

COVID-19: A Zoonosis

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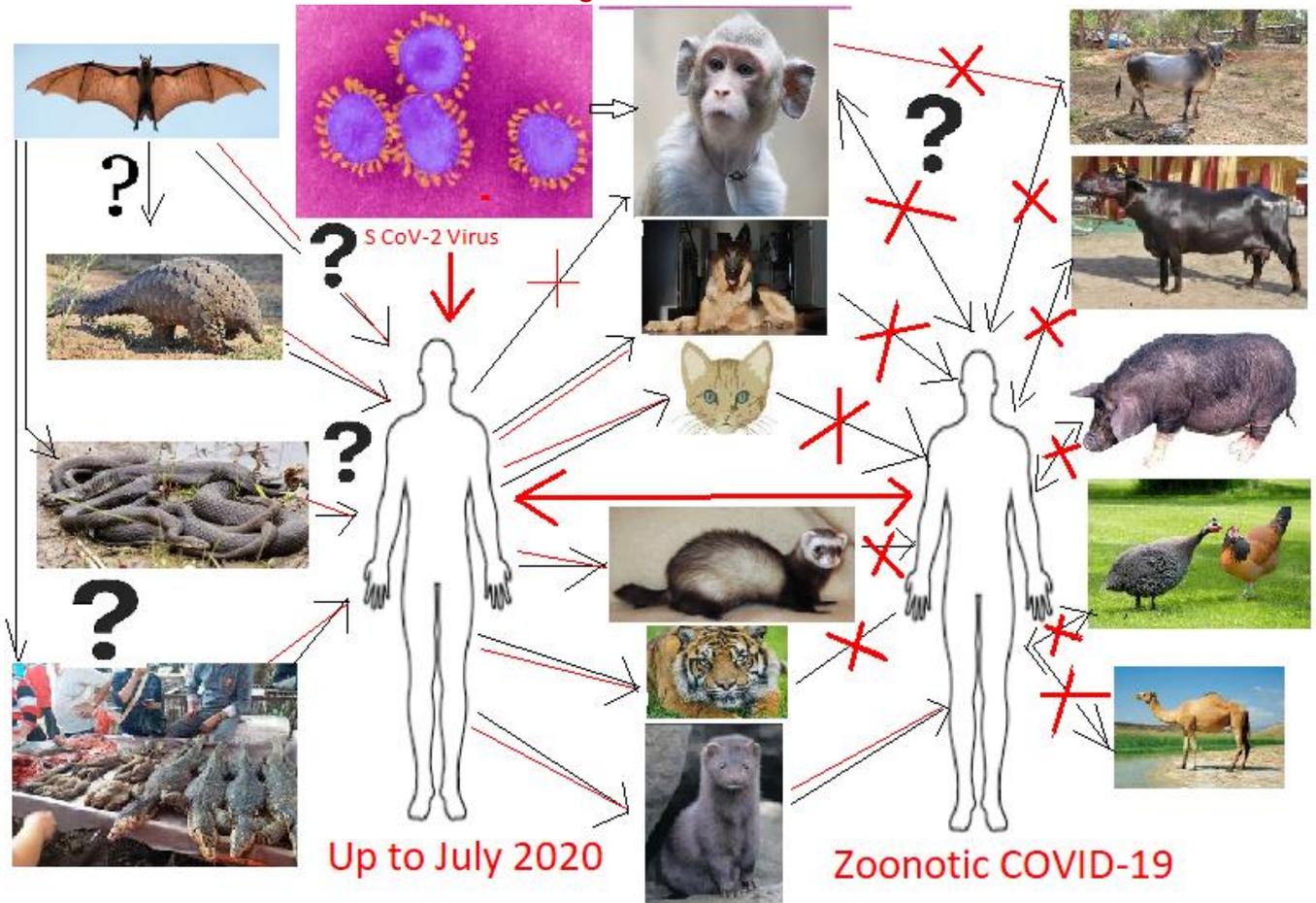
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International eConference on Immunology in 21st Century for Improvising One-Health

Sardar Vallabh Bhai Patel University of Agriculture & Technology (SVPUAT), Modipurum, Meerut-250110 (UP)

Presented on 7th August 2020 at 5.30 PM



According to UN Environment Program (UNEP) almost 60% of all known infectious diseases, and ~75% of emerging infectious diseases (as Ebola, SARS, MERS, Zika fever and Covid-19 etc.) are zoonotic in nature. Most of the emerging disease in past could be contained in time to limit spread and loss, but COVID-19 has already spread all over the world in short period of just three months and still devastating the world. It is set to cost the global economy ~\$9tn (£7.2tn) over two years. The emergence of novel CoVs and their wide host range may be due to

- Instability of the replicase enzyme,
- RNA dependent RNA polymerase,
- Polybasic furin cleavage site, and
- O-linked glycans,
- Lack of proofreading mechanism,
- A higher rate of mutations in the RBD of spike gene and
- Genetic recombination

Origin of Severe Acute Respiratory Syndrome *Corona Virus-2* (SARS-CoV-2) causing *Corona Virus* disease-2019 (COVID-19):

Theories of SARS-CoV-2 origins:

- (i) Natural selection in an animal host before zoonotic transfer.
- (ii) Natural selection in humans following zoonotic transfer.
- (iii) Conspiracy theory, laboratory synthesized virus (bio-weapon).

The comprehensive sequence analysis of the SARS-CoV-2 RNA genome identified that the SARS CoV-2 from Wuhan may be a recombinant virus of the bat Coronavirus and another Coronavirus of unknown origin probably pangolins. The recombination was found to have happened within the viral spike glycoprotein, which recognizes the cell surface receptor. Though nothing is clear, many believe it as outcome of some conspiracy and an artificial man-made virus in Wuhan Lab in China. Ji and co-workers (2020) based upon their study on codon usage bias proposed snakes as the reservoir of SARS-CoV-2. The most recent theories propose its origin from bats (Wu et al. 2020; Zhang et al. 2020) and pangolins (Andersen et al. 2020). The circumstantial evidence suggested role of snakes, pangolins, turtles, and other wild animals in the origin of SARS-CoV-2. The bats are the natural reservoir hosts of multiple Coronaviruses such as SARS-CoV and MERS-CoV (Tiwari et al., 2020). However, the virus causing COVID-19 could not be shown to infect snakes, pangolin or bats. Therefore, scientist believe that there must be an intermediate animal host responsible for the zoonotic spill-over of COVID to humans (Weiss and Leibowitz 2011; Murdoch and French 2020) as were the bats and camels in the recent SARS and MERS outbreaks in the past (Cui et al. 2019). Besides, palm civets on farms were found largely free from SARS-CoV infection but in one animal market in Guangzhou about 80% civets had high levels of antibody to SARS-CoV suggesting acquisition of infection in market rather than on farms, indicating role of civet as intermediate host for SARS. However, till now no intermediate animal host could be confirmed for SARS CoV-2.

COVID-19: A Zoonotic Disease: Though only preliminary evidence, it is a confirmed novel zoonosis caused by a Coronavirus (Mackenzie and Smith, 2020; Vinodh Kumar et al., 2020). SARS-CoV-2 is the 7th Coronavirus infecting humans and 3rd one with zoonotic linkages after SARS-CoV and MERS-CoV. The receptors of SARS CoV-2, angiotensin-converting enzyme-2 (ACE-2) modelling revealed their presence in many animal species including pigs, ferrets, cats, orangutans, monkeys, bat species, and humans with similar levels of affinity for SARS-CoV-2 indicating the possibility of existence of many hosts of the virus in nature (Jarvis 2020). Recently, transmission of virus from mink to human (two confirmed cases in The Netherlands) and human to mink has definitely proven its zoonotic nature. Considering importance of mink as animal host of COVID-19, in Spain, Joaquin Olona, agriculture minister for the Aragon region, ordered the cull of 92,700 minks. About 87% percent of the minks were infected on farms. In the Netherlands, about a million of mink have already been culled since the start of the pandemic after 20 farms were found to be infected. The recent report from FAO indicated that poultry and meat products are unlikely to transmit COVID-19 (Doughman, 2020).

COVID-19, A Reverse Zoonosis: All cases of animals were proven to be acquired infection from human contacts. The summary of animal infection is depicted in table 1. The World Organization for Animal Health (OIE) has confirmed the diagnosis of COVID-19 in both dogs and cats due to human-to-animal transmission. Buddy (a German Shepherd) was the first dog died (euthanized) after testing positive for COVID in New York; the dog developed breathing problems and thick nasal mucus in April and was euthanized on July 11 after he started vomiting clotted blood. The dog was also suffering from lymphoma. The first case of

SARS-CoV-2 infection in a dog affected a 17-year-old Pomeranian in Hong Kong it had positive results with RT-PCR in oral and nasal samples with weak seroconversion after a mild infection. Another case of SARS-CoV-2 infection was in a German Shepherd dog in Hong Kong that too with mild symptoms only. However, there is no substantial evidence that dogs get SARS-CoV-2 infection from another dog, or can transmit this virus to human beings or other dogs (Almendros, 2020).

Two cats one from Belgium and another from Hong Kong, also tested positive for SARS-CoV-2 (AVMA 2020). Cats were shown to get infection with SARS-CoV-2 under experimental conditions and can transmit it to other susceptible cats that are housed together (Mallapaty 2020; Shi et al. 2020). None of the infected cats showed any signs of illness, indicating the low potential for transmitting the infection. A serological study on cats in Wuhan revealed development of SARS-CoV-2 neutralizing antibodies. The evidence prove that cats can get SARS-CoV-2 infection under natural conditions resulting in an antibody response (Zhang et al. 2020) and a higher neutralizing antibodies' titre was seen in the cats living in close contact with SARS-CoV-2 positive owners (Zhang et al. 2020).

A Malayan tiger in the Bronx Zoo of New York City showing signs of mild respiratory illness tested positive for SARS-CoV-2. The "Big cat" was suspected to be infected by asymptomatic zookeeper tested positive for SARS-CoV-2 (USDA, 2020). Later on a lion was also reported to suffer with mild symptoms of COVID-19 in USA.

Experimentally SARS-CoV-2 caused infection in monkeys (*Rhesus macaques*) with detection of high virus amount in naso-oral and rectal swabs. Affected monkeys had apparent lesions of disease in lung radiographs and clinical signs lasting for up to 16 days (Munster et al. 2020). Shi et al. (2020) demonstrated the susceptibility of ferrets, cats, dogs, and different domestic animal species to SARS-CoV-2 by experimental inoculation and reported that SARS-CoV-2 replicates poorly in dogs, pigs, chickens, and ducks, but efficiently in ferrets and cats. Cats can spread infection via droplets too.

Other Coronaviruses and their Zoonotic Potential: Coronaviruses, identified in the mid-1960s, infect humans and other animals, including birds and mammals. Their receptors are on epithelial cells in the respiratory and gastrointestinal tract thus the viral shedding occurs via respiratory and gastrointestinal tract effusions/ excretions and virus may spread through different routes including direct contact, contacts with fomites, airborne or fecal-oral. The common human Coronaviruses include *Betacoronavirus* HCoV-OC43 and HCoV-HKU1, as well as *Alphacoronavirus* HCoV-229E, causing common colds and severe lower respiratory tract infections in infants and elderly. Another *Alphacoronavirus* HCoV-NL63 causes pseudo croup and bronchiolitis in children. Other important Coronaviruses include:

1. **Infectious bronchitis virus (IBV):** A poultry pathogen causes infectious bronchitis. Identified in the 1930s is still going strong. Repeated waves of disease due to different strains are the main causes of huge economic losses in the poultry industry.
2. **Transmissible gastroenteritis (TGE) virus:** First reported in the United States in 1946 spread through air and contact, subsequently reached the status of pandemic in pigs in Europe, Africa, South America and China. As the virus multiplies in villi in gastrointestinal tract, piglets below one month of age die due to diarrhoea and vomiting.
3. **Porcine epidemic diarrhoea (PED) virus:** It emerged in 1971 as a pig pathogen leading to global pandemic, resulting into enormous economic losses, is still a major disease in piglets. Several strains have caused waves of disease in Asia, Europe and the Americas.
4. **SARS-CoV:** The cause of severe acute respiratory syndrome, originated in China in 2003 from bats and then spreading to civet cats and then to humans. It also affected people in more than two dozen countries in North America, South America, Europe and

Asia before it was contained. It caused >8,000 illnesses with 10% case fatality ratio (CFR).

5. **MERS-CoV:** Middle East respiratory syndrome (MERS) was first reported in Saudi Arabia in 2012 and had a higher mortality rate than SARS. It had a zoonotic cycle between camel and humans besides human to human cycle. It affected about 2,500 people with almost 33% CFR. Sporadic cases are often reported in dromedary camels till date.

Control of Zoonotic COVID: Many agencies have suggested that a ban on illegal as well as legal trade of wild/game animals, their meat and other products is necessary for prevention of emergence of new zoonotic viruses like SARS CoV-2. There is a strong reason to ban unregulated wild animal sales in Chinese wet markets, particularly exotic species, both from a public health perspective and for ecological reasons. The UN report (2020) listed 10 steps to be immediately implemented to lower the risk of emergence of new zoonoses.

1. Raising awareness: For better understanding of zoonotic and emerging disease risks and prevention.

2. Governance to increase investments in interdisciplinary approaches including the One Health perspective: For strengthening the integration of environmental considerations in the World Health Organization (WHO)/ Food and Agriculture Organization (FAO)/ World Organisation for Animal Health (OIE) Tripartite Collaboration.

3. Promoting scientific enquiry attitude: Expanding scientific enquiry into the complex social, economic and ecological dimensions of emerging diseases, including zoonoses, to assess risks and develop interventions at the interface of the environment, animal health and human health.

4. Financial strengthening: Improving cost-benefit analyses of emerging diseases prevention interventions to include full cost accounting of societal impacts of disease to optimize investments and reduce trade-offs. Ensuring the development of ongoing programs and developing mechanism for well resourced preparedness and response mechanisms.

5. Monitoring and regulation: Development of effective means of monitoring and regulating practices associated with zoonotic disease, including food systems from farm to fork and improving sanitary measures, taking into account the nutritional, cultural and socio-economic benefits of these food systems.

6. Incentives: Providing incentives for sustainable food systems, including wildlife source foods. Develop alternatives for food security and livelihoods that do not rely on the destruction and unsustainable exploitation of habitats and biodiversity.

7. Biosecurity and control: Identification of key drivers of emerging diseases in animal husbandry, both in intensive husbandry systems and smallholder production. It also emphasizes the leak of pathogens from laboratories.

8. Agriculture and wildlife habitats: Providing support to integrated management of landscapes and seascapes to enhance sustainable co-existence of agriculture and wildlife, through investment in agroecological methods of food production that mitigate waste and pollution while reducing risk of zoonotic disease transmission.

9. Capacity building: Strengthening the existing and building new capacities among health of stakeholders in all countries to improve outcomes and to help them understand the human, animal and environment health dimensions of zoonotic and other diseases.

10. Operationalizing the one health approach: One Health approach in land-use and sustainable development planning, implementation and monitoring, among other fields.

Conclusion: COVID-19 is certainly a newly emerged zoonosis, not yet understood properly thus cases need utmost care in their handling both in human and animals. More observations and studies can only elucidate the origin, intermediate host and definitive host (till date)

humans) and maintenance host. For control of emerging and re-emerging zoonoses potentiating one health environmental approach is essential for understanding their drivers and control elements and strategies.

Table 1. OIE updates on SARS CoV-2 events in animals

Type of animal	Date	Country	Epidemiological comments	Number of animals tested positive
Tiger	06.04.2020	USA	The zoo animals are suspected to have been infected by an asymptomatic zookeeper	1
Lion	17.04.2020	USA		1
Dog		USA		12
Cat		USA		10
Cat	28.07.2020	UK	Positive along with Feline Herpes Virus (FHV)	1
Mink	17.06.2020	Denmark		
Cat	26.05.2020	Russia		1
Cat	13.05.2020	Germany	Cat owner died due to SARS CoV-2. Only one cat tested positive in all 3 cats in that residence.	
Cat	11.05.2020	Spain		1
Cat	08.06.2020	Spain		1
Cat	02.05.2020	France		1
Cat	12.05.2020	France		1
Mink	26.04.2020	The Netherlands	Full-genome analyses show some mutations in the virus genes in mink, which can be found also in members of the farmer's family, in several persons related to the nursing home nearby, and in persons from the same area, but without contact to either the mink farm or the nursing home.	>87%
Cat	28.03.2020	Belgium		1
Dogs	09.03.2020	Hong Kong		2

Note:

- Mostly animals are either mildly symptomatic or asymptomatic.
- Most of the reports are from samples collected from animals tested positive were analysed during normal routine analysis of SARS CoV-2 in humans.
- Even though asymptomatic, feline species and mink should be considered a potential transmission route from animals to humans.
- Experimental SARS-CoV-2 infection could be established in monkeys, ferrets and cats. In addition infected cats efficiently transmitted the disease to naive cats.

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