# Chapter 1
# Introduction to COVID-19

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## Introduction

SARS-CoV-2 is a zoonotic origin beta virus which has modified itself for man-to-man transfer (Fig. 1.1) and nowadays very famous for causing pandemic COVID-19 [1]. Till today reported cases of COVID -19 are in millions globally with thousands of reported deaths (https://coronavirus.jhu.edu). In response to the present challenges, people are facing travel bans and social distancing [2], with changes in anthropoid activity, followed by severe economic damage. Subsequently, each country is affected differentially with respect to social and economic losses by this COVID-19 pandemic. No doubt, China, which is considered as the origin land of this pandemic, is expected to recover faster than other countries like Europe and America. Other countries which will be more affected by long periods of social distancing are dependent on the tourism and automobile industries. It has also been reported that the economic growth will return to normal after three quarters 2023 (McKinsey report at https://t.co/iFC1k1A2WM). All aspects including conservation and health will be affected by this pandemic globally [3, 4].

If we look at the health aspects, the influence of this pandemic will be of three types: The first one is immediate impact which is due to rapid human limitation, inactivity, and confinement. The second medium impact includes crisis related to

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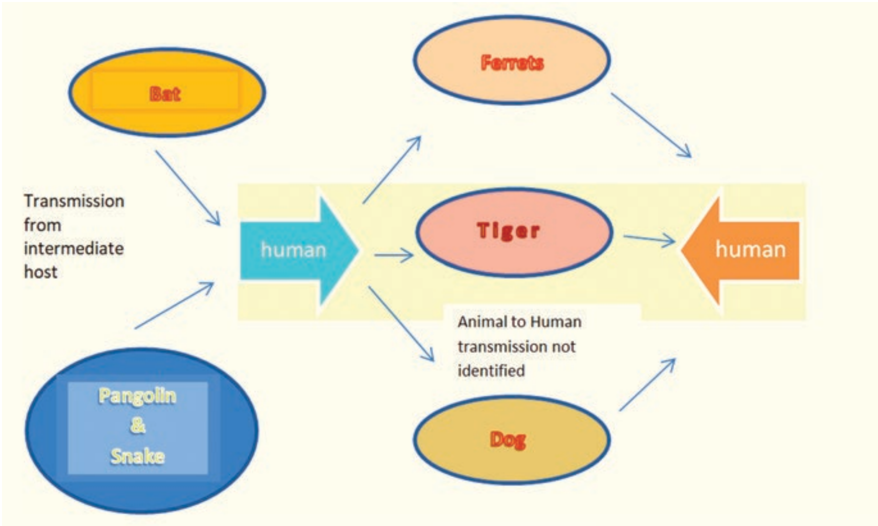


**Fig. 1.1** Zoonotic link for coronavirus and flow path

animal farming and veterinary facilities which will ultimately in the long term affect the economy. The third impact is the improved consideration toward public well-being implications of this coronavirus contagion in pets and farm animals [5–7]. During the crisis of coronavirus, all countries should maintain necessary activities like veterinary inspections, food safety, food inspection, regional regulations, emergency conditions, and other preventive measures including research, economic impact, and vaccination against COVID-19 (https://www.oie.int/en/for-the-media/pressreleases/detail/article/covid-19-and-veterinary-activities-designatedas-essential/). Farmers play an important role in the economy of a country as animals help in improving the fiscal growth and quality of life [8].

## Origin of COVID

The infectious pneumonia by coronavirus becomes a threat to humans globally. A massive pneumonia-like outbreak with strange etiology was reported in Wuhan, a city of China, in December 2019. Initial investigations reported that the patients have recently visited a market where seafood and other several animals are sold. Further results of isolated samples of pathogen showed that it is a new virus which was named as 2019-nCoV and is a member of corona family which is responsible for infecting humans. It was first identified in Wuhan. This epidemic outbreak remains different in different parts of the world. An association between the wholesale market of Wuhan and the coronavirus was reported in primary reported cases. And the possible source of this virus in that market was supposed to be the bat. Bat species are reported as the natural carrier (reservoir) of corona (SARS-CoV), as these bats which are supposed to carry alpha and beta corona are widely distributed in many areas of China.

These coronaviruses (beta viruses) can infect humans, farm animals, pets, laboratory experimental model animals, bats, whales, and other wild animals, whereas other gamma and delta viruses can cause infections in pigs, other mammals, aquatic animals like fish, and poultry birds. The researchers are working to find the truth, and till today SARS-CoV is assumed to be of animal origin. Recent report of COVID-19-infected dog who get it from his owner supports the hypothesis of transmission from animals to humans. The possibility of transmission by travelers also alerts all countries which resulted in the cancelation of events and tourist visa to all affected countries [9]. Some diagnostic methodologies were adopted like real-time PCR, and some repurposed drugs were used as vaccine is still not available. About the origin of COVID-19, there are many assumptions like some suggested snakes as outbreak source, but other studies reported bat and pangolin as source of emergence of SARS-CoV-2. The abovementioned assumptions are based on the similarity of genome sequence of COVID-19 with pangolin or bat origin coronavirus [10].

This new virus is identified as a family member of *Coronaviridae*, subfamily of *Orthocoronavirinae* and order *Nidovirales* [11], and named as SARS-CoV-2 or COVID-19. There are four genera of subfamily *Orthocoronavirinae* named as *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. Among these four, two can infect mammals which are *Alphacoronavirus* and *Betacoronavirus*. Six strains of coronaviruses which can cause severe respiratory disorders in mammals including humans have been identified [12]. These viruses can be placed in two groups on the basis of phylogenetic analysis: HCOV-229E, TGEV (transmissible gastroenteritis virus), and PEDV (porcine epidemic diarrhea virus) are in group one, whereas SARS-CoV, bovine coronavirus, and hepatitis virus of animal origin are in group two. Recently known COVID-19 is *Betacoronavirus* and its subgenus is named *Sarbecovirus*. This virus is genetically different from SARS-CoV and MERS-CoV but all are *Betacoronavirus*. This presents 52% and 78% similarity with MERS-CoV and SARS-CoV, respectively [13].

In the past, coronavirus outbreaks were twice reported as host-specific: the first case, the 2002–2003 SARS, found in human, and the origin of the virus was reported as from bats, and the second case was from Middle East countries where it was MERS which showed linked with camels. But SARS-CoV-2 seems to be able to cross the host species barriers which make these jumping phenomena a regular feature of CoV species [14]. The reason behind these phenomena may be gene configuration, enzyme or gene stability associated with replication, and abundance of mutation rates. All these reasons may help in the maintenance of hosts and emergence of novel coronavirus. The expansion in host range is associated with glycoprotein spike which helps in the adaptation of virus to hosts which can be human or any other animal [15, 16].

CoV viruses are usually known for respiratory diseases with mild infections and very low mortality rate [17–19]. These coronaviruses (beta viruses) can infect humans, farm animals, pets, laboratory experimental model animals, bats, whales, and other wild animals, whereas other gamma and delta viruses can cause infections in pigs, other mammals, aquatic animals like fish, and poultry birds [20–22]. Several other groups of animals are reported as carriers (Fig. 1.2); these are porcine, bovine, camels, equine, canine, dogs and cats, lapin, avian, bats, rodents, mink, ferrets, snakes, marmots, frogs, pangolin, and hedgehog [23–28].

Coronavirus-infected laboratory animals include mice, rabbits, rats, ferrets, and guinea pigs. COVS were blamed for the respiratory infections, hepatitis, and enteritis in lab animals mentioned above. Among the different strains, MHV were found to be important and were observed in laboratory animals [29], the most infectious viral strain observed to affect the digestive system of mouse, with mortality rate observed as 100% [30]. In other cases, it was observed that MHV affected the

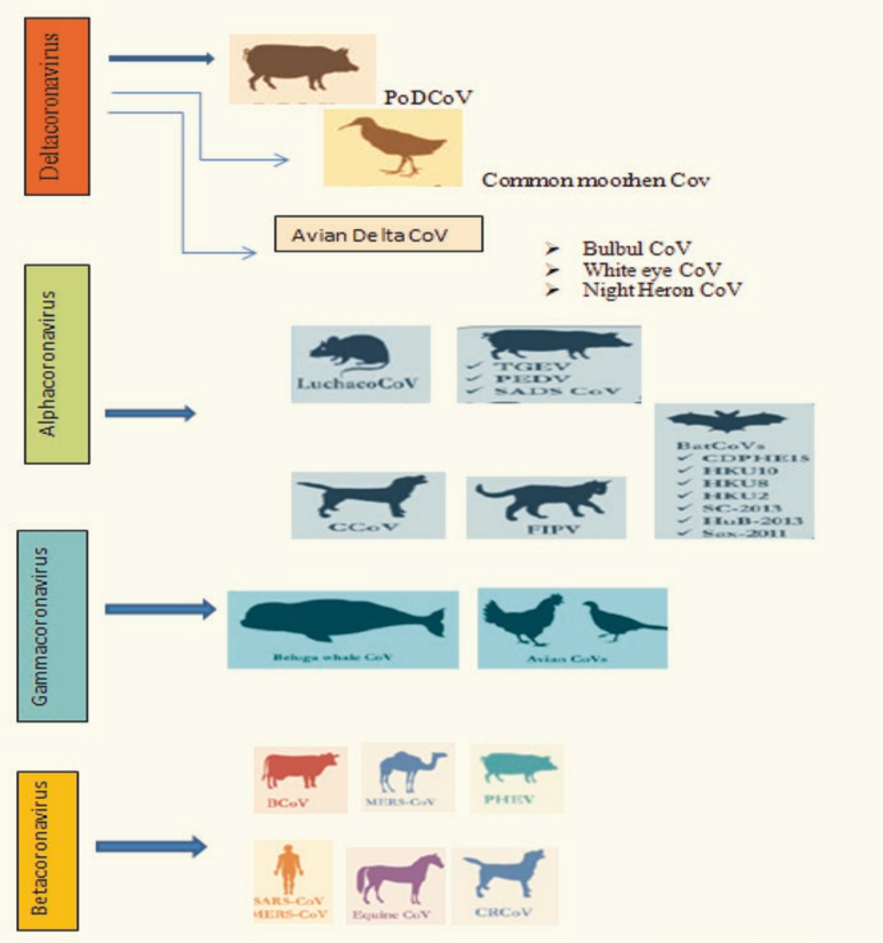


**Fig. 1.2** Different animal host and carriers of coronaviruses belonging to different genus of *Coronaviridae* family

respiratory tract, endothelium, liver, hematopoietic tissues, lymph nodes, and central nervous system. Infection of rat by coronavirus starts from the respiratory epithelium which then spreads to the salivary gland [31, 32]. In ferrets, CoV signs were observed as the green slime [33]. Very little information about CoV is in record among guinea pig and rabbits, but it is observed to be responsible for diarrhea, atrophy, and malabsorption [34].

Bovine corona is reported as having zoonotic nature as it was isolated from humans. This can further be transmitted to other cattle with symptoms of bloody diarrhea [35]. This bovine corona may cause mortality by destroying the epithelium and villi of the intestinal tract (leading in bloody diarrhea) [36]. The carriers spread virus by oral or fecal secretions and stress conditions. This CoV was reported in domestic as well as wild animals including wood bison, water deer, reindeer, waterbuck, antelopes, sheep, goat, giraffe, camel, and white-tailed deer [37–39].

In foals, coronavirus has been reported in groups of less than 2 weeks, and symptoms include mild enteritis [21, 40]. In Japan, this equine coronavirus was also observed in 2011 in horse [41, 42], causing self-limiting enteritis [43]. The immune system plays an important role for the type of infection, and antigen-antibody reactions are responsible for lesions [44]. In 2008, coronavirus was reported from the liver of a captive whale [45]; similar virus was also reported in dolphin [46]. After that bats were reported as carriers of corona, and during flight in search of food, they can shed which may infect animals and humans whoever comes in direct or indirect contact [47]. In China, bats are used as food and also are of medicinal importance. So this animal (bats) is considered to be responsible for the spread of coronavirus [48, 49].

## Emergence and Epidemiology

A massive pneumonia-like outbreak with strange etiology was reported in Wuhan, a city of China, in December 2019. Initial investigations reported that the patients have recently visited a market where seafood and other several animals are sold. Further results of isolated samples of pathogen showed that it is a new virus which was named as 2019-nCoV and is a member of corona family which are responsible for infecting humans [50–52]. Moreover, the World Health Organization named it COVID-19. A new name was also proposed by the International Committee on Taxonomy of Viruses which is SARS-CoV-2 which was not officially approved. The World Health Organization, after a massive increase in number of confirmed infected individuals, declared this pandemic on 30 January 2020 as international emergency for public health [53–55].

This family of virus is genetically diverse and is reported in a vast variety of animals belonging to different species of birds as well as mammals. In some cases corona-infected intestinal system while in others respiratory infections are confirmed in mammals and birds including humans. Corona got attention in 2002–2003, with reports of “strange pneumonia” in Guangdong Province which subsequently spread to Hong Kong. In Hong Kong, research separated the causative agent, and this pneumonia was later named as severe acute respiratory syndrome [52, 56]. This virus spread internationally and 8000 peoples were found infected in 26 countries with reported mortality rate of 10 percent (https://www.who.int/csr/sars/country/table2004_04_21/en/). This severe acute respiratory syndrome (SARS) at that time affected the economy and was globally a serious threat to health. After successive studies, it was found that the origin of SARS-CoV was bat and it came in humans via different intermediate animals (hosts) like dogs (*Nyctereutes procyonoides*) and civet (*Paguma larvata)*. Another coronavirus which also infected human was MERS-CoV (Middle East respiratory syndrome corona); the mortality rate from this virus was higher than the SARS-CoV, but its transfer from human to human was not reported [57, 58].

Bat species are reported as the natural carrier (reservoir) of corona (SARS-CoV), as these bats which are supposed to carry alpha and beta corona are widely distributed in many areas of China. The molecular evolution and diversity of SARS-CoV have been intensively studied in bats [59, 60]. As our knowledge is very limited about the COVID-19, we may review the epidemiology of corona on the basis of the previous knowledge of MERS-CoV and SARS-CoV.

There are three phases of epidemiology curve of COVID-19. The first phase is the local outbreak which started in the visitors of seafood market. From the reported starting date of outbreak (December 2019) to 13 January 2020, confirmed reported cases were 41. Epidemiological studies confirmed that even during this first initial stage, close contact was the reason of transmission between humans [61–63]. After this, a second phase started from 13 January 2020; during this phase, there was an increase in the spread and expansion, and the outbreak and spread of this disease were confirmed outside of Wuhan. The transmission of this disease from man to man may be divided into two types: nosocomial infection and close contact. Nosocomial is spread within hospital, whereas the close contact is family transmission [64, 65]. First case outside China was reported in Thailand, and history of traveling showed that the person was a resident of Wuhan and traveled from there to Thailand. On 23 January, there were 846 confirmed cases from 29 provinces and 6 countries [66, 67]. This increase was 20-fold as compared to the first phase. Before the shutting down implementations in Wuhan, five million people had already left the city for home due to the upcoming event of Chinese New Year [68, 69].

From 26 January 2020, there was a start of third phase. It showed a quick growth of constellation cases. Among the total number of conformed cases, nearly 80% were in Shanghai, Beijing, Shandong, and Jiangsu on 10 February 2020. After 20 days, this number was reached to nearly 10,000 which showed 240-fold increase in confirmed cases. However, at that time, there were 441 confirmed patients outside China in 24 countries with low death rate out of China as only 1 patient died in the Philippines, whereas in China 1114 people died. The day 3rd Feb, 2020 can be written as a tip point of COVID-19, as from this time there was a decline in the confirmed patients and it showed a success of lockdown and the health care but if the transmission was reduced due to any other reason was still unknown [70, 71]. Furthermore, some specific infection transmission causes and failure of protection among medical and health care staff still showed further research and investigations.

If we compare the basic number (reproductive number), it is 1.4–3.9 for COVID-19, 2.3–3.7 for SARS-CoV, and 0.5–0.9 for MERS-CoV. As the reproductive number for SARS-CoV is smaller, it shows the possibility of easy control for this outbreak with rapid diagnosis and isolation of infected people [72–74]. However, this is very important to take in mind that only reproductive basic number is not important as it fluctuates with social behavior and environmental and biological factors. And the interpretation must be done with caution [75, 76].

## Human-Animal Interaction as Risk Factor

Currently, we do not know about origin, detailed binding receptors of host, and natural host, as the theory of this virus as bat origin is still not confirmed [77, 78]. Some earlier studies reported SARS-CoV-2 as genetically analogous to corona of pangolin, whereas the coronavirus of bat origin did not show similarity and ancestral linkage. Recently one report confirmed this virus in pet dog which also showed some respiratory sickness and COVID-19 symptoms. Usually the dogs become affected by corona which causes severe respiratory symptoms [79–81].

Bovine corona and human corona are all related and are *Betacoronavirus* [80, 82], whereas the abovementioned viruses are different from enteric canine coronavirus which is *Alphacoronavirus* and may cause infection to dogs. Moreover, a bat origin virus was isolated, and phylogenetically it was found close relative of SARS-CoV-2, so it is considered as an intermediate host of the present outbreak strain [83–85].

If we look at the clinical picture of the COVID-19, the infection can be categorized as of four types: mild, modest, unambiguous, and acute. The symptoms and signs in patients are cough, fever, fatigue, diarrhea, and myalgia [86–88]. There was an abnormal ground glass bilateral opacity in patients when observed by chest computed tomography scan [89–91]. So the clinical and dialogical presentations of COVID-19 and SARS-CoV-2 are still further under research. There is similarity among the pathology of MERS-CoV, SARS, and COVID-19 [92–94]. Death due to COVID-19 is observed with alveolar damage, whereas the infection starts with epithelial cells which extend to the intestine, kidney, and brain [95–97].

A member of Chinese Health Commission raised an issue of evaluation of SARS-CoV-2 among animals. This issue was raised as the observations showed that the virus can move between mammals. If any pet animal come in contact with other animals or human, it can spread, so animals should be quarantined [98]. This is the first precautionary measure which must be taken to save loved ones [97, 98]. But as people came to know that corona may spread by pets, the response was severe and resulted in the killing of dogs and cats [99–101]. To change the attitude of the people, the World Health Organization gave a statement: it is not proved that cats or dogs can get infections from the virus [97, 98, 102]. Even after this statement, pet killing continued in China [103, 104]. A pet dog was reported to have infected by COVID-19 after RT-PCR testation [105]. A report from Hong Kong threatened humans as it was reported that a dog cannot be infected but can be a carrier who can spread the virus [106].

The French Food Agency requested to submit clear opinions about the role of pets and domestic animals in spreading coronavirus. A very less number of animals were experimentally proved to be infected with corona, among them a transgenic mouse was observed to be infected which expressed human ACE2 receptors for SARS-CoV-2 [105, 107]. We need further studies to observe interactions among COVID-19 and ACE2 in the tissues of other animals. Moreover, there is a need to study the dispersal of ACE2 in tissues, which is important for advance knowledge of infection and transmission to other animal species. Not only it is important to focus on the receptors' presence but also other cell factors necessary for replication of virus must be taken into consideration during intraspecific studies. To identify these factors, further studies and research are necessary [108, 109]. At the same time, there came a statement from the Ministry of Health of Singapore that pets are not a serious vector for transmission of COVID-19 but may spread this virus to human. They also not planned to isolate or quarantine animals [110].

After that, IDEXX Veterinary Laboratory tested pets for COVID-19 all over South Korea and the United States by using RT-qPCR, and there were no positive results. Although animals were from affected areas, it was confirmed from results that these pets were not living in homes with infected people [110, 111]. It was stated by the WHO that animal pets are safe from corona, but recently they admitted that they can be infected but it is not clear that they can spread the disease [112, 113]. A dog was found infected as confirmed by RT-PCR [114, 115]; after that, a cat was found COVID-19-positive [114, 116, 117]. Contrary to all previous reports, again virus was confirmed in cat as well as the presence of antigen, and it was a start of debate. But the Belgium scientist group does not recommend testing of pets as there is still unavailability of diagnostics [118]. Some scientists recommended pets as hosts of dead ending [119, 120]. It was also suggested that the risk of transmission of vector from animal to human is very less and human also must not rub their nose in front of animals [121, 122]. SARS-CoV-2-positive cats were found in New York, and their owners were also positive for this virus [123, 124].

In the respiratory and gut epithelium, antigen or RNA was present abundantly which was innervated by RT-PCR and immunohistobiochemistry assay. This was also reported that the virus in chicken, dog, pig, and duck cannot competently reproduce [125, 126]. In the studies related to then gene expression, it was noted that ACE2 was actively expressed in the lungs, retina, skin, and ear of cat, whereas in dogs it is actively expressed in the retina and skin. Moreover, cats and dogs are more affected by SARS-CoV-2 when compared with rodents [127, 128]. These results were also supported by the test positive results in lions and tigers, which become affected from their keeper.

Diagnosis of virus also faced difficulty due to the absence of clinical signs and symptoms. And radiography of chest also failed to test COVID-19 [129]. Other methods were adopted which include reverse transcription PCR, real-time PCR, computed tomography, X-ray, and enzyme-immune assay [123, 130–133]. For calorimetric detection, a loop-mediated amplification tool was designed [134]. And a web-based dash board was developed for tracking coronavirus [135, 136]. A quantitative detection (florescent-based) of N region by PCR assay has been developed [137].

## Best Suitable Animal Model

The animal models are necessary to study and explore primates or in simple words nonhuman model (Table 1.1). Although presently we do not have a model for SARS-CoV-2, some researchers have explored primates like rhesus monkey as a model. In the past, many studies evaluated different vaccines against diseases like MERS-CoV, and primates were used as animal model [125, 137, 138]. During those studies, SARS-CoV-2 affected monkey, and the animal showed different signs and symptoms for nearly 16 days and are proved to be effective in pathogenic studies with next development of antiviral drugs and vaccines [139, 140].

Different animals have been reported susceptible for ferrets, dogs, cats, and other domestic animals. However, dog, chicken, duck, and pigs have been reported less susceptible, but cats and ferrets are efficient [141, 142]. Cats were reported to spread virus by spreading droplets. In the process of finding a best model, exploration is required for animals having ACE2 receptors as in human [143, 144].

Establishment of appropriate animal model will help us in understanding the process of disease transmission and will further help in therapeutic and prophylactic improvement [127, 145–147]. Primates are considered important as best models in human disease studies, whereas for pathogenic exploration and immune response studies other animals are recommended. These other animals which are used as model animals are hamsters, rabbits, mice, and mouse [12, 148]. Among these

**Table 1.1** Animal models used to study different coronaviruses

| |
|---|
| Mouse model |
| Mouse-adapted viral strains |
| Humanized mouse |
| Receptor-transfected transgenic mice |
| Nonhuman primates |
| Old World monkeys |
| African green monkeys |
| Macaques |
| New World monkeys |
| Squirrel monkeys |
| Common marmosets |
| Animal models not usually selected |
| Hamsters |
| Rabbits |
| Ferrets |

animals, mice and hamster have been used in the studies of MERS, SARS, and SARS-CoV-2 as animal model. Golden hamster has also been studied in a SARS-CoV study for testing vaccine [148, 149] and noted as a potential model for corona pathogenic studies and vaccine efficiency testing.

Transgenic animals (lab mice) may be suitable animal model in SARS-CoV-2 studies as the receptor ACE2 is different from human in different animals [150–152]. On the basis of similarity in their ACE2 receptors, different animals like bat, monkey, cat, orangutans, ferret, and pig may be used as model animals as they have similar affinity for coronavirus as human [153, 154]. For selecting animals as model, the important thing we have to take into consideration is that the selected animal model must be small and easily manipulated as mouse or rabbit, and the other point is the selected model must be cheaper and easily available [155–157]. In the beginning, mice were difficult to be accepted as animal models but transgenic mice are now believed to be good and are accepted as models of COVID-19 [41, 91, 158–161].

Many transgenic knockout mice like ACE2, Tmpress, Stat1, inbred, and HLA have been proved to be selected as model animals for COVID-19 or SARS-CoV-2 [162–164]. As it is proved that the present pandemic is caused by coronavirus, now scientists are trying to evaluate and find the most suitable animal model for this respiratory syndrome. Animal model will be selected on the basis of questions to be answered like the airborne transmission of coronavirus among two different species like between ferrets and cats. Among monkeys, the two age groups young and old were selected, and it was found to be affected by virus in the respiratory system, but no severe symptoms appear in both groups. So these animals can answer some other questions about induction and transmission of COVID-19 [164, 165], as the human showed a great range of clinical signs: from acute to severe pneumonia. If the data is explained on the basis of one animal model, it will be misleading, and disease outcome will be challenging for human [166, 167].

If we want to select an animal model for COVID-19 from the traditional models which have been selected previously, the main point for selection is those animals must not hide the pathology of pandemic especially when our focus is to check the viral medicines and vaccines [168]. If the animal model is able to mimic the pathology, researchers will be unable to understand the transmission and infection dynamics. Previously for the MERS-CoV and SARS-CoV-1 studies, some animal models were selected. These animal models include hamster, monkey, ferret, camel, and mice [169]. It is the economic truth that mice is best suited if we focus on the price and availability of this animal, but it has been suggested that this is not suitable for COVID-19 experiments because of the differences in receptors from human. But the transgenic mice have been reported good for selecting them as model animals as they can express the human angiotensin-converting enzyme 2 (HACE2). The receptors present in cells for the entry of SARS-CoV-2 are supposed to be important for examining COVID-19. In another study, transgenic mice showed partial ruthlessness [170, 171]. Shi et al. [5] inserted coronavirus in the nasal passage of different animals including cat, dog, ferret, pig, duck, and chicken. The aim was to check the pathogenesis and replication with transmission of disease. Animals shed virus but without clinical signs and symptoms. Similar results were reported in monkey

(*Rhesus macaques*) [91, 172]. Against viral protein, antibodies were produced by insertion of SARS-CoV-2 in inactive form in selected animal models (rats, mice, and monkey). After different studies, it was suggested that ferrets and cats are susceptible and can tolerate SARS-CoV-2 [173].

In animals like ferrets and cats, no signs of infections appeared, and there was no respiratory stress or weight loss. But no virus detected in digestive or respiratory tracts of other animals. However, in two dogs, viral RNA was detected in rectal secretions, and antibodies were also produced by these animals. From other reported data, it is also suggested that the birds (chicken and duck) and pig cannot tolerate viral infection [26, 174]. Vulnerability of any animal depends upon the presence of receptors in host or enzyme activity. These two factors are important factors for coronavirus to enter in cell. It was also observed that the virus is detected not only in the respiratory tract but also in the rectum of ferrets, monkey, and cat. This may be a trustworthy initial clinical sign in COVID patients and is proof for the theory of oral-fecal administration route [24].

It has also been proven by epidemiological studies that the fatality is higher in old aged people from corona. But our model animals are usually of young age. So it is also suggested that the old model animals must be chosen for experiments. But when young and old cats were selected, opposite was found true as young cats died on day 3 after infected as compared to older ones. In monkeys, these differences in severe or mild infections were not related to age as both young and old monkeys showed similar results [25, 159, 175]. The most important thing to be noted is that not any animal showed lethal effects of SARS-CoV-2 as compared to human. During the development of animal models, age and health factors must be fully given attentions, as these factors are important for evaluation of disease in human [176].

The virus transmission through air was observed in cases of pandemics SARS-CoV-2 and influenza. But the important thing was aerosol size as its wide range specified its range. It was also proved that this coronavirus can be transmitted through air as observed by Shi et al. [5], stating that 33 percent of the virus were transmitted by air in cats [177]. The airborne nature of pandemic was also proved by experiments where animals were separated by barriers and no physical contact was possible, but the air was shared by all containers. In case of influenza, it was also observed that virus replication in the upper region of respiratory tract is important for airborne transmission. The experiments on cats confirmed that the cats are vulnerable to viruses [178, 179]. Among other animals, SARS-CoV-2 was found to be replicated in the palate of ferret and cat. The airborne transmission among ferrets was reported to be 30 percent for SARS-CoV-2.

The transfer of coronavirus from human to cat was recently observed in big cats (tiger) in zoo. But the cats may not show symptoms of disease, and it can go unnoticed even if they are infected, which proved that cats are not good animal models for coronavirus studies [180, 181]. Additional serological and coronavirus-specific antibody studies are needed to find SARS-CoV-2 virus from animals. The animal models are very important for testing the potential of antiviral medicines, vaccines, and therapeutic strategy. Among mammals, cats, ferret, hamsters, and transgenic mice are important alternate of humans to study SARS-CoV-2. Because the transgenic mice and hamster showed prominent symptoms and signs, so they may be vigorous animal models for vaccine formation [182]. Cat and ferret are best suitable models for transmissible studies and effectiveness of vaccines. So the main focus is to choose a nonhuman primate animal as model. Therefore, a continuous experimental evaluation is needed to evaluate mice as model animal.

## COVID and Animal Welfare

One factor that linked animals with COVID was that the first person who was found infected visited animal market. According to reports, that was wet market where live animals were sold [183]. This COVID has been sequenced and identified genetically as coronavirus that usually found in bats. So it is considered that bats are the natural reservoir of corona. As the coronavirus spread globally, the pets have also become victims. Some people left them home alone and some evacuated them. Although there is no evidence that pets can transmit virus, the fear of spreading the virus resulted in killing of pets [184]. So the current situation of coronavirus negatively impacted the animal welfare.

This is also very important to understand the relation between human, animal, and environment. For future and further prevention of coronavirus, one health collaborative approach of transdisciplinary help is necessary [185, 186]. As the coronavirus has resulted in shocking concerns for health and economic constancy all over the world and also appeared to be adverse, unexpected difficulties arise for animal welfare. Especially for the professionals dealing with veterinary and animal welfare, this is the time to fear how coronavirus is going to affect the pets. If we look at a picture of Wuhan (the place of origin of outbreak), many people who were evacuated from homes were forced to leave their pets behind alone. Although the owners left a sufficient amount of food and water at home as they were thinking to return soon, after more than 6 weeks, many of them still not returned [187]. It is estimated by the Chinese animal welfare organization that nearly 10,000 cats and dog were left behind in Hubei who faced starvation and death.

Concerns related to pets emerged among public and pet owners when a dog reported to be positive for corona. In another case, a dog was tested positive but apparently he was having no clinical signs. The swabs from oral and nasal cavity were weak positive [188, 189]. The dog was quarantined for 14 days, and without any clinical signs, after returning home, the dog was found dead. The cause of death remains unknown as the owner not allowed experts for postmortem. But it is believed that the death was not due to corona but age and age-related health issues may be the factor [190]. This case gives a spark of fear to public which resulted in the abuse of pets, as the public starts to believe that coronavirus may be spread among them by pets. After this case, an announcement was made from urban construction that if any cat or dog will be found on street, it will be killed to prevent the spread of coronavirus [191]. The same news about the killing of animals came from Hunan and Zhejiang also.

To stop the cruelty to animals, the Hong Kong Society makes a statement of information for public. This society informs general public that there is no need to fear from pets as there is no evidence about the transmission of virus from animals to human [192]. So people must cooperate in animal welfare. A large number of cases for uncontrolled movement of pets to become wild animals have been reported and spread widely on social media as people left them. Some people left their pets from the fear of transmission, and some left them because they become unemployed and now cannot afford a pet [193].

Another import side is that now people are isolating themselves during this outbreak and the rate for adoption of pets is rising. This is really good news that pet lovers and animals may enjoy this bond between animals and humans when this is a time of great need for all [194]. Some people who were not having pets before are now adopting animals, but some experts are also worried about the future of these pets as they think people will return these animals to shelters when life will return to normal [195].

Inclusive, the previous findings suggest that still there is no threat of transmission of SARS-CoV-2 from animals to humans. Nevertheless, the World Health Organization and the US Centers for Disease Control and Prevention tried to calm down the rising concern of people by issuing statements to not be afraid from pets, as they are not a source of spread of COVID-19 [1, 133]. According to the World Health Organization, our focus must be on the control of human-to-human transmission right now and we are not having justifications and proofs for taking any action against pets. So human activities must be restricted, and this requires reduction in community activities to reduce the spread of coronavirus [196]. However, when we critically look at the spread of pandemic, there is a complex relation between human, environment, and other living things like animals (pets or wild).

In the end, there is a need to develop one health approach strategies which will help in the prevention and control of COVID-19. One speculation that wild animals are associated with the spread of coronavirus must be elaborated and this needs some expertise and collaboration of wild life experts and forensic specialists [197]. Trading of wild animals in markets like in Wuhan must be regulated properly, as there exist poor regulation, illegal trends, and poor welfare standards. However, many experts hope for good wildlife trade globally after this crisis [198].

## Molecular Differences Between Different Animal Species

It is needed to estimate the interaction residues of S receptor binding areas of coronavirus and human, as this estimation will help in the identification on how much it will affect other species. For this, researchers bring together all available amino acid sequences of ACE2. In an experiment, N-glycosylation treatment was used near binding site [199]. N near the binding area will negatively affect the binding of

S. During this, ACE2 was glycosylated at N (N53, N90, and N322). N53 was found conserved for all species, whereas N90 was not in glycosylation site of ACE2 in pig, mouse, civet, fox, chicken, ferret, and raccoon. N322 was not a site of glycosylation in ACE2 of cattle, rat, mouse, sheep, and pangolin [200]. However, some species have an additional N glycosylation area in ACE2. In chicken, L79 is the site of N glycosylation, and in *Rhinolophus sinicus*, rats and pangolin M82 are the sites of glycosylation. In rats, it was noted that glycosylation residue 82 may prevent S binding of SARS-CoV.

In ACE2, there are amino acids that may affect the binding of S which have been reported from some species [124]. Some detail of these is presented in Table 1.2. If we look at the binding site, it is entrusting for experimentation as ACE2 binding sites for monkey and chimpanzee are similar to man. And in other animal species, the differences in ACE2 amino acid from human to chicken are 11 and to rodents 9, while from cat to human, the differences are 3. Some attraction is in ACE2 protein of pet and farm animals as another possibility is that this protein may be reservoir of coronavirus. There are six differences in ACE2 of pig, and mostly are located at the border of site for binding. The important point here is N90 T as it affects the glycosylation site and the site will be loss. In SARS-CoV, E 329 is reported to form a bridge of salt with R 426, but in COVID-19, salt bridge is formed with D30 [124, 201]. Thus, N exchange with E 329 in ACE2 of porcine also affects the S binding in SARS-CoV; however, in COVID-19, S binding is not affected. The similar pattern of effects and changes has been observed between cattle, cat, and human ACE2. A few differences and changes have also been observed in the middle of binding site which gave confidence in decision that this exchange may be a big obstacle in infecting a cell with coronavirus from one species to another [202].

**Table 1.2** Human ACE2 similarity with other animals

| Animal | Similarity | Gene bank association number |
|---|---|---|
| Human | 19/19 | AAT45083.1 |
| Chimpanzee | 19/19 | XP_016798468.1 |
| Rat | 10/19 | AAW78017.1 |
| Mouse | 9/19 | ABN80106.1 |
| Cat | 16/19 | XP_023104564.1 |
| Pig | 13/19 | XP_020935033.1 |
| Macaque | 19/19 | XP_011733505.1 |
| Horse | 14/19 | XP_001490241.1 |
| Sheep | 15/19 | XP_011961657.1 |
| Cattle | 15/19 | XP_005228485.1 |
| Camel | 14/19 | XP_031301717.1 |
| Ferret | 11/19 | BAE53380.1 |
| Fox | 14/19 | XP_0258425131 |
| Pangolin | 13/19 | XP_017505752.1 |
| Chicken | 8/19 | XP_416822.2 |

Another term used for coronavirus is that this virus is RNA positive-sense virus. The newly identified virus (SARS-CoV-2) is from *Coronaviridae* family with four genera. SARS-CoV and MERS-CoV belong to one genus (*Betacoronavirus*), but SARS-CoV-2 is genetically different from both of the above [203, 204]. But this is important to understand that nearly 89% of SARS-CoV-2 is identical to the bat-SL-COVZC45 and bat-SL-COVZXC21 (SARS-CoV of bat origin). These were also named as ZXC21, and it was found to be nearly 82% identical to SARS-CoV Tor 2 (human), and ZC45 of bat origin was found to be identical to human SARS-CoV BJO1 2003 [15, 27, 28, 93, 205]. Among SARS-CoV-2 and MERS-CoV, it was found that these two are 50% identical, whereas SARS-CoV-2 and SARS-CoV were reported to be 79% identical. Phylogenetic analysis at the molecular level proved SARS-CoV-2 to be more closely related to bat SARS-CoV [206–209].

It was reported that there are 380 amino acids between SARS-CoV-2 sequences confirmed after genome analysis. This swap of amino acid may be helpful in functional as well as pathogenesis deviation of this pandemic coronavirus [180, 210]. The most important requirement for the recovery and prevention from coronavirus is immunity, which may be innate or adaptive. The humoral immune response is very important in corona outbreak especially antibodies of titer and subtype [211]. Although it is also of concern to the coronavirus studies that mouse and some other animals may hide the clinical signs or mimic COVID infection, the genetic diversity is also linked that may guide toward wrong interpretation between the results of primate and non- primate animals. Researchers suggest humanized animals may be good models for the study of organs and tissues of human in coronavirus infection studies [212]. In addition to infection studies, these will be helpful in the vaccine preparation and elevation of target agents in host.

In previous times, to study HIV, HCV, CMV, HBV, and VZV infections and other pathogens and zoonotic diseases, mice with grafted cells or tissues have been used extensively. As we all know, lung is the major target that is infected by coronavirus [213]. In one experiment, the human lung tissue was grafted under the kidney of mice which was immune-deficient [214]. The findings suggest the rapid tissue development which was associated with supporting CMV pathogenesis. A successful association was established by using by lung grafted mouse as animal model to study VZV infection. After this infection, pro-inflammatory cytokine and viral replication were observed in grafted lung.

In recent studies, researchers worked with humanized mouse (human lung grafted). This mouse named as BLT or LOM supported Zika virus, CMV, MERS-CoV, and RSV. Response of T cell suggested that dual chimera mouse (grafted with the lung and immune cell) may be best animal model for the study of SARS-CoV-2. Multiple organs may be failed due to SARS-CoV-2, as human ACE2 can be expressed in many organs like the liver, kidney, heart, bladder, intestine, and immune-related cells or tissues. Therefore, it is also suggested that different tissues may be grafted in mice to check the severity of SARS-CoV-2 on different human organs and tissues. So we can say that the humanized animal like mice is important in improving the understanding of mechanisms involved by coronavirus for infection and immune physiology [215, 216]. In the future, these human tissues containing mice will be proved as a matchless tool in obtaining the intuition for our strategies in developing vaccine, therapy, or intervention for coronavirus.

## Vaccines for COVID from Animals

Till today, no license has been issued for any vaccine in the prevention of respiratory infection. Only vaccine for the prevention of respiratory infection from corona in chicken has been given license. Several proposals have been given for the development of vaccine for COVID-19 similar to MERS and SARS [217]. Vaccines must have to fill full the criteria of efficacy, immunity duration, and safety. However, the vaccine for COVID-19 also requires rapid production and large-scale development capacity [218]. Many traditional week and inactive vaccines have been used in experiments, but the high production of vaccines in large amount with biosafety culturing of cell is challenging. This culturing of cell with high level of biosafety is also limiting the rapid development during this emerging phase of coronavirus pandemic [219]. However, for the prevention of reversion (nsp16, exon, and accessory protein), live offset corona vaccine have been generated from clones of infected virus by deletion of many important virulence elements. But all this remains robust immunologically, inducing mucosal and humoral cell-mediated immunity with great protection. These offset vaccines remain effective in boosting immune response of host cells [220].

For the success of vaccine, it is important for a vaccine to be temperature-sensitive. The second remarks must include reverse genetics for further mutation which can be applied after generating mutant temperature-sensitive virus strain [126, 221]. A combined booster strain vaccine with S and N proteins like null (attenuated) vaccine may be potentially have cross-protection against heterogeneous mutant strain that have a potential to stumble beta COV, like bat coronavirus strain [222, 223]. It is important for vaccine technology that in this technology, subunit of viral particle is used.

New technologies for vaccine formulation also follow this principle and include viral protein, recombinant vector, and RNA. The use of viral protein and recombinant vector has advantage that these may provide a universal platform for introducing new antigen target from evolving virus [224]. Evolved viruses may mimic the week vaccines and infect the cells with the induction of antigen which will activate antibody formation and immune response from T cell. Underdeveloped vaccines for COVID-19 also have S protein and vector replicating or non-replicating with expressed S protein. There will be inconsistency between different strains so vaccines must be based on the S gene [225, 226]. Vaccines are made or classified on the basis of plasmid DNA, RBD protein, or RNA. Although DNA vaccines may be easy to produce, safe, and stable, the efficacy of these for human has not been checked. Corona DNA vaccines for SARS and MERS show great efficiency for inactive or recombinant virus and heterologous increase [227, 228].

There are still some issues related to vaccine administration, genome integration, and persistence. If we focus on the RNA vaccines, these are usually used as template which is used for protein production in animals which are vaccinated [229]. Supply of mRNA-based vaccine may be enhanced by using lipid particles for muscular administration. In the United States, a vaccine is in advance phase 1 and ready for trial on humans against COVID-19. One of the advantages of RNA vaccine is potential development in printing RNA, as it may produce massive amount of mRNA.

In recombinant vaccine scenario, vaccines are in different developmental stages for SARS including recombinant adenovirus also called Ad vector. This vector with chimpanzee's Ad63 has been used to overawe the preexisting extensive immunity in human Ad5. S or N protein of SARS-CoV or MERS-CoV, expressed from recombinant adenovirus vector, stimulated immunity or protection in animal models (ferret, mouse, and primates) [230]. Other famous vaccines for SARS include modified vaccinia Ankara (poxvirus vector), measles, and influenza, vesicular stomatitis and Newcastle disease virus [231]. These entire viruses express N and S proteins of SARS-CoV. These have been reported for protection and immunity in mouse which was used as model transgenic animal containing ACE2 and host receptor of MERS-CoV known as dipeptidyl peptidase. Intermediate hosts were also checked for the MERS vaccine. And vaccines like MVA and NCD were tested on camel which showed induction of antibodies, and MVA was reported as protected for nasal secretions and shedding [232]. The most important thing for scientists is the formulation of vaccine for livestock which may be intermediate hosts and pass on diseases to human. Similar strategy may be applied for influenza of swine and poultry; from results, we may be able to limit the risk of transmission of viruses to human [233].

During vaccination studies or formulation of vaccines, the most important point to be followed is biosafety. Even experimentation on animal studies also strictly follows the biosafety rules [234]. An experiment was designed to check the post-murine challenge of inactivated MERS-CoV vaccine or SARS-CoV vaccine with formalin in mice for effect on the lung. Addition of receptors to inactive SARS-CoV may reduce the pathogenesis of lungs. Another vaccine MVA-S is important for studying pathology of the liver in ferrets, but in other animals, it was not successful [235]. In hamsters, antibodies were enhanced by the use of S-based SARS protein vaccine. But in mice, S-based MERS vaccine was not effective. The main obstacle for the preparation of vaccine for COVID infection in cat was ADE. In this COVID infection, ADE was found to be triggered in cats as the virus-mediated antibody entered in macrophage by using the pathway of IG FC receptors. As some inconsistent events can be observed in animals, these are also important for the improvement of human immunological studies and in avoiding similar events in human [236].

The understanding with the pathogenesis, protection, and natural immunity of SARS-CoV-2 in human will be helpful in the preparation of vaccines for COVID-19 [237]. The route of pathogen infection to the specific organ is also of importance, as this knowledge will also positively help in the development of vaccines and prevention of disease from the target organ [238]. The other important point to be considered is the path to reach the target organ, e.g., lungs. There may be two routes for

SARS-CoV-2: one is by causing pneumonia by viremia and the other route is by infecting the upper respiratory tract [239]. If the other route is followed to infect, vaccines may consist of replicating vector or weak virus which may effectively encourage immunity to protect the respiratory system and may reduce nasal secretions.

On the other hand, if the infection path is viremia, parental vaccines that induce serum antibodies may successfully not only block viremia but also transduce blockage to infection [240]. This effect is the same as IM submission of slow influenza vaccine for the treatment of lung infection in humans. An annual insertion of vaccines or S subunit may be effective in humans who have been recovered from coronavirus [241]. This will be helpful in the prevention of corona infection by enhancing B- and T-cell response and immunity. Oral and nasal vaccines are reported to be effective in corona-affected people who may have diarrhea or fecal viral secretions. We can divide humans in three groups: first group includes people who have zero immunity, second group consists of immunity of different levels (these are those people who have been recovered), and third group of people has previously developed immunity for SARS. Therefore, the responses for vaccine in different groups of people will be different [242, 243]. So, the preexisting immunity levels must be studied for the effectiveness in all groups of population. But the focus must be given to the elder population, in which the death rate is reported high [244, 245].

There are different primates and non-primates who have been used for testing vaccines. These animals include African monkey, macaques, hamster, ferret, and mice. For prevention of CoV infections in animals, different vaccines to cure corona have been licensed. Not any vaccine was found effective in animals. In some animals, the digestive tract and intestine are the sites of corona infection, and this condition is severe in neonates [246]. To overcome these problems, oral vaccines have been developed which can be used for pregnant animal. These oral vaccines are helpful in preventing disease (intestinal infections) in mother and suckling neonate as antibodies will be transferred through milk. It was also observed in swine that milk antibodies were effective in passive immunity as compared to serum IgG. In bovine corona infections, diarrhea and lung infections are observed with nasal shedding. Although it has great impact on the economy, no vaccines have been developed for the prevention of bovine corona in cattle. In cattle, pneumonia and nasal shedding are associated with respiratory disease [154, 209]. This was also of great risk to use live weak coronavirus, but this type of vaccine based on bovine corona live virus has been licensed for oral administration in cattle. By using this vaccine, the risk for respiratory complex has been treated.

In camels, MERS-CoV is present in Saudi Arabia; a protein subunit (IM) or live weakened MERS-CoV may be a safe vaccine which may be helpful in controlling the transmission of virus to human and nasal shedding [177, 247]. If we observe the porcine corona, it resembles with COVID-19. As both may spread by nasal droplets, it infects the lungs. However, porcine corona infections are reported to be mild. But the dose of virus, itinerary of infection, and immunity levels are some factors which may enhance the severity of bovine and porcine coronavirus [248]. All the abovementioned factors are also important in increasing the spread and severity of

COVID-19. During pandemic, first-generation vaccine development, production, and distribution are critical. Synthesis of nucleic acid-based vaccines with S and N protein may prove to be good vaccines. Another method for speeding up veterinary vaccination during epidemic is issuance of licenses. For present mutant coronavirus, this may be based on the data from humans [249]. After that, generating a second-generation vaccine for prevention of disease and death may also be helpful for future development. Coronavirus is likely to affect as second spill of SARS-CoV-2 via animal reservoir. For generating new generation of vaccine, strong immunity is needed against corona within *Betacoronavirus* ancestors [250]. The main focus must be on S and N proteins and conservation of apoptosis that may be effective in inducing cross-reactive immunity.

Any vaccine that is successful in inducing immunity is necessary at the present scenario. The need is passive immunization to treat people both therapeutically and prophylactically. In this situation, most emphasis is also in using plasma therapy [179]. This plasma can be collected from recovered people as their plasma may contain antibodies. The induction of double-blind trials is also of importance. It has been experimented, and a comparison was made in clinical treatment; short stay at hospital and reduction in mortality rate are associated with plasma therapy. But for plasma treatment, a plasma bank is necessary. These plasma banks can collect from donors (recovered people) but proper establishment is necessary.

To control the viral proteins in host, monoclonal antibodies may be rapidly produced and also important for mapping epitopes that act as protective guards and react against immune response as established by MAB management to SARS-CoV-2-defined animals. This may also help in guiding vaccine formation and design with positive immune prophylactic against COVID-19 [138]. Encoding of mRNA is among the recent strategies used for encoding virus via intra-tracheal aerosol. Nanoparticles against MERS may provide immunotherapy in model animals.

Since the first confirmed case of coronavirus, different chemicals, vaccines, or medicines and herbs have been tested for their activities [129]. Some genetically improved antiviral therapy, drug, vaccines, and antibodies were found to be useful in reducing the global threat [152, 247]. The world has faced many epidemic and pandemic threats of Ebola, Nipah, Zika, swine flu, MERS-CoV, and SARS-CoV-2. All these are important in developing effective vaccine, drugs, and therapeutic and advanced vaccines to combat COVID-19. Some initiatives in developing new vaccines include chimpanzee vectored adenovirus vaccine [109, 171].

## Conclusion

Detection of most suitable animal models with antiviral drugs and SARS-CoV vaccines may be helpful in finding the most effective therapeutic against virus. Among animals, ferrets, cats, and hamsters are more attractive animals as models as compared to transgenic mouse and nonhuman primates. Different animals can be useful models for different parameters as for clinical symptom studies transgenic mice can be best model as they showed severe symptoms like reduction in weight. Hamsters will be proved as good models for testing the efficacy of vaccines. Cats may be suggested as model animals for viral transmission studies and for testing the bound blowout of virus and antivirus effectiveness. Nonhuman primate animals will be best suitable model animals for studying load of disease and testing vaccines and effectiveness of antiviral drugs before starting a speedy arrangement and production of vaccines for human. So we can say that continuous experiments on animal models from mice to cat, dogs, and primates will help in the establishment of data best suited for answering many problems about coronavirus (COVID-19).

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