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Investigation of Zoonotic Aspects of COVID-19

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ABSTRACT

Coronaviruses have four main types: alpha, beta, gamma, and delta. Beta and gamma types of coronaviruses are the leading causes of respiratory illnesses in humans and animals. These viruses have spread various diseases in the last 26 years. Recently, a new coronavirus disease has emerged in Wuhan, China and spread around the world. Three of these important viruses are SARS, MERS, and SARS-CoV-2. They have a natural and intermediate host in animals, especially bats. According to the gene sequence obtained from the virus, bats and pangolins are suspected to be the natural hosts of SARS-CoV-2. The virus is predicted to be transferred from bats to pangolins and then mutated and transferred to humans. Due to a large number of viruses in the corona virus family, which affects many animals, a new type of virus is likely to spread again. Based on the experiences of SARS and SARS-CoV-2, the role of veterinarians in the live animal and livestock products markets should be reconsidered.

Keywords: SARS-CoV-2, Corona virus family, SARS CoV, MERS CoV, Zoonosis, COVID-19

Introduction

Zoonotic diseases have changed human life, but unfortunately they have not been properly addressed. The transmission of pathogens from vertebrates to humans, also known as zoonotic diseases, is a deadly threat to global health. This article aimed to discuss about those coronaviruses that could infect the respiratory tract, gastrointestinal tract, liver, and central nervous system of humans, cattle, camels, birds, bats, rodents, and various types of animals.

These zoonotic viruses did not appear to be highly contagious pathogens until the outbreak of Acute Respiratory Syndrome Coronavirus (SARS-CoV) in Guangdong province, China. Before that time, coronaviruses were circulating in human communities and mostly caused mild infections in immunocompromised individuals. Ten years after the SARS-CoV outbreak, a highly pathogenic coronavirus called Middle East Respiratory Syndrome Coronavirus (MERS-CoV) emerged in Middle Eastern countries. In both cases, wild animals such as bats were the natural hosts of these viruses. In 2019, a new disease emerged in Wuhan province, China, caused by a virus called SARS-CoV-2 causing respiratory syndrome like the diseases mentioned above; according to the data obtained, the natural hosts of the virus are bats. Because SARS-CoV-2 is more transmitted from human-to-human rather than from animal-to-human, its origin and common nature have been forgotten. This article tried to address a small part of the zoonotic nature of the virus.

Coronaviridae

Coronaviruses are members of the subfamily *Coronavirinae*, the family *Coronaviridae*, and the order *Nidovirales*. Based on phylogenetic relationships and genomic structures, the subfamily *Coronavirinae* is divided into four genera, including alpha-coronaviruses, beta-coronaviruses, gamma-coronaviruses, and delta-coronaviruses. Alpha-coronaviruses and beta-coronaviruses infect only mammals (Carlo Contini et al., 2). Gamma-coronaviruses and delta-coronaviruses infect birds and some mammals such as bats. Gamma coronaviruses and beta-coronaviruses are the leading causes of respiratory diseases in humans (Carlo Contini.et al., 2). Coronaviruses are RNA based viruses. Thus, viral genes are constantly altering and producing new strains that could infect new cell types and various animal species (Chen Y et al., 9). The virus contains nucleocapsid, coat, and membrane proteins. The surface proteins form a crown on the virus. These proteins bind to cell receptors and infect them. Coronavirus is usually transmitted through airborne respiratory droplets to the nasal mucosa in closed environments as well as through close contact with people's contaminated hands (Chen Y et al., 9).

The virus multiplies locally in ciliated epithelial cells, causing cell damage and inflammation. Outbreaks appear to be exacerbated during the winter, and endemics last for weeks or months. Coronaviruses generally cause acute and chronic diseases of the respiratory, intestinal, and nervous systems in many species of animals, including humans. There is also speculation about the association of human coronaviruses with more serious human diseases such as multiple sclerosis, hepatitis, and intestinal diseases. However, none of which has been proven so far (Chan JF et al., 8).

Animal origin of HCoVs (Human coronaviruses)

All four community-acquired HCoVs (…) that cause mild symptoms are well-adapted to humans. On the other hand, it may be true that humans are also well adapted to these four HCoVs. In other words, they could be survivors of ancient HCoV epidemics. HCoVs causing severe diseases in humans as well as people with severe HCoV diseases have been eliminated. HCoVs must be sufficiently replicated in humans to be able to counteract with inhibitory factors in the host body via the accumulation of compatible mutations. The longer the SARS-CoV-2 outbreak persists, and the more people become infected, the better the virus will be able to adapt to humans. Preventing the virus transmission to humans

through quarantine or other protocols could be difficult (Zi-Wei Ye et al., 6).

For many years, the four CoVs have been circulating in human communities, causing the common cold in immunocompromised individuals. These viruses do not require animal origins. In contrast, highly pathogenic SARS-CoV and MERS-CoV are not well adapted to humans, and their transmission among humans could not be sustained. They must be preserved and dispersed among their animal reservoirs and look for an opportunity to move towards sensitive human targets. SARS-CoV-2 has characteristics similar to SARS-CoV, MERS-CoV, and the four community-acquired HCoVs (Read JM et al., 28).

Community-acquired HCoVs are highly transmissible. However, the diseases caused by HCoVs are less common in the community with less pathogenicity compared to those of SARS-CoV and MERS-CoV. For these two diseases, the question remains whether they could be fully adapted to humans and circulate among humans without a reservoir or intermediate animal host. Before discussing about the animal origin of HCoVs, it is helpful to discuss about the definitions and characteristics of their evolutionary, natural, reservoir, and intermediate hosts and enhancers. An animal acts as an evolutionary host of HCoV if it carries a close ancestor sharing a high identity at the nucleotide sequence level (Zivi et al., 6). The ancestral viruses are usually well adapted and non-pathogenic for their host. In contrast, if a virus enters a new host or human and could not be well adapt to its new host, it becomes pathogenic. In addition, if it could not maintain its transmission among the intermediate hosts, HCoV could have a dead end. In contrast, HCoVs could be well adapted to their intermediate host and even establish a long-term endemicity. In this case, the intermediate host becomes the reservoir host (de Wit E et al., 10; Chan JF et al., 8).

Coronavirus zoonotic diseases

Coronaviruses have spread several times over the past 26 years in the form of various diseases and have killed many people. These viruses infect a wide range of organisms from ruminants (cattle) to rodents, poultry, and wild animals. In humans, they usually appear as mild infections and are not taken very seriously, but they have become dangerously prevalent in humans over the last thirty years (Table1) (Lin-Fa Wang et al., 4).

Considering the genome sequence of these viruses, most EZVs (emerging zoonotic viruses) have been transmitted from their natural host (bats) to several intermediate hosts and then modified to infect humans (Lin-Fa Wang et al., 4).

Table 1: Information on zoonotic coronaviruses that have spread over the last 26 years (Cristiano Salata et al., 3)

SARS: severe acute respiratory syndrome, MERS: Middle East respiratory syndrome, nCoV: 2019 novel coronavirus

Virus Name	Year of First Major Outbreak	Bat Origin Status	Main Intermediate Animal Host Responsible for Human Infection
Hendra	1994	Confirmed	Horses
Nipah	1998-99	Confirmed	Pigs
SARS	2002-03	Confirmed	Camels
Ebola	2014	Confirmed	-
2019-nCoV	2019-20	Suspected	Presently unknown

SARS CoV

SARS was the first HCoV pandemic in human history and the third HCoV to be discovered, its etiological agent is SARS-CoV. The first case of SARS could be traced back to late 2002 in Guangdong province, China. At that time, 8096 infected cases with 774 deaths were reported in many countries. The latency period of the virus is 7 to 4 days, and the peak viral load appears 10 days after the onset of the disease (Zi-Wei Ye et al., 6).

Retrospective epidemiological data indicate that SARS has a connection with animals. Subsequent

prevalence studies have shown that animal traders have higher SARS-CoV IgG than the general population (Read JM et al., 28).

Paguma larvata and raccoons, which were on the live animal market, were identified as carriers of a SARS-like virus, which was very similar to SARS. This theory was indirectly confirmed by the fact that no one in the market got sick after killing all the civets. Further studies in wildlife showed that the coronavirus of Chinese horseshoe bats was similar to SARS-CoV. These bats are positive for anti-SARS-CoV antibodies and the SARSr-Rh-BatCoV HKU3 genome sequence. These and other bat CoVs share nucleotide sequence identity with SARS-CoV. These studies provide the basis for a new idea that bats host emerging human pathogens with similar nucleotide sequence identities (Kuiken T et al., 19).

MERS CoV

MERS-CoV was first isolated in 2012 from the lungs of a 60-year-old patient with acute pneumonia and renal failure in Saudi Arabia. Most of the laboratory-confirmed cases were in the Middle East; afterwards some cases were also reported in various European countries and Tunisia (Mu¨ ller MA et al., 24).

Another secondary MERS outbreak occurred in 2015 in South Korea with 186 confirmed cases. The clinical manifestations of MERS are similar to those of SARS, characterized by progressive acute pneumonia. Unlike SARS, many patients with MERS also show acute renal failure, making MERS unique among HCoV-induced diseases. More than 30% of patients have gastrointestinal symptoms such as diarrhea and vomiting. As of 14 February, 2012, more than 2500 laboratory-confirmed MERS-CoV cases have been reported. MERS-CoV is one of the deadliest human viruses with a mortality rate of 34.4% (Zi-Wei Ye et al., 6).

MERS-CoV pathogenesis analysis is similar to CoV-HKU4 and CoV-HKU5 in bats. CoV-HKU4 and MERS-CoV have the same cellular receptor, DPP4, for cell entry. On the other hand, studies in the Middle East have shown that livestock camels, especially those of Middle Eastern origin in various African countries, are positive for specific MERS-CoV neutralizing antibodies (…). Live MERS-CoV, similar to the human virus, has been isolated from the nasal protrusions of camels (…), further demonstrating that camels are a reasonable intermediate host of MERS-CoV. It is noteworthy that generally mild but widespread symptoms are observed in camels infected with MERS-CoV. It is also noteworthy that infected camels spread viruses not only through the respiratory tract but also through feces and mouth, which are also the main transmission routes of the bat-origin virus (Paraskevis D et al., 26).

However, questions remain because many MERS-confirmed cases did not have a history of contact with camels before the onset of symptoms. They are likely involved through human-to-human transmission route or unknown transmission routes involving unknown infected animal species.

NCoV-2019

The new species of coronavirus, designated as nCoV-2019, appeared in Wuhan, China and spread around the world in late 2019. Pneumonia symptoms of unknown causes were reported in several patients. The infection is epidemiologically linked to the Huanan seafood market in Wuhan (Wan Y et al., 20).

An important factor for an emerging virus is its ability to become epidemic. Efficient transmission to humans is a requirement for the spread of new viruses on a large scale. The proportion of patients with mild symptoms is another important factor that determines our ability to identify infected people and prevent the spread of the virus. Identifying transmission chains and tracking contacts become more complicated when several infected individuals remain asymptomatic or have mild symptoms. An important factor for efficient human-to-human transmission is the ability of the virus to attach to human cells. Coronaviruses use surface-shaped lanceolate proteins to bind to host cells.

Apparently, nCoV-2019 uses the same human angiotensin-2 converting enzyme as SARS-CoV, while MERS-CoV uses dipeptidyl peptidase 4 (also known as CD26) (Kupferschmidt K et al., 20).

Efficient human-to-human transmission involves several transmission pathways, including respiratory droplets transport, direct contact, and indirect contact. Limited human-to-human transmission may be a prerequisite for high doses of infection in people and subsequently their close contact with others. All three outbreaks of zoonotic coronaviruses in recent decades have been associated with pneumonia in patients with severe symptoms (Nishiura H et al., 25).

Although SARS-CoV and SARS-CoV-2 are very similar due to nucleotide sequence homology above 82%, they are grouped into different branches of the phylogenetic tree. SARS-CoV-2 is apparently less pathogenic but more transmissible than SARS-CoV and MERS-CoV. It has been reported that some people infected with SARS-CoV-2 may be asymptomatic and may play a role in its rapid spread worldwide (Ping-Ing Lee et al., 5).

A comparison between SARS-CoV-2 and the other six HCoVs reveals many interesting similarities and differences. First, the incubation period and duration of HCoVs diseases are very similar. In this regard, SARS-CoV-2 follows the general trend of the other six HCoVs. Second, the severity of COVID-19 symptoms lies between SARS-CoV and four community-acquired HCoVs (Rothe C et al., 22).

On the one hand, SARS-CoV-2 infection has features in common with community-acquired HCoVs infections, including nonspecific, mild, or even asymptomatic symptoms. On the other hand, a small subset of severe COVID-19 symptoms may also be observed in SARS-CoV infection, but to a lesser extent. Examination of SARS-CoV-2 transmission pathways also shows interesting patterns in common with community-acquired HCoVs and SARS-CoV. On the one hand, the transmissibility of SARS-CoV-2 is at least as high as that of community-acquired HCoVs (Li Q et al., 22).

Although a preliminary report identified codons in snakes as a possible source of the new coronavirus (…), the current consensus supports the hypothesis of mammalian or bird involvement. Phylogenetic analysis of the 2019-nCoV genome showed that the virus is similar to SARS-CoV and MERS-CoV, and bats have been identified as a possible primary reservoir of 2019-nCoV based on its similarity to bat CoVs. SARS-CoV-2 has 96.2% nucleotide similarity to CoV RaTG13 isolated from Rhinolophus affinis bats. The animal host of SARSCoV-2 is likely to be among the wildlife species sold and killed in the Huanan Seafood Wholesale Market, many of which were initially associated with COVID-19, indicating the possibility of animal-to-human transmission route (Zi-Wei Ye et al., 6).

Several recent studies based on metagenomic sequencing have shown that a group of small endangered mammals known as pangolins (Manis javanica) could also harbor SARS-CoV-2 ancestral beta CoVs. This pangolin CoV genome shares 85 to 92% nucleotide sequence homology with SARS-CoV-2, and is equally related to RaTG13 with about 90% similarity at the nucleotide sequence level. A previous study on sick pangolins also reported viral foci in lung samples, which appear to be similarly related to SARS-CoV-2. The possibility that pangolins are an intermediate host of SARS-CoV-2 could not be ruled out. However, there is currently no evidence to support the direct origin of SARS-CoV-2 from pangolins due to sequence divergence between SARS-CoV-2 and pangolin beta-CoVs. In addition, the distance between SARS-CoV-2 and RaTG13 is even shorter than that between SARS-CoV-2 and pangolin beta-CoVs associated with SARS-CoV-2 (Zi-Wei Ye et al., 6).

The evolutionary pathway of SARS-CoV-2 in bats, pangolins, and other mammals has not yet been determined. While the highest sequence homology was found in RBD between SARS-CoV-2 and pangolin beta-CoVs, the beta CoVs associated with SARS-CoV-2, SARS-CoV-2, and RaTG13 have the highest genomic sequence homogeneity. It is highly probable that the similarity between beta-CoVs RBDs is driven by SARS-CoV-2, pangolin SARS-CoV-2, and SARS-CoV-2 with selective convergence

evolution. One suggestion for recombination of beta-CoVs is related to pangolins CoV, human SARS-CoV-2, and bat CoV RaTG13 in the third species of wild animals. As a driving force of evolution, recombination is widespread among beta CoVs (Li Q et al., 22),

Conclusion

Because coronaviruses are RNA-based viruses, they are constantly mutating, and because they have different types, they could greatly infect different organisms. Therefore, a new type of virus belonging to this family of viruses is likely to spread again in the future. The experiences of SARS and SARS-CoV-2 show that the role of veterinarians in the live animal and livestock products markets should be reconsidered.

Resources

1. Alfonso J. Rodriguez-Morales D. Katterine Bonilla-Aldana,Graciela Josefina Balbin Ramon, Ali A. Rabaan, Ranjit Sah, Alberto Paniz-Mondolfi et al.2020 , History is repeating itself:Probable zoonotic spillover as the cause of the 2019 novel Coronavirus Epidemic , LIiM, Le Infezioni in Medicina. , p1-5
2. Carlo Contini, Mariachiara Di Nuzzo, Nicole Barp, Aurora Bonazza, Roberto De Giorgio, Mauro Tognon et. Al ,2020. The novel zoonotic COVID-19 pandemic: An expected global health concern ,journal of infection in developing countries,p1-3
3. Cristiano Salata, Arianna Calistri, Cristina Parolin and Giorgio Palu`. 2020 Coronaviruses: a paradigm of new emerging zoonotic diseases , femspd oxford, p3
4. Lin-Fa Wang, Danielle E Anderson, John S Mackenzie,Michael H Merson 2020, From Hendra Wuhan: what has been learned in responding to emerging zoonotic, .thelancet, p1
5. Ping-Ing Lee , Po-Ren Hsueh , Emerging threats from zoonotic coronaviruses-from SARS and MERS to 2019-nCoV ,2020 Journal of Microbiology, Immunology and Infection..p1-2
6. Zi-Wei Ye, Shuofeng Yuan, Kit-San Yuen, Sin-Yee Fung, Chi-Ping Chan, and Dong-Yan Jin. 2020 Zoonotic origins of human coronaviruses International Journal of Biological Sciences, p3-6
7. Chan JF, Lau SKP, To KKW *et al.* Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causingSARS-like disease. *Clin Microbiol Rev* 2015;**28**:465–522.
8. Chan JF, Yuan S, Kok KH *et al.* A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020; pii: S0140-6736(20)30154-9. doi: 10.1016/S0140- 6736(20)30154-9.
9. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. *J Med Virol* 2020; doi: 10.1002/jmv.25681. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol* 2019;**17**:181–92.
10. de Wit E, van Doremalen N, Falzarano D *et al.* SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol* 2016;**14**:523–34. ECDC 2020a. Novel coronavirus. Situation update 7 February 2020, 8:00 CET. https://www.ecdc.europa.eu/en/novel-coro navirus-china. Accessed 7 February 2020.
11. ECDC 2020b. Geographical distribution of 2019-nCov cases globally. Situation update 7 February 2020, 8:00 CET. https://www.ecdc.europa.eu/en/geographical-distributio n-2019-ncov-cases. Accessed 7 February 2020.
12. ECDC 2020c. Cases of 2019-nCoV in the EU/EEA and the UK. Situation update 7 February 8:00. https://www.ecdc.europa.eu/e n/cases-2019-ncov-eueea. Accessed 7 February 2020.
13. Goo J, Jeong Y, Park YS *et al.* Characterization of novel monoclonal antibodies against MERS-coronavirus spike protein. *Virus Res* 2020;**278**:197863.
14. Holmes EC, Rambaut A, Andersen KG. Pandemics: spend on surveillance, not prediction. *Nature* 2018;**558**:180–2.
15. Huang C, Wang Y, Li X *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; pii: S0140-6736(20)30183-5. doi: 10.1016/S0140-6736(20)30183-5.

16. Ji W, Wang W, Zhao X *et al.* Homologous recombination within the spike glycoprotein of the newly identified coronavirus may boost cross-species transmission fromsnake to human. *J Med Virol* 2020; doi: 10.1002/jmv.25682.
17. Jin Y, Lei C, Hu D *et al.* Human monoclonal antibodies as candidate therapeutics against emerging viruses. *Front Med* 2017;**11**:462–70.
18. Kim Y, Lee H, Park K *et al.* Selection and characterization of monoclonal antibodies targeting middle east respiratory syndrome coronavirus through a human synthetic fab phage display library panning. *Antibodies (Basel)* 2019;**8**: pii: E42.
19. Kuiken T, Fouchier RA, Schutten M *et al.* Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. *Lancet* 2003;**362**:263–70.
20. Kupferschmidt K. Study claiming new coronavirus can be transmitted by people without symptoms was flawed. *Science* 2020; doi: 10.1126/science.abb1524.
21. Letko M, Munster V. Functional assessment of cell entry and receptor usage for lineage B *β*-coronaviruses, including 2019- nCoV, 2020. https://www.biorxiv.org/content/10.1101/2020.0 1.22.915660v1. Accessed 3 February 2020.
22. Li Q, Guan X,Wu P *et al.* Early transmission dynamics inWuhan, China, of novel Coronavirus-infected pneumonia. *N Engl J Med* 2020; doi: 10.1056/NEJMoa2001316.
23. Lu R, Zhao X, Li J *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020; pii: S0140-6736(20)30251-8. doi: 10.1016/S0140-6736(20)30251-8.
24. Mu¨ ller MA, Corman VM, Jores J *et al.* MERS coronavirus neutralizing antibodies in camels, Eastern Africa, 1983–1997. *Emerg Infect Dis* 2014;**20**:2093–5.
25. Nishiura H, Jung SM, Linton NM *et al.* The extent of transmission of novel coronavirus in Wuhan, China, 2020. *J Clin Med* 2020;**9**:pii: E330.
26. Paraskevis D, Kostaki EG, Magiorkinis G *et al.* Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event. *Infect Genet Evol* 2020;**79**:104212.
27. Raj VS, Mou H, Smits SL *et al.* Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature* 2013;**495**:251–4.
28. Read JM, Bridgen JRE, Cummings DAT *et al.* Novel coronavirus 2019-nCoV: early estimation of epidemiological parameters and epidemic predictions, 2020. https://www.medrxiv.org/ content/10.1101/2020.01.23.20018549v2. Accessed 3 February 2020.
29. Rothe C, Schunk M, Sothmann P *et al.* Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *N Eng J Med* 2020; doi: 10.1056/NEJMc2001468.
30. Wan Y, Shang J, Graham R *et al.* Receptor recognition by novel coronavirus fromWuhan: An analysis based on decade-long structural studies of SARS. *J Virol* 2020; pii: JVI.00127-20. doi: 10.1128/JVI.00127-20