

Review Article

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A Review on Modes of Transmission of COVID-19

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ABSTRACT

The World Health Organization declared Covid-19 as a pandemic on March 11, 2020. It is of prime interest of a public health concern and global emergency to control its transmission. Covid-19 is caused by severe acute respiratory distress syndrome-coronavirus-2 (SARS-CoV-2) which is highly infectious agent from Corona virus family which is having many pathogenic forms like MERS-CoV & SARS-CoV experienced during past outbreaks. The disease may be transmitted by either by COVID-19-positive individuals or from a contaminated environment. SARS-CoV-2 is thought to commonly spread through respiratory droplets mainly by coughing and sneezing of an infected patient and there is a strong possibility of community transmission. Primarily, there are two methods of transmission of COVID-19 specifically direct and indirect. The direct mode includes transmission via aerosols or in the form of respiratory droplet nuclei; other body fluids and secretions (for example, feces, saliva, urine, semen, and tears) and via from mother to child. Indirect transmission may occur through fomites or surfaces present within the immediate environment of an infected patient and objects used on the infected person. Transmission dynamics of COVID-19 are heterogeneous with a major role for super spreading events in sustaining the epidemic. Based on the reported literature, studies revealed that COVID-19 is primarily transmitted human-to-human via oral and respiratory aerosols and droplets with the virus-contaminated environment play a lesser role in the propagation of disease. Besides this there are several modes of transmission reported. This review paper elaborates briefly about different modes of transmission of COVID-19 virus in the community and proposes measures to diminish the danger of spread within population.

Keywords

Covid-19, SARS-CoV-2, Pandemic and Pneumonia

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Introduction

Coronaviruses generally cause gastrointestinal and respiratory tract infections and are inherently categorized into four major types namely Gamma coronavirus, Delta coronavirus, Beta coronavirus and Alpha

coronavirus (Ge XY *et al.*, 2017). Corona virus infections were thought to infect only animals means occur animal to human infection only until a severe acute respiratory syndrome (SARS) outbreak caused by SARS-CoV, 2002 occurred in Guangdong, China. SARS-CoV causes acute lung injury and

acute respiratory distress syndrome (ARDS) which leads to pulmonary failure and result in fatality.

At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China and spread rapidly which resulted in an epidemic throughout China followed by a global pandemic. However, this virus causes rapid human to human transmission through aerosols, droplets and direct contact. In February 2020, the World Health Organization (WHO) named the disease COVID-19, which stands for coronavirus disease –2019.

Covid-19 virus is a pathogenic virus and cause of current outbreak of pneumonia (Hui *et al.*, 2020). It belongs to the β -coronavirus family in the same subgenus as the severe acute respiratory syndrome (SARS) virus. International Committee on Taxonomy of Viruses (ICTV) has proposed that Covid-19 virus be designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Gorbalenya *et al.*, 2020). Bats occur to be the COVID-19 virus reservoir, but the intermediate host(s) has not been detected till now.

COVID-19 virus is transmitted directly from bats or through some other mechanism which is unknown (Perlman, 2020). However, sequence-based analysis suggested bats as the key reservoir but zoonotic source of SARS-CoV-2 is not yet confirmed.

Similar to other viruses, SARS-CoV-2 has many potential natural hosts, intermediate hosts and final hosts. SARS-CoV-2 has high transmissibility and infectivity but a low mortality rate (Bell, 2006) as compared with severe acute respiratory syndrome and Middle East respiratory syndrome coronaviruses respectively.

Transmission

In this paper we have reviewed the extensive accumulating evidence about the transmission of Covid-19, evidence for various modes of transmission. SARS-CoV-2 is spread primarily via respiratory droplets during close contact. Infection can be spread by asymptomatic, presymptomatic and symptomatic carriers. Wiersinga *et al.*, (2020) stated that the average time from exposure to symptoms onset is 5 days and 97.5% of people who develop symptoms do so within 11.5 days. One of the reasons for cross – species transmission and rapid infection could be the involvement of spike glycoprotein which assorted SARS-CoV (CoVZXC21 or CoVZC45) with the RBD of another Beta CoV.

Respiratory transmission is the dominant mode of transmission in corona virus infection. Vertical transmission occurs very rarely and transplacental transmission has been documented. Cats and ferrets can be infected and transmit to each other, but there are no reported cases to date of transmission to humans; minks transmit to each other and to humans. Direct contact and fomites transmission are presumed but are likely only an unusual mode of transmission. Although live virus has been isolated from saliva & stool and viral RNA has been isolated from semen and blood donations (Meyerowitz *et al.*, 2020). Contact transmission (contact with nasal, oral and eye mucous membrane) and direct transmission (sneeze, cough and droplet inhalation transmission) are found to be the common mode for the transmission of novel COVID-19.

Respiratory transmission

COVID-19 can be transmitted either directly through sneeze, cough or inhalation of droplets from infected human or also through

contact with nasal mucous membranes and fomites. Previous studies have shown that besides sneezing & coughing, normal breathing and speech can also generate aerosol ranging from 0.75 to 1.1 μm , which is smaller than the aerosol generated by sneezing or coughing ($\sim 5 \mu\text{m}$) and hence it can transmit virus up to greater range (Asadi *et al.*, 2019). It is reported that the amount of aerosol generated through more than 4 minutes of speaking and breathing is equivalent to the concentration of aerosol emitted from coughing for 30 seconds (Chao *et al.*, 2009; Johnson *et al.*, 2011). Recent case studies reported also showed that transmission of aerosol emitted through these routes over a short distance in family clusters among several Chinese cities (Chan *et al.*, 2020; Yu *et al.*, 2020), restaurant in Guangzhou, China (Jiayun *et al.*, 2020) and choir group in Mount Vernon, WA, USA (Read *et al.*, 2020). Human activity can resuspend the aerosols and droplets deposited on surfaces and floors and hence comprises the majority of the aerosols within an occupied setting (Hospodsky *et al.*, 2015; Kwan *et al.*, 2020). Recent studies reported the detection of airborne levels of RNA SARS-CoV-2 virus in indoor air samples of COVID-19 patient room (Chia *et al.*, 2020; Liu *et al.*, 2020a; Santarpia *et al.*, 2020), hallway spaces outside patients' rooms (Santarpia *et al.*, 2020) and medical staff areas (Liu *et al.*, 2020a) by using quantitative RT-PCR.

Chia and his coworkers (2020) reported that the size of aerosol present in medical staff were smaller (0.25 to 2.5 μm and $>2.5 \mu\text{m}$) than those found in patient rooms (1 to 4 μm and $> 4 \mu\text{m}$) and it is observed that larger aerosols ($> 4 \mu\text{m}$) deposited in the upper and central airways (nasopharynx and tracheobronchial) and are expelled out through mucociliary clearance whereas smaller aerosols ($< 4 \mu\text{m}$) deposited in the

deep lung (alveoli) with epithelial cells rich in angiotensin-converting enzyme 2 (cellular entry receptor of SARS-CoV-2) and hence facilitates its transmission efficiency (Hamming *et al.*, 2004). ACE-2 plays an important role in human-to-human and cross-species transmission (Tortorici and Velesler, 2019) by binding with virion Spike (S) glycoprotein present on the surface of the SARS-CoV-2 virus which facilitates its entry into the host cell where genome RNA of the virus is released and uncoated into cytoplasm and translated into two polyproteins, pp1a and pp1ab (de Wilde *et al.*, 2018) forming replication-transcription complex (RTC) in double-membrane vesicle (Sawicki and Sawicki, 2005) and continues to replicate and synthesize a nested set of subgenomic RNAs (Hussian *et al.*, 2008) along with endoplasmic reticulum and Golgi (Perrier *et al.*, 2019), newly formed genomic RNA, envelope glycoproteins assemble and nucleocapsid proteins leading to formation of viral particle buds which fuses with the plasma membrane to release the virus (Guo *et al.*, 2020).

Contact transmission

Human-to-human transmission of COVID-19 virus is mainly reported between family members, relatives and friends who contacted with infected patients or incubation carriers (Guo *et al.*, 2020). Contact transmission occurs through indirect contact with the surface of contaminated objects including contaminated public transport handrails, door, handles, seats, elevator surfaces etc. or indirectly infected through contact with mucous membranes (nasal, oral, conjunctiva, etc.). It is reported that the nucleic acid of 2019-nCoV has been detected in the door handles of hospitals in Shandong and Guangzhou (New Group of Experts on the prevention and control of Chinese Preventive Medicine Association coronavirus pneumonia, 2020; Yang *et al.*, 2020).

Faeco-oral transmission

Studies have shown that besides respiratory droplets, fecal-oral route is also a potent mode for transmission of COVID-19 infection (Gu *et al.*, 2020; Tian *et al.*, 2020). Fecal oral transmission occurs through direct or indirect contact with pathogens from contaminated fecal excreta (Graaf *et al.*, 2017). Holshue *et al.*, (2020) reported first case of fecal-oral transmission by detecting the RNA of SARS-CoV-2 in the stool specimen of the COVID-19 infected patient in United States. It has been reported that ACE2 are abundantly expressed in esophageal, gastric, duodenal and rectal epithelial cells and absorptive enterocytes of ileum and colon making gastrointestinal tract susceptible to SARS-CoV-2 infection and hence suggestive of possible faecal transmission (Du *et al.*, 2020; Zhang *et al.*, 2020a; Xiao *et al.*, 2020). ACE2 of host cell binds with S1 domain spikeprotein of SARS-CoV-2 virus facilitating the viral entry (Batlle *et al.*, 2020; Liu *et al.*, 2020b; Walls *et al.*, 2020; Wrapp *et al.*, 2020) and synthesis of virus-specific RNA and protein in the cytoplasm leading to new virions formation (Weiss *et al.*, 2020) and are released into gastrointestinal tract. Recent study showed isolation of SARS-CoV-2 virus from the stool and confirmed the shedding of infectious virions to the gastrointestinal tract (Xiao *et al.*, 2020).

Various studies reported viral shedding from feces for long duration even after negative conversion in throat and pharyngeal swabs, suggestive of fecal-oral transmission may serve as an alternative infection route for SARS-CoV-2 (Chen *et al.*, 2020; Yang *et al.*, 2020) and occur even after viral clearance in respiratory tract. Zhang and his coworkers (2020b) reported high accuracy of COVID-19 nucleic acid in stool samples and presence of viral nucleic acid in stool are not correlated with severity of pneumonia or GI manifestation.

Food-borne transmission

Studies revealed that most of the initial cases originated from Huanan South Seafood Market in Wuhan where along with seafood, live and slaughtered chicken, bats, deer, snakes, pheasants, marmots, organs of rabbits and other exotic animals are sold (National Health Commission of the People's Republic of China, 2020; World Health Organization, 2020). Studies demonstrated that the genome sequence of SARS-CoV-2 virus is 96.2% identical to a bat CoV RaTG13 and hence, bat has been suspected as natural host for the origin of virus and SARS-CoV-2 may be transmitted from bats via unknown intermediate hosts to infect humans (Zhou *et al.*, 2020). Liu *et al.*, (2020c) found similar spike protein and host ACE2 receptors through protein sequences alignment and phylogenetic analysis in many species such as turtles, pangolin and snakes indicating more possibility of alternative intermediate hosts.

Water-borne transmission

SARS-CoV-2 infected patients may shed the virus in their stool and hence, wastewater-based epidemiology can quantify the prevalence of infection in wastewater among the population. Wastewater-based epidemiology is a useful approach to check the prevalence of virus in specific wastewater treatment plant catchment population as viruses are excreted from both asymptomatic and symptomatic individuals in the untreated wastewater in a catchment (Sinclair *et al.*, 2008; Ahmed *et al.*, 2020; Xagorarakis and O'Brien, 2020) and hence, used as early warning for outbreaks disease, resurgence (Kissler *et al.*, 2020), status and trends, suppression, subsidence of Covid-19 and give information regarding the efficacy of public health interventions, as demonstrated previously for enteric viruses including poliovirus, norovirus and hepatitis A virus (Asghar *et al.*, 2014; Hellmer *et al.*, 2014).

Ahmed *et al.*, (2020) confirmed SARS-CoV-2 virus from wastewater in a catchment in Australia using reverse transcriptase quantitative polymerase chain reaction. Recent studies also reported molecular detection of SARS-CoV-2 virus in wastewater samples in other parts of the world such as Netherlands and USA (Lodder and Husman, 2020; Medema *et al.*, 2020; Wu *et al.*, 2020b; 2020c; Bar Or *et al.*, 2020; La Rosa *et al.*, 2020; Nemudryiet *al.*, 2020; Randazzo *et al.*, 2020; Wurtzeret *al.*, 2020). Hart and Halden (2020) detected SARS-CoV-2 virus from wastewater computationally and also found temperature and in-sewer travel time severely impact virus detectability.

Ocular transmission

Transmission of COVID-19 infection through ocular secretion is currently unknown, however theories included migration from the nasopharynx via nasolacrimal duct or hematogenous spread through lacrimal gland or direct inoculation of ocular tissue with pathogen-loaded droplets can be the possibilities for ocular transmission of COVID-19 (Bostanci and Ozates, 2020; Loon *et al.*, 2020; Seah and Agrawal, 2020; Hu *et al.*, 2020). Various studies shown that cellular receptors for SARS-COV-2 virus is ACE2 present abundantly in the respiratory tract (Hamming *et al.*, 2004) and digestive tract (Du *et al.*, 2020; Zhang *et al.*, 2020a; Xiao *et al.*, 2020) and also in other organs of the body (skin, lymph nodes, thymus, bone marrow, spleen, liver, and brain) (Hamming *et al.*, 2004), but confirmation of ACE-2 in conjunctival epithelium still to be confirmed.

Chinese expert got infected with COVID-19 and reported first case conjunctivitis suggesting route of conjunctival infection and tear transmission (Lu *et al.*, 2020). Wu *et al.*, (2020a) reported 12 patients with ocular symptoms and two positive conjunctival

swabs from 38 COVID-19-positive patients in Hubei Province, China. Another study reported detection of SARS-CoV-2 in tears of COVID-19 infected patients by using quantitative reverse transcription polymerase chain reaction (RT-PCR) (Karimi *et al.*, 2020). National Institute for Infectious Diseases in Rome, Italy also reported ocular symptoms and confirmed SARS-CoV-2-positive RT-PCR conjunctival samples in a COVID-19 infected patient (Colavita *et al.*, 2020). Recent studies suggest that tears act as potential source for this infection and conjunctiva may sustain viral replication for an extended period of time.

Vertical transmission

Kotlyar *et al.*, (2021) stated that vertical transmission of SARS-CoV-2 in the third trimester of pregnancy is approximately 3.2% (22/936) by infant nasopharyngeal swab testing, with SARS-CoV-2 RNA positivity in other test sites ranging from 0% (0/51) in amniotic fluid and urine 0% (0/17), 3.6% (1/28) in the cord blood, 7.7% (2/26) by placental sample analysis, 9.7% (3/31) by rectal or anal swab, and 3.7% (3/81) by serology. Another case has documented evidence of a neonate tested positive for the SARS-CoV-2 infection after 30 hr. of his birth from a COVID-19 affected mother. The samples in this study were not directly collected from the amniotic fluid inside the uterus but were collected from the throat of the newborn after birth, so the evidence of vertical transmission is still obscure form this clinical case (Zhang *et al.*, 2020c).

There is no obvious proof of any intrauterine or vertical transmission form infected mother to newborn is addressed and infected pregnant women are found to show similar clinical manifestations when compared to affected non-pregnant females (Chen *et al.*, 2020b; Li *et al.*, 2020). The basic concern in regards to

the vertical transmission has shown up from the severe manifestations confirmed in previous literature where the pregnant women were found to show more severe outcome during SARS and MERS epidemics as compared with the general population (Favre *et al.*, 2020; Schwartz and Graham, 2020). Another study has reported that there is no evidence of in-utero or vertical transmission of SARS-CoV-2 virus involved 38 pregnancies and also showed similar results with previous studies on MERS-CoV and SARS-CoV epidemics. No significant and scientific establishment of in-utero or vertical transmission of SARS-CoV-2 virus has been recorded in different investigations by several countries including China (Liang and Acharya, 2020; Chen *et al.*, 2020a, 2020b; Qiao *et al.*, 2020; Favre *et al.*, 2020), Iran (Mardani *et al.*, 2020) and USA (Rasmussen *et al.*, 2020). None of the research has warranted the transmission of SARS-CoV-2 infection through breast milk but the droplets released during breast feeding could contribute for the transmission of infection from mother to the newborn (Rasmussen *et al.*, 2020).

One of the examinations in Iran has proven the death of two affected pregnant women with SARS-COV-2 infection after the delivery (out of 3) because of ARDS. However, the infants after birth were tested negative for COVID-19 disease (Tasnim Agency, 2020). In 20 January to 31 January, 2020 at Zhongnan Hospital of Wuhan University, China conducted study on affected 9 women in third trimester of pregnancy with no any chronic disease conditions (hypertension, diabetes, cardiovascular disease etc.) has addressed no proof of intra-uterine transmission after screening of the samples collected from the amniotic fluid, blood from the blood cord, breast milk and throat swabs from the neonate with RT-PCR (Chen *et al.*, 2020b).

Hong Kong, a city in China had experienced outbreak of SARS where, 30% mortality (3 died out of 10) among pregnant women has been identified, but there is no fatality among 30 affected non-pregnant women was recorded (Creanga *et al.*, 2020). Zeng *et al.*, (2020) gave evidence that COVID-19 infected neonates may get infected from their infected mothers through in utero transmission based upon elevated antibody level (IgM and IgG) and abnormal cytokines levels of blood drawn from the neonates. So, further investigation and new research related to vertical transmission of corona infection is necessary due to small size data available (Dong *et al.*, 2020; Kimberlin and Stagno, 2020).

In conclusions the novel Covid-19 virus now spread rapidly around world and primarily originated from seafood market at Wuhan city (China). Based on literature and reported data the pneumonia outbreak caused by SARS-CoV-2 is mainly transmitted by respiratory route but other modes of transmission discussed are also potential source of spread of virus in the community. Long duration of pandemic has brought disruption to the lives of people and their willingness to adhere to strict rules and lockdowns might wane. As cases of COVID-19 increase globally, we need to more fully understand the transmission routes. It is crucial that we embrace new research and do not rely on recommendations based on old data so that clearer and more effective infection control guidance can be provided in the face of pandemic fatigue.

Meyerowitz (2020) stated that we must continue to stay up to date with the new and emerging evidence and work quickly to revise our policies to reflect this new information. Even though knowledge about Covid-19 virus is still rapidly evolving and a more studies are required to assess other potential modes of transmission.

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