

POSSIBLE ROLE OF PETS, WILD AND DOMESTIC ANIMALS IN THE TRANSMISSION OF COVID-19 TO HUMANS

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INTRODUCTION

Pneumonia due to unknown cause appeared in early December, 2019 in many people residing in Wuhan city, China (Li et al. 2020a). The causal agent of this infection was verified as a novel coronavirus (nCoV), and later the disease was identified as Coronavirus Disease (COVID-19) by the WHO and the causative virus was renamed as SARS-CoV-2 (Lai et al. 2020; Yuen et al. 2020). This viral disease outbreak very rapidly spread all around the globe and WHO declared public health emergency internationally on January 30, 2020, which was afterwards announced as worldwide pandemic on March 11, 2020 (WHO 2020a). As of December 23, 2020, >76.3 million definite cases and >1.7 million deaths have been altogether reported worldwide (WHO 2020b).

This group of Coronaviruses belongs to the subfamily *Orthocoronavirinae* of family *Coronaviridae* (Dhama et al. 2020), and order *Nidovirales*. These viruses are classified on the basis of their genetic, as well as susceptibility to various species, into following four genera i.e., Alphacoronavirus (α -CoV), Betacoronavirus (β -CoV), Gammacoronavirus (γ -CoV), and Deltacoronavirus (δ -CoV) (Lau et al. 2015; Li et al. 2020a; Gennaro et al. 2020; Kiros et al. 2020; Fig. 1). Generally, viruses belong to α - and β -CoV genera can cause infection in mammalian animals including humans, while δ - and γ -CoVs viruses can cause illness mostly in birds and other animals (Li et al. 2020a; Sharun et al. 2020a).

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has appeared as the 7th member in the family of corona viruses causing infection in humans (Hasoksuz et al. 2020). Before this pandemic, atypical pneumonia due to Middle East respiratory syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) was reported in humans (Li et al. 2020a; Chang et al. 2020). Both the MERS-CoV and SARS had infected humans worldwide in 2002 and 2012 (Wu et al. 2005; Sims et al. 2008; Guillon et al. 2008; Balkhair et al. 2013; Gastañaduy 2013; Su et al. 2015).

As the SARS-CoV-2 virus has a zoonotic, as well as natural, origin, two school of thoughts can probably describe the origin of this virus i.e., i) natural selection of virus in the animal host before to its transmission to the humans; and ii) natural selection of the virus in humans subsequent to

zoonotic transfer from the animals (Yin and Wunderink 2018; Lu et al. 2020). Clinical signs and symptoms of the disease are highly variable, which make the clinical severity from asymptomatic to highly severe, leading to death of the affected individuals (Phan 2020).

Though some approved vaccines against SARS-CoV-2 are being marketed but these are beyond the approach of poor nations and even the therapeutic drugs are also not specific and clear. Therefore, it is the best policy that the transmission mechanism of this pathogen be recognized well before its prevention and control. In this context, the possible role of animals in the transmission of this virus to humans must be ruled out so that if involved, it could be curtailed. There are many studies reported (Shi et al. 2020; Kayser and Rottmann 2020; Sia et al. 2020; Kiros et al. 2020; Chan et al. 2020), while others are in progress, but information about the role of pets in spreading this virus to humans is not available. In this chapter, we have tried to review the role of various animal species in the transmission of the COVID-19 to humans.

Zoonotic Importance of SARS-CoV-2

Almost 60% of all known emerging infectious diseases are zoonotic in nature. Among the new pathogens (as SARS, Ebola, Zika fever, MERS and Covid-19 etc.) detected in humans over the period of last three decades, ~75% have originated from animals (Jones et al. 2008). Many of the emerging infectious diseases in the history were actively controlled in time to limit their spread, but COVID-19 has spread all over the world within very limited time duration and causes devastating losses all around the globe. A number of species of CoVs are circulating in mammals and birds, causing illness that leads to huge economic losses (Abdel-Moneim and Abdelwhab 2020; Li et al. 2020a). Previously observed outbreaks of both MERS and SARS-CoV also indicate the zoonotic importance of the pathogen (Kiros et al. 2020). Similarly, indications from the COVID-19 outbreaks pointed out that former cases had been linked in China to the Wholesale Seafood Market (Chen et al. 2020b) and isolation of the SARS-CoV-2 from various samples (structures, soil, people, birds, animals, discharges, etc) advocated the engrossment of some middle hosts (WHO 2020c). Possible animal-human interface, or zoonotic association towards the

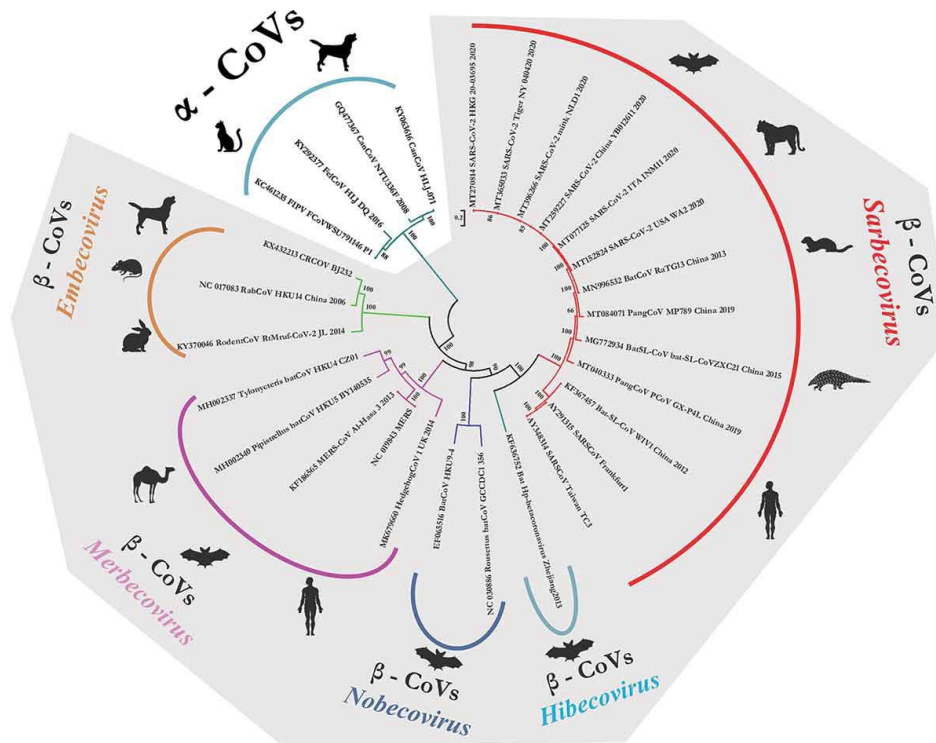


Fig. 1: Grouping of coronaviruses of human and animal origin on the phylogenetic basis (Sharun et al. 2020b).

derivation of the SARS-CoV-2 has also been pointed out recently (Fig. 2; Salata et al. 2020; Ji et al. 2020; Murdoch and French 2020; Tiwari et al. 2020). An outline of coronavirus cross-species transmission from bats to additional faunas prior to spillover to humans as zoonosis, and probable projections for additional spread to mammalian hosts, has been explained in Fig. 3.

Transmission

The transmission and adaptation of coronaviruses infection among different species are based on the existence or absence of certain receptors on the cells of different tissues of the host (e.g. ACE 2 receptors for SARS-CoV, SARS-CoV-2 and HCoV-NL63, 9-O-acetylsialic acids for HCoV-HKU1 and HCoV-OC43, human aminopeptidase N for HCoV-229E and dipeptidyl peptidase-4 for the MERS-CoV), which play an important role in the binding and entrance of the viral particles into the host cells (Tiwari et al. 2020; Salata et al. 2020). These specific receptors exist in several body systems of humans and animals, such as gastrointestinal and respiratory systems (Salata et al. 2020). Reservoir host animals of CoV, including rodents and bats, carry similar receptors as present in intermediate hosts including bovines, camels and masked palm civet (Salata et al. 2020; Wang et al. 2020; Ye et al. 2020). The presence of these receptors (ACE2 or DPP4) in humans makes them susceptible to MERS-CoV and SARS-CoV, causing MERS and SARS infections, respectively (Song et al. 2005; Tiwari et al. 2020; Ali et al. 2021). The spike present on the MERS-CoV has the capability to become accustomed to the disparity in the receptors DPP4 of the host species (Letko et al. 2018). This property of adaptation by MERS-CoV might be

present in other coronaviruses. Likewise, spike protein of SARS-CoV interrelates the angiotensin converting enzyme 2 (ACE2) receptors of the host and results in its interspecies, as well as cross-species, transmission (Wan et al. 2020). The variations in the receptors of host species bind the interaction with spike protein of CoV, which results in the formation of a barrier that results in the prevention of spillover infection. Different animal species, including pangolins, civet and snakes, are deliberated as the likely intermediate hosts of COVID-19. Though, this needs to be confirmed by tracing the origin of the virus for the prevention of viral resurgence (Amodio et al. 2020). In addition, detection of susceptible animals and investigation of SARS-CoV-2 would be of significance for the prevention of such outbreaks in the future.

Different reports suggest that the COVID-19 virus can possibly spread during the incubation period, as well as in the convalescent period, of the virus (Rothe et al. 2020). During the COVID-19 infection, the virus is present in respiratory droplets and body fluids of the infected patients with the capability to survive for up-to 9 days on polluted surfaces, leading to human-to-human, as well as nosocomial, transmission (Huang et al. 2020; Kampf et al. 2020; Lee et al. 2020). Similar to SARS-CoV, SARS-CoV-2 can be transferred from one person to another through ocular route, indicating the different ways of spread of the disease apart from respiratory tract (Belser et al. 2013; Lu et al. 2020). Later, transmission of the virus via fecal-oral route was also suggested (Huang et al. 2020). The polymorphism observed in SARS-CoV-2 through metatranscriptome sequencing in the broncho-alveolar lavage fluid has shown intra-hosts variants, proposed *in vivo* evolution, thus affecting the transmissibility, virulence and infectivity of this virus (Shen et al. 2020).

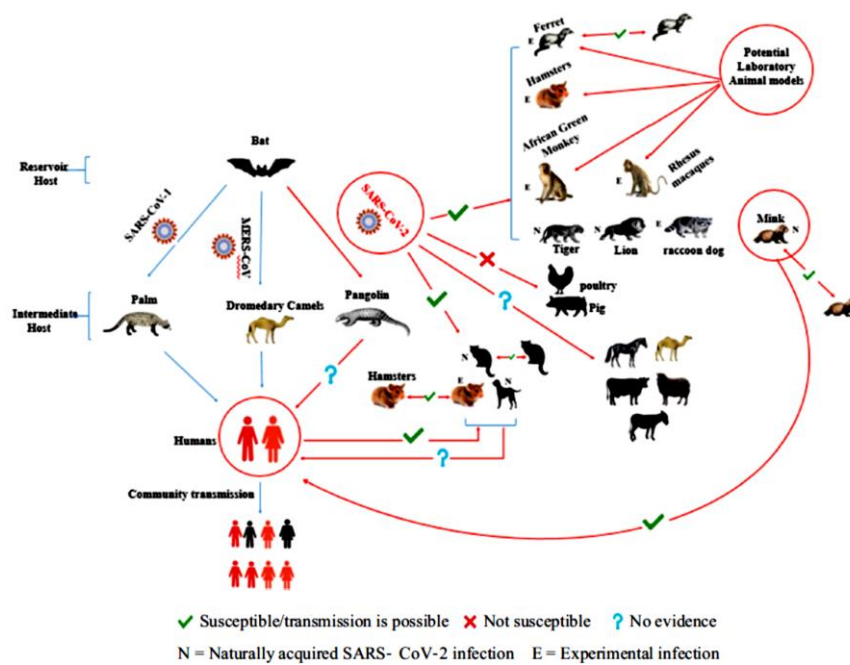


Fig. 2: The origin of the SARS-CoV-2 and its transmission along with the possible role of pets and other animals in the disease transmission. According to this figure, companion animals are prone to SARS-CoV-2 and humans could be origin of infection for the companion animals, however, probable role of companion animals in the disease spread to humans is undetermined (Kiros et al. 2020).

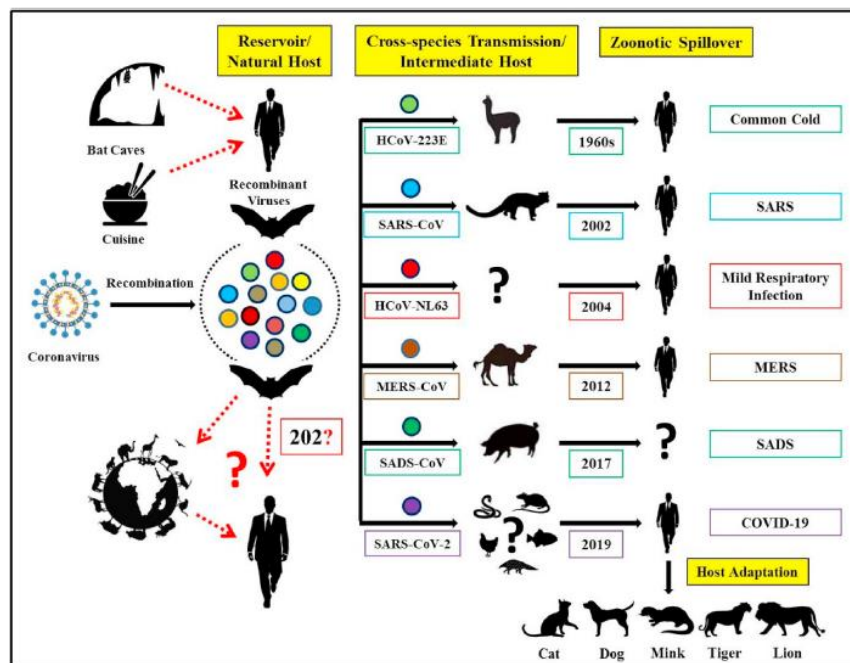


Fig. 3: The possible spread of zoonotic coronaviruses from bats to animals or cross-species spread before spillover to humans. Possible predictions of spread to mammalian hosts are also shown (Dhama et al. 2020).

Dispersion of the SARS-CoV in 2002 to palm civet from bats and afterwards to humans, whereas spread of MERS-CoV to camels from bats and subsequently to humans in 2012 has been documented (Bonilla-Aldana et al. 2020a; Ahmad et al. 2020; Bonilla-Aldana et al. 2020b; Bonilla-Aldana et al. 2020c; Bonilla-Aldana et al. 2021; Li et al. 2020b), indicating the importance of bats as reservoir host and it may have possibly been related to the current SARS-CoV-2 pandemic.

SARS-CoV affected humans (774 deaths) during 2002 in China had close contact with palm civet (Totura and

Bavari 2019). Decade after, MERS-CoV, another threat due to coronaviruses, infected humans and showed a very close relationship with camels in Saudi Arabia, where it led to 858 deaths and remained a public health concern in 27 countries (Totura and Bavari 2019). A study detected partial RNA-dependent RNA polymerase (RdRp) sequences in tissues and feces of bareback fruit bats (Anindita et al. 2015). Another study spotted 26.65% positive rate of coronaviruses in bats (Hu et al. 2018). Many other reports have shown that SARS-CoV-2 is identical to coronaviruses naturally present in bats

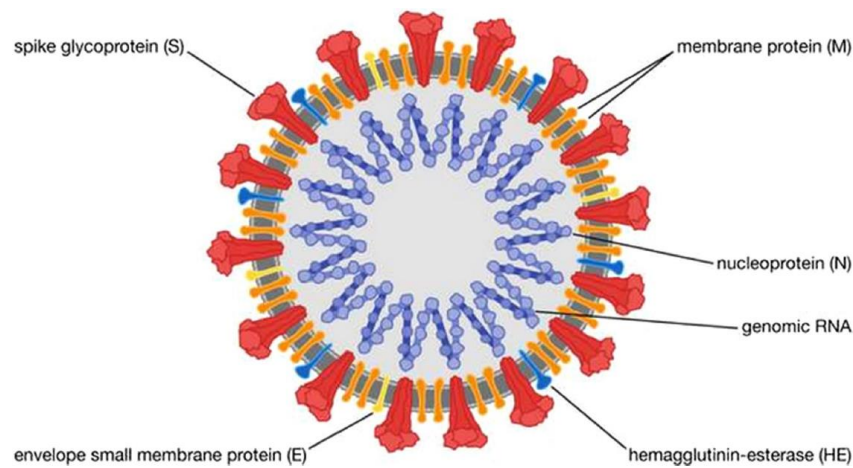


Fig. 4: Coronavirus virion structure shown with structural proteins and hemagglutinin-esterase (Kiros et al. 2020).

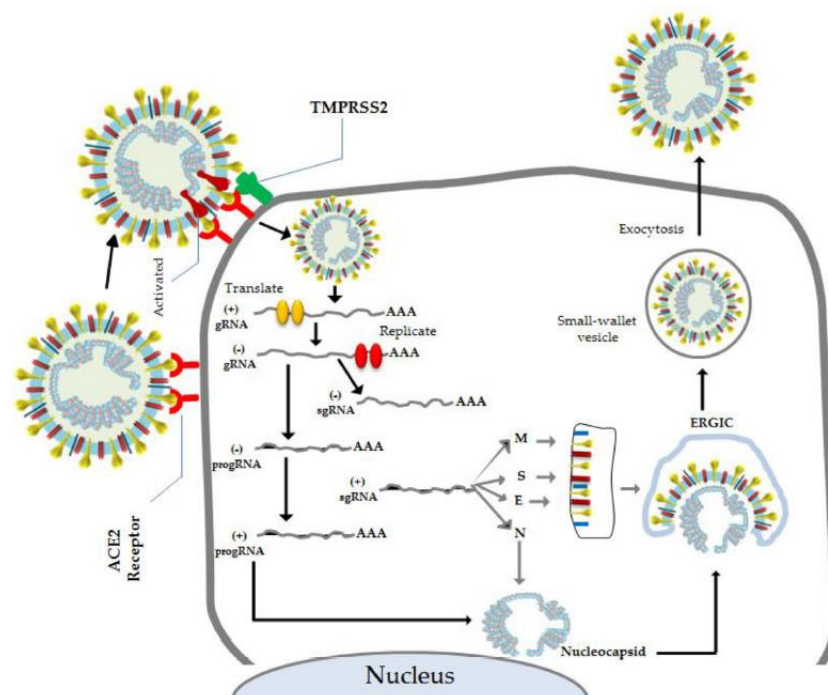


Fig. 5: Mechanism of entry and life cycle of Severe Respiratory Syndrome Coronavirus (Masters 2006; Rabi et al. 2020; Astuti and Ysrafil 2020).

(Morrison et al. 2020; Latinne et al. 2020). However, continuous mutation and evolution make it hard to find out a particular reservoir of SARS-CoV-2 (Bonilla-Aldana et al. 2021). *Rhinolophus*, a genus of bats, is assumed to be carrier host of the SARS-CoV-2. Furthermore, where different studies revealed that SARS-CoV-2 genome is very similar to the genome of coronaviruses from horseshoe bats; the receptors-binding domain of SARS-CoV-2 is found to be similar to that of pangolin corona viruses (Bonilla-Aldana et al. 2021). So, there is a possibility that pangolin CoV may be originated from some unidentified bat viruses, as an outcome of animal mixing. Therefore, SARS-CoV-2 is most likely a recombinant virus originated from bats (Lau et al. 2020). Another viewpoint related to origin of coronaviruses affecting humans, shows that all of these viruses have originated from bats or rodents (Swelum et al. 2020). At present, we have the knowledge

of conserved genome sequences of a few coronaviruses naturally found in the bats to draw the phylogenies and until now there is a need to study the reservoirs of coronaviruses in the bats, viral transmission route and the process resulting in the spillover to humans (Bonilla-Aldana et al. 2020d; Bonilla-Aldana et al. 2021). Several people afflicted with the SARS-CoV-2 owing to exposure in Wuhan City with the seafood market, which might suggest that the virus could have originated from animals and infected to humans, then persisted in the humans for further human-to-human transmission (Rothan and Byrareddy 2020; Ji et al. 2020). Bats could have been the initial reservoir of the virus (Temmam et al. 2020). Likewise, several studies have indicated with strong evidence that Malayan pangolins are supposed to be the probable intermediary host for the SARS-CoV-2 spread to humans (Lam et al. 2020).

In humans, primarily the SARS-CoV-2 targets the organs of respiratory system of the individuals, thus aerosol and/or respiratory droplets may act as major source of spread of the pathogen (Sia et al. 2020). It is believed that COVID-19 patients are the principal cause of spreading the pathogen to other individuals (Jahan et al. 2020), where transmission from one person to another is maintained via respiratory droplet within a distance of about 2 meters (Setti et al. 2020). Fomites around the infected person could also be a source of spread of the infection. Moreover, touching contaminated instruments and consecutive transfer to mouth by touching eyes and/or nose with infected hands could be other sources of transfer of the infection (Ong et al. 2020).

Possible role of animals in COVID-19 transmission

Possible role of pets

In February 2020, the first positive COVID-19 case was reported from Hong Kong, China in a Pomeranian dog (HKG 2020a). Later, another case from the same country was reported in a cat in March 2020 (HKG 2020b). In both of these cases, owners of the pets were also reported positive for the COVID-19 infection (HKG 2020a; HKG 2020b). The detailed study showed similarities in the genetic sequence of the owner and the pets SARS-CoV-2, indicating probable human-to-animal transmission. In addition, both serological tests and cultural isolation of the virus were performed for further confirmation. Results of these tests without signs and symptoms in the animals bring about interpretation that the virus was not transmissible to humans and/or another animal from the dog (Almendros 2020).

After the first reported cases of COVID-19 (HKG 2020a), further cases of COVID-19 were also reported from countries like Switzerland (Abdel-Moneim and Abdelwhab 2020), Belgium (ISID 2020a), France (ISID 2020b), Germany (ISID 2020c; ISID, 2020h), The Netherlands (ISID 2020d), South Korea, Canada (AVMA 2020), Russia (OIE 2020a), the United States (AVMA 2020; ISID 2020e; ISID 2020f; OIE 2020b) and India (ISID 2020g). From Switzerland, first case of novel coronavirus was observed on December 3, 2020 in a cat (SWI 2020). Experts believe that transmission of SARS-CoV-2 infection from humans to cats is infrequent but cannot be ruled out, that is why maintenance of fair distance from the pets is recommended by Swiss veterinary affairs (SWI 2020).

According to AVMA (2020), up to June 8, 2020, 7 million worldwide and 1.9 million people in USA were confirmed with COVID-19 infection, however, COVID-19 outbreak during the first five months (January 1 to June 8, 2020) only infected <20 pets throughout the world, which is an indication that pets are liable for SARS-CoV-2 infection (AVMA 2020). Moreover, infection of a few pets with SARS-CoV-2 was typically the result of close contact with COVID-19 positive people. Cats, ferrets and Syrian golden hamsters are also being kept as pets. These animals show potential animal models of human infection in laboratory studies (AVMA 2020; Sia et al. 2020; Chan et al. 2020),

however, chickens, ducks, pigs and dogs do not come under potentially affected pets.

Possible role of domestic animals

Similar to the companion pets/animals, domestic animals like ferrets are highly susceptible to SARS-CoV-2 (Shi et al. 2020). A recent study has shown that experimentally infected ferrets can transmit COVID-19 infection proficiently to other healthy ferrets through air and direct contact (Richard et al. 2020). On the other hand, other domestic animals including poultry and pigs do not carry and spread the SARS-CoV-2 infection (Shi et al. 2020; Schlottau et al. 2020). However, no evidence regarding the susceptibility to COVID-19 in livestock animals including horses, donkeys, camels, cows and sheep is observed yet. Raccoon dogs in another contemporary experimental study were found permissive to COVID-19 virus and could have a possibility of pathogen transmission to other animals. Following intranasal inoculation, replication of the virus was recorded in the respiratory tract of these animals (Freuling et al. 2020).

Cats seem to be more susceptible to SARS-CoV-2 with high possibility to spread disease to other un-infected cats, whereas dogs are less prone to the SARS-CoV-2 and have a very minute role in the spread of the virus to other non-infected dogs (Shi et al. 2020). Similarly, golden Syrian hamsters can acquire and spread the SARS-CoV-2 infection to naive hamsters by aerosols, as well as direct, contact (Sia et al. 2020). It can be inferred that under natural condition there is slight to no possibility that pets and other domestic animals can get infested with the SARS-CoV-2. However, people with COVID-19 must protect their pets, as they are at high risk to attain the disease and can further spread the virus. Since no evidence has so far been reported that virus has been transmitted from pets to the people, hence primary type of spread of the COVID-19 in humans is from one person to another (AVMA 2020). Though there is no proof, however, pets could have the probable role in the transmission of the infection to humans, as pets also exhibit identical cell receptors i.e., ACE2 (Schoeman and Fielding 2019; Luan et al. 2020). Hence, the traditional protective measures must always be adopted.

Possible role of wild animals

Other wild animals, such lions and tigers, have also been confirmed earlier to be prone to the COVID-19 infection (ISID 2020e; ISID 2020f). In Oregon State, USA, 2 deaths in minks have been reported due SARS-CoV-2 (OIE 2020c). The problem started on commercial premises on 24th March 2020 and cases of SARS-CoV-2 were confirmed positive at the National Veterinary Services Laboratories, based upon molecular testing results (PCR and sequencing), meeting case definition on 04 April 2020 and these cases were reported to OIE after 2 deaths on 27th November 2020. This is the first confirmed detection of SARS-CoV-2 in mink from Oregon, USA. Reported clinical signs were inappetence, coughing and mild

respiratory signs, including sneezing. Mortality rates on the affected premises remained normal for this time of year and no respiratory or gastrointestinal signs have currently been observed. The colony is reported to be free of Aleutian Disease, making it unique amongst mink colonies in the United States affected to date. The affected premises reported positive COVID-19 humans who were in contact with the mink. State Officials in Oregon are working closely with Federal One Health partners to follow up and monitor the situation (OIE 2020c).

In another study in the Netherlands, minks usually raised for fur are also found vulnerable to the SARS-CoV-2 infection and have the capability to transfer the virus to other animals (van der Poel 2020; Oreshkova et al. 2020). On 23rd April 2020, first ever case of mink infected with the SARS-CoV-2 virus was reported from the Netherlands in highly populated area of mink farms. According to the Dutch government, it is believable that some employees were infected previously with SARS-CoV-2, who transferred the virus to mink farms and created a most likely situation for the infection to farmed animals. Besides that, no other indications were found, showing that these animals served as source of infection for humans (van der Poel 2020; Oreshkova et al. 2020). Since the reporting of the first ever case, countries like France, Spain, Italy, Denmark, and other countries also testified similar COVID-19 cases in the mink as found in Greece (OIE 2021). All of this evidence indicates the possibility of human to animal spread. Thus, the persons who work on wildlife are in close contact with such animals and/or work for wildlife management and are in close contact with wildlife species, should follow stringent preventive measures to avoid the spread of the virus. SARS-CoV-2 has been detected rarely from other animal species including rhesus macaques, African green monkeys and Egyptian fruit bats; this highlights the possibility of cross-species transmission of SARS-CoV-2 (Schlottau et al. 2020; Yu et al. 2020; Munster et al. 2020; Cross et al. 2020).

A latest study from the Netherlands investigated on the spread of SARS-CoV-2 virus from mink back to humans working on the mink farm. This observation was further reinforced by finding similarities in the viral sequence isolated from mink and from an infected employee at that farm, and provided clue to the scientists that the worker was infected with the virus transferred from a mink infected with SARS-CoV-2 virus with no apparent signs of the disease (Oreshkova et al. 2020). Asymptomatic infection of COVID-19 in mink also suggests the possible probability of mink as intermediary host of the SARS-CoV-2. Since it has been described that various species, excluding rats and mouse, exhibit the ACE2 cell receptors it is reported that animal-to-human and animal-to-animal spread of the disease is conceivable, adding to human-to-human transmission of the pathogen (Schoeman and Fielding 2019).

Pathogenesis of SARS-CoV-2

The structure of CoVs is not so simple. These viruses are ~80–220 nm in diameter and enveloped with icosahedral

symmetry. These viruses consist of a non-segmented, single-stranded positive sense RNA genome, measuring ~26–32 kb (Helmy et al. 2020; Kiros et al. 2020; Wiersinga et al. 2020). Among all RNA viruses, CoVs are the largest viruses. Being spherical enveloped virus, the SARS-CoV-2 has a diameter of 50–200 nm, with a single-strand (30 kb in length), positive-sense RNA genome (Kakodkar et al. 2020; Mousavizadeh et al. 2021). The genome of SARS-CoV-2 shares sequence identification of SARS-CoV (79.6%) and Bat-CoV (96%) (Zhou et al. 2020; Kiros et al. 2020). Four main structural proteins are present in the membrane of SARS-CoV-2 virus, namely, small envelope (E) glycoprotein, spike (S) glycoprotein, nucleocapsid (N) protein and membrane (M) glycoprotein (Tok and Tatar 2017; Fig. 4). The outermost layer of the virus is composed of S glycoprotein that initiates attachment to the ACE2 receptors on the host's target cells (Luan et al. 2020). The M protein, which is the amplest protein, forms the shape of the virus. Along with other structural proteins, it plays a main role in viral get-together (Schoeman and Fielding 2019). The N protein (RNA binding protein) has the main functions of binding of the viral genome (RNA) into a long helical nucleocapsid structure (Kiros et al. 2020; Kang et al. 2020).

Though it is stated that pathogenesis of COVID-19 is not clear, however, in most of the cases, it primarily affects the lungs. Ali et al. (2021) have stated in this regards that the key mechanism for SARS-CoV-2 invasion is the binding of the virus to the ACE2 membrane-bound receptor and the host cell's internalization of the complex (Zhang et al. 2020). ACE2, a glycoprotein and metalloprotease, is present both in membrane-bound, as well as in soluble, forms (Jia et al. 2009). The membrane bound form is comprised of a transmembrane domain, which anchors its extracellular domain to the plasma membrane, whereas it is degraded and secreted in its soluble form, while the circulation of the N-terminal ectodomain is scarcely detectable (Gheblawi et al. 2020). The virus can pass through the mucous membranes of upper respiratory system, especially larynx and nasal mucous membranes, then through respiratory tract, and finally enters the lungs (Gennaro et al. 2020). At this point, the virus targets the organs including lungs, gastrointestinal tract, heart, and renal system, which express ACE2 receptors (Rose-John 2018; Chen et al. 2020a; Bennardo et al. 2020). The virus instigates a second attack, leading the patient's ailment to worsen around 7 to 14 days after onset. Reduction in the number of B lymphocytes may occur in the initial stage of the disease, which may result in the distressed production of antibody in the infected individuals. Besides, IL-6 is also increased in a significant amount, which also performs an important role in worsening the infection due to COVID-19 around 2 to 10 days after the onset of the infection along with other inflammatory factors (Weiss and Leibowitz 2011; Gennaro et al. 2020).

Precisely, it is quite fair to say that SARS-CoV-2 habits the ACE2 receptors. These ACE2 receptors are mostly found on mammalian cells for attachment (Astuti and Ysrafil 2020; Hoffmann et al. 2020; Luan et al. 2020). The binding of S glycoprotein to the ACE2 receptors paves the

admittance of SARS-CoV-2. In this regard, two pathways have been proposed (Mahmoud et al. 2020). In the first pathway, endosomes are the target for SARS-CoV-2 entry, followed by endocytosis (receptor-mediated). With upsurge in the H⁺ influx into the endosome stimulates cathepsin L, resulting in the cleavage of S glycoprotein (Lisi et al. 2020). This proteolytic cleavage within S glycoprotein exposes the interior fusion peptide, that is present close to the cleavage site. Therefore, upon S glycoprotein cleavage, the combing peptide fuses with the host cell membrane and facilitates the virus entrance into the cell (Astuti and Ysrafil 2020; Mahmoud et al. 2020). The other pathway is non-endosomal, the joining of SARS-CoV-2 S glycoprotein to the ACE2 is pursued by cleavage of the viral S glycoprotein through transmembrane protease serine 2 on the surface of the host cell (Fig. 5). This tempts straight combination of the viral and plasma membranes, resulting in the entry of viral particle into the cytoplasm (Lisi et al. 2020; Mahmoud et al. 2020). After the virus entry into the host cells, uncoating of viral genome occurs, then it is transcribed and translated (Mousavizadeh et al. 2021).

Laboratory animal models

The animals which can carry human diseases are of prime importance to develop the understanding of pathogenicity and to investigate effectiveness of vaccines and therapies. Formerly, for the study of MERS-CoV and SARS-CoV different animals including hamsters, mice and non-human primates, which showed viral replication with signs and symptoms of infection similar to human infection, were utilized as animal models (Gretebeck 2015; de Wit et al. 2020). On the basis of previous studies, non-human primates and small laboratory animals are suggested as preferred animal model for the study of SARS-CoV-2. As golden Syrian hamsters exhibited an efficient viral multiplication in epithelial cells of nasal mucosa and lower respiratory system and signs like weight loss, it is proposed as one of the suitable laboratory animal models to study SARS-CoV-2 (Sia et al. 2020; Chen et al. 2020b). Likewise, due to efficient virus replication in their respiratory organs without causing any disease for up-to eight days, ferrets are also proposed as a potent animal model detailed study about this virus (Shi et al. 2020). Other recent studies have suggested rhesus macaque as potential laboratory animal model for carrying out SARS-CoV-2 studies due to viral shedding, signs and symptoms similar to humans (Yu et al. 2020; Munster et al. 2020; Ying et al. 2020). Similar observations of infection after inoculation of virus have been reported in African green monkeys used to study COVID-19 infection (Cross et al. 2020).

COVID-19 Laboratory Diagnosis in Animals

Diagnosis/detection of the SARS-CoV-2 from the wild or domestic animals is akin to the viral diagnosis of this virus in humans. Timely identification of virus is very important to prevent community transmission. Specimens from

respiratory tract (soft palate, nasal turbinate and tonsils) are preferred for the detection of SARS-CoV-2 (Shi et al. 2020). Rectal swabs may also be used where sampling from the respiratory tract is not possible owing to risks to the humans or animals (OIE 2020c). The samples should be transported in the triple packaging system to the laboratory (WHO 2020a).

Virus culture can be performed by inoculation of nasopharyngeal samples on vero cell lines (Kim et al. 2020). Culture of the virus is valuable in its isolation and characterization. However, cell culture for isolation of the virus is not recommended for diagnostic purposes due to its high risk of transmission to the laboratory workers.

Serological assays were used extensively to study the coronavirus outbreaks in the past and these serological tests have been played an important role for the diagnosis and understanding of the disease (Chen et al. 2004). The immunological tests can provide the valuable information and aid in the diagnosis of the SARS-CoV-2 by measuring the antibodies generated by host body's, whether the host has shown any symptoms or does not exhibit any signs of the infection. Different reports documented great specificity for the detection of viral IgM and IgG for serological diagnosis of COVID-19. However, sensitivity range of 70-85% for the detection of IgG and IgM makes the testing unsuitable for active cases (Xiang et al. 2020). In general, immunoassay to detect antigen of SARS CoV-2 virus in the form of lateral flow assay are used for rapid detection of COVID-19 (Tang et al. 2020). However, the previous experience for the detection of influenza viruses using lateral flow assay for antigen detection shows that the lateral flow assay can give false negative results due to low viral load in the tested samples. Even though the serological tests have certain restrictions, these immunological tests may play a critical role in the future for the detection of recovered individuals from COVID infection. The serological results also help us in selecting the convalescent plasma used to treat COVID-19 infection (FDA 2020). According to Ali et al. (2021), myoglobin and C-reactive protein (CRP) are specific risk factors related to mortality and highly correlated to organ failure in COVID-19 disease.

Real-time RT-PCR is the widely used technique and is gold standard for the etiologic identification of SARS-CoV-2 in animals (Richard et al. 2020; Zhong et al. 2020). In the recent emergence of corona virus and need of rapid and reliable detection of virus, real time RT-PCR is one of the most reliable laboratory tests for the detection of specific target genome, pursuing and studying the COVID-19 infection in a closed system, which also reduces the chances of false positive results (Sethuraman et al. 2020). Besides real-time RT-PCR assays, many other molecular diagnostic assays are being developed and used for COVID-19 infection worldwide. These include Reverse transcription loop-mediated isothermal amplification (RT-LAMP), multiplex isothermal amplification followed by microarray detection (Tang et al. 2020).

Molecular target has been recognized within the RNA of COVID-19 virus; for example, nucleocapsid (N), helicase (Hel), envelope glycoproteins spike (S), envelope (E) and

transmembrane (M), RNA-dependent RNA polymerase (RdRp), open reading frames ORF1a and ORF1b and Hemagglutinin-esterase (HE) can be used for the SARS-CoV-2 detection through molecular tests (Tang et al. 2020). However, based on numerous studies conducted worldwide for the detection of COVID-19, it is suitable to use a minimum of two genomic targets, one specific region and one conserved region, to avoid the false negative results due to potential genomic drift in the COVID-19 virus (Corman et al. 2020; Chan et al. 2020; Tang et al. 2020).

One health approach

Keeping in view the corona virus infection, first 20 years of this century have appeared to be a nightmare for the mankind, as well as animals, in almost all the countries around the world. After SARS-CoV and MERS-CoV infections, the SARS-CoV-2 is re-emerged as third zoonotic CoV infection in December 2019, which has caused global crisis due to widespread COVID-19 infection (Anonymous 2020; Charf 2020). The emerging and re-emerging of infectious diseases capable of jumping the species barrier evolved from animal reservoirs to infect humans has increased over the past three decades. The risk of emergence with rapid spread of novel infectious agents is increasing due to increased travel and trade around the globe (Jones et al. 2008). The examples of these pathogens include highly pathogenic avian influenza (HPAI) viruses, Ebola virus, MERS, and SARS-CoV-2. The later has affected almost all the sectors regardless of underdeveloped or developed countries, including economics, healthcare system, infrastructure service, production sectors and trade of the countries (Qamar 2020). The worldwide crisis due to SARS-CoV-2 infection has strengthened the significance of principles of One Health in the global governance of infectious diseases to prevent and control the zoonotic diseases. These infections can impose vast impacts on health of the communities, as well as cause social and economic crises (Gatiso and Bureau 2020). The spread of such infections can result due to numerous limitations in domestic and global governance arrangements (Salata et al. 2020). Since COVID-19 is a novel zoonotic pathogen with many unrevealed features including modes of transmission, intermediate host, pathogenesis and ecological aspects, there is an immediate need of creation of collaborated setting to control the disease. The applied execution of the One Health approach is much difficult and challenging for many of the countries, as well as worldwide, due to certain limitations in the work structures (Zowalaty and Järhult 2020; Lee and Hsueh 2020). However, association of various authorities was sought after the widespread COVID-19 infection (Tiwari et al. 2020; Ahmad et al. 2020). The concept of One Health has been accepted by different countries during this outbreak and coordinated methodologies have been opted between public health, medical, environmental, food safety, veterinary, wildlife departments and many others for better control of the COVID-19 infection (Zowalaty and Arhult 2020). This

association involved development of infrastructure for disease surveillance in both humans and animals for the diagnosis, treatment and prevention of the COVID-19 infection. As the human, animal, and environmental health are interlinked, the prime and imminent efforts focused on finding the source of the disease, its modes of transmission among different species and humans, screening as well as monitoring of infection, contact tracing, diagnosis, treatment, proper infection control and prevention, isolation of the pathogen, quarantine and cure of infected persons, public awareness related to prevention and control of the disease and facilitation of infrastructure are required by all concerned sectors of medical, veterinary and environmental sciences and specialized persons of various departments for the effective management of current crises. COVID-19 cases in humans are increasing owing to a very efficient transmission of disease from one person to another, leading to a consequent increase in the infection among the wild, as well as companion, animal species. This could be due to some particular features of the coronaviruses that enable them to cross inter-species barriers (Leroy et al. 2020). Though the evidence of animal-to-human transmission is not available, still collective insights from environmental, social, animal, and human health sciences are required to control this pandemic virus.

Prevention and control of the COVID-19

In the early phases of the SARS-CoV-2 infection, it takes some time to implement the stringent control and preventive measurements. Early detection/recognition, isolation, and management of disease-ridden persons, as well as awareness about the essential prevention and control measures, needs to be implemented for a long-term achievement of control of the disease. Development of the specific therapeutic drugs and vaccines can play a vital role to prevent this emerging pathogen. Nevertheless, completely depending on health measures will not control the disease. So, effective restrain of this fatal pathogen can be achieved through enforcement of One Health approach. Preclusion and the control of the COVID-19 is primarily based on mitigation of person-to-person transmission of the pathogen through use of personal protective equipment like facemask, following personnel hygiene protocols, temperature screening, social distancing, timely testing, surveillance measures and quarantine of infected persons, as well as individuals with recent travel history (Gasmi et al. 2020; Lipsitch et al. 2020; Hellewell et al. 2020). As different experimental results have indicated that origin of COVID-19 virus is linked to a seafood market in Wuhan, the prevention and control of COVID-19 virus can be attained by reducing the transmission of the pathogen through identification of the susceptible animals (Xiao and Torok 2020). Different studies have shown that pets and other animals are susceptible to COVID-19 virus. So, it is highly advisable that infected and suspected individuals must have limited contact with the animals to reduce the chances of infections to the pets and other animals (WOAH 2020).

Conversely, basic hygienic procedures/measures should always be opted while restraining/handling of animals and inappropriate consumption of animal products should be avoided (Kiros et al. 2020; WOA 2020). In addition, animals should also be kept isolated at the home, specifically the pets belonging to SARS-CoV-2 infected persons to avoid animal-to-animal spread (WOAH 2020). Keeping in view both public health and ecological reasons, many agencies have proposed a ban on legal and illegal trade of wild animals for their meat and other products to thwart the advent of newly emerging viruses having zoonotic importance (Singh et al. 2020). Overall, restraint and control of the COVID-19 in both animals and humans can be achieved through application of one-health approach. As per recommendations of USDA and OIE, food safety and hygiene measures should be implemented (OIE 2020c). The spread of the virus can further be minimized by using disinfectants on different surfaces. Keeping in view the contagious nature of the SARS-CoV-2, besides public health hygiene measures and isolation of diseased individuals, implementation of environmental cleanliness and hygiene strategies are also very essential for the prevention of the COVID-19 infection (WHO 2020c; EPA 2020).

Conclusion and future perspectives

Control of coronaviruses is a matter of concern due to emerging zoonotic infections caused by these viruses over last few decades. Coronavirus is a large family of viruses which cause infection in several animals including cattle, camels and bats, as well as in humans. Viruses of this family usually cause cold-like illnesses. Some of coronaviruses only cause infection in the animals, like feline and canine coronaviruses. However, COVID-19 appeared as a newly emerged zoonosis, which has not been understood properly and requires careful handling in both humans and animals. International efforts depend greatly on the research carried at the infection location to detect/isolate viral characteristics of COVID-19. Earliest studies related to determination of origin, source and root cause of the infection revealed cross-species jumping of COVID-19 virus from animals to humans. In the future, serological studies of domestic, as well as wild, animals living in the close surroundings to humans are required to know and prevent expected spillover of other bat-related coronaviruses. The early detection of probable spillover can be achieved by a robust surveillance system for the detection and understanding the circulating viruses in animals with possible risk of zoonotic infection to humans. This may also be helpful in the prevention of human to-human transmission of a possible epidemic or pandemic. At present, around 200 viruses of different families have been identified and there are a lot of more viruses still to be discovered in the bats (Moratelli and Calisher 2015). Due to enormous reservoirs of viruses, bats are proposed to cause transmission of pathogens. However, intricacy of spread in the natural systems, variations observed in experimental designs and understanding of results is rarely definite due to

occasional evidence of transmission of virus from bats to humans and indicates need of more extensive studies. Global spread of COVID-19 infection in a very limited duration of time suggests that pets can play a vital role in the disease transmission. A recent study has suggested that mink could cause animal to human viral spill. In the light of these evidences and rapidly evolving virus, human population could be hypothetically disease-ridden with the SARS-CoV-2 via animals such as pets, domesticated species and wild animals. Thus, precautionary actions should be taken while dealing with pets and other animals. For the prevention of resurgence of COVID-19, detection of virus specifically in pets of owners who are positive for corona virus is very important. Undesirable abandonment of pets should be evaded. Side by side, prevention of further transmission of virus can be achieved through tracing and surveillance in the animals. Moreover, zoonotic threats due to COVID-19 need to be evaluated in more details to prevent the re-emergence of SARSCoV-2 in the future.

Different technologies for the diagnosis of the pathogen are available for the community. Among these, real time RT-PCR assay is the test of choice for the diagnosis of the SARS-CoV-2. Moreover, serological tests work as supplementary tools for the screening of individuals and community. Both assays in combination can help us to confront against this outbreak, which imposes huge impact on global economy and life of the people. For the proper diagnosis of the case, it is necessary to take the correct specimen sample at correct time. In summary, through appropriate use of these tests, we can identify the SARS-CoV-2 at the earliest to save the lives and prevent the further spread of the disease.

During the initial period of disease spread, public health measures are implemented for the effective control of the COVID-19 outbreak, which may play a vital role in the long-term prevention and control in the predisposed group of people. However, crises due to COVID-19 infection cannot be resolved by depending on public health measures alone. Therefore, efforts need to be imposed under One Health approach for effective control of COVID-19. The rapid spread of this emerging zoonosis worldwide potentiates environmental health approach to understand drivers and control elements of the disease. Furthermore, implementation of One Health approach including public health, wildlife, veterinary and other associated professionals could be helpful in tracing/detecting the infection, identification of associated risk factors, reducing threat to susceptible and formulating improved prevention and control strategies. So, we recommend that all countries improve their strategy through key concept, with human, animal and environmental health be considered in a unified way to control the crises due to COVID-19.

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