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Insight into SARS-CoV-2: Epidemiology, Hosts and One Health

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Abstract

The outbreak of the new coronavirus SARS-CoV-2 is a serious threat to human health and has caused a huge economic loss. The intermediate animal host for the transmission of SARS-CoV-2 to humans in yet to be known. It is of immense importance to identify the intermediate hosts of SARS-CoV-2 to counter its transmission for both preventing the re-emergence and control of the epidemic to ensure public health safety. This study summarizes the latest research on hosts involved in SARS-CoV-2 transmission. Based on the epidemic facts, we hypothesized that there are several intermediate hosts of SARS-CoV-2 ranging from bats to humans. Therefore, it is essential to apply an integrated human–veterinary medicine based approach along with the novel concepts of "One Health" for the prevention and control in the late stage of the SARS-CoV-2 epidemic and in any future re-emergences.

In December 2019, an increasing number of new cases of the new coronavirus (CoV) SARS-CoV-2 associated with pneumonia (COVID-19) have been reported in Wuhan, Hubei Province, China [1-5]. The epidemic did not limit itself only to China, but now it acquired the state of a massive pandemic by hitting more than 200 countries around the globe. In an early study by Chinese Center for Disease Control and Prevention, a total of 5.6% environmental samples from Wuhan South China Seafood Market were found SARS-CoV-2 positive, while some studies also proposed other sources causing infections because some infected individuals had not been exposed to seafood markets [4,6,7,]. Li et al. estimated that SARS-CoV-2 outbreak in Wuhan had probably begun in November 2019 (95% CI, 2019.9.25–2019.12.19) based on analysis of genetic diversity, temporal origin, and evolutionary history [8]. In this tug of war situation to control and prevent SARS-CoV-2, scientists, researcher community and, pharmaceutic industry are putting all their energies and resources to overcome this pandemic.

Based on research and data available, we hypothesize that the source of SARS-CoV-2 transmission is semi-wild animals (bamboo rats, mink, pangolins and crickets) reared in farms for human consumption, where they might have infected by the natural virus host (bats). Poor sanitary conditions, carcasses and blood after slaughtering attract rats, stray dogs, and cats, may also promote the spread, recombination and mutation of the virus across different species including humans. This leads us to two questions which may be of great significance to prevent further epidemics and re-emergence of SARS-CoV-2 like pandemics to ensure public health safety

Firstly, which animals may serve as intermediate hosts and contribute transmission between the original host and humans? Cell experiments confirmed that SARS-CoV-2 gains intracellular access via angiotensin-converting enzyme 2 (ACE2), which is also used by SARS-CoV [7,9,10]. In fact, the ACE2 protein is distributed widely across human organs including lung and small intestinal epithelial cells, which provides a possible route of entry for SARS-CoV into cells [11]. Given the wide host range and genome structure of CoV, genetic recombination and mutation events are likely to occur during the evolution of the virus. Malayan Pangolins (*Manis javanica*) that were illegally smuggled to Guangxi China for both food source and utilizing their scales in traditional Chinese medicine, six of 43 samples showed 99.83-99.92% similar genomic organizations to SARS-CoV-2 (August 2017-January 2018) while among the archived

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samples (May-July 2018) 12 among the 19 samples were coronavirus positive. Archived pangolin samples obtained in anti-smuggling operations (Guangzhou) performed in March 2019 were re-examined after the start of the SARS-CoV-2 outbreak. High-throughput sequencing revealed 72% of the SARS-CoV-2 genome sequence similarity. In an another study in Guangdong, 85.5% to 92.4% sequence similarity to SARS-CoV-2 was observed in novel pangolin coronavirus genomes with 97.4% amino acid similarity in the receptor-binding domain [12]. The wide spread of CoV in rodents indicates that mice could act as reservoir hosts of human CoV infection [13]. Susceptibility of SARS-coronavirus-2 was tested through intra-nasally inoculating pfu of CTan-H in ferrets, cats and dogs. Ferrets are mostly used as an animal model in human respiratory viruses while cats and dogs are the closest in contact animals to humans. Replication of SARS-coronavirus-2 was observed among all tested ferrets and adult cats while young cats showed more server clinical signs with efficient transmission via respiratory droplets among cats. A total of two among five dogs were also tested seropositive for SARS-coronavirus-2 after intra-nasally inoculating pfu of CTan-H, showing low susceptibility to SARS- CoV-2 in comparison to cats. Same investigations were also conducted on pigs, chickens and duck but the results were all seronegative for SARS-CoV-2, showing their non-susceptibility to SARS-CoV-2 [14]. Serological prevalence investigation of SARS-CoV-2 by enzyme linked immunosorbent assay (ELISA), virus neutralization test (VNT) and western blot test in cats were made. The presence of SARS-CoV-2 antibodies in 15 (14.7%) cats was observed by ELIZA while 11 (10.8%) were further positive with VNT among the total 102 cats in Wuhan during COVID-19 outbreak. It is of importance to mention here that the cats owned by COVID-19 patients showed the highest neutralization titer [15]. According to National Veterinary Services Laboratory in Iowa, a female Malayan tiger at the Bronx Zoo in New York City has tested positive for the coronavirus. This is the very first animal infected case with Covid-19 in the US [16].

CoVs were first discovered in humans, the non-human hosts origin of these viruses has been confirmed; particularly bats, which despite species barrier, resulting in SARS-CoV and MERS-CoV infections in humans [17].

Bats have been identified as natural hosts of multiple viruses including hepatitis viruses (Nipah virus and Hendra virus), CoVs (SARS-CoV, MERS-CoV, and SADS-CoV), and linear viruses (Marburg virus, Ebola virus, and Mengla virus) [18-21]. The high temperature increasing innate and adaptive immune systems during flight is one possible mechanism for bats to reduce the impact of virus attacks in comparison to terrestrial mammals during movement [22-24]. Genome sequencing indicates that the genomes of bat-originating SARS-like CoVs shares a high similarity (88%-92%) with SARS-CoV isolated from humans and the masked palm civet [25,26]. Hao et al., observed same structure with no difference in the 3D structure of the receptor-binding domain (RBD) while comparing S protein of SARS with SARS-CoV-2 [27]. In a study by Shi et al., similar whole genome sequence we observed at 79.5% between genome sequences of SARS-CoV-2 and SARS-CoV, while SARS-CoV-2 was 96% identical to Bat CoV RaTG13 from *Rhinolophus yunnanensis* [28]. They also found that SARS-CoV-2 uses the same cell entry receptor, i.e., ACE2, as SARS-CoV, suggesting that the natural host of SARS-CoV-2 is bats [28]. Zhu et al., predicted that bats and mink are two potential hosts of the new CoV, with mink being the reservoir host [29]. They found that the infection pattern of SARS-CoV-2 is more similar to that of SARS-like CoVin bats than in others. More recent studies have also indicated that SARS-CoV-2 originates from bats [9,30-32]. We propose further researches to answer some critical scientific questions pertaining to the identification of intermediate hosts and overall transmission pattern of SARS-CoV-2 between humans and animals, along with the mutation events involved in the evolution of the virus.

In summary, there are many potential intermediate hosts of SARS-CoV-2 such as semi-wild animals that are in frequent contact with humans including stray dogs, cats, and domestic mice.

One Health Approach in China

No one knows, when exactly will the coronavirus outbreak end and how many lives will it takes. Here it is important to mention that World Health Organization (WHO) also delayed in declaring the emergency situation of the pandemic, the consequences of which can be seen in developing or third world countries. It is of immense importance to know, how many infectious diseases are inter-transmittable among human, animals and, their environment and how closely connected and prone we are to these infections. These infections do not discriminate in cultures, societies and communities and seek no distances, barriers, borders or any other means of separations. We need to understand the fact to suffer now or bear such infections with more severity in future [33].

Deforestation, agricultural encroachment, road construction, faulty irrigation, dam building, mining, hunting, ecological tourism, climatic changes, pollution, and intensive urbanization had disturbed the habitat, behavior, spacial distribution, biodiversity, population of animals and bring humans close to wildlife and other domestic animals. This enabled wildlife or other domestic animals to migrate, increasing exposure of humans to new pathogens. Private possession, illegal trading and the use of wildlife for human consumption has increased the demand of wildlife business in China [34].

Livestock production have become the second largest sources of pollution after industrial pollution in China. The byproducts of livestock and poultry industry highly contribute in polluting and contaminating the environment with substantial number of pathogenic microorganisms, leading to the spread of zoonotic diseases [35]. Farmers use many antibiotics to prevent disease, promote growth or as prophylactic drugs, which has increased the antibiotic resistance. The abusive use of food additives in food processing industries also very common, posing serious threats to human health.

In addition to the most popular pets, such as dogs and cats, other rare species including, guinea pigs, lizards, and other wildlife have become members of the family. These pets may carry a number of zoonotic infectious diseases, such as rabies, salmonella, tuberculosis, leptospirosis, or toxoplasmosis via direct or indirect contact and by being bitten.

According to WHO, 75% of recently emerging infectious diseases are zoonotic. Due to the increased regional and global human interactions, the transmission of emerging and re-emerging zoonotic diseases is a serious threat to human health [36]. Unlike Western countries, developing countries and in specific rural areas are found to be in close contact with wildlife. Bio-safety measures are mostly compromised in such areas by consumption of these wild animals directly or indirectly via contact between wildlife and domestic animals [37,38]. Human health is closely related to animal and environment which drives the attention towards the importance of "One Health" approach [39]. The Global Environmental Institute Beijing (TGEIB) have somewhat adopted One Health concept in broader term by limiting its scope to private enterprise and not giving key interest in tracing infectious diseases. TGEIB hunts for resolving domestic environmental issues by engaging local communities, research groups, civil societies, government agencies and private sector. Kunming Medical University in collaboration with the World Agro forestry Centre has been addressing national Eco Health issues by developing projects and programs in the scope of One Health [40]. In 2014, Sun Yat-sen University, the Academy of Military Medical Sciences, South China Agricultural University, and Duke University jointly hosted a One Health symposium on "zoonosis, food safety and security, environment science, wildlife ecology, and antibiotics resistance" in Guangzhou city [41]. Experts from more than seven countries having expertise in public health, clinical medicine, veterinary medicine, environmental and agricultural science attended the conference. The initial success of One Health in China can be observed by the joint researches conducted on H3N2 [42], rabies and dengue fever outbreak [35].

China's economy was hit by the outbreak of SARS in 2003 with a total loss of $25.3 billion [43]. After the end of the SARS outbreak, the investigation team of WHO includes seven veterinarians or experts in animal health among the total eight experts, but the Chinese team of six members had only one veterinarian. The failure to predict or monitor the spread of disease in animals and subsequently to humans gives a wake-up call to the regulatory authorities for the need of incorporated cross-sectoral collaboration between human and animal health sectors. Farm-to-fork issues in food production chain can occur as a result of compromise in biosecurity and food safety measures, which may lead to a number of infectious diseases. It is important to have common understanding to work together. Food safety and security justifies the need of understanding the link between humans, animals and environment. It is of utmost importance to collaborate and share information regarding emerging and reemerging zoonotic pathogens. An in-depth collaborative research need to be conducted on the prevalence, incidence, variation, genomic data, life cycle of the natural reservoir,

intermediate hosts, antibiotic resistance patterns and spacial distribution of the pathogens. A multi-sector scientific and, early warning database should be available nationally and globally as well. As an example, to control microbial resistance, we can learn it from the automated program in Denmark named Vetstat, which collect quantitative data from all prescribed animal medicine sources, including veterinarians, pharmacies, and feed mills [44]. We recommend that a professional and comprehensive "One Health" team should participate in the investigation of emerging zoonosis in the future to strengthen the prevention and control of integrated human-veterinary medicine, which will heavily influence the control of emerging zoonotic diseases, harmony, and health among humans, animals, and environment.

Funding Information

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