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Two-Year History of COVID-19: A Review

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Abstract

In the two years since the outbreak of COVID-19, scientific advancement in relation to SARS-CoV-2 and COVID-19 has been rapid and extensive, covering virus identification, development of testing methods, epidemiological characterization, understanding of pathogenesis and immune responses, development of therapeutic agents, analysis of emerging variant strains, and development and deployment of several types of vaccines. Through trial and error in research and development for COVID-19, a certain degree of knowledge has been obtained: RT-PCR tests appear negative for some infected individuals with low levels of viral nucleic acid and appear positive for some un infectious convalescent individuals with fragmented nucleic acid; the main mechanisms of severe disease are hyper-inflammation and hyper-coagulopathy; Antiviral therapeutics may be expected to be efficacious in early phases of the disease when viral loads are still low, whereas anti-inflammatory therapeutics may be expected to be efficacious in late phases of the disease; Pre-existing cross-reactive immunity exists in some proportion of population people and modifies the immune response to emerging pathogens; Infection-induced immunity against reinfection wanes over time and upon the emergence of variants; MRNA-based vaccines may be highly effective for a short period of time, but vaccine-induced immunity wanes in half of a year; In vaccination schedules with two doses, a longer interval between the first and the second doses may lead to a higher vaccine efficacy; MRNA-vaccines may cause myocarditis, whereas virus-vectored vaccines may cause thrombosis by the production of abnormal antibody that activate platelets; Heterologous vaccination strategies may be feasible to broaden the selection of vaccines to be used for booster vaccination; Multiple-antigen exposure by infection or vaccination induces stronger and broader immunity that is effective for variants. This learning will facilitate research and development in the next pandemic.

Keywords: Nucleic acid; Vaccines; Platelets; COVID-19 vaccines; Immunity

Introduction

Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Distress Syndrome Coronavirus 2 (SARS-CoV-2), is the fifth documented pandemic following the 1918 Spanish flu (H1N1), the 1957 Asian flu (H2N2), the 1968 Hong Kong flu (H3N2), and the 2009 Pandemic flu (H1N1) and is the largest pandemic since the 1918 flu. COVID-19 has become a major burden on the social lives of researchers and changed biomedical research practices in many ways. For most researchers, this was their first experience participating in scientific meetings via remote systems. Globally, almost all academic society meetings in 2020 and 2021, regardless of research area, included COVID-19 as one of the main issues, and many researchers who do not normally study infectious diseases have engaged in COVID-19 research in various ways. Because the 2009 pandemic was mild and had limited social impact, the COVID-19 pandemic was the first pandemic in human history to limit socioeconomic activities in a highly networked information-driven society. In this article, we provide an overview of how COVID-19 research has been conducted in the past two years since the first outbreak in December 2019 in China and describe how humans have combated a pandemic the first time after the spread of information technology. The past two years of research and development in this pandemic involved a great deal of trial and error, which consequently led to the development of a wide variety of the viral tests with appropriate use for different situations, an explanation of the main pathological mechanisms, strategies for the development of treatments, the elucidation of the relationship to immunity to similar pathogens, an understanding of the properties of vaccines using new technologies, and an explanation of the process of attenuation of immunity elicited by infection or vaccination [1]. This article aims to provide a comprehensive view of this trial-and-error process from the perspective of the history of technological developments in medical science in order to serve as a guide for more efficient research and development in responding to future pandemics.

Identification and potential origin of SARS-CoV-2

To combat it, we must first know what our enemy is. Naturally, the first studies were focused on identifying SARS-CoV-2. Fortunately, the whole SARS-CoV-2 genome sequence was reported quickly from China and research was conducted worldwide. SARS-CoV-2 is a new RNA virus strain from the family Coronaviridae family consisting of approximately 29,900 base-pairs. It was first identified in December 2019 in patients who were workers at the seafood and wildlife market of Wuhan, Hubei-Province, China, experiencing severe respiratory symptoms that included fever, dizziness and a cough. The sequences share 79.6% sequence identity with SARS-COV but are 96% identical to RaTG13 bat coronavirus at the whole-genome level 4. Although phylogenic analyses suggest that bats are the probable original host of this virus, whether bat coronaviruses directly adapted to transmit to

humans or transmitted to intermediate hosts that facilitated animal-to-human and human-to-human transmission remains inconclusive. Proteins of a coronavirus isolated from a Malayan pangolin (pangolin-CoV) have strong amino acid similarity to SARS-CoV-2 proteins, with an almost perfect similarity in the Receptor-Binding Domain (RBD) of the Spike (S) protein and SARS-CoV-2 is suggested to have originated in the recombination of a virus similar to pangolin-COV with one similar to RaTG137. Since early in the initial outbreak of SARS-CoV-2 infections, SARS-CoV-2 was rumored to have originated from human manipulation in a laboratory, and even scientific papers suggested this might be the case. Indeed, it is extremely difficult to completely rule out the possibility that serial passage through a cell culture could mimic a natural zootonic jump or that a chimeric virus could arise *via* human genetic intervention. Although SARS-CoV-2 is believed to be a spillover of an animal coronavirus that later adapted the ability to transmit human-to-human by most of scientists, there are still some disputes about the origin of the virus as of this writing [2]. SARS-CoV-2 may have had a history of abortive human infections before a variant established a sufficiently productive infection to create a transmission chain with pandemic potential. Wuhan is the first location where cluster of infections was identified but may not necessarily represent the location of initiating events. A study using molecular clock interference and epidemiological simulation identified a period between mid-October and mid-November 2019 as the plausible interval when the first case of SARS-CoV-2 emerged in Hubei province, China. A remarkable phylogenetic and genomic diversity of bat coronaviruses, including close relatives of both SARS-CoV-2 and SARS-COV, were identified in Southeast Asia and southern China to which humans may be routinely exposed [3]. Indeed bat-borne SARS-CoV-2 -related viruses infectious for human cells were found to circulate in the Indochinese peninsula. In addition, SARS-CoV-2 has been identified in diverse kinds of naturally infected animals, regardless of whether such animals are wild or domestic, including pangolins white-tailed deer, minks, dogs and cats. Surveillance efforts covering a broad range of animals may be necessary to track ongoing spillovers of SARS-CoV-2 and SARS-CoV relatives and other coronaviruses from animals to humans [4].

Biology of SARS-CoV-2

Once the genome sequence of SARS-CoV-2 was revealed, its function and structure became focuses of studies with particular interest in similarities and differences between SARS-CoV and SARS-CoV-2. SARS-CoV-2 uses the Angiotensin Converting Enzyme 2(ACE2) on human cell surfaces as its cell entry receptor4 and the serine protease TMPRSS2 for S protein priming, as does SARS-COV. The SARS-CoV-2 S glycoprotein harbours a furin cleavage site at the boundary between the S1/S2 subunits, which is processed during biogenesis and sets this virus apart from SARS-COV of note, a four-amino-acid residue (PRRA) insertion in the furin cleavage site, which may be relevant to patho genicity is a distinct feature of SARS-CoV-2 that differs from other SARS-related coronaviruses, including RaTG13S. The predominant state of the trimer S glycoprotein has one of the three RBDs rotated up in a receptor-accessible conformation, which is stabilized by proline substitutions. Biophysical and structural studies demonstrated that the SARS-CoV-2 S protein binds to ACE2 with significantly higher affinity than SARS-COV. The expression of ACE2 is high in human nasal secretory and ciliated cells alveolar pneumocytes and intestinal enterocytes which SARS-CoV-2 preferably infects. SARS-CoV-2 conists of 13 structural proteins (S), Envelope (E), Membrane (M), Nucleocapsid (N) and nine accessory structural proteins and 16 non-structural proteins (NSP 1 to NSP 16). RNA dependent RNA polymerase, which functions as a complex of NSP 12 and its co-factors NSP 7, NSP 8 and require NSP 13 as a accessory factor and main protease NSP 5 are essential for viral RNA replication and transciption and are therefore an attractive target of antiviral drugs. Tests for SARS-CoV-2 the presence and shedding of SARS-CoV-2 and protective measures against infection to prevent viral infection, we first need to know where the virus is. For this purpose, measures to detect invisible viruses must be established [5]. Although a Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) using a nasopharyngeal swab is a standard method to detect the presence SARS-CoV-2, false negative rates vary 20% to 60%, depending on the time since exposure. Therefore, close contacts of individuals diagnosed with COVID-19 were required to quarantine for 14 days, even if they tested negative [6]. Furthermore, RT-PCR tests detect only viral RNA and positive results do not indicate the presence of infectious viruses. The use of saliva specimens and patients self-collected specimens for RT-PCR tests has increased convenience, but the accuracy of such specimens compared to nasopharyngeal webs is controversial and the problem of limited sensitivity has not changed. Research was conducted to understand where the virus is by collecting samples from the environment or patients mostly using RT-PCR tests [7]. In an experiment, live SARS-CoV-2 was found to be viable in aerosols for three hours but for longer on solid surfaces and was stable on plastic and stainless steel for 72 hours. Considering this, rigorous sanitization of hands, tables and handrails, etc. has been ubiquitously implemented and continues to date to prevent infection from the environment. However, there is little evidence to support the idea that SARS-CoV-2 passes from one person to another through contaminated surfaces. On the other hand, infectious viruses were readily isolated from samples derived from the throats or lungs of hospitalised patients but not from stool samples, in spite of high concentrations of virus RNA [8]. A study from Seoul including 21 hospitalised patients found that the latest positive viral culture was 12 days after symptom onset and those viable viruses were identified until three days after fever had subsided. In this study, a viral culture was positive only in samples with a RT-PCR cycle-threshold value of 28.4 or less. In contrast, the shedding of viable SARS-CoV-2 was prolonged in immune compromised patients. The COVID-19 pandemic is also the first occasion where the universal wearing of face masks has been recognized as a meaningful way to control infectious disease outbreaks [9]. In an experiment, a slightly damp washcloth mask over the speaker's mouth almost completely cut off forward-moving droplets during speech. Surgical masks are effective in preventing virus spread in most environments and contacts where virus abundance is low; for virus-rich indoor environments, including medical centres and hospitals, masks are effective in combination with other protective measures. A study with Healthcare Workers (HCWs) showed that universal masking was associated with a significantly lower rate of SARS-CoV-2 positivity among HCWs, which may be related to a decrease in transmission between patients and HCWs and among HCWs. A large reduction in risk of SARS-CoV-2 infection by face mask use was confirmed in a systematic review and meta-analysis [10].

While emerging infectious diseases originate locally, it is human mobility that spreads them to pandemic proportions [11]. COVID-19 provided the first opportunity to scientifically capture the progression

process from local outbreak to pandemic. Phylogenetics has proved its significance for discriminative identification of distinct strains that were prevalent during the same periods. Repeated independent international or domestic introductions of SARS-CoV-2 in the early phase of the pandemic, which eventually resulted in sustained transmission of the infectious disease although some of these introductions extinguished or were substantially controlled by public health measures, including travel restrictions [12]. Furthermore, the SARS-CoV-2 pandemic is historically the first time since computer technology became commonplace that lockdown measures were actually implemented. Whether and how the lockdown policies suppress infectious disease in real-world settings were defined scientifically using mathematical models [13].

Epidemiological and clinical characterization of SARS-CoV-2 infection

In order to consider countermeasures against new infectious diseases, understanding their infection characteristics is indispensable. For this reason, research on the epidemiological characterization of SARS-CoV-2 was also diligently conducted. Studies revealed that 30% to 90% of people that tested positive for SARS-CoV-2 had no symptoms at the time of testing, depending on the study and that 30% to 90% of people with no symptoms at the time of testing remained asymptomatic throughout the course of infection. The percentage variations in the studies may at least partly reflect the limited capacity of RT-PCR tests, especially in the early stages of the pandemic. Modelling and sero prevalence studies have estimated that there must have been nearly ten times as many infections as confirmed cases [14]. The risk of transmission from an index case increases approximately two days before and three days after symptom onset, peaking at or just after symptom onset which may be congruent with viral volume in the index case's throat. Although a significant proportion of SARS-CoV-2 transmissions are caused by asymptomatic individuals the incidence of COVID-19 among close contacts of a symptomatic index case is approximately four times higher than for close contacts of an asymptomatic index case 90. SARS-CoV-2 infection is characterized by transmission heterogeneities with 80% of secondary cases traced back to less than 20% of infection [15]. The risk of transmission markedly increases where the implementation of preventive measures to control infection is difficult due to limited space, including households care facilities ships and prisons. Clinical manifestation is the one of the issues of greatest interest when outbreaks of a new infectious disease occur. For COVID-19, reports from China, the original epicenter in December 2019, and United States, more severely affected than China since March 2021, described symptoms and clinical features of COVID-19 early in the pandemic. Fever, cough, and dyspnea are the most common symptoms with lymphocytopenia found in 70% to 80% of patients. Anosmia and insomnia are reported by over half of the patients often as the first symptoms and were a discriminative feature of COVID-19. Ground-glass opacity is a typical finding in chest CT scans of COVID-19 patients which can be used to detect asymptomatic individuals with a SARS-CoV-2 infection. Progression to severe disease or death distinctly increases with age an d with preexisting comorbidities, including cardiovascular disease diabetes chronic respiratory disease, hypertension obesity and cancer [16]. The estimated risk of COVID-19-related mortality varies depending on testing capacity to detect asymptomatic individuals or patients with mild disease. The case fatality risk and the infection fatality risk of COVID-19 is estimated to be approximately 1% to 2% and 0.1% to 2% respectively, with a markedly higher risk in older individuals than younger individuals. The mortality risk is approximately five times higher than seasonal influenza. ACE2, the cellular receptor for SARS-CoV-2, is an enzyme that regulates the renin-angiotensin-aldosterone system by converting angiotensin II to angiotensin. Initially, concerns were expressed that renin-angiotensin-aldosterone system inhibitors, such as ACE Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs), which are widely used as antihypertensive agents, may increase the expression of ACE2 and promote COVID-19 infection [17]. However, large-scale case-control studies and randomized clinical trials repeatedly confirmed that there was no evidence that use of ACEIs or ARBs affected the risk of COVID-19-related admission severe COVID-19 or COVID-19-related mortality. Randomized clinical trials confirmed no significant differences between discontinuing and continuing of ACEI or ARBs in disease progression or mortality related to COVID-19. Histopathological studies of fatal COVID-19 patients revealed diffuse alveolar damage with pronounced macrophage infiltration and diffuse micro thrombi indicating two major mechanisms of disease progression: Hyper-inflammation and hyper-coagulopathy. In relation to hyper-inflammation, an elevation in cytokine levels, a so-called "cytokine storm," was found to be associated with worse clinical outcomes with impaired coordination of interferons identified in severe disease. Moreover, some studies showed an approximately ten to 20% prevalence of autoantibodies for immunomodulatory proteins, such as interferons, in patients with severe COVID-19 pneumonia which may impede immune functions and impair virological control by inhibiting immune receptor signaling and by altering peripheral immune cell composition. Children and adolescents infected with SARS-CoV-2 mostly develop only mild disease while some develop Multisystem Inflammatory Syndrome in Children (MIS-C), a severe disease characterized by persistent fever, hypotension, multi-organ involvement (including myocarditis and aneurysms of coronary-artery) and an elevated level of inflammatory cytokines. Higher pediatric innate interferon-responses in airway cells may restrict viral replication and disease progression, while a systemic interferon-stimulated subpopulation of immune cells is introduced in adults upon SARS-CoV-2 infection. Pregnant women may be in a state of immune tolerance, and, compared to non-pregnant women, pregnant women with COVID-19 were less likely to have symptoms but had higher odds of admission to an intensive care unit, invasive ventilation, and the need for extracorporeal membrane oxygenation. Although in-hospital mortality was low, it was significantly higher in pregnant women with COVID-19 than in those without COVID-19. Pregnant women with COVID-19 had higher odds of preterm birth than those without COVID-19. In relation to hyper-coagulopathy, thrombotic events, both venous and arterial, are associated with COVID-19 mortality and pulmonary thromboembolism is a frequent direct cause of COVID-19-related deaths. The risk of myocardial infarction and ischemic stroke increased following SARS-CoV-2 infection. Early in the pandemic when the positive rate of SARS-CoV-2 tests in the community was high, the incidence of acute myocardial infarction and ischemic stroke significantly decreased, while incidence of out-of-hospital cardiac arrest significantly increased which is suggestive of patients' hesitancy to visit hospitals resulting in increased mortal ischemic cardiovascular events in out-of-hospital settings. It was reported that a considerable proportion of COVID-19 patients suffered from a continuous variety of symptoms or functional impairments in the post-acute phase of COVID-19. A substantial health loss burden spanning the pulmonary and several extra pulmonary organ systems is experienced by patients who survive after the acute phase of COVID-19, with a risk of the readmission or death four to eight times

higher. Approximately half to 70% of COVID-19 convalescent patients suffered from at least one sequelae symptom at 4 months-6 months which was decreased with time. Although the proportion of patients with symptoms or functional impairments in the post-acute phase of COVID-19 was greater with an increased severity of the acute phase of COVID-19 these symptoms and impairments were also observed in the post-acute phase of patients with mild COVID-19. Long-term symptoms could occur in children but were generally mild and had low prevalence. Hyper-inflammation and hyper-coagulation are well associated. SARS-CoV-2 infection induces a process known as immune-thrombosis, in which activated neutrophils and monocytes interact with platelets and the coagulation cascade leads to intravascular clot formation in small and larger vessels , while the activation of coagulation pathways during the immune response to infection results in overproduction of proinflammatory cytokines leading to multi-organ injury. In this way, epidemiological and clinical studies of COVID-19 revealed that the two key determinants of disease severity of COVID-19, hyper-inflammation and hyper-coagulation, mostly relate to host factors, whereas viral factors did not significantly affect outcomes.

Adoptive immune response in SARS-CoV-2 infection

In relation to host factors, adoptive immune responses are most responsible for protection from emerging infectious diseases, along with natural immunity and cytokines. Since early in the pandemic, efforts have been made to illustrate the immune response against SARS-CoV-2 that contributes to the various pathologies of COVID-19 patients. Most of SARS-CoV-2 -infected individuals seroconvert within one to two weeks post symptom onset with over 95% seropositivity within four weeks. Neutralizing antibodies also rapidly develop in a majority of SARS-CoV-2 -infected individuals, in parallel with seroconversio. Most antibody studies revealed a positive correlation between antibody levels and disease severity [18]. Antibody levels also correlate with increasing age probably reflecting severe COVID-19 in older populations. SARS-CoV-2 -specific IgG levels in asymptomatic individuals were significantly lower than those in symptomatic patients, and 40% of asymptomatic individuals became seronegative for IgG in the early convalescent phase 187. Therefore, there was a concern that a certain percentage of SARS-CoV-2 -infected individuals with no symptoms or mild symptoms often develop only suboptimal antibody responses and are susceptible to repeated infections. On the other hand, although most convalescent individuals with mild COVID-19 do not possess high levels of neutralizing antibodies approximately 40 days after symptom onset, rare but recurring RBD-specific antibodies with potent antiviral activity were found in all individuals tested 188. Low antibody titres could be a consequence of efficient and rapid clearance of the virus. Antibodies alone frequently cannot clear an ongoing infection. Studies of acute and convalescent COVID-19 patients observed that SARS-CoV-2 -specific T-cell responses are associated with milder disease, both for CD4+T and CD8+T cells while neutralizing antibodies correlated with disease severity 186-190, suggesting the predominance of T cells over neutralizing antibodies in controlling SARS-CoV-2 . Evidence of no increased risk of mortality in patients with ongoing B-cell depletion therapies suggests that the control of SARS-CoV-2 may be possible without substantial contribution of an antibody response, as long as a robust T-cell response is present. While the antibody responses coordinated with CD4+T and CD8+T cells are protective, uncoordinated responses frequently fail to control disease 193. Lymphocytopenia, especially in relation to reduced CD4+T and CD8+T-cell counts, is a pronounced feature of severe COVID-19 and is also predictive of disease progression 136. Importantly, an increased proportion of cytotoxic CD4+T cells responding to SARS-CoV-2 was found in hospitalised patients or patients with moderate-to-severe COVID-19, indicating an imbalance of regulatory and cytotoxic SARS-CoV-2-reactive CD4+T cells, which is a distinct feature of moderate-to-severe COVID-19 compared to mild COVID-19.

Literature Review

Therapeutics for COVID-19

In general, the objectives of pharmacological interventions against infectious disease are the reduction of the volume of parasites and symptomatic remission by reducing inflammation. This theory also applies to COVID-19, and pharmaceuticals for COVID-19 are largely classified into two types: antiviral and anti-inflammatory pharmaceuticals. When a new viral endemic emerges, use of existing medicines for similar pathogens is a prompt and plausible response. Since early in the pandemic, several available drugs already approved for anti-RNA viruses and other pathogens were repurposed and vigorously tested for COVID-19. Most of these drugs, including lopinavir/ritonavir an anti-Human Immunodeficiency Virus (HIV) drug, favipiravir an anti-influenza virus, hydroxyl-chloroquine an anti-malaria drug, azithromycin an anti-bacterial drug, and ivermectin an anti-intestinal strongyloidiasis and onchocerciasis drug, failed to demonstrate efficacy against COVID-19 in randomised controlled clinical trials. Remdesivir, an anti-ebola virus nucleotide analogue targeting the RNA-dependent RNA polymerase of RNA viruses, showed efficacy in shortening the recovery time of patients with COVID-19 pneumonia who needed hospital admission due to hypoxemia in a randomised controlled clinical trial, but this efficacy was limited only to patients who need oxygen support but did not need high-flow oxygen or non-invasive ventilation. Moreover, remdesivir failed to demonstrate dose-effect consistency or any clinical benefits in other randomised controlled trials involving hospitalised patients with COVID-19 pneumonia. In contrast, remdesivir demonstrated a clear effect among non-hospitalised patients who were at high risk for COVID-19 progression, which resulted in an 87% lower risk of hospitalization or death than in the placebo group. Generally, antiviral drugs exerted no significant beneficial effect in the term of disease progression or survival of patients whose disease has already progressed to a high viral load, and efficacy could be expected when used for patients in the early post-infection period. However, intravenous drugs, such including remdesivir, must be administered to patients at clinics or emergency departments and are inconvenient for homecare patients. Recently, molnupiravir, an oral nucleotide analogue developed for influenza, was reported to reduce the risk of hospitalization or death by approximately 30% over a placebo in non-hospitalised adult patients with mild-to-moderate COVID-19, and nirmatrelvir, an oral compound of a main protease inhibitor with ritonavir, reportedly reduces the risk of hospitalization or death by 89% over a placebo in patients treated within three days of symptom onset [19]. Remdesivir and these two oral antiviral agents were shown to be effective against the newly emerged B.1.1.529 variant in an in vitro study and are expected to be standard therapeutics for outpatients with mild-to-moderate with COVID-19, possibly mitigating the real-world pathogenicity of COVID-19.

In contrast to antiviral agents, anti-inflammatory pharmaceuticals successfully demonstrated distinct clinical benefits in the treatment of

moderate-to-severe COVID-19 in randomized clinical trials, reflecting the fact that the key drivers of disease progression are host factors causing hyper-inflammation. Dexamethasone, a widely used anti-inflammatory glucocorticoid for a long time, repeatedly showed efficacy in the survival or recovery time of hospitalized patients with moderate-to-severe COVID-19 in randomized clinical trials and became a standard therapeutic for hospitalized patients with moderate-to-severe COVID-19 since early in the pandemic. Later, tocilizumab and sarilumab, Interleukin (IL)-6 receptor antagonists, demonstrated efficacy in improving clinical outcomes, including the survival of hospitalized patients with severe COVID-19, in powered randomized clinical trials although some other underpowered randomized trials failed to show their clear efficacy. Tofacitinib and baricitinib, Janus kinase inhibitors, also demonstrated efficacy in reducing the risk of disease progression and death in hospitalized patients with COVID-19 in randomized clinical trials. Furthermore, baricitinib, in combination with remdesivir, showed superiority to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with COVID-19, notably among those receiving high-flow oxygen or non-invasive ventilation. Early treatment with anakinra, an IL-1 α/β inhibitor, reduced the risk of a worse clinical status in patients with a high soluble urokinase plasminogen activator receptor. Inhaled budesonide, a widespread inhaled glucocorticoid, improved time to clinical recovery time in outpatients with mild COVID-19.

Convalescent Plasma (CP) therapy, a classic adaptive immunotherapy, has been applied to the prevention and treatment of many infectious diseases, including SARS, MERS, and 2009 H1N1 pandemic. In the absence of effective antiviral therapeutics, the efficacy of CP against COVID-19 was assessed in randomized controlled clinical trials. CP is also an antiviral therapy, and it seems advantageous to start treatment early in the disease when the viral load is still low using CP with high antibody titres, as evidenced in a retrospective cohort study in which CP with higher anti–SARS-CoV-2 IgG antibody levels was associated with a lower risk of death than that with lower antibody levels. However, CP failed to demonstrate a clinical benefit in most randomized controlled clinical trials. In a randomized controlled clinical trial, an early administration of high-titre CP against to mildly ill older COVID-19 patients reduced the disease progression, but a systematic review and meta-analysis determined that treatment with CP compared to a placebo or standard of care was not significantly associated with a decrease in all-cause mortality or any benefit for other clinical outcomes [20]. Monoclonal antibodies seem to be a plausible and highly specific strategy for the treatment of infectious disease. With recent progress in techniques of cell sorting and genetic recombination, many monoclonal antibodies (mAbs) with robust neutralizing potencies against SARS-CoV-2 identified in convalescent sera were vigorously developed for the treatment COVID-19. Almost all of these neutralizing mAbs target epitopes on SARS-CoV-2 S protein, and most of them target epitopes within the RBD of S proteins, which inhibits interaction between RBD and ACE2. Some neutralizing mAbs target the N Terminal Domain (NTD) of S proteins. In these therapeutic mAbs pipelines, bamlanivimab monotherapy reduced the risk of the onset of COVID-19 in residents and staff of care facilities with SARS-CoV-2 index cases compared to placebo , and the combination of bamlanivimab and etesevimab led to a lower incidence of COVID-19–related hospitalizations and deaths than a placebo among high-risk ambulatory patients in randomised trials. As treatment with mAbs is also an antiviral therapy, bamlanivimab, when co-administered with antiviral drug remdesivir, failed to demonstrate efficacy among the hospitalized patients whose disease may have already progressed and who have higher viral loads.

One critical issue for mAbs is that they are susceptible to antigenic drift of their directing epitopes due to their high specificity of epitopes. Most mAbs pipelines are designed based on the genome sequence of the original Wuhan strain, and mAbs can therefore lose their neutralizing potency against variants that harbour mutations within their directing epitopes. After the emergence of SARS-CoV-2 variants with mutations within RBD, bamlanivimab and etesevimab lost efficacy against some of these variants. REGN-COV, a cocktail of the mAbs casirivimab and imdevimab was designed based on a concept that a pair of mAbs that do not compete in binding to the RBD, would be resistant to S mutations, because mutations rarely occur in two different sites simultaneously. Even if an immune escape mutation occurred for one of the two mAbs, the neutralizing ability of the pair would be maintained. When administered intravenously, REGN-COV reduced the risk of COVID-19-related hospitalization or death by approximately 70% and resolved symptoms more rapidly than a placebo among COVID-19 outpatients with risk factors for severe disease. Furthermore, when administered subcutaneously as a preventive therapeutic, REGN-COV reduced the risk of symptomatic COVID-19 and asymptomatic SARS-CoV-2 infection in household contacts of infected persons by 66%, and reduced the risk of sympathetic COVID-19 in asymptomatic SARS-CoV-2-PCR-positive individuals living with infected household contacts by 46%. However, when administered to patients admitted to hospital with COVID-19, REGN-COV reduced 28-day mortality in patients who were seronegative (and therefore had not mounted their own humoral immune response) at baseline but not in those who were seropositive at baseline. Furthermore a substantial reduction in REGN-COV efficacy against the newly identified B.1.1529 variant was reported in the preliminary results of studies. Along with cocktail of mAbs, selecting mAbs that target epitopes within highly conserved regions of S proteins among pan-sarbecovirus is another possibility for resistance against emerging variants. In these pipelines of pan-sarbecovirus mAbs, sotrovimab reduced the risk of disease progression by 85% compared to a placebo, among high-risk patients with mild-to-moderate COVID-19. Sotrovimab was reported to have retained activity against the full combination of mutations in the spike protein of the B. 1.1529 variant in a preliminary study. Pan-sarbecovirus mAbs may also be useful for the treatment of and design of vaccines for future SARS-CoV-2 variants, as well as other future sarbecovirus infections.

For hyper-coagulopathy, anticoagulation was also applied to patients with COVID-19, similarly to prophylaxis of disseminated intravascular coagulation in infectious diseases. The focus of the studies was to compare the effectiveness of anticoagulation regimens of therapeutic doses, prophylactic standard doses, or prophylactic intermediate doses [11]. Although therapeutic anticoagulation failed to improve clinical outcomes in hospitalised COVID-19 patients with elevated D-dimer levels over standard anticoagulation, therapeutic anticoagulation was shown to increase the probability of survival to hospital discharge, with reduced use of organ support or reduced occurrence of thromboembolism compared to standard thromboprophylaxis in noncritically ill patients but not in critically ill patients. Among patients admitted to th e Intensive Care Units (ICUs) with COVID-19, intermediate-dose prophylactic anticoagulation, compared to standard-dose prophylactic anticoagulation, did not result in a significantly improved clinical outcome in a randomised controlled trial, which does not support the routine empirical use of intermediate-dose prophylactic

anticoagulation in unselected patients admitted to the ICU with COVID-19. In addition, aspirin failed to reduce the mortality rate of hospitalized COVID-19 patients in a large-scale randomized clinical trial. In patients discharged after hospitalization due to COVID-19 who were at high risk of thrombotic events, thromboprophylaxis with rivaroxaban improved clinical outcomes compared to no extended thromboprophylaxis [12].

Discussion

Pre-existing immunity

A pandemic is caused by a novel human pathogen that has evolved from existing ancestral pathogens [13]. Therefore, it is possible that some people have acquired immunity against the ancestral pathogens that also cross-reacts to the novel pathogen causing the pandemic. This was the case for SARS-CoV-2. Studies found antibodies and B cells and CD4+T and CD8+T cells, cross-reactive to SARS-CoV-2 in samples from healthy naïve individuals or blood donors before the SARS-CoV-2 pandemic who had previous exposure to Human Common cold coronaviruses (HCoVs). These SARS-CoV-2 cross-reactive antibodies are found in 20% to 30% of naïve healthy individuals especially in individuals recently infected with HCOVs, children and adolescents. On the other hand, cross-reactive T cells are reported to be observed in 20% to 60% of naïve healthy individuals, depending on the study with frequencies decreasing with age. The majority of SARS-CoV-2 cross reactive T cells are CD4+T cells which recognize epitopes conserved among HCoVs or animal coronaviruses. SARS-CoV-2 cross reactive CD8+T cells are found less frequently but may still have biological relevance. The most important issue is whether these cross-reactive immune cells really function for protection against SARS-CoV-2 infection and COVID-19 severity. In relation to humoral cross-immunity, a majority of studies showed the SARS-CoV-2 neutralizing potency or protective activity of these cross-reactive antibodies found in naïve donors, while other studies reported that SARS-CoV-2 cross-reactive antibodies in individuals with previous HCoV infection do not have SARS-CoV-2 neutralizing activity or that these cross-reactive antibodies do not correlate to protection against SARS-CoV-2 infection or hospitalization [14]. A longitudinal profiling study of the B cells of COVID-19 patients reported that pre-existing cross-reactive seasonal coronavirus memory B cells contribute to an early anti-SARS-CoV-2 response. Regarding cellular cross-immunity against SARS-CoV-2, results from a vast majority of studies are indicative of protective activity of cross-reactive T cells in SARS-CoV-2 naïve individuals. Pre-existing memory CD4 +T cells were cross-reactive with comparable affinity to SARS-CoV-2 and HCoVs-291 and were recruited into an immune response to SARS-CoV-2 infection, suggesting that pre-existing cross-reactive cells account in part for the high rate of asymptomatic or mild COVID-19 disease courses. Pre-existing cross-reactive memory CD8+T-cell responses were observed in individuals with mild disease following SARS-CoV-2 infection, suggesting their contribution to immune protection in mild COVID-19 infection. A pre-existing memory T-cell response with cross-protective potential against SARS-CoV-2 may expand to support rapid viral control, aborting infection. More direct evidence showed that hospitalized patients with a previously detected HCoV infection (HCoV+) had significantly lower odds of ICU admission compared to those without (HCoV-) and a trend toward lower odds of the mechanical ventilation, with more than threefold lower hospitalized patients who eventually died than the HCoV–group, suggesting that preexisting immune responses against HCoVs can mitigate disease manifestation from SARS-CoV-2 infection.

Immunity against reinfection

Simplistically, the way to contain and eventually end the pandemic is for more people get immunized through natural infection or vaccination, which is the achievement of herd immunity [15]. Early research in the COVID-19 pandemic identified that the basic reproduction number (Ro; The average number of secondary infections transmitted from an infected index individual to a fully susceptible population) of the wild type of SARS-CoV-2 is approximately implying a theoretical herd immunity threshold for a homogenous population of approximately 70%. In a real-world setting, however, a study of blood donors showed an estimated 76% of the population infected by October 2020 in Manaus, Brazil, but an increase in the number of COVID-19 related hospitalization occurred in 2021 [16]. Similar evidence against a simple notion of herd immunity was found in Karnataka, India, which a large pandemic wave severely affected in the spring of 2021, despite the fact that an estimated 53.8% of seroprevalence in urban areas had been achieved by August 2020 and in Nairobi, Kenya, where an estimated 61.8% of population had been infected with SARS-CoV-2 by February 2021 before a large third wave of infections began in March 2021. While not resulting from natural infection alone, a study in the United States showed an estimated 87.2% of seroprevalence in the Northwest through natural infection and vaccination by May 2021 although the region was still affected in September 2021.

Clinical evidence of reinfection

The earliest reports of phylogenetically confirmed cases of SARS-CoV-2 reinfection included relatively young and healthy individuals without any specific previous comorbidities including those with more severe diseases during reinfection than in primary infection. These cases simply indicate that immunity obtained through natural infection is not necessarily sterilizing nor even protective against more severe illness [17]. Studies with a large number of samples repeatedly confirmed an association between the presence of anti-SARS-CoV-2 Spike IgG antibodies or previous RT-PCR positive results for SARS-CoV-2 and a reduced risk of reinfection demonstrating the protective efficacy of infection-elicited antibodies against reinfection, with a failure rate around ten to 15% in working-age individuals within about a half of a year and a failure rate of over 50% in individuals at 65 years of age or older. The protective efficacy of antibodies against severe disease was also confirmed. For a person who has already had a primary infection, the risk of a severe reinfection seems to be only approximately 1% of the risk of a previously uninfected person having a severe primary infection. One possible explanation of the susceptibility to reinfection is low antibody levels elicited by asymptomatic or mild illness in individuals with SARS-CoV-2 infection which may subsequently result in high seronegative conversion in the early convalescent phase. However, direct evidence has not fully established that individuals with low antibody titres during the recovery period from the initial infection are more likely to be reinfected [18]. Although antibody levels also correlate with older age individuals 65 years or older with previous SARS-CoV-2 infection are at high risk of reinfection compared to younger individuals with previous SARS-CoV-2 infection.

Waning immunity and durability of immune memory

Immunity waning may be a more plausible explanation of reinfection. Infection with SARS-CoV-2 could fail to elicit a functional germinal centre response which would interfere with the generation of long-lived plasma cells that produce a continuous supply of immune effector molecules [19]. Moreover, concerns arose from the fact that infection with common cold coronaviruses fails to induce durable infective immunity. The major components of immunological memory to viruses are antibodies, memory B cells, memory CD4+T cells and memory CD8+T cells. Longitudinal studies in convalescent COVID-19 patients showed that antibody titres were more or less attenuated over time after initial infection, with some studies emphasizing decay in early convalescence while others rather suggested persistence of several months. Neutralizing antibody response dynamics in convalescent COVID-19 patients vary greatly indicating that the prediction of immune longevity can only be accurately determined at an individual level. Although antibody titres decreased among seropositive individuals over time, the proportion of seropositive individuals did not necessarily decrease. Moreover an improvement in neutralizing potency per antibody was observed despite decay in antibody titres, indicating antibody response maturation and improved affinity, which suggests that declining antibody titres may not be indicative of declining protection. It is still unknown whether antibody titres are more closely related to protection against infection or severe disease. In relation to immune attenuation, antibody titre level does not necessarily seem to be a reliable indicator of protective immunity in individuals previously infected with SARS-CoV-2.

Memory B cells form an essential arm of humoral immunity following the primary infection. After exposure to a pathogen, antigen-specific memory B cells rapidly proliferate and differentiate into protective antibody-secreting plasma blasts. Studies identified memory B cells in convalescent COVID-19 patients with a durability of more than six months and 12 months after the initial infection. These cells were induced by natural infection even with mild disease, which accounts for the majority of COVID-19 patients. Notably, frequencies of spike or spike-RBD memory B cells increased over time after initial infection with more spike-specific memory B cells at six months after infection than at one month after infection. Neutralizing SARS-CoV-2 RBD-specific clones accumulated with time and contributed to a stable memory B-cell pool, showing the germinal centre response maturation with an accumulation of somatic mutations in their variable region genes over time [20].

Memory CD4+T cells and memory CD8+T cells were found to persist longer than six months and were identified in approximately 90% and 70%, respectively, of convalescent individuals at six months after infection. Upon reinfection, re-activated memory CD4+T cells expand, help activate memory B cells, and secrete cytokines to activate innate immune cells, while memory CD8+T cells also secrete cytokines and kill virus-infected cells through the delivery of cytolytic molecules. Some studies show that memory CD4+T cells and memory CD8+T cells decline with a half-life of three to five months while other studies report that SARS-CoV-2-specific T-cell responses remained robust and even developed over time in frequency and intensity. It is probable that the decay of T-cell memory slows over time, which is consistent with the observation that long-lasting SARS-CoV memory T cells are detected 17 years after an outbreak of SARS-CoV296. Importantly, persistent memory T cells were observed in individuals with asymptomatic infection even in antibody-seronegative exposed family member.

Memory B and T cells can take several days to reactivate and generate a recall response, and sterilizing immunity against viruses can only be accomplished with high-titer neutralizing antibodies 191. Repeat infection possibly occurs in individuals with decreased antibody titres, who will, nevertheless, subsequently develop a robust adaptive immune response based on immune memory generated through the initial infection within several days and recover early without developing severe disease. Thus, protection against symptomatic or severe COVID-19 can be mediated by durable memory B and T cells, despite the decay of antibody titres over time.

SARS-CoV-2 Variants of Concern (VOCs)

Characterization of SARS-CoV-2 VOCs: The emergence of variants that evolved to transmit more efficiently and/or evade immunity induced by previous infection is one of the most problematic issues in pandemics. Since early in the pandemic, the emergence of SARS-CoV-2 variants was thought to be one of major concerns for antiviral immunity or a vaccine strategy. Theoretically, a SARS-CoV-2 variant can inhibit the establishment of herd immunity in two distinct ways: By increased transmission and by altered antigenicity. The evolutionary rate of SARS-CoV-2 is very low and transmission-enhancing and/or immune-escape SARS-CoV-2 variants are likely to arise infrequently. However, amino-acid substitutions in the immune-dominant SARS-CoV-2 S protein, especially those within the RBD that binds to human cellular receptor ACE2, may change binding affinities between the RBDs and ACE2 or structural characteristics of the epitopes recognized by humoral or cellular immune molecules, possibly resulting in enhanced transmission and pathogenesis or immune escape, respectively. Mutations within the epitopes outside RBD can also enhance transmissibility and pathogenesis by stabilizing pre-fusion spike conformation or evade immunity by impairing the neutralizing potencies of antibodies targeting epitopes outside RBD. Variants that evade immunity are likely to emerge particularly in immune compromised individuals who develop only suboptimal immune responses and whose recovery has been delayed despite various treatments, including CP and antibody therapies. In February 2020, SARS-CoV-2 variants with a D614G mutation in the spike protein emerged in Europe342 and rapidly spread globally by replacing variants without D614G in a manner consistent with selective advantage, eventually establishing almost 100% dominance worldwide. The SARS-CoV-2 D614G mutation increased viral infectivity to human cells but did not increase COVID-19 severity nor evade antibody/serum neutralization induced by viral infection. To date, diverse SARS-CoV-2 variants have been identified, among which five Variants of Concern (VOCs) that harbor multiple amino-acid substitutions of biological importance within RBD and NTD have circulated globally: B.1.1.7 (alpha), which was first identified in late September 2020 in the United Kingdom and has an N501Y mutation in RBD and a 69/70 deletion in NTD; B.1.351 (beta), which was first identified in May 2020 in South Africa and has N501Y, E484K, and K417N in RBD; P.1 (gamma), which was first identified in November 2020 in Brazil and has N501Y, E484K, and K417T in RBD; B.1.617.2 (delta), which was first identified in October 2020 in India and has L452R in RBD; B.1.1.529 (omicron), which was first identified in late November 2021 in South Africa. B. 1.1.7 was demonstrated to have a 40% to 100% higher reproduction number and 30% to 50% higher transmissibility, than prior non-B. 1.1.7 strains and spread globally

from late 2020 to spring 2021. Among the eight substitutions or deletions in the S protein of B.1.1.7, only the 501Y substitution exhibited consistent fitness gains for replication in the upper airway epithelial cells, suggesting that this is a major determinant of increased transmissibility of this variant . Moreover, COVID-19 with B.1.1.7 is associated with an increased risk of admission of 1.4 to 2.2 times and an increased risk of mortality of approximately 60%, compared to prior non-B.1.1.7 strains and linages grew in South Africa and Brazil respectively, demonstrating higher transmissibility than their respective ancestral strains. Extensive dominance however, has not been observed outside South Africa and Brazil, although cases with B.1.351 and P.1 have been reported globally. Which has an estimated transmission advantage of 76% over B.1.1.7, rapidly spread and replaced ancestral lineages, including B.1.1.7, establishing dominance globally in late spring to early autumn? It is theoretically possible that a highly infectious variant can grow even with a high (e.g. over 80%) seropositivity in population. The percentage of persons who would need to be immunized against B.1.617.2, which is has a basic reproduction number of somewhere between 5 and 8, would need to be 80% to 87.5%. Thus, the high infectiousness of B.1.617.2 could be a factor contributing to a new hike in infection counts in countries with previous extensive infections. The mechanism of heightened transmissibility of B.1.617.2 is still not clearly defined. B.1.617.2 RBD mutations did not increase ACE2 binding markedly suggesting that its emergence was due to reduced immune recognition. Other studies showed the efficient membrane fusion capability of the B. 1.617.2 S protein, possibly associated with a P681R mutation or the contribution of specific nucleocapsid mutations of B.1.617.2 to efficient mRNA delivery and accelerated production of viruses. Along with increased transmissibility, infection with B.1.617.2 was associated with more severe COVID-19 than B.1.1.7, with a two to 2.5-folded increased risk of hospital admission. We observed that both the transmissibility and virulence of SARS-CoV-2 increased during the replacement of the dominant strain from ancestral variants to B. 1.1.7 and from B.1.1.7 to B.1.617.2. This deviates from the traditional “transmissibility-virulence trade off theory” which asserts that parasites balance virulence (the increased death rate of infected hosts), which shortens the infectious period and thus reduces transmission opportunities, against transmissibility (the probability of transmission given contact).

To maximize overall transmission the validity of this theory is controversial for a variety of infectious diseases and should be studied beyond COVID-19. Recently, B.1.1.529 a newly identified SARS-CoV-2 variant that had unprecedently diverse mutations on the S protein was reported to have a substantial growth advantage over previous VOCs including and rapidly spread in South Africa. It was designated as the fifth VOC (omicron). Preliminary results from *in vitro* studies have suggested a higher infectivity to human cells of this variant compared to other VOCs268. As the binding affinity of B. 1.1.529 to human ACE2 is reported to be comparable to the prototype strain or B.1.617.2, the higher infectivity of B.1.1.529 than other variants may be explained by a mechanism other than ACE2-binding affinity. The ineffective usage of TMPRSS2 and higher dependency of B.1.1.529 on other proteases (cathepsins) to enter human cells compared to other variants suggest that the omicron variant enters cells by different routes than other variantsincluding endocytotic pathways389. The proportion of hospitalised patients and those with severe disease is reported to be significantly lower in relation to B. 1.1.529 than other variants in preliminary clinical observations which may reflect the ineffective replication and reduced pathogenicity of B. 1.1. found in ex *vivo* explant cultures of human lower airways or lungs and in studies using animal models.

Immune escape by VOCs

Immune escape by SARS-CoV-2 variants is also a plausible mechanism of reinfections in individuals previously infected with SARS-CoV-2 ancestral strains. Studies of neutralizing activity against these VOCs or pseudo-viruses carrying key amino-acid substitutions of these VOCs in serum/plasma samples from individuals previously infected with prior SARS-CoV-2 strains showed that some of these VOCs or key amino acid substitutions of these VOCs are resistant to the neutralizing activity of convalescent sera/plasma compared to corresponding ancestral strains. B.1.1.7 is comparably susceptible or only modestly (2-3 folds) less susceptible than ancestral strains. By contrast, B.1.351 is markedly resistant to convalescent serum/plasma from individuals infected with ancestral strains. Studies revealed that more than 40 to 70% of convalescent sera/plasma failed to neutralize B.1. or that the neutralizing activity of convalescent sera/plasma was reduced significantly or seven- to 13-fold against B.1.351 compared to ancestral strains. E484K substitution within the RBD of the S protein has been shown to be the main driver of increased resistance to neutralization by convalescent sera/plasma. P.1, which also has E484K substitution, was found to be approximately 2.5 to fivefold resistant to convalescent sera/plasma over ancestral strains which is comparable 409 to or more resistant than B.1.1.7 but less resistant than B. 1.351405, 409. B.1.617.2 is also less susceptible to convalescent sera/plasma from individuals infected with ancestral strains was shown to be approximately four times more resistant than, but does not cause the extensive immune evasion observed with B.1.351. Recently, has been reported to be more resistant to convalescent sera than even B. 1.351with ten to 40 times more efficient evasion of neutralization by convalescent antibodies compared to B.1.617. These studies defined the extent of resistance of each VOC to neutralization by antibodies induced by previous infection with prior strains *in vitro*. It is still unknown, however, whether these results correctly predict reinfection in humans where cellular immunity is also present. In contrast to neutralizing antibodies, functional T-cell responses were reported to be preserved at a high level even to such variants.

Athough B.1.351 was poorly cross-neutralized by plasma from individuals with previous infections and the efficacy was reduced by 15.1-fold relative to the neutralization of B.1.351 by plasma from individuals infected with B. 1. the efficacy of natural infection against reinfection was estimated at approximately 85% to 90% for the B.1.351 variant in a real-world setting, which is just slightly lower that for the B.1.1.7 variant of approximately 90% to 95%. For P.1, a modeling study estimates that previous non-P.1 infection provides 54% to 79% of the protection against infection with P.1 that it provides against non-P.1 lineages365. For B.1.617.2, the protection provided by prior infection against reinfection was reported to be approximately 85% to 90% 419. Lastly a study reported that the effectiveness of previous infection in preventing reinfection with B.1.1.529 was estimated to be 56.0% 419, although the rapid spread of B.1.1.529 has been observed in regions with over 60% of population immunity in South Africa. These antibody neutralization studies and real-world studies collectively show that some of variants, such as B.1.351, P.1, B.1.617.2 or B. 1.1.529 partially evade immunity induced by previous infections with ancestral strains but to limited extent.

Conclusion

In these two years, through trial and error in research and development for COVID-19, a certain degree of knowledge has been obtained: RT-PCR tests appear negative for some infected individuals with low levels of viral nucleic acid and appear positive for some un infectious convalescent individuals with fragmented nucleic acid; The main mechanisms of severe disease are hyper-inflammation and hyper-coagulopathy; Antiviral therapeutics may be expected to be efficacious in early phases of the disease when viral loads are still low, whereas anti-inflammatory therapeutics may be expected to be efficacious in late phases of the disease; pre-existing cross-reactive immunity exists in some proportion of population people and modifies the immune response to emerging pathogens; Infection-induced immunity against reinfection wanes over time and upon the emergence of variants; MRNA-based vaccines may be highly effective for a short period of time, but vaccine-induced immunity wanes in half of a year; In vaccination schedules with two doses, a longer interval between the first and the second doses may lead to a higher vaccine efficacy; mRNA-vaccines may cause myocarditis, whereas virus-vectored vaccines may cause thrombosis by the production of abnormal antibody that activate platelets; Heterologous vaccination strategies may be feasible to broaden the selection of vaccines to be used for booster vaccination; multiple-antigen exposure by infection or vaccination induces stronger and broader immunity that is effective for variants. This learning will facilitate research and development in the next pandemic.

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