

SPECIAL ARTICLE

Covid in Animals and Upcoming Vaccine Based on Rabies Virus

Dr. Shivaji Bhattacharya

B.Sc.; B.V.Sc. & A.H.; P.G.D.H.R.M.;

P.G.(Wildlife); M.Sc. E.E.; Ph.D. (Toxicology)

The family Rhabdoviridae consists of more than 100 viruses that infect a wide variety of hosts, including vertebrates, invertebrates, and plants. Under this family, genus *Lyssavirus* includes rabies virus and at least five other pathogenic rabies-like viruses. Whereas corona viruses (CoVs) are a group of viruses under the family Coronaviridae and based on their genetic properties, distributed among four genera viz. Alphacoronavirus (α -CoV), Betacoronavirus (β -CoV), Gammacoronavirus (γ -CoV), and Deltacoronavirus (δ -CoV). Both rabies and corona viruses are enveloped RNA virus. CoVs are known to circulate in mammals and birds. Both α and β -CoV genera are known to infect mammals, where δ - and γ -CoVs infecting birds.

Generally, seven CoVs are affecting humans, out of which four are common human CoVs (HCoVs) comprise HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1 and usually lead to common self-limited upper respiratory disease. Rest three CoVs are recently emerged and zoonotic in nature and usually infect humans responsible for atypical pneumonia and severe acute respiratory syndrome which include (i) Severe acute respiratory syndrome (SARS)-CoV, (ii) Middle East respiratory syndrome (MERS)-CoV and (iii) Severe acute respiratory syndrome (SARS)-CoV-2.

Zoonotic link of SARS-CoV, MERS-CoV & SARS-CoV-2 is now established. The zoonotic link of SARS-CoV was revealed when similar virus was isolated from masked palm civets (*Paguma larvata*) and raccoon dogs (*Nyctereutes procyonoides*); and antibodies against SARS-CoV were detected in Chinese ferret badgers (*Melogale moschata*) found in a live-animal market of China (2002 AD). Similarly, MERS-CoV in humans was transmitted from dromedary camels (*Camelus dromedaries*) in Saudi Arabia (2012 AD). SARS-CoV-2 is the most recent example of an emerging zoonotic infectious virus that has converted 'pandemic potential' to reality. Though the origin of SARS-CoV -2 has not yet been confirmed, the preliminary evidence suggests that SARS-CoV-2 emerged from Wuhan, China, via animal-to-human transmission (most likely candidate is the bat, the pangolin or a combination of both). However, all three zoonotic CoVs are reported to originate from bats and were transmitted to humans through an intermediate animal host.

Some reasons of SARS Cov-2 susceptibility in different species of animals and human have been identified like (a) Similarity of Angiotensin-converting enzyme 2 (ACE2) and (b) High similarity of amino acid sequence alignment of ACE2 among humans and different animals. Many animal species have similar or identical SARS cellular receptors, Angiotensin-converting enzyme 2 (ACE2) to those found in humans. This potentially provides SARS-CoV-2 with a related cellular entrance mechanism to infect a varied series of hosts without requiring further significant genetic changes. Genetic changes randomly acquired when the virus replicates could lead to it developing the ability to become endemic in some animal populations, including domestic pets. The key ACE2 residues that are responsible for recognizing the spike/S protein were analyzed to identify the potential host range of SARS-CoV-2. Mammals such as different monkeys, Sumatran orangutan, chimpanzee, olive baboon, common marmoset, stoat, civets, fruit bats, wild boar, domestic pig, ferret, dog, red fox, cat, pangolin, horse, cattle, sheep, rabbit, hamsters, naked mole-rat, thirteen-lined ground squirrel etc. possess ACE2 residues that may have the potential to bind to the S protein of SARS CoV-2. Genomic analysis has identified bats as original host, camel as the reservoir host and other animals such as cattle, sheep, goat, pigs, rabbits, rhesus macaques and common marmosets acting as the susceptible or intermediate hosts. Snakes and turtles are cannot be considered as the intermediate hosts of SARS-CoV-2.

In another study, the amino acid sequence alignment of ACE2 was compared among species such as humans, non-human primates (gibbon, green monkey, macaque, orangutan, and chimpanzee), cats, dogs, bovines, sheep, goats, swine, horses,

***Corresponding Author:** Dr. Shivaji Bhattacharya, Assistant Director, ARD (Microbiology), Institute of Animal Health & Veterinary Biologicals (IAH&VB), Kolkata

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chickens, ferrets, civets, mice, rats, and Chinese horseshoe bats, and a high sequence similarity was found, with the exception of chickens.

Studies on nucleotide similarity index among different animal CoVs with respect to SARS-CoV and SARS-CoV-2 reveal that canine and feline CoVs shared a low nucleotide similarity index with respect to SARS-CoV and SARS-CoV-2 which ranged from 44.0% to 44.5%, whereas, SARS-CoV-2 isolated from Tiger (MT065033) and Mink (MT396266) shared a high nucleotide similarity percentage of 99.6% to 99.9%. Nucleotide similarity index between SARS-CoV-2 and other animal origin CoV species like Pangolin (MP789; MT081071), Bat-SL-CoVs (CoVZXC21; MG772934), Bat-CoV (RaTG13; MN996532) in subgenus Sarbecovirus varies between 86.6%, 88.4% and 96.3%, respectively.

Susceptibility of animals and birds to SARS-Cov-2: SARS-Cov-2 has been recorded in pets as well as wild animals. SARS-Cov-2 transmission to cats, tigers, and lions has been documented, with clinical signs i.e. vomiting, diarrhoea, difficulties in breathing, dry cough, and wheezing. Dogs have the exception which contract the disease but show none of these symptoms and comparatively less susceptibility to SARS-CoV-2. Experimental inoculation of SARS-CoV-2 in several animal species indicated that Ferrets and Cats are highly susceptible to the disease; and they had the potential to transmit the virus to susceptible animals cohabiting with them via droplets and successfully maintain the infection chain. Researchers found that animals such as chickens, turkeys, ducks, quail, geese and pigeons are not infected by SARS-CoV-2.

Reported SARS-Cov-2 in Pets:

In dogs: On February 28, 2020, a Pomeranian dog in Hong Kong tested positive for SARS-CoV-2 without showing any signs of the disease. The genetic sequences of SARS-CoV-2 obtained from the Pomeranian and its human contacts were very similar, indicating human-to-animal transmission. It was the first report of the human-to-animal transmission of COVID-19. On July 31, 2020 -- Buddy, a 7-year-old German shepherd, that was the first dog to test positive for the SARS-CoV-2 in the United States, has died after being sick for three months. Some researchers put forward the possibility of dogs acting as intermediate hosts in the transmission of SARS-CoV-2 within the human population in Italy.

In cats: SARS-CoV-2 was detected in two cats, one each from Belgium and Hong Kong. Researchers at Harbin Veterinary Research Institute recently reported that cats can be infected with SARS-CoV-2 and can spread it to other cats.

In minks: There have been reports of large animal outbreaks of SARS-CoV-2 in mink farms in several countries viz. Netherlands, Denmark, USA, Spain etc. SARS-CoV-2 can change while infecting minks. It has been observed that these mink variants are able to transmit back into humans through close contact with the mink. Preliminary results suggest that the mink variants infecting humans appear to have the same properties as other variants of the SARS-CoV-2 virus. Netherlands, after outbreak of SARS-CoV-2 in two separate mink farms, initiated mass culling of minks (>1million as on 02.08.2020) fearing the possibility of minks acting as a viral reservoir for this pandemic virus. Denmark culled all 17 million minks on its farms last year.

SARS-CoV-2 in wild animals:

In otters: Otters at Georgia Aquarium in the Atlanta city, USA have tested positive for Covid-19.

In Malayan pangolins: SARS-CoV-2 virus was identified in Malayan pangolins seized from southern China.

In Malayan tiger: SARS-CoV-2 diagnosed in a tiger in the Bronx Zoo of New York City. This tiger, along with other tigers and lions, was tested immediately after showing signs of respiratory illness. This was the first report of SARS-CoV-2 transmission from humans to a wild animal in USA.

In snow leopard: Samples were taken from the three large cats after they showed signs of respiratory illness and a snow leopard in the Louisville Zoo in Kentucky, USA was test positive for the SARS-CoV-2. The cats were likely infected by an asymptomatic staff member, despite precautions that included caretakers wearing personal protective equipment.

SARS-CoV-2 in Asiatic lions: On 19.04.2021, Eight Asiatic lions (4 male & 4 female) at Hyderabad's Nehru Zoological Park have tested positive for Covid-19 after they showed symptoms including fever. This is the first case of lions or any other animals testing positive in an Indian zoo and this is the first time in India that transmission of the virus to animal through human has been detected. An Asiatic lion at Etawah Safai Park in Uttar Pradesh had tested positive while another was suspected to have contracted the contagion. On 12.05.2021, Tripur, an Asiatic lion, in Jaipur zoo, tested positive for Covid-19. On 03.06.2021, Neela, an Asiatic lioness becomes first animal to die from Covid-19 in India while nine others in the pride tested positive for the infection at Arignar Anna Zoological Park at Vandalur.

Preventive measures initiated against Covid-19 in animals: Some preventive measures have been initiated in different countries like (a) Covid-19 vaccination for animals: Russian scientists have developed the first Covid-19 vaccine for animals. The vaccine was registered after it showed effective results in dogs, cats, foxes and mink, (b) Physical

distancing with animals: The US Centers for Disease Control and Prevention (CDC) recommended laboratory-confirmed COVID-19 people to limit their contact with their companion animals such as dogs and cats, including snuggling, petting, and getting licked, and (c) General precautions and hygiene measures: General precautions and hygiene measures are suggested while visiting live-animal markets, wet markets, and animal product markets, to avoid contact with diseased animals or spoiled animal products and to avoid contact with stray animals (cats and dogs), rodents, birds and bats.

Rabies virus-based COVID-19 vaccine: In animal model, some researchers have developed a novel, highly efficient, and safe COVID-19 vaccine (e.g. CORAVAX™) using a rabies virus-based vector that has proven to be an efficient vaccine against several emerging infectious diseases. This study reports that both a live and an inactivated rabies virus containing the SARS-CoV-2 spike S1 protein induces potent virus-neutralizing antibodies at much higher levels than seen in the sera of convalescent patients. These types of vaccines have ample scope to be used for mass vaccination to prevent SARS-Cov-2 in human as well as susceptible animals.

In Conclusion - an appeal to WHO, OIE & Law makers is that the SARS-CoV-2 pandemic and subsequent panzootic potential highlights the need for a One Health approach. It is important that harmonized guidelines for surveillance and intervention in wild, captive, and companion animals are developed to facilitate a better understanding of viral spread in novel host populations. The proposed interventions should include quarantine and care packages for infected animals. Whilst potentially at lower risk, food animals may still be considered in future guidelines as the cellular receptor mechanisms render the target species jump possible even though the risk of close contact with humans is lessened.