*Clinical Infectious Diseases*

SPECIAL SECTION/INVITED ARTICLE

# COVID-19—Lessons Learned and Questions Remaining

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In this article, the editors of *Clinical Infectious Diseases* review some of the most important lessons they have learned about the epidemiology, clinical features, diagnosis, treatment and prevention of SARS-CoV-2 infection and identify essential questions about COVID-19 that remain to be answered.

> "You will draw from your errors the very lessons which may enable you to avoid their repetition."
>
> - Sir William Osler, *Aequanimatus*

In January 2020, the World Health Organization announced a Chinese outbreak of a respiratory illness caused by a novel coronavirus. Since that time the COVID-19 pandemic has caused more than 38 000 000 infections and 1 000 000 deaths worldwide [1], with no end yet in sight. This has been paralleled by an explosion of the biomedical literature relating to SARS-CoV-2 and COVID-19, with more than 64 000 papers at the time of this writing. *Clinical Infectious Diseases* has received a considerable share of these manuscripts, with over 4500 COVID-19-related papers submitted to the journal in the first nine months of 2020, representing more than the total number of submissions the journal ordinarily receives in an entire year, and more than 500 papers published thus far. Clinicians and researchers battling SARS-CoV-2 are finding it challenging to surf the COVID literature tsunami. In this overview, the CID Editors distill several of the most important and surprising lessons that they have learned thus far during the pandemic (Table 1) and identify some of the most important unanswered questions moving forward (Table 2).

## EPIDEMIOLOGY

### Asymptomatic/Presymptomatic Transmission and Superspreading

Many COVID-19 infections are asymptomatic or only mildly symptomatic, and SARS-CoV-2 is frequently transmitted by infected individuals before they develop symptoms [2]. In fact, patients with COVID-19 are most contagious 1–2 days prior to the onset of symptoms [3]. One reason may be the ability of the virus to dampen the initial interferon-dependent innate immune response [4, 5], which ordinarily coincides with symptom onset in many viral infections. Asymptomatic or presymptomatic transmission has complicated efforts to identify cases and prevent spread. Tracing chains of transmission in well-defined COVID-19 outbreaks in regions without previous widespread community transmission has provided direct evidence of presymptomatic and asymptomatic viral spread [6]. Asymptomatic individuals often shed large quantities of virus in their respiratory secretions [7], and modeling studies have determined the usual incubation period of COVID-19 to exceed the serial interval between symptom onset in index and secondary cases, indicative of presymptomatic transmission [3, 8]. As observed during the SARS and MERS epidemics, episodic "superspreader events" are often associated with explosive COVID-19 transmission [9]. Epidemiologists estimate that as few as 10% of infected persons are responsible for 80% of SARS-CoV-2 transmission [10], suggesting that recognition and prevention of events at high-risk for superspreading can have a major impact on limiting the epidemic. Analysis of superspreader events in settings as diverse as choir rehearsals, call centers, nightclubs or research conferences have suggested common features to be avoided: closed poorly-ventilated indoor spaces, crowds, and close contact (the "three C's") [11–15]. A synthesis of current data suggests that exposure risk can be estimated on the basis of ventilation, density, face coverings, exposure duration and activity [16].

### Airborne versus Droplet Spread

Perhaps the biggest surprise about the issue of airborne spread of SARS CoV-2 is that it has been surprising to so many people. From the beginning of the epidemic, the ability of the virus to

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**Table 1. COVID-19: Lessons Learned**

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| **Epidemiology** |
| • Presymptomatic transmission plays an important role in community spread. |
| • 10–20% of individuals may be responsible for 80% of transmission. |
| • Short range aerosol transmission is an important route of spread, and longer-range transmission can occur in closed, poorly-ventilated spaces. |
| • Racial and socioeconomic disparities in illness are similar those seen in the HIV pandemic. |
| **Virology** |
| • Type I interferon responses play a critical role during early infection. |
| **Clinical** |
| • Age, sex and comorbidities have a major impact on disease severity and mortality. |
| • Children have generally mild illness but rarely can develop an immune-mediated Multisystem Inflammatory Syndrome (MIS-C). |
| • Severe illness with respiratory failure is associated with a proinflammatory immune dysregulation that includes a robust type 2 response. |
| • Inflammatory vascular and thromboembolic complications are frequently encountered in severe infections. |
| **Diagnosis** |
| • Nucleic acid amplification tests to detect viral RNA are recommended for diagnosis. |
| • Sensitivity of diagnostic tests can depend on specimen and assay type and is time-dependent. |
| • Antibody responses may be short-lived, particularly in mild or asymptomatic infections. |
| • IgM and IgG appear at approximately the same time. |
| • Biomarkers can predict disease progression and complications. |
| **Treatment** |
| • Large coordinated multicenter randomized clinical trials are superior to observational studies or small fragmented trials to assess novel therapies. |
| • Hydroxychloroquine appears to be ineffective. |
| • Remdesivir can shorten illness duration if given early. |
| • Corticosteroids are beneficial in critically ill patients requiring mechanical ventilation. |
| • Early superinfections are uncommon but late infections, including invasive pulmonary aspergillosis, are a risk in critically ill patients. |
| **Prevention** |
| • Vaccines are being rapidly developed and tested. |
| • Universal face mask use can reduce the efficiency of transmission. |
| • Health care workers are at risk but can be protected by appropriate PPE. |

**Table 2. COVID-19: Questions Remaining**

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| **Epidemiology** |
| • How can superspreader events be avoided? |
| • Why do infection rates and severity vary so widely among individuals and countries? |
| • Why are global COVID-19 mortality rates falling? |
| **Virology** |
| • Does viral diversity influence illness severity? |
| • Can early administration of agents such as vitamin D, famotidine or interferon prevent infection or arrest disease progression? |
| • What is the impact of prior exposure to endemic seasonal coronaviruses? |
| **Clinical** |
| • What are late complications and how can they be managed and/or prevented? |
| **Treatment** |
| • What is the treatment for mild disease? |
| • When should antifungal prophylaxis be considered? |
| • Is there a role for immunomodulatory agents in addition to corticosteroids? |
| • How should the timing of immunomodulatory interventions be optimized? |
| • Is convalescent plasma beneficial? |
| • What is the role and optimal dosing of anticoagulant therapy? |
| **Diagnosis** |
| • What is the accuracy of antigen compared to viral RNA testing? |
| • What are the correlates and durability of protective immunity? |
| **Prevention** |
| • Can effective vaccines and other targeted immunotherapeutics be found? |
| • Does low-level viral exposure lead to protective immunity? |
| • How can communities reopen and resume essential activities without incurring new waves of epidemic spread? |
| • Can upgrading ventilation systems in businesses and schools facilitate reopening? |

spread from person to person has been regularly downplayed by public health officials despite clear evidence of exceptional transmissibility, from the initial explosive spread in Wuhan to its rapid dissemination across China and to the rest of the world. A key lesson learned from this pandemic is that the distinction between "droplet" and "aerosol" spread is a false dichotomy that is inconsistent with contemporary knowledge about respiratory aerosols [17, 18]. Aerobiologists have demonstrated that particles produced in the human respiratory tract represent a continuum of sizes [19, 20].

In general, larger droplets are derived from the nasopharynx, and aerosols emerge from deeper in the lungs, including the alveoli. Larger particles are heavier and contain larger volumes and thus are less likely to hang in the air and traverse long distances. The distribution of infectious virus among larger and smaller particles is likely to be influenced by where a virus predominantly replicates. Replication of seasonal influenza (generally Influenza A H1N1 or H3N2) occurs primarily in the upper airway because of the preference of the viral hemagglutinin for 2,6-linked sialic acid receptors that dominate the nasopharynx [21], whereas as COVID-19 progresses, SARS CoV-2 preferentially replicates deeper in the lungs where its favored ACE-2 receptors predominate [22]. H1N1 and H3N2 influenza A strains cause mainly upper tract disease and spread when people sneeze and cough and expel larger droplets produced in the upper airway over short distances. In contrast, SARS CoV-2 replicates to high titers in the lungs [23] and is shed in the smaller aerosols with the air produced in breathing, talking, singing and shouting (in order of increasing magnitude) [24]. Large and small particles are both present in high quantities close to the mouth and nose of a person who is talking, and both can transmit pathogens at these distances. As one moves farther from the source, the concentration of larger and smaller particles each decline as a function of distance, but the concentration of larger particles falls more steeply because of the effects of gravity [19]. Pathogen transmission rates are inversely proportional to distance from the source whether a pathogen is carried by large or small droplets, as both are concentrated closest to the source. Interpretations of transmission data have frequently misunderstood this relationship and assumed that the relationship between distance and transmission implies the involvement of large droplets.

In the case of SARS CoV-2, virus is present in the full size range of exhaled particles, but most of it is likely to be carried in the more numerous smaller particles that originate where the greatest amount of virus is produced. Small particles may remain airborne for 30 minutes or more and can easily travel distances greater than 6 feet [17, 25]. The likelihood of infection becomes a function of the quantity of virus being produced by the source patient, distance from the source, ambient air flow and whether the producer and potential recipients of the virus are wearing face masks [19, 26, 27]. Smaller particles are much more likely to accumulate in enclosed places with poor air flow and to be transmitted where people are not wearing masks – hence providing a simple explanation for the clear epidemiological evidence that crowded bars, restaurants and gyms favor viral outbreaks and suggesting engineering interventions to reduce the risk of spread [28].

A single SARS-CoV-2-infected person talking normally can exhale millions of SARS CoV-2 viral genome equivalents every hour [29]. Like SARS-CoV, spread of SARS-CoV-2 from inadequate sewage systems is another potential, albeit uncommon, route of airborne transmission [30–32]. Outlier events in which many people have been infected, such as the infamous Skagit Valley Chorale cluster or the distant windborne spread of the virus wafting from untreated sewage, are thankfully infrequent but nevertheless provide a clear public health demonstration of what aerosol scientists have been telling us: "It is time to address airborne transmission of COVID-19" [33].

#### Comparisons with HIV

Almost 40 years ago the first cases of what we now know as HIV/AIDS were reported [34]. Since then the disease has become a major global pandemic that has infected about 76 million people with around 33 million having died. HIV defined the careers of a generation of infectious disease and HIV specialists and taught the importance of research, community engagement and politics in the response to any pandemic [35]. The first appearance of HIV generated concern about possible acquisition by health care workers in the workplace, just as COVID-19 does now. As we now confront COVID-19, there are many similarities and lessons from HIV, although the uniformly grim prognosis during the early years of the HIV/AIDS pandemic is an obvious difference.

One of the most important similarities is that SARS-CoV-2, like HIV, disproportionately affects racial and ethnic minorities and those who are marginalized and made more vulnerable by society. Published data thus far suggest that the risk of COVID-19 infection and its attendant severe complications in people with HIV is mostly attributable to underlying socioeconomic conditions and comorbidities [36]. Lowering the excess prevalence of comorbid conditions such as obesity, diabetes and hypertension in minority populations [37] should be a public health priority. Higher rates of SARS-CoV-2 infection seen across all age groups rather than differences in age-adjusted case-fatality rates suggest that a primary cause of racial disparity in COVID-19 may be differences in household, community and workplace exposure [37, 38], although biological factors may also be contributory [39].

As with COVID-19, test availability to identify infected individuals was also a major concern early in the HIV epidemic [40], as was uncertainty regarding potential routes of transmission [41]. In general, people living with HIV who are on effective antiretroviral therapy have similar risks and outcomes for

COVID-19 compared to people without HIV. However, studies from some regions such as the Western Cape in South Africa suggest that HIV may increase the risk of death from COVID-19 [42].

### Global Responses

Since the first case of COVID-19 emerged in China, many millions of people have been infected in countries as distant as the United States, Brazil, India and the Russian Federation, exemplifying the global nature of this pandemic. Only a small number of Pacific Island nations have not yet reported cases. Public health responses have been highly variable, even within individual countries. At one extreme, in New Zealand, initial cases were clearly associated with acquisition overseas and subsequent importation into the country. In that setting, attempts were made to completely eliminate the infection from the population by extremely strict border control [43–45]. However, even with this intervention, cases of unknown origin have arisen, leading to isolated community transmission. At the other extreme, in the setting of poor testing availability and overcrowding, some parts of Africa and South America have seen rapid spread within communities that is unlikely to be controlled until herd immunity is achieved or an effective vaccine becomes available, although thus far the fatality rate has been lower in Africa than on other continents, possibly due to a low seeding rate, effective mitigation measures, youthful population, warm weather, and the influence of BCG immunization or endemic viral infections [46]. Most countries lie between these extremes, with interventions based on wide scale testing and partially effective measures such as quarantine, social distancing, wearing of face masks and varying degrees of contact tracing. In almost all studies a clear relationship has been found between increasing age and poor outcomes from the infection. In this context, nursing homes have faced a high burden of cross-transmission and high mortality [47]. First Nations people in developed countries have also represented a vulnerable group [48]. Future rollout of vaccination will need to be global and targeted to the highest risk populations in each individual country.

## VIROLOGY

### Host and Viral Determinants of Virulence

A striking feature of COVID-19 is the wide spectrum of clinical manifestations and severity, which vary by region and country [49]. The complexity of factors responsible for this variation has been challenging to unravel. Age, gender and the prevalence of comorbidities such as obesity, diabetes and cardiovascular disease are important risk factors for disease progression and poor outcomes [50, 51]. In addition to the disproportionate impact of COVID-19 on racial and ethnic minorities mentioned above, potential contributing factors include population density, nonpharmaceutical infection control measures, host genetics, viral genetics, and pre-existing immunity.

Case incidence and fatality rates per capita are approximately 10-fold higher in U.S. counties in the top population density decile compared to those in the lowest quartile [52]. The potential for younger persons to transmit SARS-CoV-2 to older family members living in multigenerational households is a concern, although a clear relationship between COVID-19 fatality rates and intergenerational relationships has not yet been shown [53]. Non-pharmaceutical measures, in particular social distancing, can clearly have a major impact on reproduction number ($R_0$) [54]. Host factors are presently less well-defined, but intriguing recent observations have linked deficient type I interferon responses to coronavirus susceptibility [55, 56]; trials are in progress to determine whether the early administration of interferon can prevent disease progression. ABO blood type, HLA variants and vitamin D levels have also been suggested to influence host-viral interactions [57–60]. Randomized clinical trials will be required to determine whether agents such as vitamin D or famotidine that have been associated with improved outcomes in observational studies can ameliorate the clinical course of COVID-19 [60, 61]. Another intriguing observation is the presence of pre-existing cellular immune responses in approximately one-third of the population, possibly as a result of prior exposure to seasonal endemic coronaviruses [62]. Recent infection with endemic seasonal coronaviruses has been associated with a milder clinical course following SARS-CoV-2 infection [63]. However, it is possible that certain cross-reactive immune responses might be associated with immunopathology and more severe illness [64]. Perhaps least well understood is the contribution of viral variants. The D614G spike variant has become dominant as the pandemic has progressed, and also attains higher titers in culture and higher viral loads in patients [65]. Other variants have been associated with milder illness [66], and it remains to be seen whether differences in viral genotypes have an important influence on COVID-19 severity in individuals and communities.

Intriguingly, mortality rates from COVID-19 appear to be falling in multiple countries as the pandemic is continuing to evolve [67]. Although demographic changes, with more infections occurring in younger age groups, appear to be part of the explanation, other contributing factors may include testing rates, nonpharmaceutical interventions, pre-existing immunity, weather, improvements in management, and changes in circulating viral strains.

## CLINICAL

### Infections in Children

The clinical manifestations of SARS-CoV-2 infection in children are relatively benign, with 90% remaining completely asymptomatic or having mild-to-moderate disease [68–70]. The reasons for milder disease in children are presently unclear. Possible contributing factors include more robust early innate

immune responses [71], cross-protection from seasonal coronavirus exposure, differences in ACE2 expression, nonspecific effects of vaccination and greater memory T-cell diversity [72, 73]. The mild course of COVID-19 is quite different from other respiratory illnesses in children, such as influenza and respiratory syncytial virus, which impact children more severely than adults and in which children are the major mediators of transmission. COVID-19 incidence in adolescents aged 12–17 years is approximately twice that in children aged 5–11 [74]. Children may transmit SARS-CoV-2 to other children and adults, but are not generally thought to play a major role in community spread. As in adults, higher rates of disease and hospitalization are seen in Hispanic and Black children in comparison to non-Hispanic White children [70]. Although the number of COVID-19-related pediatric hospitalizations remains low, one in three children who are hospitalized require admission to the Intensive Care Unit, similar to adult rates [70].

An uncommon but serious manifestation of pediatric COVID-19 disease is Multisystem Inflammatory Syndrome in Children (MIS-C), an acute inflammatory syndrome characterized by fever, rash, conjunctivitis, abdominal pain, shock, and cardiac dysfunction [75–86]. MIS-C is more common in older children (average 8–11 years) and generally presents between 2 to 4 weeks after SARS-CoV-2 infection, suggesting that it is a postinfectious immunologic phenomenon. A similar syndrome has been recently described in adults as well [87]. Treatment of MIS-C usually entails the administration of immunomodulatory agents such as high-dose intravenous immunoglobulin, corticosteroids, aspirin, or rarely more targeted anti-inflammatory medications [75–78, 83, 84, 86]. Most children with MIS-C recover completely, but some may exhibit long-lasting cardiac dysfunction.

#### Clinical Presentations

Following an incubation period that averages 5 days [88], cough, dyspnea and fever are the symptoms most frequently associated with COVID-19, but no symptoms are sufficiently sensitive nor specific to rule-in or rule-out the diagnosis [89]. Nevertheless, some differences in the usual presentation of influenza and COVID-19 have been observed. Influenza is more likely to exhibit an abrupt onset of upper respiratory tract symptoms, fever, sputum production and myalgias, while COVID-19 is more likely to be gradual in onset, with nonproductive cough, disturbances of taste or smell (dysgeusia and anosmia), diarrhea, and frontal or retro-orbital headache [90]. Disturbances of taste or smell are especially common in mild cases [91, 92]. Chilblain-like lesions ("COVID toes") have been reported, but their relationship to COVID-19 is presently controversial [93]. The ability of SARS-CoV-2 to infect sustentacular cells of the olfactory epithelium has been suggested as an explanation for the frequent occurrence of anosmia and dysgeusia [94, 95]. Although primarily a respiratory tract infection, severe COVID-19 is characterized by multiorgan system involvement, and cardiac or renal injury are poor prognostic indicators [96, 97]. Prolonged gastrointestinal shedding has been observed in convalescent patients [98], but its importance in transmission has not yet been well defined. Hospitalized patients frequently report persistent fatigue, dyspnea and arthralgias for weeks after discharge, and further study is required to understand the frequency and nature of long-term complications [99–101].

#### Immune Dysregulation

A striking aspect of severe COVID-19 disease is the development of respiratory failure progressing over days to weeks with an increasing requirement for supplemental oxygen, peripheral patchy ground glass infiltrates on chest CT, and the frequent presence of pleuritic pain not often seen with other viral pneumonias. Plasma cytokine measurements provide evidence of immune dysregulation with the simultaneous activation of every arm of the immune system, including type 1, 2 and 3 responses. Although some have questioned characterizing the hyperinflammatory state of COVID-19 as a "cytokine storm" since IL-6 levels are less markedly elevated compared to sepsis [102], IL-6 levels ≥80 pg/ml are associated with a substantially increased risk of respiratory failure and death [103]. An alternative hypothesis suggests a central role for bradykinin in the inflammation and increased vascular permeability observed in COVID-19 [104]. Respiratory failure appears to be associated in particular with a type 2 immune response, typified by IL-13 production, which is higher in patients requiring mechanical ventilatory support [105]. Although type 2 immune responses are protective in the gut [106, 107], they are deleterious in the lung [108]. Eosinophils can cause alveolar damage and increase airway hyperreactivity, in part through goblet cell metaplasia, mucus hypersecretion, fibrosis and smooth muscle changes. IL-13 induces eosinophils to migrate to the lung via the induction of IL-5 and eotaxins [109, 110]. Therefore type 2 immunity may be contributing to the respiratory failure of patients with COVID-19. Studies in animal models have been initiated to determine whether type 2 immunity is causally related to respiratory failure associated with SARS-CoV-2. The presence of eosinophils, neutrophils and monocytes in alveoli support a pathogenic role of type 2 immunity [111]. Future research will determine whether the blockade of type 2 immunity can protect patients with COVID-19 from lung injury.

#### ARDS and Vasculopathy

One of the most serious complications of severe COVID-19 is the development of acute respiratory distress syndrome (ARDS) [112]. Diffuse alveolar damage, the characteristic pathologic correlate of ARDS, is a common finding in autopsy studies [113]. However, controversy has arisen over whether COVID-19 causes classical ARDS or a distinct form of lung injury requiring different treatment approaches [114, 115]. An emerging

consensus is that the ARDS observed in COVID-19 is typical in many respects and usually responds to proven interventions for ARDS [116], but some patients have an unusually prominent component of an inflammatory vasculopathy that can result in occlusion of large and small pulmonary blood vessels and may require specific intervention [117–119]. Endotheliitis, complement activation, dysregulated inflammation, neutrophilic extracellular traps, autoantibodies and a hypercoagulable state may contribute to the development of COVID-associated vasculopathy [120–125]. Full dose heparin and even thrombolytic therapy have been used with some evidence of clinical benefit in patients with ongoing thrombosis but have yet to be proven effective in clinical trials [126, 127] (current guidelines favor LMW heparin to minimize staff exposure [128]). The discovery that cell surface glycans interact with the ACE2 viral receptor suggests that heparin may have an antiviral effect in addition to its anticoagulant actions [129]. Although heparin shifts the SARS-CoV-2 spike protein to an open conformation that binds ACE2, heparin competes with cell surface heparan sulfate and can block virus binding to cells [129].

#### *Aspergillus* Superinfections

Bacterial and fungal superinfections are generally uncommon in patients with COVID-19 [130], but can become more frequent with prolonged ICU stays and the administration of immunomodulatory agents [131]. Secondary invasive pulmonary aspergillosis (IPA) has been previously reported in patients with influenza and SARS pneumonia [132–134], and recent observations from China and multiple European countries suggest that secondary IPA is also encountered in patients with critical COVID-19 [135–140]. The reported incidence of COVID-associated pulmonary aspergillosis (CAPA) in critically ill patients varies (7–35%), with potential reasons including different diagnostic methods, diagnostic criteria, and patient populations. The radiographic diagnosis of IPA superimposed on viral pneumonia is challenging, and CT scans are difficult to obtain in critically ill patients, especially in those receiving extracorporeal membrane oxygenation. Reluctance to perform bronchoscopy due to infection control concerns and a lack of fungal antigen test availability in many centers may contribute to underrecognition [141]. Importantly, treating CAPA may result in lower mortality [135]. Many gaps currently exist in our understanding of CAPA, including the role of diagnostic sampling by nonbronchoscopic methods, the utility of antigen or nucleic acid amplification testing, and the potential use of antifungal prophylaxis. Immunologic risk factors for CAPA and the importance of hyperinflammation, immunosuppression and respiratory mucosal injury remain to be defined [142].

#### Immunocompromised Hosts and Solid Organ Transplant Recipients

The reported susceptibility of immunocompromised individuals to SARS-CoV-2 has been variable. Cancer patients who recently received chemotherapy may be at higher risk for severe illness, while outcomes in hematopoietic cell transplant recipients or patients receiving immunosuppressive agents are generally favorable, and outcomes in persons with HIV are largely dependent on other comorbidities [143–146]. The field of solid-organ transplantation (SOT) has been profoundly impacted by the COVID-19 pandemic, with a substantial reduction in the number of life-saving transplants performed during the initial phases of the pandemic [147]. This resulted from concerns about the general impact of the epidemic on health systems and specific concerns about the potential for higher morbidity and mortality in patients with SOT-associated immunosuppression, as seen with other respiratory viral infections, as well as the potential for SARS-CoV-2 to be transmitted via transplant. All of this has occurred in the context of regulatory guidance that SOT should be considered a tier 3b procedure, ie, a procedure that should not be delayed because the benefits significantly outweigh the risks [148]. The clinical manifestations of COVID-19 in SOT recipients are likely to reflect a balance between the consequences of calcineurin inhibitor effects on host pathways required for viral replication and impaired T cell activation and expansion [149, 150]. Several observations have emerged from cohort studies focusing on the clinical presentation and outcome of COVID-19 in SOT recipients. The frequency of certain clinical manifestations (fever, gastrointestinal symptoms) may differ in SOT patients, perhaps related to effects of immunosuppression [151–153]. Limited data suggest that the risks for acquisition and progression of infection to clinical symptoms may be higher than in the general population, related to behavioral factors such as more frequent contact with the healthcare system and biological factors such as co-morbidities and the effects of immunosuppression [151]. For patients requiring hospitalization due to COVID-19, short-term morbidity and mortality appear to be high and generally similar to non-SOT populations. Available evidence suggests that COVID-19-related mortality in SOT recipients is largely driven by underlying co-morbidities rather than by immunosuppression [151–153]. In fact, similar mortality despite higher comorbidities is seen in hospitalized SOT COVID patients, hinting at the possible modulation of illness severity by immunosuppression. This interesting possibility warrants further study. SOT recipients may be less likely to respond to vaccines and may require broader preventive strategies, including passive immunity and behavioral interventions to limit exposure.

## DIAGNOSIS

#### Innovations in Diagnostics

Diagnostic testing has been front and center in the COVID-19 pandemic, and IDSA guidelines on SARS-CoV-2 viral RNA and antibody testing have been prepared and published in record time [154, 155]. Laboratory supply chain challenges have

also been unprecedented, but are driving testing innovations that will hopefully facilitate COVID-19 control and also lead to improvements in other microbial diagnostics in the future. Viral RNA detection by nucleic acid amplification testing continues to play a central role in diagnosis, but imperfect sensitivity and prolonged shedding of RNA in the absence of viable virus require careful test interpretation [156–158]. Some assays exhibit differences in sensitivity [159]. Antigen tests may improve speed and accessibility of testing; however, their accuracy is incompletely defined in the published literature and will have to be carefully assessed in order to minimize any consequences of false-positive or -negative results [160, 161].

Nasopharyngeal viral shedding peaks shortly before the onset of symptoms and declines thereafter, making the timing of sampling relative to symptom onset an important determinant of test performance [3, 162]. Viral load in the lungs or plasma may be more reflective of disease progression [163]; the detection of viral RNA in plasma ("RNAemia") correlates with more severe illness [164–168]. Some studies have correlated nasopharyngeal viral load at the time of presentation with clinical outcomes and the ability to isolate SARS-CoV-2 in culture [157, 169–173]. Viral load varies inversely with cycle threshold (Ct) or crossing point values measured in a quantitative real-time PCR assay. However, the accuracy and precision of current assays have not been validated with regard to quantitative interpretation, and Ct values may vary based on the quality of sample collection and between methods [174]. Although chest CT abnormalities may be evident in some patients with COVID-19 who have negative viral RNA tests [175], the positive predictive value of a viral RNA test is far superior to radiographic imaging [176].

Patient self-collection of respiratory tract specimens and the use of alternative samples such as mid-turbinate swabs, anterior nasal swabs, throat swabs and saliva may help to alleviate shortages of testing supplies and personal protective equipment [177, 178]. Easy-to-collect specimen types such as saliva, being used for the first time in clinical practice, provide convenience and cost advantages for mass screening [179]. Whether findings with SARS-CoV-2 will generalize to other infectious diseases in the future remains to be determined.

A variety of inflammatory biomarkers are predictive of COVID-19 progression and may be monitored and used to guide immunomodulatory therapy, including lymphopenia, the neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, and IL-6 [103, 180]. SARS-CoV-2 serologic testing has revealed a few surprises. In contrast to most other viral infections in which IgM precedes the presence of IgG, SARS-CoV-2 IgM and IgG appear at approximately the same time, rendering IgM detection of questionable utility [155]. It is hoped that SARS-CoV-2 infection will confer protective immunity in most cases, but robust supporting clinical evidence is still awaited [181]. IgG and neutralizing antibodies may start to decline as early as the first three months following symptom onset in individuals with mild infections [182]. Laboratory correlates of protective immunity remain to be defined, including in specific populations (eg, newborns, the elderly, the immunocompromised) [155].

## TREATMENT

### Observational and Retrospective Studies

It was predictable that a pandemic caused by a novel pathogen would expose critical knowledge gaps ranging from transmission to disease complications, and from management to prevention. The scientific community has had to balance the need to fill these gaps as quickly as possible with limited quality evidence available in most early reports, unavoidably based on observational and often retrospective studies, with inherent limitations including small sample sizes, confounding, selection bias, inadequate controls, lack of blinding, uncertain generalizability and variable follow-up. Many early studies tested drugs that were readily available but accompanied by little or no in vitro evidence specifically relating to the susceptibility of SARS-CoV-2. As a result, much of the early COVID-19 treatment literature is of lower quality than the standard to which the clinical research community had become accustomed. All too often this has resulted in the publication of low quality evidence that is difficult to interpret. For example, after treatment of more than 20 000 individuals with convalescent plasma, considerable uncertainty remains as to whether it is beneficial and which patients are most likely to benefit [183, 184]. Editorial commentaries have played a critical role in helping to contextualize published data and its limitations.

Ultimately it is anticipated that preliminary results of smaller studies will give way to the results of larger, higher quality multicenter randomized controlled clinical trials. Hype, misinformation, and social and political pressures may have sometimes led to false hopes and hasty decisions. Several initial reports regarding the utility of hydroxychloroquine and the detrimental effects of corticosteroids turned out to be incorrect as the pandemic proceeded, and higher quality studies superseded earlier ones, necessitating the revision of treatment guidelines. Looking to the future, these experiences suggest that procedures to rapidly organize, fund and implement large clinical trials should be substantially improved. Federally funded rapid start-up networks to support pandemic research may play an important role in a time of crisis. The ACTT (Adaptive COVID-19 Treatment Trial) program provides a good example, in which innovative trial design led to an Emergency Use Authorization for remdesivir [185]. In the United Kingdom, a national effort to recruit into a single platform of trials (the "RECOVERY" trial) yielded practice-changing results on the roles of dexamethasone, hydroxychloroquine and lopinavir-ritonavir within months of the onset of the pandemic [186–188]. As we move into the next phase of COVID platform clinical trials, it will be

critical to ensure the rapid dissemination of results and a resetting of expectations on the quality of evidence required to meet evolving standards.

#### Clinical Trials

The urgent need for high quality clinical trials to inform treatment and prevention has been all too clear during the COVID-19 pandemic. Approximately one-third of respondents in a recent CDC survey engaged in nonrecommended high-risk practices in the hope of preventing SARS-CoV-2 transmission, including the application of bleach to food and household disinfectants to skin, and inhalation or ingestion of cleaners and disinfectants [189]. Physicians, desperate to help their patients who were dying of COVID-19, also tried a variety of similarly unconventional therapies. As mentioned above, a plethora of retrospective case series reported survival benefit for a host of treatments. Some, such as lopinavir/ritonavir, were quickly shown to not provide benefit [190], while others such as hydroxychloroquine/chloroquine, persisted amidst significant controversy.

On March 28, 2020, the FDA granted Emergency Use Authorization (EUA) for hydroxychloroquine for the treatment of COVID-19-infected patients. However, in the ensuing months, a series of well-designed randomized controlled trials demonstrated that neither hydroxychloroquine nor chloroquine improved outcomes in hospitalized and nonhospitalized patients with COVID-19 infection [187, 191–194], nor reduced rates of COVID-19 infection when administered as postexposure prophylaxis following high-risk exposures to SARS-CoV-2 [195, 196]. In response, the FDA revoked the EUA for hydroxychloroquine on June 15, 2020 [197].

The RNA polymerase inhibitor remdesivir was also evaluated for the treatment of COVID-19. A multinational, randomized, double-blind, placebo-controlled trial in hospitalized patients with laboratory-confirmed SARS-CoV-2 infection found that remdesivir significantly reduced the median time to recovery compared to placebo (11 vs. 15 days; $P < .001$). This benefit was most pronounced in the subgroup of patients who required supplemental oxygen at the time of randomization. Although remdesivir appeared to confer a mortality benefit at day 14 in a *post hoc* analysis of this subgroup (HR for death 0.22; 95% CI: .08–.58), the mortality difference in the entire study cohort did not achieve statistical significance (7.1% remdesivir vs. 11.9% placebo, HR 0.70; 95% CI: .47–1.04) [185]. An industry-sponsored trial subsequently demonstrated that remdesivir treatment for either 5 or 10 days had similar clinical benefit among hospitalized COVID-19 patients not on mechanical ventilation [198]. Based upon these findings, the NIH and IDSA COVID-19 Treatment Guidelines Panels recommend using remdesivir for 5 days or until hospital discharge for patients with COVID-19 requiring supplemental oxygen without the need for a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO [199, 200]. Whether remdesivir confers a mortality benefit is unknown [201, 202].

Most recently, the WHO made available the interim results of its SOLIDARITY trial [203]. Over 11 000 adults from over 400 hospitals in 30 countries who were hospitalized with COVID-19 were randomized to receive either remdesivir, hydroxychloroquine, lopinavir, interferon plus lopinavir, interferon only, or no study drug. The intent-to-treat primary analysis was in-hospital mortality in the four pairwise comparisons of each study drug vs. its control. In a preprint version of the manuscript that has not yet undergone peer-review, none of the regimens appeared to improve mortality, rates of progression to mechanical ventilation, or length of hospitalization. The hydroxychloroquine and lopinavir treatment arms were discontinued for futility on June 18 and July 4, 2020, respectively. These findings dampen prospects of repurposing existing antivirals to treat moderate-to-severe COVID, although the possibility that one or more of these agents may benefit subsets of patients remains a possibility, particularly during the early stages of infection when antiviral agents are most likely to be beneficial [204, 205].

Several clinical trials have evaluated interventions to attenuate the host immune response. Some host immunomodulatory strategies, such as the IL-6 receptor antagonists sarilumab and tocilizumab, have thus far not been proven to improve clinical outcomes in patients with severe COVID-19 [206, 207]. Although observational data suggest a possible mortality benefit, at the expense of an increased risk of secondary infection [131, 208], a reduction in mortality from IL-6 inhibition has not yet been demonstrated in randomized clinical trials. However, dexamethasone has been shown to confer a significant mortality benefit in a multicenter, open-label, adaptive randomized trial involving over 6400 hospitalized patients with severe COVID-19 infection. Patients receiving dexamethasone were significantly less likely to die within 28 days of enrollment than patients receiving standard of care (22.9% vs. 25.7%; age-adjusted rate ratio 0.83; 95% CI, .75–.93; $P < .001$) [186]. The benefits of dexamethasone were most apparent in hospitalized patients who were mechanically ventilated (29.3% dexamethasone vs. 41.4% standard of care; rate ratio 0.64; 95% CI, .51–.81), with no benefit observed in patients not requiring oxygen support. Other trials of immunomodulatory drugs are in progress, and it remains possible, if not likely, that some will be shown to be beneficial. Patient selection and the timing of therapy are likely to be important factors, as immunomodulation is a two-edged sword, and some agents have been found to reduce signs of inflammation but increase the likelihood of opportunistic superinfections.

As noted above, the COVID-19 pandemic has already led to advances in how clinical trials are conducted. Several studies have adopted ordinal scales of disease severity as a primary endpoint [185, 194, 198]. These scales can provide a

more comprehensive representation of the patient experience and accommodate a superiority analysis of endpoints, which often reduces the required sample size. Several clinical trials groups have also successfully employed adaptive clinical trial design. Adaptive trials improve efficiency by simultaneously testing several treatments and allowing the addition of new trial arms based on emerging evidence. A final lesson re-learned from the COVID-19 pandemic is the importance of scientific rigor. Several studies have been underpowered due to inadequate enrollment [192, 209] or because the primary study endpoint was changed without a re-calculation of statistical power [194]. Such shortcomings limit confidence in the interpretation of study results. Nowhere is the need for scientific rigor more pressing than in the current and planned clinical trials to test vaccines for COVID-19, in part because of the need to ensure both efficacy and safety. The possibility of paradoxical adverse immunological effects from a SARS-CoV-2 vaccine is real and has been observed with other vaccines against dengue, *Staphylococcus aureus* and respiratory syncytial virus [210–212]. Reassuringly, the CEOs of nine companies with candidate COVID-19 vaccines in late stage clinical trials have announced a united commitment to uphold the integrity of the scientific process as they work towards approval of the first COVID-19 vaccines [213].

## PREVENTION

### Duration of Immunity and Implications for Vaccines

Virus-specific antibodies develop within 1 to 2 weeks after COVID-19 symptom onset, and levels of antibody to the SARS-CoV-2 spike domain correlate with a fall in plasma RNA levels and clinical recovery [165]. SARS-CoV-2-specific neutralizing antibodies target the receptor-binding domain (RBD) of the viral spike protein S1 subunit and compete with its binding to human angiotensin converting enzyme 2 (ACE2), thereby decreasing viral entry and subsequent replication [214, 215]. Pre-existing immunity to common seasonal human coronaviruses is associated with some cross reactivity to the SARS-CoV-2 spike and nucleocapsid proteins but does not confer neutralizing activity against SARS-CoV-2 in vitro [216]. In an observational study of 175 hospitalized adults with mild COVID-19 infection requiring hospitalization, neutralizing antibody responses varied considerably and correlated with sex, age, CRP levels and lower lymphocyte counts [217]. Levels of neutralizing antibody correlate with illness severity and decline within 2 months in a third or more of patients, suggesting that humoral immunity to SARS-CoV-2 can be short-lived [165, 218, 219]. However, a large, population-based study in Iceland found that more than 90% of persons were seropositive by two different pan-immunoglobulin (IgM, IgG, IgA) assays 2 months after recovery from COVID-19, and antibody levels remained stable for at least 4 months after recovery [220].

IgG antibodies against SARS-CoV-2 are unlikely to provide durable protective immunity against reinfection. Based on experience with endemic seasonal human coronaviruses (229E, OC43, NL63 and HKU1), for which re-infection may occur as soon as 90 days after infection onset, the possibility of SARS-CoV-2 re-infection has been anticipated [221]. As of eight months after the beginning of the pandemic, there have been at least five reported cases of reinfection with SARS-CoV-2 (Hong Kong, Nevada, Netherlands, Belgium, India). In the first report, re-infection with a phylogenetically distinct strain of SARS-CoV-2 was detected in a 33-year-old-man who was routinely screened on return from Europe 147 days following his initial COVID-19 infection [222]. This patient remained asymptomatic although he developed elevated CRP and IgG seroconversion, consistent with true re-infection. This anecdote suggests that pre-existing immunity may ameliorate the severity of re-infection, but also raises concern that herd immunity will not be adequate to eliminate ongoing SARS-CoV-2 circulation and that vaccines may be unable to provide long-term protection against COVID-19. Although serum antibody levels wane rapidly after infection, persons with asymptomatic or symptomatic COVID-19 infection develop SARS-CoV-2 specific memory B and T cell immunity that might provide protection against symptomatic or severe re-infection [223, 224]. Following mild infection, SARS-CoV-2-specific CD4+ T cells activate memory B cells to produce virus RBD-specific neutralizing antibodies [223]. SARS-CoV-2-specific CD8+ memory T cell responses are directed primarily to the S and M proteins, and the highest response frequencies are seen among those who have recovered from severe COVID-19 infection [225]. These CD8+ memory T cells produce effector cytokines (IFN-γ), and upon antigen reencounter, can expand and directly kill virus-infected cells [223, 225]. Similar B and T cell activation profiles have been observed after successful immunization and suggest that cellular immunity may mitigate the severity of COVID-19 re-infections [226]. However, much remains to be learned about SARS-CoV-2 immunity, and other observations have correlated CD4+ T cell responses with immunopathology.

It is hoped that an effective vaccine will play a key role in terminating the COVID-19 pandemic. Monoclonal antibodies are also under active investigation as targeted immunotherapeutics for both prevention and treatment of COVID-19 [227]. Monoclonal antibodies directed to non-overlapping epitopes of the SARS-CoV-2 spike protein have been shown to reduce viral load and ameliorate virus-induced pathology in primate and hamster models [228]. Emergency use authorization from the FDA has been applied for. Potential vaccine platforms include protein-based vaccines, inactivated whole virus and live attenuated viral vaccines, viral vector-based vaccines, and DNA- and RNA-based vaccines, and all are being developed simultaneously [229]. An analysis of 18 514 sequenced viral genomes found limited diversity and suggested

that a single vaccine could cover currently circulating SARS-CoV-2 lineages [230]. Among the four structural proteins of SARS-CoV-2, the spike (S) protein receptor binding domain (RBD) is a target of neutralizing antibodies that interfere with RBD-ACE2 binding and is the primary focus of current vaccine development. Inactivated/killed or live attenuated vaccines have an advantage over novel vaccine platforms in utilizing existing manufacturing infrastructure and a greater potential to induce sustained immunity, but are likely to require more time and safety testing. Challenges with new vaccine platforms include reactogenicity (RNA), cold-storage requirements (RNA, DNA), delivery method (DNA), antigen integrity (protein) and antivector immunity, which can limit vaccine effectiveness [229]. Although antibody-dependent enhancement as seen in dengue is unlikely, animal tests of previous SARS and MERS vaccines have suggested the potential for vaccine-induced immunopathology, which will have to be monitored carefully [212]. The WHO list of vaccines under development was updated on September 28, 2020, and includes 40 vaccines in clinical evaluation and 151 in preclinical development [231]. As of September 2020, eleven candidate vaccines have entered into international Phase 3 clinical trials, including three inactivated whole virus vaccines, two mRNA vaccines, four replication-defective viral vectors, one protein-based vaccine and one BCG trial to assess its impact on COVID-19 infection. A two-dose (prime-boost) strategy with doses spaced 3–4 weeks apart will likely be needed to achieve protective immunity. The timeline for candidate vaccine approval and licensure is likely to stretch into 2021.

#### Protecting Health Care Workers

Health care workers are at increased risk for SARS-CoV-2 acquisition. One study of nearly 100 000 health care workers and more than 2 million nonhealth care workers found a 3.4-fold higher hazard ratio in health care workers after adjustment for testing rates [232]. However, although some health care workers have developed severe or fatal COVID-19 [233], several studies suggest that they are more likely to experience mild or subclinical illness [234], possibly due to the protective effects of personal protective equipment and universal masking in the hospital setting, which can reduce the concentration of viral inoculum reaching mucosal surfaces [235]. Although the infective dose in humans is not known, inoculum is a determinant of disease severity in COVID-19 animal models [236]. For comparison, the 50% infectious dose of SARS-CoV is estimated to be 280 viral particles [237, 238]. Break rooms and common work areas may be important sites of nosocomial transmission where PPE is removed and social distancing is inconsistently observed [239]. Not surprisingly, health care workers are exposed to SARS-CoV-2 in the community as well, and community transmission rates are reflected in the health care workforce [240]. Shortages of PPE have increased risk as well as worker stress, although the ability to sterilize and reuse N95 respirators has helped to alleviate shortages [241].

Recommendations for PPE use are evolving, and this has correlated with a reduction in COVID-19 infections in the health care workforce over time [242]. Although increasing evidence suggests that short-range airborne spread is the predominant route of SARS-CoV-2 transmission, medical/surgical masks used for droplet precautions appear to be nearly as effective as N95 respirators [243], which are more effective at blocking micron-sized aerosols. Although this is often misinterpreted as evidence against airborne spread, the reason may be that medical or surgical masks have fairly high effectiveness in blocking aerosols in the supermicron size range [244]. A graded approach to prevention that balances exposure risk, provider tolerability and PPE availability is now advocated [245].

#### Reopening Safely

After gaining control of local SARS-CoV-2 spread by social distancing and other nonpharmaceutical interventions, many communities are now grappling with the challenge of reopening safely while the viral threat remains. Growing awareness of settings in which superspreading events are most likely to occur (see above) form the basis of a gradual resumption of lower risk activities while continuing to restrict high-density close contact in poorly-ventilated indoor settings [246]. The recognition of airborne transmission should focus greater attention on upgrading ventilation systems in businesses and schools to allow safe reopening [247, 248]. Once ongoing transmission is sustained at a low level, rapid contact tracing, testing and isolation assume an important role, requiring a substantial investment in local public health and laboratory resources. However, contact tracing efforts can easily become overwhelmed as transmission rates accelerate [249]. The use of masking and PPE in public and health care settings is essential. Although fomites are no longer thought to play a major role in SARS-CoV-2 transmission [250], the ability of SARS-CoV-2 to survive for hours on human skin or environmental surfaces [25, 251, 252] underscores the continuing importance of hand hygiene and environmental decontamination.

Thus far, the most successful outcomes have been achieved by countries that have rigorously enforced a broad range of nonpharmaceutical interventions until community transmission rates reach an reproduction number ($R_0$) < 1, or surrogate measures such as a local test positivity rate <1–2% have been achieved [253]. The initial $R_0$ for SARS-CoV-2 was estimated to be 2.5, comparable to that of SARS-CoV and the 1918 influenza pandemic, and higher than that of MERS-CoV ($R_0$ 0.9) and the 2009 H1N1 influenza pandemic ($R_0$ 1.5) [254]. However, limitations of the $R_0$ as a guide to COVID-19 prevention must be noted. Superspreader events illustrate that methods to calculate $R_0$ are imprecise [255, 256] and fail to represent the heterogeneity of transmission within a population [9]. It remains

to be seen how effectively communities will be able to control transmission rates with targeted interventions without resorting to recurrent lockdowns as new waves of infection occur [257]. Many believe that an effective vaccine will be necessary to truly end the pandemic, although experience with the HIV pandemic suggests that highly effective treatment and prophylactic measures might be able to accomplish a similar outcome (although this may be more challenging for a respiratory virus capable of airborne spread). Some countries such as Taiwan and New Zealand have largely been able to re-open their economies and resume many normal activities by continuing to enforce some control measures even in the absence of an effective treatment or vaccine, while the U.S. has unfortunately learned the consequences of inconsistently applied public health measures, leading to recurring waves of new infections and deaths. Examples of best practices for safely re-opening schools, places of employment, and local businesses and venues are increasingly reported but may depend on local socioeconomic and sociocultural factors for successful implementation [258, 259].

Since COVID-19 emerged in China in late 2019, we have been humbled by its unique features and devastating consequences. Although this is by no means a comprehensive review, we are grateful for the opportunity to share some of what we have learned as we look to the future in the hope that this terrible pandemic can soon be brought to an end.

## Notes

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