no competing interests.

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