COVID-19 and Lessons to be Learned from Prior Coronavirus Outbreaks

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A novel coronavirus was quickly recognized as the cause of a cluster of severe pneumonia cases in China circa December 2019. Now known as COVID-19, the epidemic caused by the SARS-CoV-2 virus rapidly surged to pandemic proportions with sweeping global public health and economic consequences. In this review, we aim to discuss the emergence of this novel coronavirus in the context of the virus characteristics and pathogenesis, transmission, clinical syndrome, and potential therapeutics or vaccines.

COVID-19 Virology

Coronaviruses are large RNA viruses that are endemic among bats globally. These bat viruses are known to readily recombine and present an ever-present potential to jump host species, allowing for emergence into novel hosts.[1] Four seasonal human coronaviruses (hCoV) circulate yearly as mild "common cold" viruses causing upper respiratory symptoms: OC43, HKU1, NL63, and 229E. Additionally, three novel coronaviruses have emerged as zoonotic human infections in the past 17 years. SARS-coronavirus (SARS-CoV), Middle East Respiratory Syndrome coronavirus (MERS-CoV), and the 2019 novel coronavirus (SARS-CoV-2)[2] have each been associated with lower respiratory symptoms, progressing in a subset of individuals to acute respiratory distress syndrome (ARDS) and death.

The full genome sequence of SARS-CoV-2 shares some striking similarities to SARS-CoV.[2] SARS-CoV-2 is a member of the betacoronavirus 2b clade that includes the original SARS-CoV (sharing 79.5% sequence homology), as well as a more distant seasonal hCoV, OC43.[3] SARS-CoV-2 also uses the same human host receptor as SARS-CoV for viral entry, angiotensin

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converting enzyme 2 (ACE2) (Figure 1). [3] Although many questions about the increased pathogenicity of emergent zoonotic coronaviruses remain unanswered, the receptors used for host cell entry play a pivotal role. The spike glycoprotein of the virus is responsible for receptor binding and entry, and is the main determinant of host range. Both SARS-CoV and SARS-CoV-2 use ACE2, while MERS-CoV uses dipeptidyl peptidase 4 (DPP4). Interestingly NL63, a hCoV which also uses ACE2 as the host receptor but typically causes mild upper respiratory disease, was the cause of a cluster of severe pediatric pneumonias in China in 2018, during which half of the patients were identified with viruses containing a specific substitution in the Spike glycoprotein that enhanced binding to and entry via ACE2.[4] The same substitution does not have a role in the current COVID-19 outbreak, as SARS-CoV-2 has a structurally dissimilar spike glycoprotein and recognizes a different epitope of ACE2 (Figure 1). Nonetheless, the acquisition of “minor” changes in the Spike glycoprotein may contribute to the increased virulence of zoonotic coronaviruses. The SARS-CoV-2 Spike binds ACE2 with 10- to 20-fold higher affinity than SARS-CoV Spike, which may affect transmission or pathogenesis.[5]

COVID-19 Pathogenesis

The severe respiratory compromise of SARS and COVID-19 are likely mediated by mechanisms including: a combination of direct cytopathic effects, immune-mediated pathology, and downregulation of ACE2 within the lung.[6] Severe pulmonary damage in SARS was associated with increased inflammatory cytokines, recruitment of macrophages and neutrophils to the lungs, and higher viral titers.[7] Autopsy data showed histologic evidence of acute lung injury

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with denuding of the ciliated epithelia, diffuse alveolar damage, and hyaline membrane formation indicative of ARDS.[7] A pathology report from a single COVID-19 patient shows similar histology.[8] ACE2 is normally expressed on type II pneumocytes and the apical surface of ciliated airway epithelial cells, serving as an entryway for direct cytopathology.[9] Functionally, ACE2 acts as a negative regulator of angiotensin II in the renin-angiotensin-system (RAS), potentially providing a protective role in ARDS by promoting anti-inflammatory and anti-fibrotic effects.[9] In animal models, downregulation of ACE2 increased lung pathology (pulmonary edema and acute lung failure), which was restored by supplemental recombinant ACE2.[9] SARS-CoV infection prompted shedding of the ACE2 ectodomain, removing the catalytic function of ACE2 and possibly potentiating the development of ARDS.[6] This shedding can be induced by the SARS-CoV Spike glycoprotein alone, and is more rapid than the shedding elicited by the Spike glycoprotein of NL63 (seasonal hCoV).[6] It can be hypothesized that the Spike glycoprotein of SARS-CoV-2, with its structural similarity and higher affinity binding to ACE2, provokes a similar mechanism of lung pathology leading to ARDS with severe COVID-19.

The overall case fatality rates for SARS and MERS was 10% and 35%, respectively.[10] Although crude case fatality is hovering around 4% for COVID-19 this estimation is exaggerated by limitations in testing and underestimated by the lag in deaths, with the adjusted CFR estimated to be between 0.25 and 3%.[11,12] The three emergent coronavirus infections share the trend of high mortality rates among older adults. The mortality rate was >50% for individuals over 65 years with SARS and a mortality rate of 86.2% was published for individuals over 80 years of age with MERS.[10] An analysis of 72,314 COVID-19 cases by the China CDC showed a strong association between older age and mortality.[13] While individuals under 50

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years of age showed a case fatality rate less than 0.5%, mortality increased with each subsequent decade, to 1.3% in those 50-59 years up to 14.8% in individuals 80-89 years old.[13] Furthermore, severe outcomes have been observed for both COVID-19 and MERS in individuals with comorbidities, such as chronic kidney disease or diabetes.[13] In contrast, cases in children appear to be rare and more mild, with asymptomatic cases and no deaths reported for children under 10 years of age.[13–15]

Transmission and Prevention

Unique among the severe coronavirus outbreaks, SARS-CoV-2 appears to be efficiently transmitted person to person, including from individuals with minimal symptoms. Viral transmissibility is not as simple as the basic reproduction number, or R_0, but it provides a clue to understand transmission potential. The early R_0 for SARS-CoV-2 was estimated at 2.2, indicating that on average one individual would transmit the virus to 2.2 additional people.[16] The R_0 for SARS-CoV (2003) was estimated as 3, but severe symptoms typically preceded transmission thus facilitating epidemiological measures to control the pandemic.[17] In comparison, MERS infections have continued in Saudi Arabia over the past 8 years, without efficient human-to-human transmission (an R_0 below 1) but with ongoing spillover events from camels sustaining the outbreak.

Epidemiological and social dynamics can further alter the transmission dynamics of an emergent virus. The incubation period of SARS-CoV-2 is estimated to be approximately 5 days (range of 1.3 to 11.3 days), and respiratory shedding in mild cases may be as long as 14 days,

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leading to the current 14 day quarantine recommendation.[18] The transmission of SARS-CoV-2 has been slowed by either broad-reaching limitation of personal movement and gatherings, as in China, or by aggressive contact tracing and isolation of suspect cases, as in South Korea. Both strategies result in a lower R_0 and significant decline in COVID-19 cases. Importantly, early recognition of suspect cases is essential to limit transmission, particularly in hospital environments. Hospital employees comprised 29% of the individuals included in one of the early clinical case series and 3.8% of those identified by records review, emphasizing the importance of early recognition and appropriate personal protective equipment to protect healthcare workers.[13,19]

COVID-19 Clinical Course

The clinical syndrome of COVID-19 can range between asymptomatic or mild illness (e.g., fever with or without cough) to severe respiratory distress, multi-organ failure, and death. Currently, 80% of cases are mild, 15% develop lower respiratory tract disease (i.e., worsening pneumonia), and 3-5% require intensive care. For those who progress to severe disease the clinical course has an insidious onset, with minimal symptomatology progressing to worsening respiratory distress around week two of illness.[20] Two case series have been published from hospitals in Wuhan detailing the clinical course of 99 patients at the Jinyintan hospital January 1 through Jan 20, and 138 cases at the Zhongnan Hospital January 1 through January 28, 2020. [19,20] The vast majority of hospitalized patients presented with fever (83 to 99%) and a cough (59 to 82%), with 30% in each series having dyspnea on admission. Additionally, a subset presented with

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only diarrhea and nausea as initial symptoms, potentially delaying recognition of infection.[19] In these series, 17-20% of admitted patients had ARDS, 11-13% required noninvasive ventilation, 4-12% required mechanical ventilation, and 3% were placed on extracorporeal membrane oxygenation (ECMO).[19,20]

Radiologic findings, as described in the above case series and another series of 51 patients with COVID-19, demonstrated the vast majority (≥90%) of these hospitalized patients had abnormalities on CXR or CT, usually bilateral.[19–21] CT findings showed ground-glass opacities, with or without septal thickening, or consolidation, located predominantly in the peripheral or posterior lungs.[21] Later in the disease course (after 4 days inpatient) imaging is more likely to show consolidation.[21]

Samples from bronchioalveolar lavage fluid appear to have higher viral loads than oropharyngeal washes.[3] With higher viral loads detected in deeper lung samples, intubation and bronchoscopy are suspected to be high-risk procedures for providers of patients with COVID-19, and therefore should be minimized as able and performed in an airborne isolation room under airborne precautions when necessary. Prevention of hospital-acquired infections will require aggressive screening, early recognition and diagnosis, and strict adherence to precautions, particularly for potentially aerosolizing procedures such as intubation. The demands of airborne isolation precautions for any large number of patients can easily overwhelm medical systems with finite numbers of trained personnel, airborne isolation rooms, personal protective equipment, and dedicated equipment.

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Therapeutics and Vaccines

There are no approved drugs or vaccines for human coronaviruses. Multiple vaccine candidates utilizing different platforms are in preclinical development, and two have advanced to phase 1 clinical trials. Although this speed in unprecedented, progression through the necessary steps of development, safety testing, efficacy analyses, and manufacturing may take over a year until publicly available.[22] In the interim, rapid evaluation of potential therapeutics may provide an earlier intervention to mitigate disease. Antivirals targeting the RNA-dependent RNA polymerase (such as remdesivir) showed in vitro activity, as did the immune modulator chloroquine.[23] The protease inhibitors lopinavir and ritonavir have been used, but they lack a clear antiviral mechanism for coronavirus proteases and were ineffective in a controlled clinical trial.[23–25] Clinical trials for remdesivir and hydroxychloroquine have begun, and additional therapeutics are in development.[23] Host-targeted therapeutics are also under consideration, including inhibitors of host proteases required for viral entry, or anti-IL-6 therapeutics that are hypothesized to blunt the cytokine storm in severe cases.[26] Based on evidence from SARS and MERS, current recommendations are to avoid the use of corticosteroids for COVID-19 patients.[27] Corticosteroid use for patients with SARS-CoV was associated with higher plasma RNA levels at weeks two to three into illness (reflecting likely prolonged viremia) and increased 30-day mortality (adjusted OR 26, 95% CI 4.4-154.8).[26] Convalescent sera, including the neutralizing antibodies isolated from recovered cases, is a promising but not yet scalable option.[28]

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Conclusions

SARS-CoV-2 is the most recent emergent coronavirus, and having already demonstrated a greater facility for transmission than SARS-CoV or MERS-CoV, it threatens to be a devastating pandemic. Current recommendations to reduce transmission include social distancing, hand hygiene, cough etiquette, and aggressive recognition and isolation and quarantine of cases and contacts; for the health care environment, early and judicious PPE use to prevent respiratory droplet and short distance aerosol transmission and appropriate environmental control of rooms housing patients are critical. While the majority of infections are have been mild, hospitalized patients have high rates of complications including the need for aggressive supportive care including mechanical ventilation, CRRT, and ECMO. These complications place a heavy burden on hospital systems that may be ill-prepared for large numbers of patients who will require airborne isolation and prolonged durations of stay. There are no approved therapeutics, although there are some promising antivirals under study. While the first severe coronavirus epidemic was halted by non-pharmacologic interventions alone, the COVID-19 outbreak has become a pandemic due to the efficient transmissibility of the virus. However, several countries have demonstrated that aggressive non-pharmacologic intervention and control measures can slow the spread, blunting the impact on the healthcare systems and allowing the time needed for the testing of potential therapeutics and vaccines. Beyond this pandemic we must continue work towards sustained preparedness against future emergent infectious diseases.

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Figure Legend:

Figure 1: Crystal structures of coronavirus receptor binding domains complexed with their host receptor: MERS-CoV (pdb 4l72), SARS-CoV (pdb 6cs2), SARS-CoV-2 (pdb 6m0j), and NL63 (pdb 3kbh). Images rendered in PyMOL version 2.3.4. Summary table includes select characteristics of each coronavirus.

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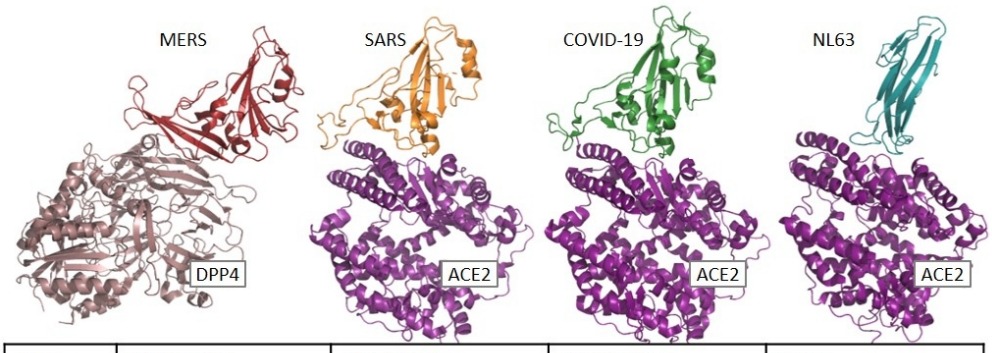

Virus	MERS-CoV	SARS-CoV	SARS-CoV-2	NL63
Disease	Middle East respiratory syndrome (MERS)	Severe acute respiratory syndrome (SARS)	Coronavirus disease 2019 (COVID-19)	*Mild upper respiratory syndrome, not named.*
Host Receptor	DPP4	ACE2	ACE2	ACE2
Mortality	35%	10%	0.25-4%	minimal
Risk for severe disease	Increased age, kidney disease, diabetes	Increased age, kidney disease, diabetes	Increased age, kidney disease, diabetes, hypertension	Immunocompromise
Year identified	2012	2003	2019	2004
Clade (genus)	2c (betacoronavirus)	2b (betacoronavirus)	2b (betacoronavirus)	1 (alphacoronavirus)

Crystal structures of coronavirus receptor binding domains complexed with their host receptor: MERS-CoV (pdb 4l72), SARS-CoV (pdb 6cs2), SARS-CoV-2 (pdb 6m0j), and NL63 (pdb 3kbh). Images rendered in PyMOL version 2.3.4. Summary table includes select characteristics of each coronavirus.

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