

Review Article

An Overview on Transmission of Diseases in Special Reference to COVID-19 and Potential Targets to Control this Pandemic

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Abstract

With its initial outbreak in China, the virus was referred as “coronavirus”. WHO has named it “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2). It has been described as the successor to SARS-CoV-1 which is a positive-sense single-stranded RNA virus. The virus spreads mainly between people who are in close contact (less than two metres or six feet) through small droplets produced during coughing, sneezing, or talking. Infected people exhale the contaminated droplets which are then inhaled into the lungs, or settle on other non-infected people’s faces his/her mucosae (mouth and nose) or conjunctiva (eyes) get exposed to potentially infective respiratory droplets to cause new infection. Organism may enter to human cells by binding to the receptor angiotensin converting enzyme 2 (ACE2). Research works are in progress to find potential targets to control the pandemic. To control and treat the virus various targets are under study and these targets range from modulating host cell receptor for the virus entry to generate an effective adaptive immune response.

Keywords: Angiotensin; Coronavirus; SARS-CoV-2

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Introduction

In present scenario, the term Corona has become an appalling word, which is not limited to the single country or continent but has been pandemic. The World Health Organization (WHO) recommended initially in January 2020 as “2019 novel coronavirus” as per its guideline of 2015 [1-3]. Before it during the initial outbreak in Wuhan, China, the virus was commonly referred to as “coronavirus”, “Wuhan coronavirus” or “Wuhan virus” [4,5]. On 11 February 2020, “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2) was adopted by the International Committee on Taxonomy of Viruses. The WHO sometimes refers to SARS-CoV-2 as “the COVID-19 virus” in public health communications to avoid confusion with the disease SARS and the name HCoV-19 was included in some research articles [6,7].

The National Institutes of Health has described it as the successor to SARS-CoV-1 (NIH, 2020) which is a positive-sense single-stranded RNA virus. It is contagious in nature to humans, and the World Health Organization (WHO) has designated the ongoing pandemic of COVID-19 a Public Health Emergency of International Concern [8]. Taxonomically, SARS-CoV-2 is a strain of severe acute respiratory syndrome-related coronavirus (SARSr-CoV) [9]. It is found to have zoonotic origins and has close to genetic similarity of bat coronaviruses (approx 99%), it emerged from a bat-borne virus [10-12]. There is no prove yet to link an intermediate animal reservoir, such as a pangolin, to its introduction to humans [13]. There is little genetic diversity in the virus, that indicates the spread of SARS-CoV-2 to humans which has occurred in late 2019.

Common symptoms are fever, cough, fatigue, shortness of breath, loss of smell and taste. Most of the cases result in mild symptoms, some leads to acute respiratory distress syndrome (ARDS) likely precipitated by a cytokine storm, multi-organ failure, septic shock, and blood clots (CDC, 2020). The incubation period is typically around five days but it may range from two - fourteen days [14]. If no members of the community are immune and no preventive measures have been taken then it has been estimated that each infection results in 1.4 to 3.9 new ones. The virus primarily spreads between people through close contact and via respiratory droplets produced from coughs and sneezes [15]. It mainly enters human cells by binding to the receptor angiotensin converting enzyme 2 (ACE2) [16].

Transmission of Infectious Diseases

Infectious diseases result due to invasion of host by a pathogenic agent. The continuous survival of infectious agents depends on their successful transmission to a susceptible host. Infection and replication of infectious agents is necessary to maintain the cycle of infection. Knowledge of life cycle of an infectious agent is essential for selecting the most applicable or approximate contact technology. There are horizontal and vertical two major modes of transmission of infectious diseases.

Horizontal transmission

In this mode of transmission infection takes place from a segment of population to another segment of population [17]. It may occur in following ways viz. Direct or indirect.

- i. **Direct transmission:** When susceptible host get infection by contact with infected discharge of sick animal or come in direct physical contact with infected animal [18]. No vehicle is involved here.
- ii. **Indirect transmission:** It involves an intermediate vehicle which, may be living or inanimate object that transmit infection between infected and susceptible host. Factors associated with spread of infection are characteristic of host, characteristic of pathogen and effective contact.

Vertical mode of transmission: Transmission of disease from one generation to another viz. transovarial, transplacental or transcolostral [19].

Routes of transmission: Most important, to study the epidemiology of pathogen because patterns of contact may vary between different populations and different groups of populations depending on socio-economic, cultural and other features. The route of transmission varies with different pathogens which are as follows:

Airborne infection: In airborne transmission, viral particles spread through droplet nuclei containing infective microorganisms, which can survive outside the body and remain suspended in the air for long period. Here infection goes to infect others via the upper and lower respiratory tracts. The size of the particles for airborne infections needs to be $< 5 \mu\text{m}$ [20]. Higher levels of isolation required because it contains both dry and wet aerosols which can stay suspended in the air for longer periods of time. Mainly separate ventilation systems or negative pressure environments are required to avoid general contamination. e.g. tuberculosis, chickenpox, measles.

Droplet infection: It is most common form of transmission in diseases affecting respiratory system. In these disease conditions respiratory droplets are generated by coughing, sneezing, or talking. When respiratory droplets reach susceptible mucosal surfaces, such as in the eyes, nose or mouth then only infection occurs. Droplet infection may also happen indirectly via contact with contaminated surfaces. The size of the particles for droplet infections is $> 5 \mu\text{m}$. Due to larger size they remain suspended in the air for short period of time and travel to short distances [21]. e.g., influenza virus, parainfluenza virus, *Streptococcus pyogenes*, diphtheria, rubella and corona viruses.

Faecal-oral: In the faecal-oral route, the pathogens of faeces are transmitted from one person to the mouth of another person. Faecal oral transmission can occur by contaminated foodstuffs or water which may happen due to inadequate sanitation and poor hygienic practices e.g. cholera, hepatitis A, polio, Rotavirus, *Salmonella* and parasites (e.g. *Ascaris lumbricoides*).

Sexual: The infections transmitted during sexual activity with another person, including vaginal or anal sex or through less commonly by oral sex. Transmission occurs direct between surfaces in contact during intercourse or from secretions. Some of the diseases transmission by the sexual route includes HIV/AIDS, chlamydia, genital warts, gonorrhea, hepatitis B, syphilis, herpes, and trichomoniasis.

Oral sexual: Here infection does not occur through mouth-to-mouth contact, although it is possible to transmit some sexually transmissible diseases (STDs) between the genitals and the mouth during oral sex e.g. HIV, hepatitis B and herpes simplex virus 1.

Oral: Diseases which are transmitted primarily by oral means may spread through direct oral contact such as kissing or by indirect contact such as by sharing a drinking glass or a cigarette e.g. herpes viruses namely cytomegalovirus infections, herpes simplex virus (especially HSV-1) and infectious mononucleosis.

Direct contact: Diseases that may be transmitted by direct contact are called contagious. All the contagious diseases are infectious but all infectious diseases are not contagious. Few diseases that are transmissible by direct contact include athlete's foot, impetigo, syphilis (on rare occasions, if an uninfected person touches a chancre), warts and conjunctivitis.

Vertical: This is inherited from mother to child more rarely father to child, it may be perinatal infection or postnatal. In mammals, including humans, it occurs also via breast milk (transmammary transmission). e.g. HIV, hepatitis B and syphilis. Many mutualistic organisms are transmitted vertically [22].

Iatrogenic: The infections occur during medical procedures such as touching a wound, an injection or transplantation of infected material.

Vector-borne: A vector is an organism that does not cause disease itself but that transmits infection by conveying pathogens from one host to another. Vectors may be mechanical or biological. A mechanical vector picks up an infectious agent on the outside of its body and transmits it in a passive manner. e.g. housefly. In contrast, biological vectors contain pathogens within their bodies and deliver pathogens to new hosts in an active manner, usually through bite e.g. malaria, viral encephalitis, Chagas disease, Lyme disease and African sleeping sickness.

Infection and Transmission of COVID-19

Human-to-human transmission of SARS-CoV-2 was confirmed on 20 January 2020, during the COVID-19 pandemic. It spreads mainly between people who are in close contact (less than two metres or six feet) through small droplets produced during coughing, sneezing, or talking. Infected people exhale the contaminated droplets which are then inhaled into the lungs, or settle on other non-infected people's faces his/her mucosae (mouth and nose) or conjunctiva (eyes) get exposed to potentially infective respiratory droplets to cause new infection.

The humans are most infectious who show even mild or non-specific symptoms, but may be infectious for up to three days before symptoms appear i.e. pre-symptomatic transmission. People remain infectious up to six to twelve days in moderate cases and an average of thirteen to fourteen days in severe cases. During incubation period, degree of viral infection is uncertain, but research has showed that the pharynx reaches peak viral load approximately four days after infection or in the first week of symptoms, and it declines after [23,24]. On 1 February 2020, the World Health Organization (WHO) indicated that «transmission from asymptomatic cases is likely not a major driver of transmission». However, an epidemiological model of the beginning of the outbreak in China suggested that «pre-symptomatic shedding may be typical among documented infections»

and that subclinical infections may have been the source of a majority of infections [25]. Similarly, a study of ninety-four patients hospitalized in January and February 2020 estimated patients shed the greatest amount of virus two to three days before symptoms appear and that «a substantial proportion of transmission probably occurred before first symptoms in the index case» [26].

There is some evidence of human-to-animal transmission of SARS-CoV-2, including examples in felids [27]. Institutions have advised, those infected with SARS-CoV-2 to restrict contact with animals [28].

Indirect contact occurs via contaminated surfaces, is another possible cause of infection. Previous research indicates that, virus may remain live on plastic (polypropylene) and stainless steel (AISI 304) for up to three days, but does not survive on cardboard for more than one day or on copper for more than four hours [29]. Transmission may also occur through fomites in the immediate environment around the infected person. Therefore indirect contact with surfaces or with objects used on the infected person (e.g., stethoscope or thermometer) plays an important role in the transmission [30]. Surfaces can easily be decontaminated with household disinfectants which kill the virus outside the human body or on the hands. Disinfectants or bleach are not a treatment however, it may cause health problems when not used properly, particularly when used inside the human body. This virus is easily inactivated by soap, which destabilises its lipid bilayer [31].

Sputum and saliva contain large amounts of virus. Although it is not a sexually transmitted infection but kissing, intimate contact and faeco-oral routes are supposed to transmit the virus. Viral RNA has also been found in stool samples and semen from infected individuals [32,33]. There is some evidence that infection may lead to intestinal infection and may be present in faeces. However, till date only one study has cultured the virus from a single stool specimen. There have been no reports of faecal-oral transmission of this virus till date. The aerosol-generating medical procedures such as endotracheal intubation, bronchoscopy, open suctioning, administration of nebulized treatment, manual ventilation before intubation, turning the patient to the prone position, disconnecting the patient from the ventilator, non-invasive positive-pressure ventilation, tracheostomy and cardiopulmonary resuscitation enhance the viral transmission more easily than normal.

Factors affecting COVID-19 transmission

Spread of viral diseases is affected by different factors viz. host, vectors, virulence of virus and environmental conditions. In case of SARS-CoV-2 following different factors are involved.

Close contact

Virus is easily transmitted between people who are at very close distance to one another approximately less than 1.8 meters. Thus to avoid the infection one should maintain social distance (WHO).

Air currents

This factor affects the spread of infection because of size of respiratory droplets. With size more than 5 µm droplet stay in air for shorter time and travel only short distances and aerosolized droplets of size less than 5 µm remain in the air for longer time and travel long distances. The strong air flow of air conditioner play an important role in propagation of droplets [34].

Relative humidity

Humidity can modulates the viability of virus by influence the properties of viral surface protein and lipid membrane. It affects all types of respiratory viruses independent of their source and location. In spite of affecting all transmission routes relative humidity affects mostly the air born transmission. There is good correlation between the stability of winter viruses at low RH (20-50%) while the stability of summer or all year viruses enhanced at higher RH (80%) [35,36].

Air distance

This virus can travel in aerosol form approximately 4 meters (13 feet). US CDC has reported that SARS-CoV-2 is widely distributed in the air and on object surfaces in both the ICU and general ward.

Air duration

In a study published on 17 March, in The New England Journal of Medicine found that virus remain viable in aerosols upto 3 hours.

Objects and surfaces

Zhonghua reported in a study regarding contamination of ICU and general ward (GW) having different percentage of surface contamination with virus as follows:

Computer mouse (75%, 20%), Trash cans (60%, 00%), sickbed handrails (43%, 00%), doorknobs (00%, 8.30%) in ICU and GW respectively. Cellular phones 83.30% positive for viral RNA, remote controls in room T.Vs. 64.7%, toilets 81% and room surfaces 80.4% were found positive [37].

Floor: The rate of positivity was relatively high for floor swab samples i.e. 70% and 15.4% for ICU and GW respectively. With walk of medical staff around the ward 100% rate of positivity was reported from floor of pharmacy where there were no patients. Furthermore, half of the samples from the soles of ICU medical staff shoes tested positive and it might function as carriers. These findings are probably due to gravity and air flow which affect virus droplet to float to the ground.

Potential Target to Control and Treat the COVID-19

Scientists are working potential targets to control the pandemic. The targets range from modulating host cell receptor for the virus entry to generate an effective adaptive immune response, which are discussed in brief as follows.

Target Angiotensin I Converting Enzyme 2 (ACE2) Receptor to inhibit the virus entry to the host

Interaction of a virus receptor with its ligands at the host cell (e.g., host cell receptor) is the first step in virus infection. Studies with SARS COV2 showed virus S protein interacts with host receptors such as angiotensin-converting enzyme 2 (ACE2) or Transmembrane protease serine 2 (TMPRSS2) to initiate the infection. ACE2, a homologue of ACE, is a multifunctional zinc metalloprotease consisting of 805 amino acids, which can be functionally divided into the amino-terminal catalytic domain and a carboxy-terminal domain [38]. High expression of ACE2 in the human mouth and airway epithelium make this virus easy for aerosol transmission [39]. A small molecule which can disrupt or reduce the interaction between host cell receptor (e.g. (ACE2) and virus (e.g. Spike protein)

can significantly reduce virus infection. Scientists identified at least 77 such small molecules which can interfere these protein-protein interaction can be used as therapeutic drugs for COVID 19 [40]. Additionally, telmisartan, an angiotensin II receptor blocker which is frequently used to treat high blood or soluble recombinant ACE2 could be used to inhibit virus interaction to the host cell [41].

Preventing virus entry to the host cell by inhibiting cellular Cathepsin L activity

Following interaction of the host cell (e.g. ACE2) and virus receptor (Spike e.g. protein), virus in endocytosis for uncoating and replication. A recent study with SARS-CoV-2 showed that cathepsin L is involved in virus endocytosis and treatment of cathepsin L-selective inhibitor SID26681509 significantly reduced SARS-CoV-2 to the host cell [42]. Therefore SID26681509 or other of cathepsin L-selective inhibitor can be used to prevent SARS-CoV-2/COVID-19 infection.

Interfere the virus trafficking in the cellular compartment

During virus infection, virus enters to the host cell and transported to the cellular compartment for its replication. Among various adaptor proteins, GAK (cyclin G-associated kinase) is an important protein which regulate clathrin-coated vesicle trafficking and has been shown its effect in various virus replication such as dengue, Ebola and hepatitis C virus [43]. Therefore could be explored for its effect in COVID19 infection.

Targeting cellular autophagy to control COVID-19 replication

Autophagy is a normal cellular physiological process, which recycle unused/damaged cellular components/ misfolded proteins [44]. This self-digestion not only provides nutrients to maintain vital cellular functions during fasting/stress but also offer a pathway to eliminate superfluous or damaged organelles, misfolded proteins [45]. Studies showed that energy and macromolecules released by autophagosomes is utilized by many viruses utilize for their efficient replication [46-48].

Corona virus such as mouse Hepatitis Virus (MHV: Murine, betacoronavirus) and PEDV showed autophagy enhanced virus replication. Therefore reducing the cellular autophagy may inhibit the COVID 19 replication [49].

Used of nucleoside analogs as antiviral drugs

There are number of nucleoside analogs which show the antiviral properties, however recent study with Remdesivir, is an adenosine analogue which inhibits RNA dependent RNA polymerase showed beneficial effect in reducing virus replication [50]. The similar beneficial effect was observed in an American patient with intravenous administration [51]. In addition to Remdesivir, other analogues such as umifenovir, lopinavir, ritonavir treatment, favipiravir and oseltamivir need to be tested for COVID-19 as they has been successful in reducing other RNA viruses.

Conclusion

It can be concluded that COVID-19 is a highly contagious disease and mainly transmitted through exposed mucosae (nasal, oral and conjunctival) or inhalation of respiratory droplets exhaled by the infected person. These droplets may be inhaled directly or indirectly by touching the infected surfaces, contaminated food and water or fomites

The aerosol-generating medical procedures have been another major source of infection. However, it is a new disease and its modes of transmission and the details of spread are still under investigation. To control and treat this pandemic various targets have been identified where virus acts but still is under study.

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