Viral Transmissibility of SARS-CoV-2

Subjects: Virology

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The emergence of coronavirus disease 2019 (COVID-19), caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to a global health calamity unprecedented in the modern world. The disease spread worldwide, and to date, there have been over 230 million confirmed cases of COVID-19, including approximately 4.7 million deaths. Mutant variants of the virus have raised concerns about additional pandemic waves and threaten to reverse our progress thus far to limit the spread of the virus.

Keywords: COVID-19 ; SARS-CoV-2 ; viral transmissibility

1. Introduction

The emergence of the coronavirus disease 2019 (COVID-19), caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to a global health calamity that is unprecedented in the modern world. Part of the Genus ‘Coronaviruses’ belonging to the family ‘Coronaviridae’, SARS-CoV-2 is the third virus of its kind responsible for an outbreak (albeit with greater global impact), succeeding SARS-CoV in 2003 and MERS-CoV (the Middle East Respiratory Syndrome Coronavirus) in 2012–2015 and 2020 [1]. COVID-19 emerged as novel pneumonia in Wuhan, Hubei Province, China, in December 2019 and is believed to have originated via zoonotic transmission. The disease quickly spread worldwide, prompting the World Health Organization (WHO) to declare the outbreak a pandemic on 11 March 2020. To date, there have been over 230 million confirmed cases of COVID-19, including approximately 4.7 million deaths [2]. The pandemic has also disrupted the global economic landscape due to widespread lockdowns, leading to loss of income for individuals and precipitating staggering negative trends in global stock markets [3].

2. Viral Transmissibility

The primary mode of transmission of SARS-CoV-2 is human-to-human via respiratory droplets produced during exhalation, as shown in **Figure 1** [4][5][6]. However, there is also evidence that suggests the virus is transmissible via viral aerosol particles produced by individuals with COVID-19 disease [7][8][9]. In order to assist in the development of prevention guidelines, a group from the Nebraska Medical Center further investigated the transmission routes of the virus. Their studies reveal that viral RNA is present in nearly two-thirds of the air samples from rooms housing COVID-19 patients [9]. However, there is insufficient evidence at this time that would suggest that these particles indicate a viable virus that could be transmitted [9]. While the transmissibility of the virus via inanimate surfaces is generally low [10][11], aerosol to surface studies reveal that SARS-CoV-2 is more stable on plastic and stainless steel surfaces, showing a presence for up to several days, **Figure 1** [12].

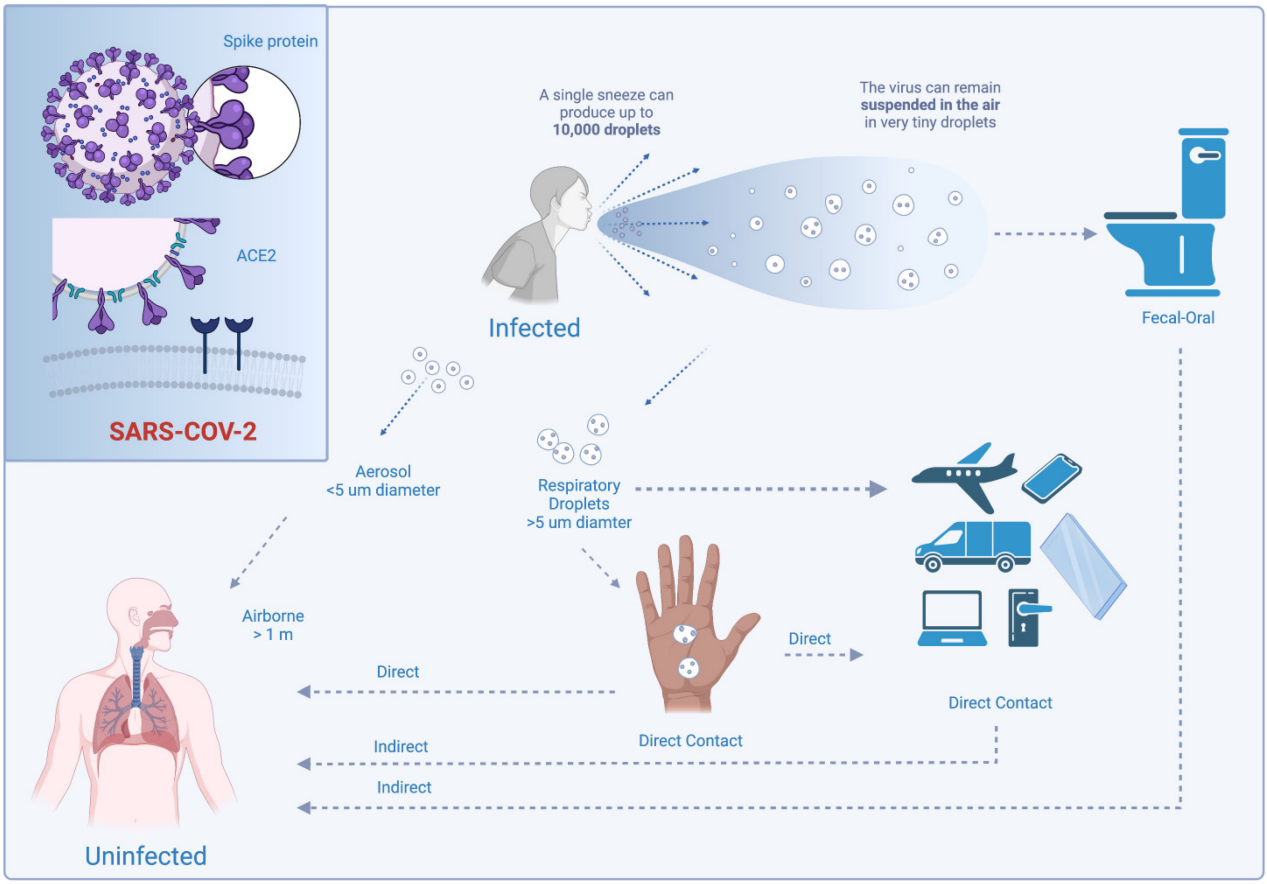

Figure 1. Modes of transmission of Sars-Cov-2. Created with BioRender.com.

An additional potential transmission route is fecal-oral transmission, **Figure 1** [13][14][15][16]. Clinical characterization data from pediatric patients in China has suggested that rectal swab testing is more efficacious than nasopharyngeal testing. Several patients had tested negative for the nasopharyngeal swabs while positive for the rectal swabs [14][15][17]. However, the number of SARS-CoV-2 particles and the length of exposure necessary to cause infection are unknown [7].

Yet, the epidemiological and clinical findings indicate that the transmissibility of COVID-19 depends on the viral load at the time of the onset of the disease. Researchers have observed a short serial interval (time between symptom onset of the index case and secondary case) of 4–5 days for COVID-19 and a decreased risk for secondary infection over time. This suggests that there is a high risk of secondary transmission right before or at the onset of symptoms [4][18][19]. The recent data from South Korea reveals that the mean serial interval in the Delta variant is one day longer than when compared to the wild-type [20][21]. This trend is consistent with the viral shedding duration, as viral load peaks around symptom onset and decreases thereafter [4][18][22][23][24]. However, in more severe diseases, viral load was found to have peaked later in the second week of illness, suggesting a potentially longer period of infectiousness in cases of severe disease [25].

Recent discovery-based control design studies reveal that mutations in the viral nucleocapsid protein bring to light an association with the hospitalization rate [26]. Some single nucleotide variants increased the hospitalization rate, whereas a handful decreased it. Specifically, nonsynonymous variants R203K, R203S, and G204R occur in the linker region between the N-terminal RNA binding domain and the C-terminal dimerization domain, however this region has yet to be resolved [26][27]. It is hypothesized that the mutations in the linker region may potentially affect RNA binding interactions [26]. In addition, nucleocapsid mutations in the endoRNAse are also found to play an important role in the hospitalization status of the patients.

Several studies have examined the relationship between viral load and secondary transmission among symptomatic versus asymptomatic COVID-19 patients, although these findings have been inconsistent and contradictory. For instance, one study found comparable viral load in nasal and throat swabs at symptom onset among symptomatic and asymptomatic patients [24], while another found higher viral load in nasopharyngeal swabs in symptomatic patients [18]. Notably, a study by Hasanoglu et al. identified significantly higher viral load in asymptomatic patients in six types of specimens (nasopharyngeal/oropharyngeal, oral cavity, saliva, rectal, urine, and blood), suggesting higher infectiousness for asymptomatic patients than previously thought [28]. These findings highlight an important gap in the literature regarding the viral load and transmission risk of symptomatic versus asymptomatic COVID-19 patients that warrant further investigation.

Similarly, there are a limited number of studies in the literature that assess the relationship between SARS-CoV-2 viral load and disease severity. As was previously stated, disease severity may be associated with a higher risk of secondary transmission; however, this hypothesis must be examined further. Nonetheless, several studies have identified an association between disease severity and SARS-CoV-2 RNA shedding [29][30][31], while others report no such correlation [8] [16]. For instance, the longer the duration of SARS-CoV-2 RNA shedding, the longer it takes to recover body temperature (when the fever was present at illness onset) compared to patients with early SARS-CoV-2 RNA clearance [31]. Additionally, patients admitted to the Intense Care Unit experienced longer viral shedding time than non-ICU patients [32]. A similar pattern is identified for the relative amounts of viral load over time, where higher viral load is associated with increased disease severity and mortality [33][34]. However, other studies have found that viral load in severe patients is lower [28] than in mild cases, encouraging further research in this area.

One possible reason for these discrepancies in the literature relating to viral load and transmissibility may be due to the wide range of reported viral shedding times for SARS-CoV-2. For instance, the average reported duration of viral shedding from the onset of the illness ranges from 11 days [29] to 17 days [31] to 31 days [35]. The median duration of viral shedding also differs in the type of specimen collected. Major shedding routes for SARS-CoV-2, such as the nasopharyngeal, sputum, and stools [30], are expected to show a longer median duration of viral shedding than other collected specimens. Interestingly, sputum specimens exhibit longer viral shedding than nasopharyngeal specimens [30] [36], almost twice as long according to some accounts [36]. Hindson et al., 2020 determined that the digestive system may exhibit longer viral shedding than the respiratory tract [14]. These findings are supported by the fact that patients with COVID-19 can simultaneously test positive for SARS-CoV-2 RNA on some samples but not on others. For instance, patients simultaneously tested positive for COVID-19 on rectal swabs but tested negative on nasopharyngeal swabs within the same testing period [13][14]. COVID-19 patients may also test negative for SARS-CoV-2 on samples that later test positive [14][37], further limiting the generalizability of viral shedding times in the literature.

There are other factors that have been associated with the transmission. One of them is individuals' behaviors toward public health measures, such as physically distancing, masking, or staying home while they are sick. For example, those who had lower concerns about spreading the virus reflected the least uptake of public health measures [38]. Transmission dynamics were also affected among close contacts. Specifically, the transmission potential was at its peak in the first two days and after three days of the onset of the symptoms. When individuals were exposed to mild and moderate COVID-19 patients, they were exposed to a higher risk of COVID-19 when compared to asymptomatic carriers, and it worsens when exposed to patients with moderate cases of COVID-19 [39]. Moreover, environmental conditions play an important two-fold role; the initial viral load, and the immune response. Generally, higher temperatures and humidity have been associated with a lower fatality rate [40]. Another factor that has played an important role in Sars-CoV-2 transmission is long diagnostic delays (LDDs). A study in Japan concluded that the portion of long diagnostic delays with unknown exposure was correlated with a significant increase in the virus spread [41].

Moreover, the range of reported viral shedding times of SARS-CoV-2 may also be explained by independent risk factors such as age and gender. In some reports, old age—a major risk factor for COVID-19 severity—is associated with prolonged viral shedding duration [31][36]. Contrary to Xu K et al., 2020 and Wang K et al., 2020, another study finds no significant difference in viral shedding time between patients less than 65 years of age and those aged 65 years and older [35]. Similarly, some studies find viral shedding duration in males to be higher [31] or equal to females [35]. Concomitant hypertension has also been identified as a potential risk factor for prolonged viral shedding [31].

Conversely, the differences in the duration of viral shedding may be due to features that vary on a case-by-case basis, such as a longer time from the onset of symptoms to hospitalization or treatment, which increases the risk for prolonged viral shedding [29][31][42]. Other factors that are associated with an increased duration of viral shedding include cough [30], fever, and hydrocortisone use [29], specifically high-dose corticosteroids [43]. The presence of diseases other than COVID-19, such as diabetes mellitus and chronic lung disease, is associated with viral RNA detection [18]. Overall, these studies highlight the need for additional research on the factors affecting viral shedding duration and the detection of SARS-CoV-2.

As is the case with other coronaviruses, SARS-CoV-2 relies on the spike (S) glycoprotein to successfully bind to and enter host cells. Components of the SARS-CoV-2 S protein include subunit S1, subunit S2, the transmembrane anchor, and the intracellular trail [44][45][46]. However, while SARS-CoV-2 related coronaviruses today contain a monobasic cleavage site between S1 and S2, SARS-CoV-2 garners a multibasic cleavage site, **Figure 2** [47][48][49], believed to be the result of a recombination event [16][35][47]. This specialized motif enables SARS-CoV-2 to exploit a greater variety of widespread cellular proteases in the body, thereby allowing the virus to have a more rapid spread [44][46]. Additionally, newly

synthesized virions can bypass the requirement of binding to host cell receptors and still continue to infect cells as they can be secreted in a preactivated state [46].

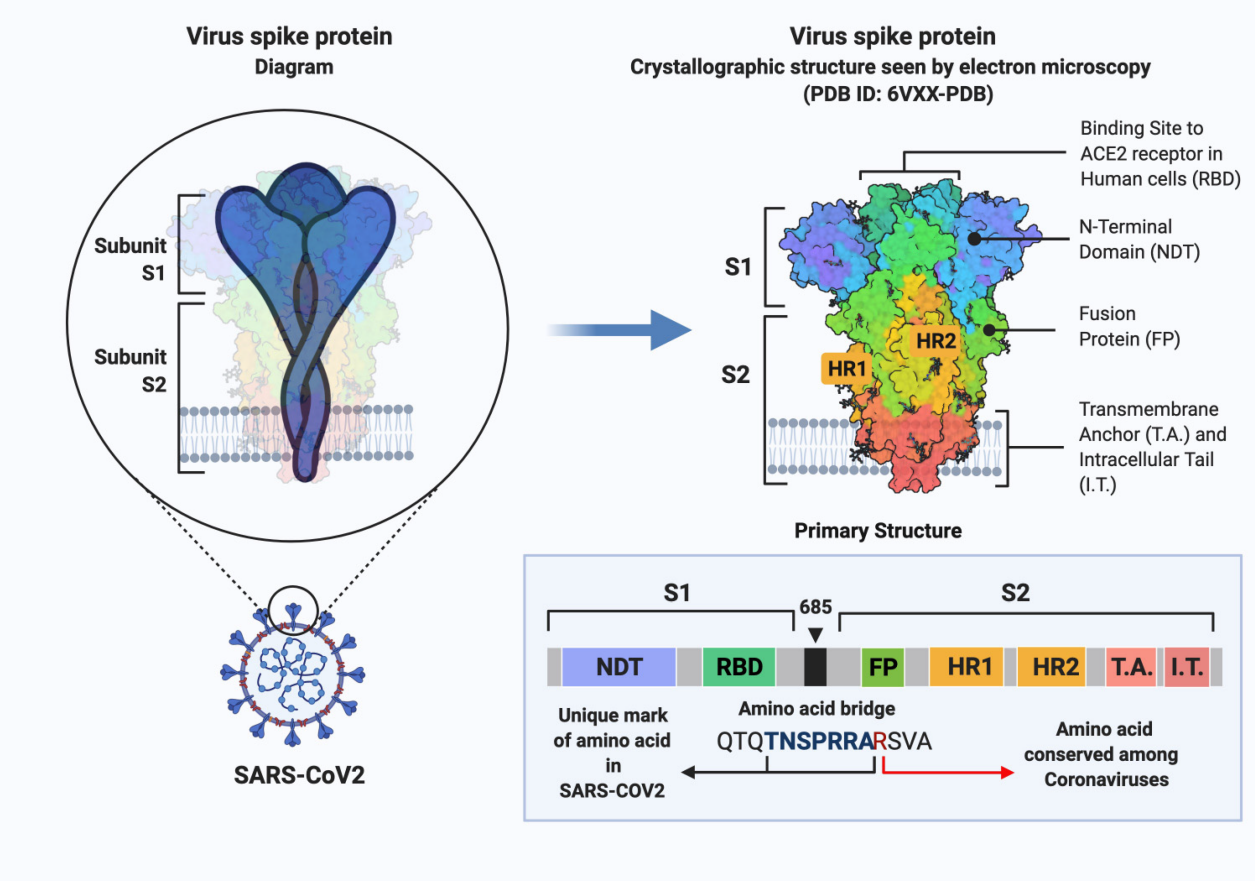

Figure 2. Schematic representation of SARS-CoV-2 spike protein primary structure. Domains are depicted with different colors. NTE, N-terminal domain; RBD, receptor-binding domain; FP, fusion peptide; HR1, heptad repeat 1; HR2, heptad repeat 2; TM, transmembrane domain; IT, intracellular tail. Created with BioRender.com.

Moreover, the SARS-CoV-2 S protein can trigger cellular entry independent of proteases but dependent on receptor binding, leading to augmented viral spread [46]. However, when the S1/S2 site is damaged, it can severely inhibit the S protein cleavage and proteolytic processing [47]. Moreover, structural studies suggest that the addition of basic residues to the S1/S2 site of SARS-CoV-2 exhibits an increased viral spread via cell–cell fusion but no change to virus–cell fusion [47]. In sum, the structural studies stress the importance of recognizing which viral mutants lead to inhibition or augmentation of viral spread to develop effective therapeutic strategies against SARS-CoV-2 and its variants.

For viral spread to occur, the S protein of SARS-CoV-2 must first be activated. This process starts when the receptor-binding domain (RBD) of the S1 subunit binds to the host cell surface receptor angiotensin-converting enzyme-2 (ACE2) [44][46][47][50] via its peptidase domain [51][52]. Compared to SARS-CoV, the receptor binding capacity of SARS-CoV-2 to ACE2 is at least 10-fold higher [44][49]. This high affinity is partially due to the specialized RBD of SARS-CoV-2, which contains a residue motif at 482–485 (Gly-Val-Glu-Gly) that allows for better contact with ACE2 and two key residues (Gln493 and Leu455) that stabilize ACE2 binding [46][53]. Interestingly, the data reveals that this high-affinity results in increased virulence of SARS-CoV-2 [4][48][49]. Once SARS-CoV-2 and ACE2 bind together, it alters the conformation of the S protein, exposing a cleavage site on the S2 subunit, which the host cell proteases will act upon in the next step [46][54]. Then, the host cell proteases, such as transmembrane protease serine S1 member 2 (TMPRSS2), carry out proteolysis of the S protein at the cleavage site between the S1/S2 boundary, resulting in a new S2 site (S2′) [46][55][56]. Following the S2′ cleavage and the release of the S2 subunit, the activation of the protein concludes, allowing for the subsequent initiation of the endocytosis of the virus through the fusion of the viral and cell membranes [46][54][55][56].

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