



COMMENTARY

High-Priority Pathogens with Potential to Cause “Disease X” Pandemics

Qi Shi^{1,*} and Xiaoping Dong^{1,2,*}

Abstract

In past decades, numerous emerging infectious diseases have markedly affected global health and social-economic development. Consequently, the concept of “disease X” has been developed, and lists of the pathogens with potential to cause future pandemics have been proposed and updated several times by the World Health Organization. Herein, we analyzed the major features of pathogens with high probability to cause future COVID-19-like pandemics, on the basis of their transmission routes, animal-human interfaces, herd immunity barriers, and evolutionary and mutational characteristics. We also evaluated high-priority viral infectious diseases with potential to become disease X in the future, on the basis of their transmission pathways, including airborne/respiratory, vector-borne, and direct contact. Overall, viruses had much greater likelihood of becoming “pathogen X” than either bacteria or other microorganisms. Respiratory viruses, particularly RNA viruses, have notably high potential to become pathogen X. Vector-borne viruses might also become pathogen X, and mosquito-borne viruses would be more likely than tick-borne viruses to do so. Many contagious viral infectious diseases lead to severe clinical outcomes but have relatively low likelihood of causing global pandemics. Coronaviruses in the *Coronaviridae* and influenza viruses in the *Orthomyxoviridae* were identified as top-priority pathogens X with potential to cause the next COVID pandemic.

Key words: disease X, pathogen X, pandemics, priority

*Corresponding authors:

E-mail: shiqi@ivdc.chinacdc.cn (QS);
dongxp238@sina.com, dongxp@chinacdc.cn, Fax: +86-10-58900815 (XPD)

¹National Key-Laboratory of Intelligent Tracking and Forecasting for Infectious Disease, National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Chang-Bai Rd 155, Beijing 102206, China

²Shanghai Institute of Infectious Disease and Biosafety, Shanghai, China

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Infectious diseases not only threaten human life and survival, but also drive social change. They have repeatedly reshaped population structures and altered civilization by profoundly affecting scientific, cultural, religious, and geopolitical landscapes. Before the 20th century, bacterial infectious diseases were the most important threat to humans. Bacterial infectious diseases have markedly decreased with the invention of antibiotics, antitoxins (antisera), toxoids, and vaccines, as well as the implementation of modern public health and improved human living conditions. However, the

threat of viral infectious diseases has become increasingly apparent. Since the 1970s, pathogens have increasingly been discovered to cause emerging infectious diseases (EIDs), such as AIDS in the 1980s [1]; bovine spongiform encephalopathy in cattle and the variant Creutzfeldt Jakob disease in humans in the 1990s [2], SARS in the 2000s [3]; new influenza (new A/H7N9), MERS, and Zika virus disease in the 2010s [4–6]; and COVID-19 and monkeypox in the 2020s [7,8].

In 2017, 2018, and 2022, the World Health Organization (WHO) proposed lists of infectious diseases with pandemic

characteristics, on the basis of the evaluation and assessment of more than 30 families of viruses, and one major group of bacteria and other microorganisms (Table 1). All infectious diseases on the lists are caused by viruses. The term “disease X” was first included in the list for 2018, and COVID-19 was the first known disease X in the list for 2022. The listed viruses are *Coronaviridae* (causing SARS, MERS, and COVID-19), *Filoviridae* (causing Ebola disease and Marburg disease), *Arenaviridae* (causing Lassa fever), *Bunyaviridae* (causing Crimean-Congo hemorrhagic fever and Rift Valley fever), *Paramyxoviridae* (causing Nipah and henipavirus disease), and *Flaviviridae* (causing Zika virus disease). In 2024, experts organized by the WHO systematically assessed 1625 pathogens from 28 families of viruses and one major group of bacteria, and proposed priority pathogen families, priority pathogens, priority prototype pathogens, and pathogens X. Among them, 34 pathogens from 18 families were listed as pathogens X.

MAJOR FACTORS ASSOCIATED WITH PATHOGENS X

Evaluating the potential threat of the new microorganisms to humans and the epidemic potential requires careful consideration of multiple factors, including the transmissibility among humans, disease severity, extent of pathogen distribution, speed of pathogen evolution and mutation, human-animal interfaces, herd immunity barriers, occupational exposure risks, public health capacity, and response capabilities of government and society (Fig 1).

Transmission routes

Pathogens with airborne or respiratory transmission routes frequently have high transmissibility (Fig 1). Historically, smallpox, measles, influenza, and Pneumonic plague have

caused severe pandemics lasting for years or even decades. Three new coronaviruses in the 21st century have also caused pandemics [9]. Insect-borne transmission also plays important roles in pandemics; examples include the yellow fever and Japanese encephalitis pandemics. Zika virus disease spread to South America and Southeast Asia between 2015 and 2016. Moreover, malaria, dengue fever, chikungunya fever, and other diseases transmitted through mosquito species have been prevalent in tropical regions [10]. Another transmission route is through contact. In addition to hepatitis B, AIDS, and various sexually transmitted diseases, many severe hemorrhagic diseases, such as Ebola disease, Marburg disease, Nipah virus diseases, and Rift Valley fever, can spread and cause cross-border outbreaks. Recently, monkeypox has also rapidly spread among populations through sexual or close contact, particularly among gay men.

Human-animal species barriers

Many EID pathogens come from wild or domesticated animals and directly infect humans. Examples include avian influenza viruses, Ebola viruses, and Lassa fever viruses. These diseases are known as zoonoses [11]. Some pathogens may originate from animals but undergo adaptive mutation evolution in one or more intermediate host animals before fully adapting to humans [12]. Examples include HIV, coronaviruses, and some types of avian influenza viruses. Clear barriers exist in the transmission of microorganisms between host species (Fig 1). For example, the biological species barrier refers to the natural or evolutionary limitations between species that hinder cross-species transmission of microorganisms. The species barrier is based on natural physiological structural differences, such as cell receptors, tissue and organ structures, the immune system, and the intracellular environment. However, microorganisms’ genetic and protein

TABLE 1 | Disease X lists issued by the WHO.

2017	2018	2022
Arenaviral hemorrhagic fevers (including Lassa fever)	Crimean-Congo hemorrhagic fever	COVID-19
Crimean-Congo hemorrhagic fever	Ebola virus disease and Marburg viral disease	Crimean-Congo hemorrhagic fever
Filoviral diseases (including Ebola and Marburg)	Lassa fever	Ebola virus disease and Marburg virus disease
Middle East respiratory syndrome coronavirus (MERS-CoV)	MERS and SARS	Lassa fever
Other highly pathogenic coronaviral diseases, such as severe acute respiratory syndrome (SARS)	Nipah and henipaviral diseases	MERS-CoV and SARS
Nipah and related henipaviral diseases	Rift Valley fever	Nipah and henipaviral diseases
Rift Valley fever	Zika disease	Rift Valley fever
Severe fever with thrombocytopenia syndrome	Disease X	Zika
Zika disease		Disease X

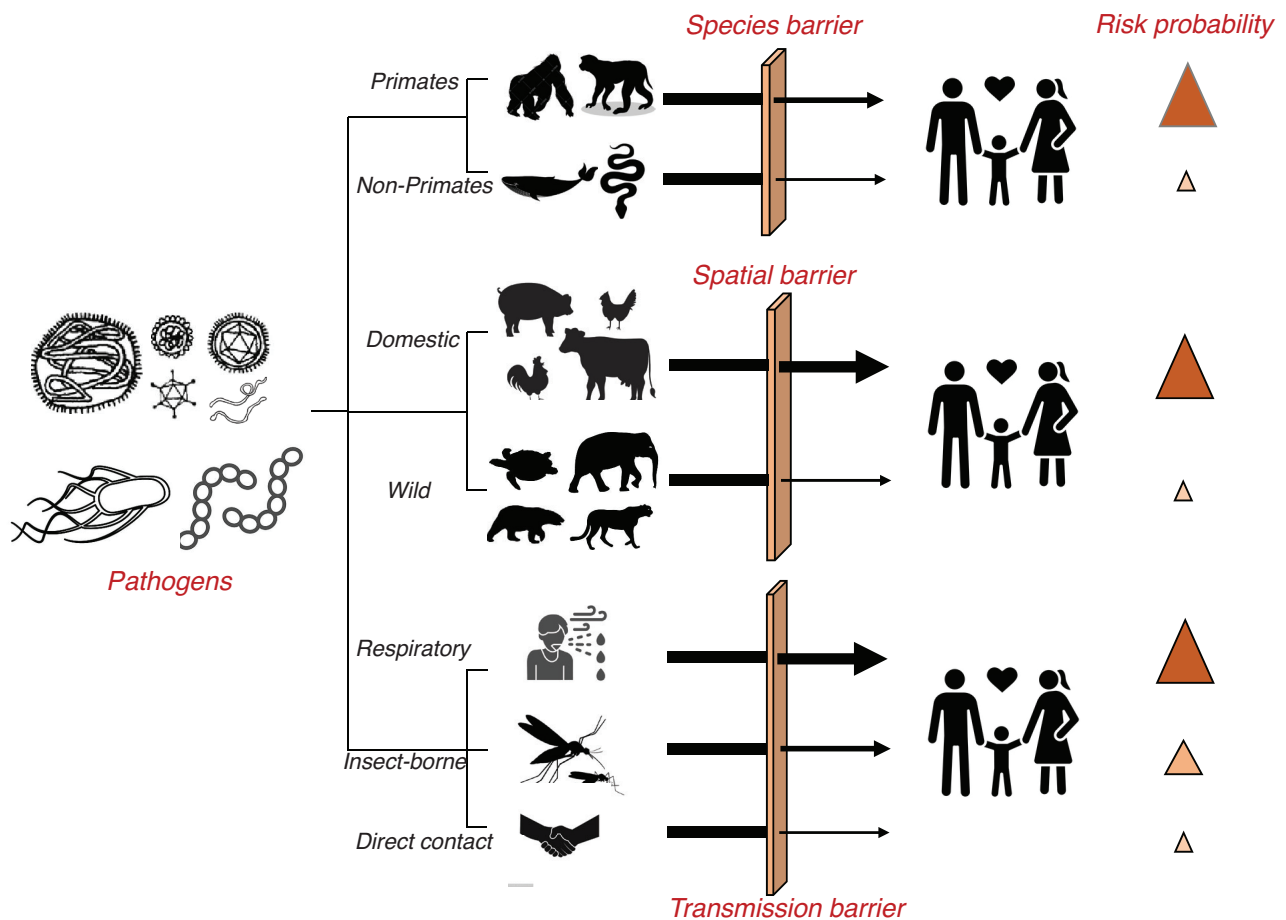


FIGURE 1 | Barriers to cross-species transmission of pathogens from animals to humans. The size of the triangular areas represents the risk probability.

structures have acquired high host specificity during long-term evolution. Another barrier, the transmission barrier, refers to the efficient transmission routes for microbial cross-species transmission. Contact frequencies and behaviors between species markedly affect transmission efficiency. Animals with biology similar to that of humans (such as non-human primates), animals with activities similar to those of humans (such as domesticated animals), and animals carrying high levels of microorganisms in their bodies (such as bats) are most likely to transmit microorganisms to humans and to potentially become pathogen X.

Herd immunity barrier

One characteristic of EIDs is humans' “blank” or “naïve” immunity to the new pathogens, thus resulting in population susceptibility. The pathogens associated with EIDs are either directly derived from animals or carry large-scale mutations formed through gene recombination and reassortment, and genetic material exchange. However, most such pathogens remain within the scope of known

biological families or genera. Despite the marked differences with respect to the ancestral strains, several similarities have persisted. In populations, preexisting immunity to ancestral microorganisms affects disease transmission and severity. New pathogens with greater genetic distance from their ancestral strains that previously infected humans, particularly in key gene loci, usually have greater potential for becoming pathogen X.

Microbial evolution and mutation

Microorganisms have clear evolutionary advantages arising from their simple structures, rapid replication speed, and susceptibility to genomic mutations. Microorganisms may achieve immune escape through small-scale mutations, thereby generating new mutant strains or new clades. Large-scale genetic variations, recombination, or reassortment may lead to the formation of new serotypes or species with altered transmissibility and pathogenicity. RNA viruses are prone to mutation during replication, owing to the poor correction mechanism of RNA polymerase and the high rate of base mismatch.

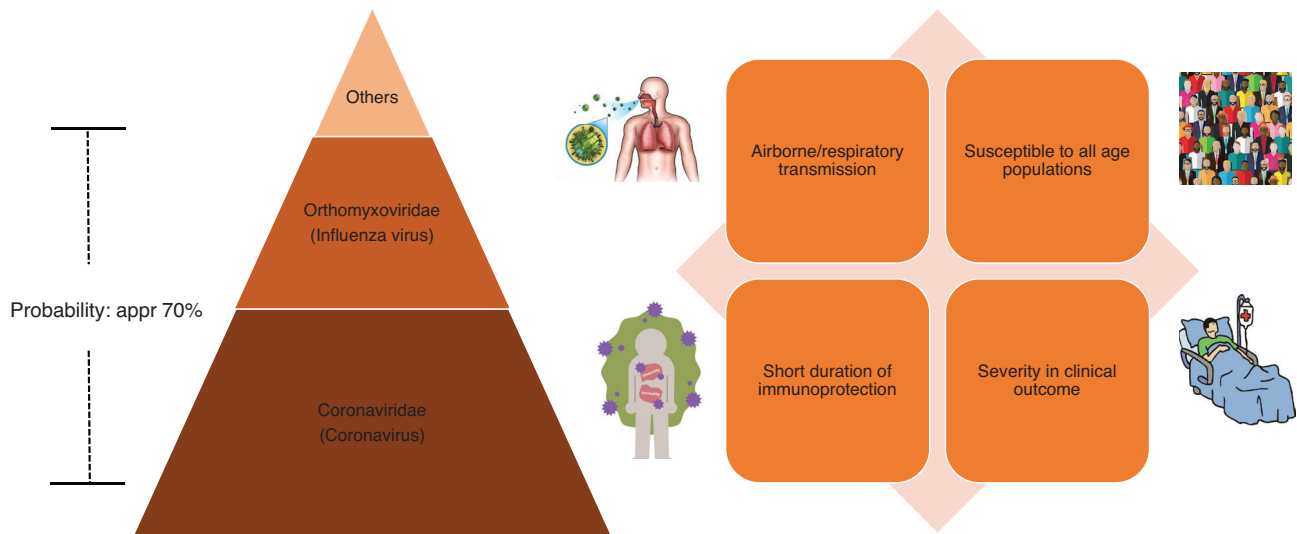


FIGURE 2 | Probability and major features of priority pathogens with potential to cause pandemics.

PRIORITY PATHOGENS WITH POTENTIAL TO CAUSE DISEASE X

An important feature of pathogen X is the potential to cause pandemics. Newly emerging pathogens with respiratory transmission, whole-population susceptibility, severe clinical consequences, rapid mutation and evolution, and host inability to achieve long-lasting and herd immunity after infection are highly likely to cause global pandemics in short time periods; examples include SARS-CoV-2 (Fig 2). Diseases transmitted primarily through insects are often limited by breeding grounds and tend to cause local or cross-border epidemics. Climate and environmental changes affect the scope of epidemics. Infectious diseases, primarily those with contact and gastrointestinal transmission, often cause local outbreaks associated with poor sanitation conditions and high population density; examples include Ebola and Marburg disease. In addition, some chronic infectious diseases transmitted via sexual contact and blood have become global problems after years or even decades; examples include HIV, hepatitis B, and hepatitis C. In the above scenario, influenza virus and coronavirus are the two major pathogens causing global pandemics.

Respiratory viral infectious diseases

Influenza virus

Influenza virus belongs to the *Orthomyxoviridae*, which comprises four serotypes. Influenza A (H1, H2, and H3 subtypes) and B viruses are pathogenic to humans. Influenza A viruses caused five pandemics, in 1914, 1957, 1968, 1977, and 2009 [13]. One important reason for those pandemics was the viruses' proneness to genomic mutation. Currently, the subtypes of seasonal influenza are H1N1 and H3N2, whereas the H2 subtype has nearly disappeared. When the H2 subtype virus reappears, or a new serum subtype virus emerges, it will inevitably trigger a

new influenza pandemic. Influenza virus infects people of all ages and spreads rapidly. The immunoprotection times after illness or vaccination are short, and the cross-immunoprotection between sub-serotypes or strains is limited. In addition, influenza viruses are widely present in various animal species, particularly avian influenza viruses, which not only occasionally directly infect humans but also provide an important biological basis for the emergence of new influenza viruses.

Coronaviruses

Coronaviruses comprise four genera, among which α and β infect primarily mammals including humans, bats, and pigs, whereas γ and δ infect primarily birds. Since the 21st century, a new coronavirus has emerged every decade, thereby triggering three markedly different pandemics. SARS in 2003 caused 8422 cases worldwide, with a 9–10% case fatality rate. MERS in 2012 was highly pathogenic and caused a global average fatality rate of approximately 35%; dromedary camels were the main host and source of infection. SARS-CoV-2, since the end of 2019, has presented severe pandemic characteristics; infected nearly 10% of humans globally and caused more than 7 million deaths; and resulted in historically notable public health hazards, and economic and social turmoil. SARS-CoV-2 displays rapid and sustained mutation features, and several variants of concern have emerged and triggered several global epidemic peaks [14]. The immune protection time after illness is short. Moreover, available vaccines achieve weak cross-protection across variants and low protection against infection. After the existing SARS-CoV-2 undergoes large-scale variations and forms a new variant of concern, it will inevitably trigger new epidemics. In addition, the wide distribution of coronaviruses in animals, particularly bats, might potentially enable formation of a new coronavirus through “spill-over”

infection. Consequently, substantial uncertainty exists regarding coronavirus-induced human infection and pandemic status.

Other respiratory viruses

Smallpox has been eradicated globally through vaccination and therefore cannot become pathogen X. Measles has extremely high transmissibility and has caused many pandemics worldwide. Measles virus has only one serotype, and protection is sustained after illness or vaccination. Measles has been listed as a disease to be eliminated by the WHO, and its potential for becoming pathogen X is very low. Respiratory syncytial virus (RSV) can cause severe lower respiratory tract infections in infants, young children, and older people, yet usually elicits mild symptoms in adults. Generally, a local epidemic peak occurs every 2–5 years. RSV vaccines and preventive monoclonal antibodies have been approved for the market, and RSV’s potential for becoming pathogen X is low. Adenovirus comprises more than 100 serotypes and can be transmitted through respiratory, contact, and digestive tract routes. Adenovirus has caused clustered outbreaks in schools, military camps, and childcare institutions, but no global pandemic. Other respiratory viruses, such as metapneumovirus, parainfluenza virus, and mumps virus, have caused outbreaks of a small scale, but their potential for becoming major infectious diseases is relatively low.

Vector-borne viral infectious diseases

Mosquito-borne virus

Yellow fever virus is transmitted through *Aedes aegypti* and *Aedes albopictus* mosquitoes, and monkeys are the storage hosts. Yellow fever has been widely prevalent historically and was listed as an international quarantine infectious disease in 1907. With vaccination, the incidence and mortality of yellow fever have significantly decreased. Dengue viruses comprise four serotypes and are transmitted through bites of *Aedes aegypti* and *Aedes albopictus* mosquitoes. The animal hosts are primates. Dengue fever remains widely prevalent in tropical and subtropical regions. The WHO has estimated approximately 50 million annual infections globally. A dengue fever vaccine has been approved but has not yet achieved widespread use. Japanese encephalitis virus is transmitted through *Culex* mosquito bites. Its animal hosts include livestock, poultry, various wild animals, and birds. Eastern and southeastern Asia are the most severely affected regions, in which infections peaked in the 1950s and 1970s. Large-scale vaccination significantly decreased the incidence rate and mortality. Zika virus is transmitted through the bites of *Aedes* mosquitoes. Mother-to-child and sexual transmission have also been described. Zika disease is prevalent primarily in countries and regions of the Americas, Africa, Southeast Asia, and the Pacific Islands. The symptoms in infected individuals are mild. From 2015 to 2017, Brazil experienced a large-scale outbreak, involving 3894 cases of neonatal microcephaly. No approved vaccine for Zika virus disease is currently on the market. Chikungunya

virus is transmitted primarily through mosquito bites, and its animal hosts include primates, rodents, and bats. Chikungunya fever is prevalent in tropical and subtropical regions of Africa, Asia, the Americas, and Indian Ocean regions. No chikungunya fever vaccine has received market approval.

Tick-borne virus

Crimean–Congo hemorrhagic fever is distributed in Europe, Asia, and Africa, and causes a high mortality rate. The virus is transmitted primarily through tick bites but can also be transmitted through direct contact with infected people or animals. The main animal hosts are sheep, cattle, horses, and wild rabbits. Severe fever with thrombocytopenia virus is a newly discovered virus distributed primarily in East Asia, including China, Japan, and South Korea. This virus is transmitted primarily through tick bites, and infected people may experience severe bleeding. The diverse animal hosts include livestock, poultry, rodents, and some wild animals. Forest encephalitis is common in temperate forest areas of Europe and Asia, and causes a high mortality rate. The virus is transmitted through tick bites, particularly by the full ditch tick.

Other arboviruses

Sandfly fever virus is transmitted through bites of sandflies, and its main animal hosts are rodents. Sandfly fever is common in the Mediterranean, the Middle East, Africa, and West Asia. Oropuche fever is distributed primarily in South America and the Caribbean. The main vector of transmission is *Paracoides*, which is hosted by primates, sloths, and birds. Vesicular stomatitis virus is transmitted by flies and mosquitoes, and its main animal hosts are livestock, rodents, primates, and fish. The epidemic areas are primarily in the Americas.

Contagious viral infectious diseases

Ebola virus and Marburg virus are filamentous viruses whose animal hosts include fruit bats and primates. Human infection occurs primarily through direct contact with patients or animal blood, body fluids, secretions, excreta, pollutants, or corpses. The main epidemic areas are in countries in Central and West Africa. During 2014 and 2015, a large-scale Ebola outbreak affected Guinea, Sierra Leone, and Liberia in West Africa, and caused more than 28600 reported cases and 11325 deaths. Several years later, Ebola disease occurred in the Democratic Republic of Congo and Uganda. An Ebola vaccine has been approved for the market. Marburg epidemics were reported in the Democratic Republic of Congo from 1998 to 2000; in Angola in 2004 and 2005; and in Tanzania and Rwanda in 2024. No Marburg disease vaccine is available. The mortality rates of these two diseases are extremely high, thus frequently causing social panic and garnering attention from the international community.

Lassa fever is prevalent in West Africa and Central Africa, and causes high mortality rates among pregnant

people and children. The natural storage host of Lassa fever virus is *Mastomys natalensis*. Humans are infected primarily through direct or indirect contact with infected animals and their excrement. Human-to-human transmission occurs via direct contact with the blood, urine, feces, or other secretions of infected individuals. No Lassa fever vaccine is currently available. Nipah virus disease is prevalent primarily in Southeast Asia and South Asia, and was first reported in Malaysia in 1998. Its mortality rate is as high as 60–90%. Fruit bats are natural hosts and sources of infection of Nipah virus, whereas pigs, horses, and other animals serve as intermediate hosts. The saliva or urine of fruit bats contaminates the food of humans, pigs, and horses, and subsequently further infects humans and livestock. The transmission route involves direct contact with infected animals and individuals. No vaccine is currently available for Nipah virus disease. Rift Valley fever, a zoonotic disease caused by the Rift Valley fever virus, infects primarily ruminants and is widely distributed in sub-Saharan African countries, where it causes periodic outbreaks. Beyond mosquito bites, direct contact with blood, tissues, or secretions from infected animals and people is also important in transmission. The infected population has clear occupational relevance. No Rift Valley fever vaccine for human use has been approved for marketing.

CONCLUSION

Overall, viruses have a markedly greater likelihood of becoming pathogen X than either bacteria or other microorganisms. Respiratory viruses, particularly RNA viruses, have notably high potential for becoming pathogen X. Viruses to which populations of all ages are susceptible are most likely to become the pathogen X inducing the next COVID-19-like pandemic. Orthomyxovirus and Coronavirus viruses have high probability to become pathogen X (Fig 2). Mosquito-borne viruses also have potential to be pathogen X, but they affect primarily tropical and subtropical regions. The regions affected by tick-borne viral diseases are often limited to temperate forest and/or rural areas. Diseases caused by filoviruses and Nipah virus have extremely high mortality rates and can easily trigger public panic and social unrest; however, the likelihood of either disease becoming a global pandemic is relatively low.

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CONFLICT OF INTEREST

Xiaoping Dong is Co-Editor-in-Chief of Zoonoses. Qi Shi is an editorial board member of Zoonoses. Neither was involved in the peer review or handling of the manuscript.

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