SARS-CoV-2 Virology

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KEYWORDS
- SARS-CoV-2 • COVID-19 • Viremia • Receptor-binding domain
- Monoclonal antibody

KEY POINTS
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genome is homologous to several Sarbecoviruses, but its proteins have unique features.
- SARS-CoV-2 viral evolution is more prominent in immunocompromised hosts.
- There are several variants of concern and variants of interest, with Omicron, followed by Delta variants, being the most dominant variant currently.
- Upper and lower respiratory tract SARS-CoV-2 infection follows different viral dynamics.
- Systemic dissemination serves as a marker and mechanism for COVID-19 disease severity.

INTRODUCTION
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has not ceased to wreak havoc since its identification in early 2020.1,2 Despite its homology with several Betacoronavirus strains including SARS-CoV-1 and bat-derived SARS-related coronaviruses (SARSr-CoVs),1 SARS-CoV-2 owns several unique features accounting for its pathogenesis and transmission. Clinically, coronavirus disease 2019 (COVID-19) demonstrates the full spectrum of symptomatology, ranging from asymptomatic, to mild/moderately symptomatic, to critical illness with acute respiratory distress syndrome (ARDS) and death.3 In addition, presymptomatic transmission has greatly contributed to SARS-CoV-2 community spread.4 Asymptomatic, pauci-symptomatic, and presymptomatic transmission has made it difficult to trace and contain its transmission, leading to this global pandemic that has lasted more than 2 years, with more than 330 million confirmed cases and 5.5 million reported deaths, although the attributable mortality to the COVID-19 pandemic has been estimated to be 12 to 22 million by January 2022.5 In this review, the authors discuss key aspects of SARS-CoV-2 virology that contribute to its variable clinical manifestations, evolution, replication dynamics in the respiratory tract, and systemic dissemination.

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SARS-CoV-2 is part of the Betacoronavirus genus and Sarbecovirus subgenus. It is a single-stranded, positive-sense, 29.9-kilobase (kb) RNA virus. This virus shares 96.2% identity with a bat SARSr-CoV strain RaTG13 and 79.6% with SARS-CoV-1. SARSr-CoV have also recently been recovered from pangolins (Manis javanica) and different species of bats (eg, RpYN06 from Rhinolophus pusillus in southern China and RshSTT182/RshSTT200 from Rhinolophus shameli in Cambodia) with variable degrees of recombination detected in different regions of genome.

The SARS-CoV-2 genome consists of the following genes: open reading frame (ORF) 1a/1b, S, 3a/3b, E, M, 6, 7a/7b, 8, 9b, N, 10, with overlaps in certain regions (Fig. 1). The S (Spike), E (Envelope), M (Membrane), and N (Nucleocapsid) genes encode essential structural proteins, whereas the rest of the genes encode nonstructural proteins (Nsps) from ORF1a/1b and accessory factors (ORFs 3–10). Of note, ORF1a/1b encode polyproteins that are subject to viral protease-mediated cleavage into Nsp1–Nsp16. Nsps serve a variety of functions. For example, Nsp1 interacts with the ribosome subunit 40S and interrupts host protein translation, whereas Nsps 7 to 10, 13 to 16 coordinate with Nsp12 to complete the replication cycle, RNA capping, and proofreads. In addition, accessory factors carry additional functions necessary for immune evasion and viral replication. For example, ORF3b, 6, 7a, 8, 9b proteins have been reported to interfere with innate immune responses by antagonizing the interferon (IFN) signaling pathway. In an in vitro cell model, Lei and colleagues demonstrated that ORF6 protein inhibits both upstream type I IFN promoter activation and downstream IFN-stimulated gene expression. In another in vitro cell model, Xia and colleagues further noted that the ORF6 protein could inhibit inter- feron regulatory factor 3 nuclear translocation, thus blocking its binding to IFN-α/β gene promoter. In addition, ORF7a/7b and ORF3a proteins in conjunction with nsp6, nsp1, and nsp13 inhibit signal transducer and activator of transcription 1 (STAT1)/STAT2 phosphorylation or nuclear translocation, thus further blocking the type I IFN downstream signal. SARS-CoV-2 accessory proteins are also capable of antagonizing other aspects of the home immune response. For example, the ORF8 protein is capable of downregulating human leukocyte antigen-I (HLA-I) by enhancing autophagy-related HLA-I degradation, which may enhance escape from T-cell-mediated immunity in SARS-CoV-2 infection. Finally, many of the Nsps, accessory proteins, and structural proteins are polyfunctional. In an affinity-purification–mass spectrometry–based proteomics study, Gordan and colleagues reported that almost 40% of SARS-CoV-2–interacting host proteins are associated with endomembrane and vesicle trafficking/rearrangement, in addition to their previously identified functions. For example, Nsp8 participates in forming primase for RNA-dependent RNA polymerization, interaction with signal recognition particle to hijack protein translocation pathway, glycosylation, and extracellular matrix regulation; N protein, as a structural protein, also participates in RNA processing and stress granule regulation.}

**Fig. 1.** SARS-CoV-2 genome structure. In SARS-CoV-2 genome, ORF1a/1b encodes polypeptides that undergo viral protease–mediated cleavage to nonstructural proteins 1 to 16. Spike (S), Envelope (E), Membrane (M), and N (nucleocapsid) genes encode corresponding structural proteins. Accessory factors including ORF3a, 6, 7a, 8, and 9b contribute to viral pathogenesis and immune evasion. ORF, open reading frame; UTR, untranslated region; −1PRF, −1 programmed ribosomal frameshifting.
Of all the Nsps, Nsp12 and Nsp5 have been the primary focus of therapeutic development. Nsp12 is the RNA-dependent RNA polymerase (RdRp) that is crucial for viral replication. Remdesivir, an adenosine analogue inhibitor of RdRp, has been shown to shorten recovery time for hospitalized COVID-19 patients and has been approved by the Food and Drug Administration (FDA). Accumulating evidence has also demonstrated its efficacy in decreasing hospitalization and death in the outpatient setting. Nsp5 is the main protease of SARS-CoV-2 (3C-like protease) and is responsible for viral polypeptide cleavage and viral maturation. Nirmatrelvir/PF-07321332 (boosted by ritonavir), a protease inhibitor targeting 3C-like protease, has been reported to decrease the risk of hospitalization and death and has been granted Emergency Use Authorization in the outpatient setting.

Of all the structural proteins, Spike protein has been the center of research and therapeutic development. Spike protein consists of 2 subunits: S1 and S2. The S1 subunit contains the N-terminal domain and the receptor-binding domain (RBD) that mediate host cell binding, whereas the S2 domain is responsible for cell membrane fusion. Host proteases are required to prime the Spike protein by cleavage at the boundary between S1 and S2 and the S2* site in S2 domain. Similar to SARS-CoV-1 and SARSr-CoVs, SARS-CoV-2 binds to human angiotensin-converting enzyme 2 (ACE2) through interaction with the RBD. However, SARS-CoV-2 Spike protein contains a unique polybasic cleavage site at S1/s2 boundary that is recognized by Furin, an ubiquitous host protease, which contributes to SARS-CoV-2 pathogenesis and host adaptation. Furin cleavage allows for the S2 subunit to mediate host cell fusion, promoting viral entry into target cells. The Spike protein is further cleaved at target cell surface by TMPRSS2 and on endocytosis, by Cathepsin L in the endosome. Given its key role in SARS-CoV-2 lifecycle and cell entry, the Spike protein has been targeted by several monoclonal antibodies that can neutralize the virus, especially by targeting the RBD.

Evolution and Variants

Similar to other RNA viruses, the SARS-CoV-2 RNA-dependent RNA polymerase has a relatively high error rate, although the error rate is mitigated in part by the presence of a proofreading mechanism mediated by the nsp14-encoded exonuclease. There was initial optimism about the lack of genetic diversity seen in the early stages of the pandemic, including relatively limited intrahost viral diversity in next-generation sequencing studies. Lythgoe and colleagues demonstrate that average intrahost single-nucleotide variant (iSNV) count is 1.4 iSNVs per sample (0.47 base substitution per 10kb), and this observation was only seen at high viral loads, sampled a median of 6 days apart. In addition, the bottleneck size for intrahost variants is very small, indicating the difficulty of transmitting intrahost mutant variants to others. However, in immunocompromised hosts, the situation seems different. In patients with cancer infected with SARS-CoV-2, intrahost diversity is far higher than in the immunocompetent control group (iSNV 0.77 vs 0.45 base substitution per 10kb), and immunocompromised individuals are at risk of persistent COVID-19 infections. One of the most extreme cases that has been reported is an individual with antiphospholipid antibody syndrome, who was receiving a broad spectrum of immunosuppressants targeting T cells, B cells, complement system, and innate immunity. This patient suffered from persistent COVID-19 over a 5-month period and harbored constantly evolving virus and eventually succumbed to COVID-19, despite Remdesivir and monoclonal antibody administration. Viral genome sequencing at different time points demonstrated a dynamic pattern of mutations, with an overall accumulation of mutations.
was an average of 4.67 base substitutions per 10kb (excluding the deletions in Spike protein region; compared with 0.45–0.47 in the aforementioned immunocompetent hosts), with mutations overrepresented in the Spike protein gene that highlights the Spike protein as the site of intense immune pressure. In addition, the mutations that emerged in this patient were subsequently identified as key mutations in several variants of concern, suggesting that immunosuppressed individuals may be a source for the emergence of new variants. Similar cases in immunocompromised patients infected with SARS-CoV-2 further support the negative correlation between host immunity and accelerated intrahost evolution.

From the population level, interhost mutations and evolution have certainly complicated this pandemic by multiple folds. D614G mutation on Spike protein was the first major mutation discovered since the beginning of this pandemic. D614G was rare before March 2020 but rapidly became the globally dominant mutation since May 2020. This mutation is associated with enhanced infectivity and replication compared with the original strain with D614. This enhanced infectivity is mediated by an increase in Furin cleavage efficiency and more frequent RBD “up” state that characterizes a conformation facilitating ACE2 accessibility. However, G614 and D614 strains have similar level of susceptibility to neutralization from convalescent plasma/serum. With further global spread and replication, SARS-CoV-2 continues to diversify and has developed into multiple circulating variants. By the beginning of 2022, there have been 5 major variants of concern (VOC) and 6 variants of interest (VOI) documented on the GISAID database. The VOCs and certain VOIs are summarized in Table 1.

Among all these VOC and VOI strains, the Delta variant merits further discussion. This variant was first detected in India in December 2020 and caused a disastrous surge in COVID-19 cases and death in early 2021. By July 2021 it has already supplanted the then-dominant strains (Alpha, Beta, and Gamma) to become the dominant strain in most countries of the world. The Delta variant has several features that seem to enhance transmission. First, it contains several antibody evasion mutations. Several neutralization studies have demonstrated that the Delta variant is associated with decreased sensitivity to convalescent sera, vaccinated sera, or bamlanivimab (a monoclonal antibody targeting the Spike protein), compared with the wild-type strains or the Alpha variant. In addition, real-world data demonstrate that certain adenovirus-vector–based vaccine (ChAdOx1 nCoV-19) and mRNA-based vaccine (BNT162b2) have a modestly decreased vaccine efficacy against symptomatic disease. Second, the Delta variant contains certain mutations that may escape preexisting cellular immunity from prior infection or vaccination. Two groups have demonstrated that L452R, the signature mutation in the Delta variant, is associated with decreased sensitivity to convalescent sera, vaccinated sera, or bamlanivimab (a monoclonal antibody targeting the Spike protein), compared with the wild-type strains or the Alpha variant. In addition, real-world data demonstrate that certain adenovirus-vector–based vaccine (ChAdOx1 nCoV-19) and mRNA-based vaccine (BNT162b2) have a modestly decreased vaccine efficacy against symptomatic disease. Second, the Delta variant contains certain mutations that may escape preexisting cellular immunity from prior infection or vaccination. Two groups have demonstrated that L452R, the signature mutation in the Delta variant, is associated with decrease in HLA-A24– or HLA-A02–restricted CD8+ T-cell response to the T-cell epitope containing this mutation. Third, the Delta variant is associated with more efficient membrane fusion independent of better ACE2 binding. Zhang and colleagues demonstrated that Delta strain had higher fusion activity toward target cells in an in vitro system without having higher affinity to ACE2 compared with other variants. Last but not the least, Syed Abdullah and colleagues used an SARS-CoV-2 virus-like particle model and demonstrated that key nucleocapsid mutations found in Delta variant, including R203M, are associated with enhanced viral RNA packaging and replication. Although the Beta and Gamma variants mediate a greater degree of escape against vaccine or natural immunity–mediated immune responses, the greater transmissibility of Delta allowed it to supplant these variants. Together, the features discussed earlier enable Delta variant to transmit efficiently and evade preexisting adaptive immunity, leading to higher viral shedding in the upper respiratory tract.
<table>
<thead>
<tr>
<th>Variants</th>
<th>First Identified</th>
<th>Key Spike Mutations</th>
<th>Impact on Antibody Neutralization</th>
<th>Impact on Viral Entry and Transmission</th>
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<tbody>
<tr>
<td><strong>VOC</strong></td>
<td></td>
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<tr>
<td>Alpha^a</td>
<td>United Kingdom</td>
<td>69–70del, <strong>144del</strong>, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H</td>
<td>+/-</td>
<td>+ +</td>
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<tr>
<td><strong>VOI</strong></td>
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<tr>
<td>Lambda^a</td>
<td>Peru</td>
<td>G75V, T76I, R246N, del247–253, L452Q, F490S, D614G, T859N</td>
<td>+++</td>
<td>+ +</td>
</tr>
<tr>
<td>Iota^a</td>
<td>United States</td>
<td>L5F, T95I, <strong>D253G</strong>, E484K, D614G</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Kappa^a</td>
<td>India</td>
<td>L452R, <strong>E484Q</strong>, D614G, P681R, Q1071H</td>
<td>+++</td>
<td>+ +</td>
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Bold font, adaptive immunity escape mutations. Underline, increase in ACE2 binding affinity and transmission.

^a Currently listed as Variant Being Monitored (VBM) by US CDC.

*Data from* Refs 50, 51, 54, 61, 78, 117–123
tract more rapid transmission and vaccine “breakthrough” infection compared with ancestral strains. Fortunately, vaccination is still associated with more rapid viral clearance in those Delta breakthrough cases compared with unvaccinated cases.

The Omicron variant, first reported in South Africa in November 2021, has further led this pandemic into an uncharted water. The rate that the Omicron variant has spread world-wide has been unprecedented, and it has become the dominant strain worldwide. The Omicron variant has developed an extensive set of mutations in the Spike protein; this unfortunately leads to escape from multiple FDA-authorized monoclonal antibody treatments and leads to substantial reductions in vaccine-induced neutralizing titers. Somewhat reassuringly, CD4 and CD8 T cells from vaccinated and/or previously infected people retain activity against the Omicron strain, although as many as 21% of the participants in one study has shown significant reduction in Omicron spike recognition by the CD8 T cells. In addition, Omicron is not as efficiently antagonizing IFN signaling pathway as other variants and remain susceptible to most of the available antiviral small molecules authorized by the FDA. Last but not the least, several in vitro and animal studies have demonstrated that the Omicron strain preferably replicate in the upper respiratory epithelium and does not replicate well in the lungs, causing less severe inflammation in the lung tissue in animal models. These findings could potentially indicate differences in its clinical phenotypes and outcomes, as reported in a recent study from South Africa suggesting milder disease and lower morbidity/mortality, but more evidence is needed.

Animal Reservoirs

SARS-CoV-2 seems to have broad tropism across species, and infection has been observed in a wide range of animals besides the bats. Gu and colleagues demonstrated that SARS-CoV-2 developed a de novo mutation in the Spike protein gene after 6 passages of a viral strain from clinical isolate in early 2020 (BetaCov/human/CHN/BeijingIME-BJ05/2020), when VOCs/VOIs had not yet arisen. This mutation N501Y confers higher affinity to mice ACE2 and is associated with adaptation to mice and is subsequently found in 4 major VOCs: Alpha, Beta, Gamma, and Omicron. Similarly, in domestic cats, a consensus mutation at Spike protein, H655Y, has been detected, which is also found in the Gamma and Omicron VOCs. In addition, SARS-CoV-2 transmission among minks is associated with a mutation at Spike Y453F, suggesting adaptation to mink ACE2. A very recent study evaluating free-ranging white-tail deer in Ohio, US has demonstrated a shockingly 35.8% SARS-CoV-2 nucleic acid detection rate from nasal swabs between January and March 2021. This study further identified multiple independent human-to-dear transmission events based on the phylogenetic analysis from sequences obtained from human and deer at different locations and timepoints. Surprisingly, certain mutations that are rare in humans (<0.5%–0.05% globally) are seen in deer, including Δ141 to 144 and E484D; this indicates a possibility of deer-to-deer transmission and independent evolution. The significance of animal reservoirs of SARS-CoV-2 remains to be determined but has important implications for our efforts to eradicate the pandemic and prevent the emergence of new variants.

Upper and Lower Respiratory Tract Infection and Replication

SARS-CoV-2 replication follows different virological dynamics in upper and lower respiratory tracts. The biological mechanism behind this finding could be due to different levels of ACE2 and entry factors expression in upper and lower airways. In an early study synthesizing multiple preexisting single-cell RNA sequencing (scRNA-seq)
datasets generated from healthy donors, Sungnak and colleagues demonstrated that ACE2 and TMPRSS2 expression levels are higher in cells derived from nasal cavity than lungs and bronchi. This finding is further confirmed by a study using a more sensitive technique, RNA-in situ hybridization, demonstrating that upper airway epithelial cells express higher levels of ACE2 and TMPRSS2 compared with lower respiratory tract. In this study, in vitro cell line models from both upper and lower respiratory tracts, and autopsy results demonstrating patchy segmental/subsegmental viral infection, further suggest that SARS-CoV-2 viral replication starts from the upper respiratory tract followed by aspiration and subsequent lower respiratory tract infection. This theory is further supported by an animal model study in which only intranasal challenge was conducted in rhesus macaque. In this study, an early peak of viral load in the upper respiratory system at days 2 to 6 postinfection was noted, in comparison to peak viral load at day 9 in the lower respiratory tract. In a clinical cohort where the date of infection was known and only mild cases were included, Wölfel and colleagues described that viral level peaked later in sputum sample compared with upper respiratory tract swab; in addition, 2 participants with lower respiratory tract involvement showed prolonged viral persistence in sputum, significant delay in viral level peak in sputum compared with the upper respiratory sample, and more than one viral level peaks in sputum. These findings indicate ongoing replication in the lower respiratory tract that is disconnected from upper airway viral replication. Similarly, in a cohort study of 196 hospitalized participants, the viral level from upper respiratory tract peaked within 7 days after symptom onset, whereas sputum viral level peaked between 7 and 14 days after symptom onset, highlighting the temporal and spatial gradient of SARS-CoV-2 viral spread and replication in different respiratory compartments.

**Systemic Dissemination and Disease Severity**

Plasma viremia can be detected in several respiratory viral infections including SARS-CoV-1, influenza virus, respiratory syncytial virus, and adenovirus infection and has been associated with more severe disease. In contrast to SARS-CoV-1 infection, where almost 80% of patients have viremia within first 3 days of symptom onset, a lower proportion of patients with COVID-19 have had detectable SARS-CoV-2 RNA in the blood, although rates of plasma viremia detection may be affected by disease severity, duration of symptoms, and sensitivity of the tests. The authors’ group and other investigators have demonstrated that SARS-CoV-2 viremia (or referenced as RNAemia in other literature) is associated with worse disease outcomes including ARDS and death. Furthermore, those hospitalized in critical care settings have higher odds of having viremia than in noncritical care settings. Similarly, lower respiratory tract viral loads tend to correlate with disease severity; this is in stark contrast with viral levels in the upper respiratory tract, which does not seem to correlate well with severity of symptoms and disease. As discussed in the previous section, SARS-CoV-2 may have comparable replication levels in upper respiratory tract across different severity spectrum due to expression of high levels of ACE2 and other entry factors, but the determinant of severe disease is mainly due to lower respiratory tract infection and subsequent hematogenous dissemination. This hypothesis is further supported by a proteomic study showing that SARS-CoV-2 viremia is associated with severe disease and death, along with higher levels of lung damage–related proteins, fibrosis markers, and extrapulmonary organ damage markers from gastrointestinal (GI) system, and vasculature- and coagulation-related factors. Several autopsy studies have also demonstrated detection of SARS-CoV-2 RNA in multiple extrapulmonary tissues, including tissues from the GI,
cardiovascular, endocrine, lymphatic, urinary, bone marrow, reproductive, and central nervous systems. This extrapulmonary dissemination theory is further supported by mounting evidence of SARS-CoV-2 replication and virion detection in in vitro organoid models and ultimately clinical samples including GI tract, pancreatic islets, placenta, kidney tissue, and endothelium. However, caution is warranted when interpreting some of the transmission electron microscopy (TEM) results, as some subcellular structures can be misconstrued as virions and further clarification methods are warranted. In addition to extrapulmonary involvement, several studies have shown that SARS-CoV-2 viremia is further associated with complement system activation and elevated proinflammatory cytokine levels.

Given that SARS-CoV-2 infection can cause extrapulmonary involvement and dissemination from lungs, an ongoing question is the mechanism by which SARS-CoV-2 disseminates. A few studies have shown that SARS-CoV-2 virions, rather than just RNA fragments, can be detected in the blood vessels and blood. Ackermann and colleagues first reported prominent endothelial injury and inflammation in COVID-19 lung autopsy compared with influenza-infected lung tissue; furthermore, SARS-CoV-2 virions are visible in endothelial cells through TEM. This result suggests that SARS-CoV-2 can infect the endovascular system, leading to systemic dissemination. From plasma samples, Jacobs and colleagues demonstrated that SARS-CoV-2 virions can be detected via TEM and further confirmed by immunostaining. These findings further support the theory that SARS-CoV-2 may first gain entry to the circulatory system from the pulmonary vasculature due to extensive lung damage, followed by infection of endothelial cells, leading to systemic dissemination of virions. However, it remains elusive whether SARS-CoV-2 virions are carried within certain cellular or acellular components in the blood during dissemination (ie, monocytes, platelets, and so forth) and how they infect extrapulmonary tissues.

SUMMARY

Understanding the virology behind SARS-CoV-2 infection has provided key insights into our efforts to develop antiviral agents and control the pandemic. However, there remains substantial gaps in our knowledge of SARS-CoV-2 biology and pathogenesis. Studies are needed to further dissect the functions of each nonstructural and accessory proteins and how they contribute to the pathogenesis of SARS-CoV-2. In addition, we need to understand the roles of the multiple mutations in the newly emergent variants (eg, Omicron variant) and how they contribute to increased transmission and immune evasion. There are also increasing questions on the role of systemic viral dissemination in the pathogenesis of severe disease and the detection of viremia as a prognostic marker. Furthermore, we know relatively little about the animal reservoirs of SARS-CoV-2 and their potential to fuel the emergence of new variants. The answers to these questions will be crucial as we devise improved vaccine strategies and antiviral therapies.

CLINICS CARE POINTS

- Immunocompromised patients are at higher risk of developing immune escape mutations and prolonged SARS-CoV-2 infection.
- SARS-CoV-2 has different replication dynamics in the upper and lower respiratory tracts.
SARS-CoV-2 viremia and dissemination are associated with worse outcomes.

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**DISCLOSURE**

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