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Covid 19: a new emerging zoonotic disease

(The role of animals in disease transmission).

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بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

فَتَعَٰلَى ٱللَّهُ ٱلْمَلِكُ ٱلْحَقُّ ۗ وَلَا تَعْجَلْ بِٱلْقُرْءَانِ مِن قَبْلِ أَن يُقْضَىٰٓ إِلَيْكَ وَحْيُهُۥ ۖ وَقُل رَّبِّ زِدْنِى عِلْمًا ﴿١١٤﴾

صَدَقَ اللهُ العَظِيمُ

من سورة طه

Certificate of Supervisor

I certify that the project entitled (**Covid 19: a new emerging zoonotic disease :The role of animals in disease transmission)** was prepared by **Abdullah Karim** under my supervision at the College of Veterinary Medicine / University of Al-Qadissiya.

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Certificate of Department

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Summary

Coronavirus Disease 2019 (COVID-19), caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome - Coronavirus-2) of the family *Coronaviridae*, appeared in China in December 2019. This disease was declared as posing Public Health International Emergency by World Health Organization on January 30, 2020, attained the status of a very high-risk category on February 29, and now having a pandemic status. This ongoing pandemic has now been reported in 221 countries with more than 133 million confirmed cases and more than 2.8 million deaths worldwide as of April 7, 2021. t is now known that SARS-CoV-2 can affect not only humans but also pets and other domestic and wild animals, making it a one health global problem. The COVID-19 outbreak once again proves the potential of the animal-human interface to act as the primary source of emerging zoonotic diseases. Several published scientific evidences have shown that bats are the initial reservoir hosts of SARS-CoV-2, and pangolins are suggested as an intermediate hosts. So far, little is known concerning the role of pets and other animals in the transmission of COVID- 19. Exploring the possible zoonosis and revealing the factors responsible for its initial transmission from animals to humans will pave ways to design and implement effective preventive and control strategies to counter the COVID-19. Therefore, this review discusses in brief about the COVID-19/SARS-CoV-2 with a particular focus on the potential role of pets and other animals in the current outbreak and transmission to humans, and associated zoonotic links and highlights the new advances in diagnosis, along with prevention and control strategies based on One-health approaches.

Key word: COVID-19, zoonotic, transmission, pets, host range.

1. Introduction

In the 21st century, we have faced a few deadly disease outbreaks caused by pathogenic viruses such as Bird flu caused by Avian influenza virus H5N1, Swine flu caused by reassorted influenza virus H1N1 pandemic 2009 (H1N1pdm2009), Severe Acute Respiratory Syndrome (SARS) caused by SARS-CoV (coronavirus), the Middle East respiratory syndrome (MERS) caused by MERS-CoV and Ebola (Baharoon & Memish,2019).

In the early days of December 2019, several patients with pneumonia of unknown etiology emerged in Wuhan City, Hubei Province, Central China. The causative agent for this illness was later confirmed as a novel coronavirus by a laboratory and was initially named as a 2019 novel coronavirus (2019-nCoV) (Lai et al.,2020). The World Health Organization (WHO) subsequently recommended the disease name as Corona Virus Disease (COVID-19). On March 11, 2020 the WHO declared the situation as a pandemic which is threatening mankind to a great extent. As of now, SARSCoV-2 is considered as the seventh coronavirus that infects humans. The other coronaviruses (CoVs) include HKU1, NL63, OC43, 229E, SARS-CoV, and MERS-CoV. Among which SARS-CoV and MERS-CoV are zoonotic and have resulted in high mortality outbreaks in the last two decades, while the others are usually associated with mild upper-respiratory tract illnesses, and sometimes leading to complicated disease, when occurring in immunocompromised individuals (Wei et al.,2020). Coronaviruses (CoVs) are a group of viruses that belong to the subfamily *Orthocoronavirinae* in the family *Coronaviridae*, Order *Nidovirales*. They are classified into four genera based on their genetic properties within the subfamily *Orthocoronavirinae*, namely Alphacoronavirus (α-CoV), Betacoronavirus (β-CoV), Gammacoronavirus (γ-CoV), and Deltacoronavirus (δ-CoV) (Li et al.,2019). Both α- and β-CoV genera

are known to infect mammals, whilst δ- and γ-CoVs infecting birds. Seven CoVs, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) being the seventh member of the family, have been found to infect humans and cause respiratory diseases so far. Among these, the common human CoVs (HCoVs) are HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1, and they usually lead to common self-limited upper respiratory disease (Hasoksuz et al.,2020). On the other hand, the recently emerged SARS-CoV and the Middle East respiratory syndrome (MERS)-CoV (including SARS-CoV-2) are responsible for atypical pneumonia . Despite its rapid spread, there are no approved vaccines against SARS-CoV-2 nor specific therapeutic drugs so far. Thus, a better understanding of the virus's transmission vehicles is key to the overall prevention and control of this virus. In this connection, understanding animals' involvement in the transmission dynamic must be an important component of the efforts to interrupt the pace of its communicability and spread. The close association between humans and their pets has led to an examination of the potential risks of transmission. Viral RNA has been detected in two dogs and two cats, belonging to SARS-CoV-2 infected owners, in Hong Kong. Although so many studies are on progress, little is known so far concerning the role of pets, which are always in close contact with humans, and other animals in the spread of COVID-19 to humans. In this review, we summarized the current evidence about the role of pets and other animals in the spread of COVID- 19 infection.

2.Structure of virus

CoVs are enveloped viruses with icosahedral symmetry and measures ~ 80–220 nm in diameter. They are composed of a non-segmented, single-stranded positive-sense RNA genome that measures ~ 26–32 kb in size, which makes them the largest viruses among all other RNA viruses (Helmy et al.,2020). The SARS-CoV-

2 is a spherical enveloped virus that measures 50–200 nm in diameter with a single-strand positive-sense RNA genome (30 kb in length). The genome of SARS-CoV-2 shares 79.6% and 96% sequence identity with SARS-CoV and Bat-CoV respectively (Zhou et al.,2020). Structurally, the SARS-CoV-2 membrane contains four major structural proteins; namely, spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M) glycoprotein, and nucleocapsid (N) protein (Fig. 1). S glycoprotein, which is found in the uppermost layer of the virus, mediates viral attachment to the Angiotensin-converting Enzyme 2 (ACE2) receptor on the host's target cell. The M protein determines the shape of the virus is the most abundant protein than other structural proteins. Together with other structural proteins, it plays a major role in viral assembly. The N protein is an RNA binding protein and as being so its main function is for binding and packaging of the viral RNA genome into a long helical nucleocapsid structure (Kang et al.2020).

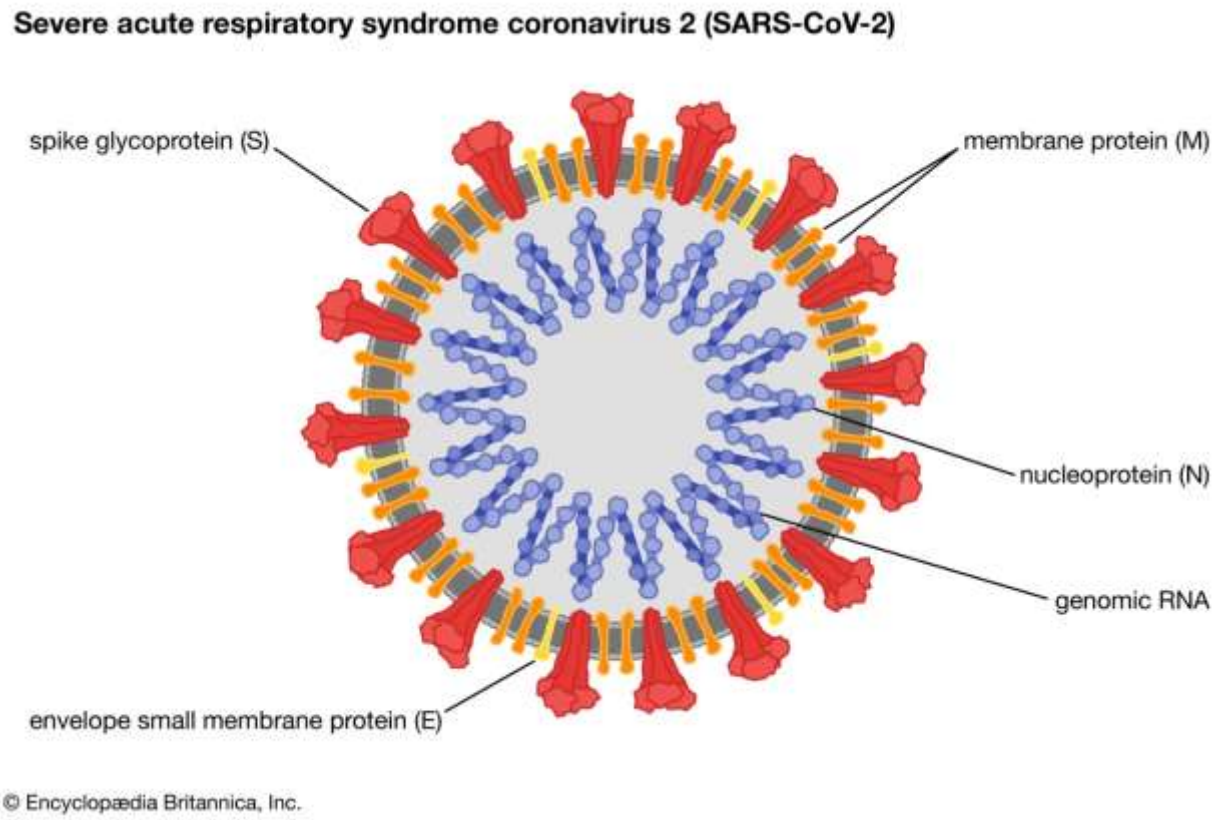

Fig.1: The structure of corona virus

3. Host range of corona virus

Coronaviruses have a broad animal host range, it infect man as well as domestic and wild animal species and usually infections remain sub-clinical in most cases (Ji et al.,2019). The clinical form varies from enteritis in cattle, horses and swine, upper respiratory tract disease in cattle, dogs, felines, and poultry, and common cold to highly fatal respiratory infections in humans. Among the four genera in the Coronaviridae family, Alphacoronavirus and Betacoronavirus usually infect mammals and have probable bat origin, while Gammacoronavirus and Deltacoronavirus infect birds, fishes, and mammals and are assumed to have swine origin (Cui et al.,2019). The genus Betacoronavirus possess potential zoonotic

pathogens like SARS-CoV and MERS-CoV which have bats as primary host and palm civet cat and dromedary camels as intermediate hosts, respectively (Ramadan & Shaib,2019). Many CoVs have been recovered from birds such as Wigeon coronavirus HKU20, Bulbul coronavirus HKU11, Munia coronavirus HKU13, White eye coronavirus HKU16, Night-heron coronavirus HKU19 and Common moorhen coronavirus HKU21. A list of other animal species also reported harboring the CoVs such as cattle, horses, swine, dogs, cats, camels, rabbits, rodents, birds, ferrets, mink, bats, snake (such as Chinese cobra and krait), frogs, marmots, hedgehogs (Erinaceus europaeus), Malayan or Javan or Sunda pangolin (Manis javanica), many other wild animals and their role as carrier/reservoir needs urgent attention (Ji et al.,2019). Among large animals, bovine coronaviruses (BoCoVs) have zoonotic potential as being isolated from asymptomatic children and also found affecting several domestic and wild ruminants, in which calf diarrhea in neonates, bloody diarrhea in adult cattle and respiratory form of shipping fever in all age groups of cattle are universal implications (Suzuki et al.,2020). Feline CoVs affect the respiratory tract, central nervous system, abdominal cavity, and gastrointestinal tract to produce enteritis and infectious peritonitis. Canine enteric coronavirus of Alphacoronavirus and canine respiratory coronavirus of Betacoronavirus genera affect the enteric and respiratory tract, respectively (Licitra et al.,2014). In the poultry industry, infectious bronchitis virus (IBV), member of the genus Gammacoronavirus cause extensive economic loss by producing respiratory illness, urinary tract infection, and reproductive problems.

4.Zoonotic origin and transmission of SARS-CoV-2

Coronaviruses have crossed the species barrier twice in the past during SARS and MERS outbreaks, and thus SARS-CoV-2 looks to be the outcome of species barrier jumping for the third time. Amongst CoVs, recent zoonotic ones such as

SARS-CoV, MERS-CoV, and SARS-CoV-2 gained higher importance due to the severity of disease in humans and their global spread (Rothan and Byrareddy 2020). SARS-CoV emerged in humans that had contact with palm civets in China in 2002 and resulted in a global SARS epidemic that lasted 8 months and took 774 lives. Ten years later, in 2012, MERS-CoV appeared in humans that had close contact with dromedary camels in Saudi Arabia where it remains a major public health concern, spread to 27 countries claiming 858 lives. Similarly, for SARS-CoV-2, due to evidence of several infected people's exposure to seafood in the wet animal market in Wuhan City, it is assumed that the virus was likely originated from animals and transmitted to humans, then maintains human-to-human transmission (Ji et al.,2020). It is now suggested that bats are the initial reservoir of the virus. Based on evidence from studies that investigated the animal sources of the virus pangolins are believed to be the most likely intermediate host responsible for SARS-CoV-2 human transmission (Fig. 2).

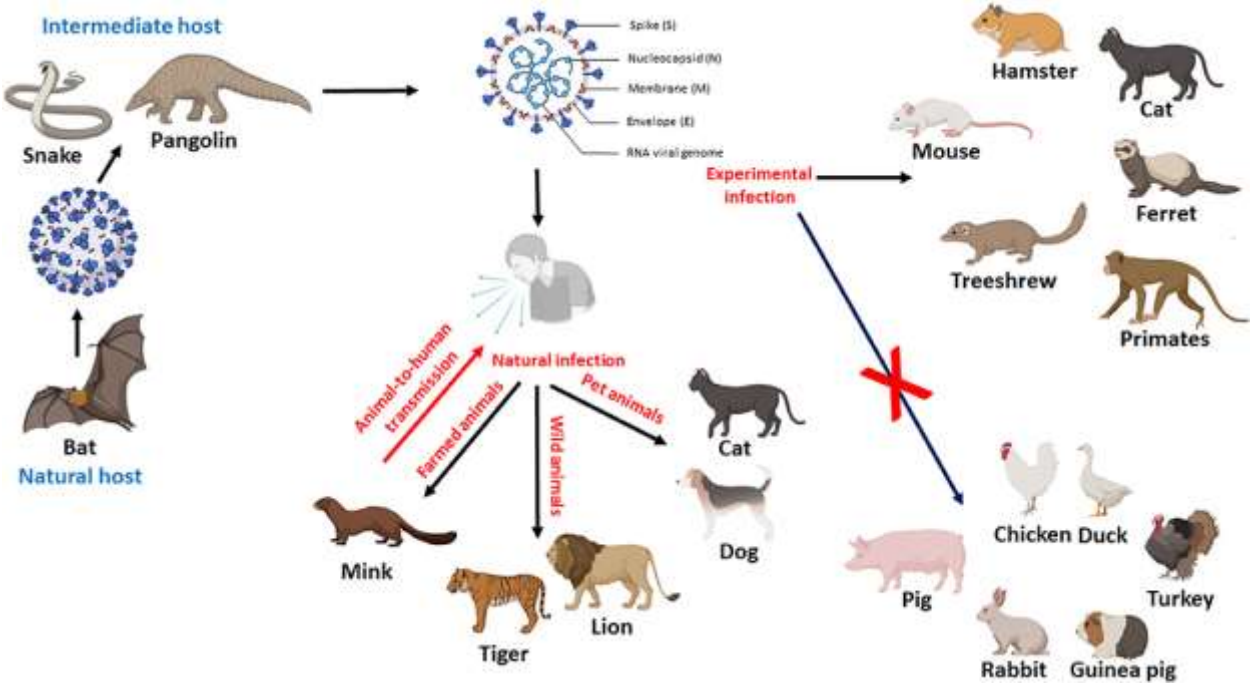

Fig.2: Transmission of SARS-CoV-2

4.1. Zoonotic spillover

Zoonotic spillover is the transmission of pathogens to humans from vertebrate animals. At present, these spillovers are of significant concern as in the past, many spillovers in the form of Nipah, Hendra, Ebola, SARS, MERS, and ongoing COVID-19 involving many animal species like pigs, horses, monkeys, camels, civets, among others, were documented.

SARS-CoV-2 has been implicated to be originated from animals, and associated with animal linkages, spillover events, cross-species barrier jumping and zoonosis. Since the beginning of 2002 till the end of 2019, three coronaviruses have caused havoc in the human population globally and will continue to do so. Earlier identified betacoronaviruses (SARS-CoV and MERS-CoV) were reported in Guangdong province of China in November 2002 and Saudi Arabia in 2012, respectively. SARS-CoV-2 is the third zoonotic betacoronaviruses recognized in this century.

Added to the involvement of bats and pangolins, the recent reports revealing SARS-CoV-2 infection in cats, dogs, tigers, lions and minks have raised concerns over this virus affecting multiple animal species, and also points out towards the incidences of reverse zoonosis (Tiwari et al.,2020). The ferrets, cats, and primates are suggested to be good candidates for susceptibility to SARS-CoV-2. COVID-19 research and surveillance in companion and pet animals, livestock animals, zoo animal species, wildlife animal species as well as their handlers, veterinarians, and owners need to be enhanced during the pandemic, which would help to follow better integrated one health strategies and appropriate preventive and mitigation to counter SARS-CoV-2 effectively (Leroy et al.,2020). Significance of COVID-19

monitoring and implementation of suitable public health measures among workers involved in meat and poultry processing facilities/industries has been emphasized, which would protect them as well as aid in preserving the critical meat and poultry production infrastructure and the meat products.

4.2. Transmission to humans

The involvement of intermediate hosts in maintaining and transmitting the virus to susceptible host predisposes humans to novel CoVs leading to the emergence of new diseases in humans. The currently ongoing SARS-CoV-2/COVID-19 pandemic has put on hold the entire world. The CoVs have frequently been associated with animal and human diseases and have a zoonotic interface. Usually, one or more types of animal hosts are involved in the transmission cycle of CoVs to humans . That can be natural host, reservoir host, intermediate host or definitive host. Bats have been the natural hosts for human CoVs of *Alphacoronavirus* (HCoV-NL63, HCoV-229E) and *Betacoronavirus* (SARS-CoV, MERS-CoV, SARS-CoV-2*) genera whereas for Betacoronavirus members HCoV-OC43 and* HCoV-HKU1, *rodents are the natural hosts*. Genome sequence analysis has revealed bats as a natural host for SARS-CoV-2 (Salata et al.,2020). In natural or reservoir hosts, CoVs adapts well, however, being unstable RNA viruses, they keep multiplying continuously without producing disease thereby enabling persistence or survivability and accumulation of mutations over the time resulting in the emergence of newer and novel strains of viruses. These unique strains or viruses occasionally spill over to other species including animals or humans, adapting to their body systems and hence broaden the biological host range for evolutionary sustainability; however, results in epidemiological widening of disease sphere as well (Tiwari *et al*.,2020). This transmission and adaptation scenario initiates a host-pathogen response resulting in the novel usually severe

diseases that can at times be fatal in initial stages or over extended periods until virus pathogen adapts to host or the host develops sufficient immune defense. Interestingly, bats play a crucial role in all the spillovers mentioned above, indicating their importance in the emergence of new viruses. The reason behind the emergence and broad host range of CoVs in the past and present might be due to unstable RNA-dependent RNA polymerase (RdRp), lack of proof-reading ability, high frequency of mutations in the receptor-binding domain of spike gene and genetic recombination (Chen *et al*.,2020).

Role of pets in disease transmission

The first COVID-19 case in companion animal was reported in a Pomeranian dog from Hong Kong, China in February 2020. Later in March 2020, COVID-19 was reported from a cat in the same country (The Government of Hong Kong,2020). These two cases were found after their owners were reported positive for COVID-19. The persistent positive reverse transcription-polymerase chain reaction (RTPCR) result of the Pomeranian dog was accepted as a true positive by the experts from the University of Hong Kong and the World Organization for Animal Health as a true positive result for a true infection. This was further supported by the absence of contamination as the dog was confined in quarantine at government kennels. Genetic sequence similarities of the SARS-CoV-2 from the owner and the pets indicated the potential of human to-animal transmission. Besides, both viral culture and serological tests were done to check whether the dog was contagious or not and becomes negative. These tests coupled with the absence of any sign and symptom lead to deduce that the dog was not contagious to humans and/or another animal (Almendros ,2019).

After the first reported case of COVID-19 in a cat, other COVID-19 cases were similarly reported from other countries like Belgium, France , Germany, Russia, and the United . Based on these reports and other evidence from experimental studies, it is now accepted that these two companion animals are susceptible to SARS-CoV-2 with cats being highly susceptible and having the potential to transmit the illness to other naive cats while dogs are less susceptible (Shi *et al.*,2020). Besides cats and dogs, the golden Syrian hamsters have been also confirmed to be susceptible to SARS-CoV-2 in recent laboratory experiments. It was demonstrated that golden hamsters exposed to SARS-CoV-2 can be infected and were able to efficiently transmit the virus to naive hamsters by direct contact and via aerosols (Sia *et al.*,2020). Altogether, pets living in the household of people with COVID-19 are at risk of contracting the disease and can spread the virus to other naive pets. Hence, owners should protect their companion animals from being infected, which will have a positive effect on COVID-19 prevention. Unless pet owners do so, this would pose difficulties for the overall prevention and control of the disease. However, there is currently no evidence on the potential role of pets on SARS-CoV-2 transmission to humans. Although there is no evidence, these pets might have the potential to transmit the virus to humans as they express the same cell receptor ACE2 (Schoeman & Fielding, 2019). Hence, the usual precautionary measures must always be there.

Role of domestic and wild animals in disease transmission

Domestic animals such as ferrets were also reported to be highly susceptible to SARS-CoV-2. A recent experimental study verified that infected ferrets can transmit SARS-CoV-2 efficiently to other naive ferrets via direct contact and air (Richard *et al.*,2020). In contrast, other domestic animals like pigs and poultry are not susceptible to SARS-CoV-2 (Sia *et al.*,2020) while there is no evidence so

far on the susceptibility of livestock animals like camel, horse, sheep, cow, and donkey. Concerning other wild animals, tiger and lion were confirmed to be susceptible to SARS-CoV-2.

In April 2020, five tigers (Two Malayan and three Amur tigers) and three African lions that exhibited respiratory signs (dry cough and some wheezing) were tested positive in the Bronx Zoo in New York City, USA. It is assumed that an asymptomatic zoo employee infected the animals (OIE. SARS-CoV-2/COVID-19, United States of America). Minks, which are farmed for their fur, are also susceptible to SARS-CoV-2 with the ability to transmit the virus among each other A recent research finding from the Netherlands suggested that there has been a transmission of a new case of COVID-19 from mink back to human (an employee who worked in a mink farm).

An overview of coronaviruses jumping the cross-species barriers, zoonotic CoVs transmitted from bats to animals before spillover to humans, and possible prospects for further transmission to mammalian hosts is depicted in Fig. 2

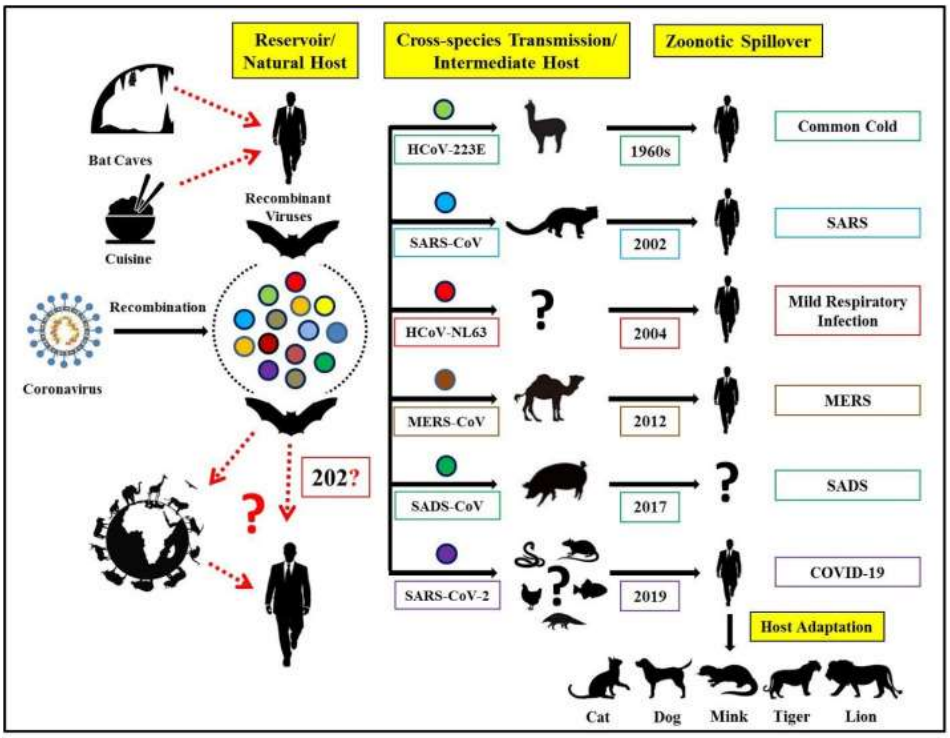

Fig 2: Cross-species transmission of known zoonotic coronaviruses from bats to animals before spillover to humans and probable prospects of further transmission to mammalian hosts.

Laboratory diagnosis of COVID-19 in animal

Laboratory diagnosis of SARS-CoV-2 in animals is similar to the viral diagnosis among humans. For diagnosis, respiratory tract specimens from the nasal turbinate, soft palate, and tonsils are preferred [Shi et al.,2020]. Although specimens from these sites are preferable, other specimens from other sites like rectal swabs may also be used in situations where direct sampling is not possible due to risks to the animal or testing staff (OIE. 2020). The molecular test developed for use in human samples; the real-time Reverse-transcription polymerase chain reaction (RT-PCR), is the gold standard and widely used method to diagnose SARS-CoV-2 in animals using the above-mentioned samples (Richard *et al.*,2020). Besides, viral isolation in cell culture, viral genome sequencing, and other molecular tests like Reverse

transcription loop-mediated isothermal amplification (RT-LAMP) can also be used for the detection of SARS-CoV-2 in animals. Furthermore, rapid immunochromatographic tests and other serological immunoassays such as enzyme-linked immunosorbent assay (ELISA) and Virus neutralization tests can be also used for the detection of antibodies against SARSCoV-2 in animals (OIE.2020).

Prevention and control

Although many vaccines and antiviral drugs are being tested, there is no known effective treatment for COVID-19 so far. As of March 20, 2020, WHO has tabulated approximately 44 vaccine candidates targeting SARSCoV-2, among which few are under clinical evaluation and some under development by various companies and institutions. They included live attenuated, formaldehyde inactivated, protein subunit, DNA, m-RNA, VLP, replicating, and non-replicating vector-based SARS-CoV-2 vaccines. Effective prevention and control strategy is primarily through the mitigation of human to-human spread. This includes personal protection (like personnel hygiene, wearing a facemask), social distancing, temperature screening, early testing, quarantine of peoples of suspected or infected individuals' travel history, and preventing further global spread (Gasmi *et al.*,2020). Since studies have shown that the origin of the virus is connected to a seafood market in Wuhan, identification and reduction of transmission from the susceptible animal sources might also another means for prevention and control of viral spread (WHO,2020a). Given the susceptibility of pets and other animals to SARS-CoV-2, it is still recommended that people who are suspected or confirmed for COVID-19 should limit contact with these animals as this will minimize animal infection from human sources. Companion animals may also have the potential to spread COVID-19 to other people in the household or people being in close contact

with the animals. It is thus advisable that humans to avoid unnecessary contact with animals and care, like basic hygiene measures, should always be there when handling and caring for animals and/or animal products. Additionally, animals belonging to owners infected with SARS-CoV-2 should be kept indoors in line with similar lockdown recommendations for humans to prevent animal-to-animal spread. Overall, countries should have a one-health approach in their prevention and control strategy to protect both humans and animals from being infected, which can have a positive impact on prevention and control and consecutively in the economy (WHO,2020b).

Conclusion

Our knowledge and understanding of SARS-CoV-2 and the resulting disease COVID-19 is growing by the day, and while there is a lot still to discover, it would be worth taking the time not only to look at historical records of the emergence of betacoronaviruses in the human population but also engage with the veterinary community who have been working with coronaviruses in animals for many years.

The possibility of inter-species transmission of CoV infections is a point of concern to human beings due to the adaptive genetic recombination that occurs in these viruses. it is better to regulate the trade of wild animal species all around the country. The emergence of newer zoonotic infections like SARS-CoV-2 is inevitable in the future. The SARS-CoV-2 outbreak is just another critical example that proves the existence of a close but straight forward interaction between humans, animals, and the environmental health that can potentially result in the emergence of a deadly pandemic. The past decades have shown us the destructive potential of several zoonotic coronavirus infections like SARS, MERS, and now SARS-CoV-2 that calls for the implementation of One Health as a framework to protect humankind from emerging pathogens soon.

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