

## Emerging infectious diseases never end: The fight continues

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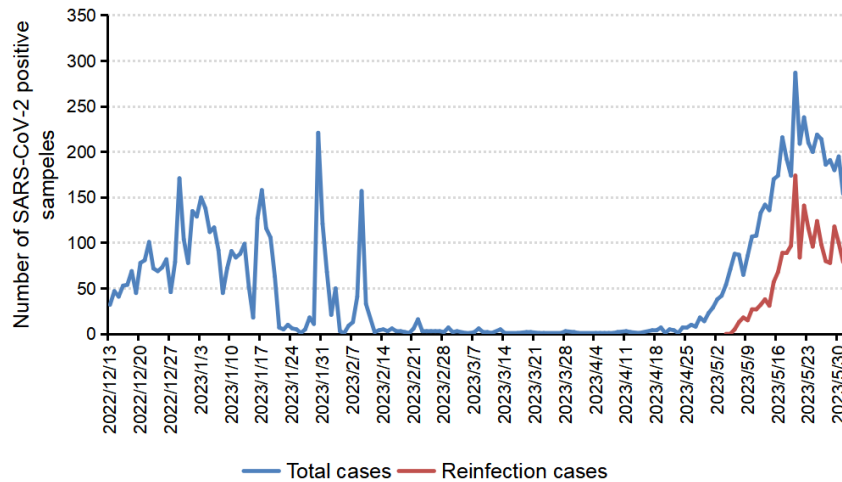
**SUMMARY** Emerging infectious diseases have accompanied the development of human society while causing great harm to humans, and SARS-CoV-2 was only one in the long list of microbial threats. Many viruses have existed in their natural reservoirs for a very long time, and the spillover of viruses from natural hosts to humans *via* interspecies transmission serves as the main source of emerging infectious diseases. Widely existing viruses capable of utilizing human receptors to infect human cells in animals signal the possible outbreak of another viral infection in the near future. Extensive and close collaborative surveillance across nations, more effective wildlife trade legislation, and robust investment into applied and basic research will help to combat the possible pandemics of new emerging infectious diseases in the future.

**Keywords** SARS-CoV-2, coronavirus, emerging infectious diseases, interspecies transmission, zoonosis

For 12,000 years, ever since human hunter-gatherers settled in villages to domesticate animals and cultivate crops, emerging diseases like the "Black Death" (1340s, ~50 million deaths), "Spanish influenza" (1918, ~50 million deaths), and H1N1 "swine flu" (2009, 284,000 deaths) have been threatening human beings and have killed substantial proportions of the population (1). Over the past 40 years, constantly emerging and re-emerging infectious diseases have been found almost every year, such as acquired immune deficiency syndrome (AIDS, a sexually transmitted disease), severe acute respiratory syndrome (SARS, a respiratory disease), H1N1 "swine" influenza (a respiratory disease), Middle East respiratory syndrome (MERS, a respiratory disease), and Zika fever (mosquito-borne disease) (1,2). The ongoing coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in particular has led to unprecedented challenges to public health and devastating economic losses (3). As of 3 May, 2023, SARS-CoV-2 has accounted for more than 765 million infections and 6.9 million deaths globally (<https://covid19.who.int/>). Based on the decrease in COVID-19 deaths, the decline in COVID-19 related hospitalizations and intensive care unit admissions, and the high levels of population immunity to SARS-CoV-2, the World Health Organization (WHO) declared that COVID-19 is now an established and ongoing health issue that no longer constitutes a public health emergency of international concern (PHEIC) on May

5, 2023 (4). However, RNA viruses are inherently genetically unstable which allows their rapid evolution, resulting in the predominance of new variants of SARS-CoV-2 with a higher capacity for immune evasion and transmissibility (5). Moreover, the zoonotic characteristics of SARS-CoV-2 increase the risk of virus spread and mutation (6).

Studies have indicated that the spike (the main target of neutralizing antibodies) protein of SARS-CoV-2 is evolving at twice the rate of a similar protein in seasonal influenza and about ten times as quickly as "seasonal" coronaviruses (7). A variety of evidence has also shown that newly emerging variants are better able to evade vaccine-induced, infection-induced, or 'hybrid' immunity and that the protection provided by vaccination was short-lasting (8,9). Therefore, scientists believe that the combination of rapid mutation and short-lived human immunity will result in SARS-CoV-2 circulating in mini-waves rather than seasonal surges in the future, so explosive, hospital-filling COVID-19 waves are unlikely to return (7). China has experienced one wave dominated by BA.5.2 and BF.7 variants following the adjustment of prevention and control policies in December, 2022 (10). As studies have shown that XBB related variants possessed strong antibody escape against breakthrough infections with previous variants including BA.5 and BF.7 (11-13), it seems that the second wave dominated by XBB related variants is ongoing according to the data from our hospital (Figure 1) and GISAID database (<https://www.gisaid>.

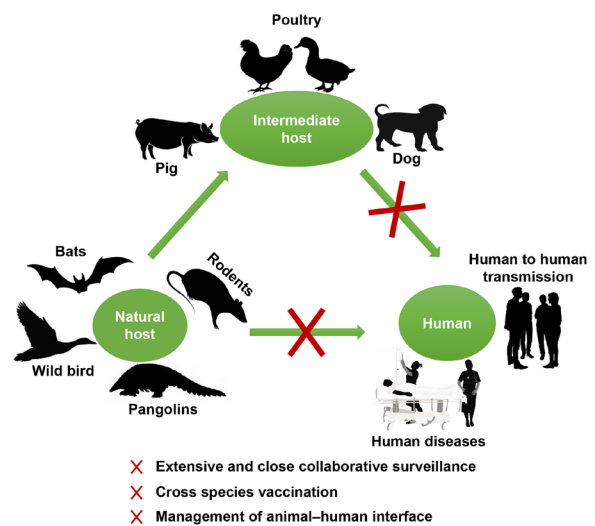


**Figure 1. Dynamics of SARS-CoV-2 infections (blue line) and reinfections (red line) in patients diagnosed at Shenzhen Third people's hospital during Dec 13, 2022 and May 31, 2023.**

org/). Undoubtedly, the elderly and individuals with an immune deficiency or underlying medical condition should be the focus of the medical system, and more effective vaccines and oral antivirals still serve as key weapons in the battle against SARS-CoV-2 (14).

Interspecies transmission plays a key role in the emergence of new human infectious diseases like human coronavirus infections and human avian influenza virus (AIV) infection (Figure 2) (15,16). Coronaviruses, for example, are characterized by a higher rate of mutation and recombination than other viruses, facilitating host adaptability and interspecies transmission (17). Notably, all known human coronaviruses are believed to be zoonotic pathogens that crossed the species barriers to infect humans based on current sequence databases (5,15). SARS-CoV, MERS-CoV, HCoV-NL63, and HCoV-229E are considered to have originated in bats and HCoV-OC43 and HKU1 in rodents (5,15,18). Although the accurate reservoir of SARS-CoV-2 has not yet been determined, there is no doubt of its zoonotic origins via the wildlife trade (19,20). Many coronaviruses that are capable of utilizing human receptors to infect human cells were found to circulate in bats and pangolins during the last decades, such as SARS-CoV, MERS-CoV and SARS-CoV-2 related coronavirus (21-28). These coronaviruses are potentially likely to spilled over from an intermediate host, and domestic animals in particular, into human beings (29). A novel HKU2-related bat coronavirus named swine acute diarrhea syndrome coronavirus (SADS-CoV) that has been found to infect human cells emerged in Guangdong Province, China in 2016, causing large-scale mortality in piglets on several farms (30,31). Recently, human infections with a novel recombinant canine coronavirus were found in East Malaysia and Haiti (32,33). These findings signal the possible outbreak of another coronavirus in the near future.

Many viruses have existed in their natural reservoirs



**Figure 2. Typical cycle of interspecies transmission and possible countermeasures.** Mutation and recombination of viruses during their circulation in natural hosts enable host adaptability and interspecies transmission via an intermediate host or direct contact. Extensive and close collaborative surveillance, cross-species vaccination, and management of animal-human interface are important countermeasures against interspecies transmission.

for a very long time and the spillover of viruses from natural hosts to humans and other animals serves as the main source of emerging infectious diseases (Figure 2) (1,5,34). The spread of infectious diseases is not limited by geographic boundaries, so extensive and close collaborative surveillance among nations will be crucial to the prevention and control of future pandemics (2). The identification of key reservoir species could enable targeted prophylactic cross-species vaccination campaigns or intervention strategies to minimize contact between natural reservoirs and humans (28,35). Over the past three decades, most new human pathogens with substantial impacts on human health or economics

have originated in wildlife, so enactment of legislation effectively addressing the wildlife trade, protection of habitats, and reduction of the wildlife-livestock-human interface is another effective way to prevent future zoonoses (36,37). Basic science has brought us many life-saving drugs, vaccines, and diagnostics as it did during the COVID-19 pandemic (38). Therefore, robust investment into applied and basic research on virus pathogenesis, interspecies transmission, vaccines, and antivirals is needed to combat possible pandemics of new emerging infectious diseases in the future.

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