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SARS-CoV2 in Different Body Fluids, Risks of Transmission, and Preventing COVID-19: A Comprehensive Evidence-Based Review

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Abstract

The world is combating a common and invisible enemy severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), a highly transmissible virus responsible for serious respiratory illness coronavirus disease-2019 (COVID-19). As with all respiratory viruses, public health measures are focused on contact tracing, isolation, and treatment of affected individuals, who have respiratory symptoms. However, it is spreading efficiently, and it can be explained from its stealth transmission from presymptomatic and asymptomatic individuals. Droplet and contact precautions are followed universally. Healthcare workers are at higher risk of acquiring infection and they are additionally required to follow airborne and eye protection. Recent studies indicate viral particles can be isolated from many body fluids including feces, saliva, semen, and tears, suggesting transmission could be possibly occurring through some of these routes as well. We have done an evidence-based review of all potential modes of transmission and discussed preventive measures to stop the spread. There is an urgent need for educating the healthcare professionals, governments, and public regarding other potential modes of transmission. Strict preventive measures need to be used to stop the spread.

Keywords: *COVID 19*, *novel coronavirus*, *Pandemics*, *SARS-CoV2*, *transmission*

Coronaviruses are positive-sense single-stranded RNA viruses and are known to cause diseases in a variety of hosts including humans, bats, civet cats, camels, and other mammals.[1] Until December 2019, only six strains of pathogenic human coronaviruses were known and four of these strains cause approximately one-third of the common cold infections in all age groups. Two other strains of coronaviruses namely severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome-coronavirus (MERS-CoV) that were identified in 2002 and 2012, respectively, caused severe respiratory illnesses with high case fatality rates and infected about 10,500 individuals.

In 2019, an investigation into a cluster of cases of pneumonia of unknown origin led to the discovery of a novel coronavirus of zoonotic origin (2019-nCoV) linked to a seafood market in Wuhan, Hubei province involved in the sale of illegal game animals including pangolins, birds, and rabbits. The analysis of genetic makeup revealed 2019-nCoV likely originated from bats and transmitted to humans through intermediate reservoirs such as pangolins.[1] It was also found out that 2019-nCoV shared 79% similarities with SARS-CoV and 50% similarities with MERS-CoV.[1] Within no time, widespread human to human transmission in Wuhan was documented. The Novel coronavirus was christened SARS-CoV2 by the International Committee on Taxonomy of Viruses and the disease from it coronavirus disease-2019 (COVID-19) by World Health Organization (WHO) on January 11, 2020.[2]

Since the discovery, SARS-CoV2 spread rapidly in China, which led to a strictly enforced lockdown of affected areas by the country in an effort to the spread of the epidemic. Prior to governmental action, a large number of people living in Wuhan left the region by aeroplanes and this likely resulted in the spread of the virus globally.[3] Documented COVID-19 cases multiplied at a dizzying pace prompting WHO to declare a pandemic on March 11, 2020.

As of May 8, 2020, more than 4 million individuals are diagnosed with COVID-19 worldwide and about 276,000 deaths are reported. The ongoing pandemic is causing great disruptions to the daily lives of people forcing them to stay indoors and made to practice social distancing. Several countries responded with drastic measures such as lockdown to prevent the spread as well as improve health care resources to care for the sick.

In the USA, the first COVID-19 case was confirmed in Washington state on January 19, 2020 and was successfully treated. Soon communities spread was suspected as more cases were identified and first deaths due to COVID-19 happened in Washington state on February 26, 2020.[4] Documented infections have now grown to 1.3 million cases and 78,615 deaths in the USA despite strict public health measures to prevent spread. With no end in sight for this pandemic currently, the vaccine is the only hope to check the spread of this life-threatening disease.

A search for a vaccine is underway and is estimated to be available on a large scale no sooner than 18 months, if successful. Meanwhile, identifying all potential modes of transmission of SARS-CoV2 and preventing spread is the only solution to combat this global public health threat killing thousands of lives every single day.

SARS-CoV2 is known to infect individuals of all age groups including neonates. Patient present with a wide variety of respiratory, gastrointestinal, neurological and constitutional symptoms including fever, cough, sputum, dyspnea, myalgia, malaise, diarrhea, nausea, and vomiting and sometimes with no symptoms at all. The spectrum of this disease appears to be wide ranging from mild URI symptoms in most to severe conditions such as acute respiratory failure, acute encephalopathy, renal failure, myocarditis, sepsis, acute respiratory distress syndrome and death in few others and so a better understanding of pathophysiology of disease process is needed. Infections in children are generally mild and self-limited and rates of hospitalization are comparatively markedly lower. Elderly patients and/or

those with comorbidities are the most affected with severe COVID-19 disease. Since the disease appeared in a season when influenza is common co-existing infections were also noted in few cases, although uncommon, complicating the diagnosis.

In this article, we provide a comprehensive evidence-based review of various modes of transmission of SARS-CoV2 including few suspected modes which are currently under investigation and may gain prominence depending on further data. Public awareness campaigns and measures are focused on well-recognized transmission modes of SARS-CoV2 such as droplet and contact with fomites. In healthcare settings, airborne precautions during specialized aerosolizing procedures and barrier precautions for eye are also followed at the minimum in most countries. Other potential modes of transmission at this time are feco-oral, saliva, conjunctiva/ tears, and vertical transmission.[5,6,7] We must identify all potential modes of transmissions and prevent spread effectively to eradicate the COVID-19 pandemic.

Droplet Route

The concept of microorganisms expelled from the respiratory tract of an infectious person in the form of droplets can transmit the infection to another was first discovered at the end of the 19th century. Droplet transmission then became recognized as one of the main modes of transmission of all respiratory viruses and this is true for SARS-CoV and SARS-CoV2 as well. SARS- CoV2 replicates in the respiratory tract and spreads to one another mainly through respiratory secretions. SARS-CoV2 is mainly transmitted through the air in the form of droplets as well as aerosols.[8] Nasal and oropharyngeal swabs have shown high viral load.[9]

Droplets are small particles that carry viable viruses and bacteria and usually fall to ground soon after they are released owing to their relatively larger size (>5 μm). Droplets can be produced with coughing, sneezing, talking, and even normal breathing. These infected droplets, by depositing on the mucosal membranes of mouth, nose, or eyes of susceptible individuals can give rise to an infection. Also, those that are deposited on environmental surfaces may contribute to indirect spread via fomites as well. Surgical masks and N95 masks provide good protection against droplet transmission.

Fomites

This is also thought to be the other main transmission route of SARS-CoV2 virus.[8] Human-to-human transmission of the SARS-CoV2 virus can occur through contaminated intermediate objects by droplets and aerosols. Environmental contamination of SARS-CoV-2 from infected persons has been proven in experimental and real-life settings in multiple studies.[10,11] In healthcare settings, shoe soles of medical staff shoes were noted to have functioned as carriers and have spread the virus to distant areas.[10] The SARS-CoV-2 aerosol distribution characteristics indicated that the transmission distance of SARS-CoV-2 might be 4 metres.[10] Given high transmissibility and sustainability, as long as one family member is infected the chances of others in the family being infected are very high. In an experimental project SARS-CoV2 aerosols generated remained viable longer on plastic and stainless steel compared to copper and cardboard.[11] Live virus was detected up to 72 hours.[11] Virus in fomites may be destroyed in less than a minute by a variety of disinfectants including hydrogen peroxide.

Airborne Route

Many respiratory viruses including influenza have known to spread via air in the form of aerosols causing outbreaks that are challenging to control.[12] Majority of SARS-CoV and MERS-CoV spread was in healthcare settings likely due to airborne spread.[13,14,15] Aerosol-generating procedures such as positive pressure ventilation, nebulizers, and intubation are more likely to generate aerosols that can travel long range and cause an infection. Besides, Aerosols can be produced during normal breathing and talking. Further, a droplet generated through coughing or sneezing may convert to an aerosol in no time. According

to WHO, there is no evidence of airborne transmission of SARS-CoV2. However, this does not explain the infection of patients for whom contacts cannot be traced. Of note, many health organizations including WHO, CDC, and others have admitted that they are still learning the modes of transmission. Therefore, absence of evidence should not be treated as evidence of absence. A recent study from Wuhan, China demonstrates air samples in hospitals showed evidence of airborne SARS-CoV2.[16] Interestingly, higher aerosol virus concentration was noted in patient's toilet room with poor ventilation suggesting the possibility of aerosolization of virus particle during flushing of feces or stool[16] CDC acknowledges the possibility of airborne transmission but does not believe it is a significant mode of transmission except in special situations like above. Another recent study showed that coronavirus like other respiratory viruses is commonly emitted in aerosols rather than droplets with normal breathing.[17] This suggests spread via airborne route may be more common compared to via droplet transmission and this may explain why infections in healthcare workers are more common despite widespread use of surgical face masks. A large proportion of presymptomatic and asymptomatic individuals infected with SARS-CoV2 are likely transmitting viruses to others via aerosols generated during normal breathing and talking. This is highly evident from studies of SARS-CoV2 transmission in nursing homes.[18]

Feco-Oral Route

Fecal shedding is not uncommon with respiratory viruses like rhinoviruses and Influenza.[19] Besides, Feco-oral transmission is an accepted mode of transmission for Coronaviruses such as SARS- CoV and MERS CoV.[20,21] SARS-CoV2 infects gastric, duodenal, and rectal epithelial cells and the ACE2 receptor in them acts as co-receptor for virus entry and replication leading to gastrointestinal infection and further viral replication.[22] Digestive symptoms including nausea, vomiting, and diarrhea are commonly noted in patients with COVID-19. Sometimes, gastro-intestinal symptoms are prominent and no respiratory symptoms leading some to propose there are two types of SARS-CoV2, one with gut tropism and another with lung tropism.

Fecal viral shedding has been noted in many studies involving patients with COVID-19.[7,23,24,25,26] Higher rates of familial clustering have been attributed to shared toilets according to one study.[25] In a study published from China, involving 10 children, SARS-CoV2 was detected in stool samples of 8 of 10 children after the nasopharyngeal swab turned negative.[27] Many other studies indicate prolonged fecal viral shedding after nasopharyngeal swab turning negative.[22,28] All these, suggest fecal shedding may occur for a prolonged period beyond patient is considered negative based on nasopharyngeal swab and during this time patient may be potentially infectious.

We however do not know if the positive fecal test results are due to inactive viral RNA amplified by PCR or due to active virion particles. Data are therefore limited as to the possibility of developing an active infection by feco-oral route, and above studies only indicate indirect evidence of feco-oral transmission.[26] Interestingly, first confirmed US case of COVID-19 had diarrhea, and the stool sample was positive for viral RNA.[29] In a research letter published in JAMA, live virus was isolated from stool samples of two patients even in the absence of diarrhea strengthening the possibility of feco-oral transmission.[5] These findings have wide implications in infection control and nosocomial spread. On the light of the above evidence, it is reasonable to suggest routine feces testing should be performed in all hospitalized patients and isolation to be maintained for those whose respiratory specimens have turned negative, until there is evidence of clearance of virus in stool samples.[22] Also, viral clearance from stool may be used as a guidance for determining quarantine duration.[30]

Saliva

Prior studies indicate many respiratory viruses including SARS-CoV can be detected in saliva specimens with good co-relation to nasopharyngeal swab positivity.[7,31] SARS-CoV2 RNA has been isolated from self-collected saliva of 11 of 12 patients raising a possibility of this being a source of transmission.[7] Viral

culture showed that live viruses were present in the saliva of three patients.[7] In another study, one-third of patients had viral RNA in saliva even 20 days after presentation and up to 25 days. Viral RNA was detected in salivary samples even after nasopharyngeal samples turned negative.[31] Given the ease of obtaining salivary samples compared to nasopharyngeal or oropharyngeal samples, it may be used for serial viral load monitoring. Viral load was found to peak shortly after presentation. In SARS-CoV infection, patients with higher initial viral load were noted to have higher mortality.[31] So besides assisting with diagnosis, this may provide prognostic data and alert physicians for the early need for intervention during clinical worsening. The advantages of using saliva for detection include no discomfort to patients, easily obtainable, and less risk to health care workers.[7] SARS-CoV2 could be transmitted via saliva even in the absence of respiratory symptoms.[7] Of note, FDA has recently approved a saliva-based test for diagnosing SARS-CoV2 infection.

Tears

Many respiratory viruses are known to use eye as a port of entry as well as the site of replications before causing a respiratory infection and may also cause minor eye manifestations during the process.[32] SARS-CoV has been shown in tear specimens and direct or indirect contact with mucous membranes of the eyes can be a possible source of transmission.[33] In a study involving SARS-CoV, healthcare workers who did not have eye protection were noted to have increased infection rates suggesting the possibility of direct or indirect exposure of droplet to the eyes.[34] According to few studies, tears were found to be positive for RT- PCR of SARS CoV2 indicating it may be a potential source of transmission.[35,36,37] Based on limited evidence from these studies, the prevalence of SARS-CoV2 in tears is low, however, may be still be a possible route of transmission.[37] Of note, only viral RNA was identified and no live virus has been isolated.

Interestingly, health care workers in China were urged to use eye protection after a physician on national pneumonia expert panel developed conjunctivitis followed by fever soon after, postulating virus spread through conjunctiva and causing pneumonia.[38] Now, it is being followed universally. Low prevalence rate of SARS-CoV2 in these studies may be explained by the incorrect testing methodology of testing, late sampling during the illness or low sensitivity of RT-PCR testing. Nevertheless, based on SARS-CoV experience and given droplet can transmit SARS-CoV2 virus through the eye by direct or indirect means and cause respiratory infection, the current level of eye protection involving the use of goggles is recommended in healthcare settings

Vertical Transmission

There is no documented evidence of intrauterine vertical transmission occurring with SARS CoV and MERS CoV. Whether SARS CoV2 can be transmitted vertically to the fetus from the pregnant mother in utero or during labor is unclear and current data is conflicting.[39,40,41] Given COVID-19 was discovered only recently, due to short study period, available data could help us determine the possibility of transmission during the third trimester of pregnancy only. It is unknown if materno-fetal transmission can occur during the first or second trimester.

In a case report published in JAMA, an infant of COVID-19 positive mother was noted to have negative nasopharyngeal swabs but positive IgM antibodies and elevated cytokine levels immediately after birth suggesting infection occurred in utero.[39] Mother developed symptoms of COVID-19 about 25 days prior to delivery. Vaginal secretions of mother and breast milk were negative for SARS-CoV2 virus. In another study involving three infants with early onset symptomatic SARS CoV2 infected born to COVID-19 mothers, vertical transmission could not be ruled out.[40] In another report involving a delivery of stillborn during second trimester of a pregnant women with SARS-CoV2 infection, although the nasal swabs for

infant were negative, placental infection was confirmed raising vertical transmission is very much possible.[41] A case series of 9 pregnant women did not have any evidence of transmission from mother to child.[42]

Semen

Presence of viruses in semen is not uncommon. In a recent report, SARS-CoV2 was identified in semen in 6 of 38 individuals tested. Likely, SARS-CoV2 seeded to the reproductive system during viremia. With this finding, the likelihood of transmission through semen cannot be ruled out. If proven, sexual abstinence and condom use may be beneficial to eliminate the risk of infection through this route.[43]

Special Populations

Nosocomial spread

Healthcare workers are at higher risk of contracting COVID-19 infection. For example, an infected patient who underwent endoscopic pituitary surgery ended up infecting 14 healthcare workers.[44] In China, more than 2000 healthcare workers were infected by February 20, 2020 according to their National Health Commission data. In the USA, preliminary data as of April 9, 2020 suggests that more than 9000 healthcare workers have been infected.[45] Serum antibody testing should be done for healthcare workers on a priority basis to identify asymptomatic infections early on as they pose a greater risk of transmitting infection to other healthcare workers, patients and the public.[46] Not only that, they are part of critical workforce necessary during surging needs due to pandemic and are vital to the smooth functioning of healthcare systems.

Challenges with preventing spread

Interestingly, few patients who were discharged and asymptomatic were noted to have virus RNA reappear in their respiratory samples and the reason is being investigated. It is unknown whether these patients continue to be contagious.[23] The duration of viral shedding from nasopharyngeal specimens was prolonged up to at least 24 days after symptom onset.[47] Longest duration of viral shedding noted was 37 days.[48] The basic reproductive number (Ro-R naught) which is an indication of the transmissibility of a virus, representing the average number of new infections generated by an infectious person was estimated to be between 2.2 and 2.5 in Wuhan, China.[49] Coinfections by other viruses such as influenza and rhinovirus which seem to be far common can during flu season mimic symptoms of COVID-19 and can make diagnosis challenging.[50] Viable virus could be isolated from 6 days before to 9 days after symptoms developed.[18] False-negative rates of oropharyngeal samples seem high is some studies and so should be interpreted with caution. Since the virus replicates in multiple sites including the throat, lungs, and gastrointestinal tract, simultaneous collection of samples from multiple sites may be required at the time of diagnosis as well as evaluating infectiousness risk at the time of discharge from the hospital or coming of isolation.[51,52] In summary, SARS-CoV2 viral RNA has been found in multiple clinical specimens such as saliva, tears, feces, placenta, semen as well as the surrounding environment. The evidence for spread through feces, saliva, and tears, as well as vertical transmission, is not strong and merits further investigation, however, cannot be ignored for a rapidly transmissible virus such as SARS-CoV2.

Mitigation and Prevention Strategies

Patient's history, clinical manifestations, lab tests, and radiological data are all important elements and should be collectively considered for diagnosis of this disease. Depending on one modality alone can lead to missed diagnoses. Identification of high-risk individuals who may be asymptomatic or presymptomatic transmitters by aggressive contact tracing and quarantine is essential.

It is not known when and how this pandemic will end. It is common for the virus to have genetic mutations and recombinations during transmission and spreading.[53] It is hoped, virulence will decrease through long term host–parasite relationships at the cost of transmission.[54] Co- infections of various other viruses, bacteria, and fungi can happen, and an alternate diagnosis should not prevent clinicians to forego further testing for COVID-19. Aggressive case detection, isolation, and contact tracing is essential. Testing capabilities for infection detection, as well as antibody detection, should improve to identify infected individuals, those at risk and those that have recovered. Neonates of pregnant women with suspected or confirmed COVID-19 infection should be isolated for at least 14 days after birth.

Apart from isolation measures, frequent and regular hand-hygiene, wiping down surfaces that are frequently touched, and community use of masks are encouraged. A simple soap and water preparation is more than sufficient to kill the virus and will help prevent the spread of the virus via feces, saliva, and respiratory droplets, tears on surfaces and fomites. Safe and careful food handling-practices are also vital. N-95 masks should be restricted to health care professionals who risk exposure to COVID-19 patients, until supplies become surplus for widespread use. Additionally, making sure that the patient has a mask on helps reduce aerosolized virus particles.

When available, a negative pressure room should be used in hospital settings. Minimal to no direct contact should be encouraged as much as possible. Minimizing daily blood work, reducing the frequency of investigations are useful ways of preventing transmission in healthcare settings. Hemodialysis centers and nursing homes or care-homes are increasingly becoming clusters of outbreaks. In congregate settings such as nursing homes, early and repeated testing of all staff and residents including those who are asymptomatic should be done for rapid detection and isolation. Very high level of prevention strategies should be used and followed.

In conclusion, SARS-CoV2 virus is a highly contagious with viral RNA particles being detected in multiple body fluids. Strict measures are needed at all times until the pandemic is over and/or a vaccine becomes available.

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Conflicts of interest

There are no conflicts of interest.

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