

Unignorable public health risk of avian influenza virus during COVID-19 pandemic

To the Editor,

Human infections with the newly emerging reassortant H5N6 avian influenza viruses (AIV) were reported.¹ AIV has been prevalent persistently worldwide, which results in a devastating impact on the poultry industry and even public health. Highly pathogenic AIV (HPAIV), including H5Ny lineages (H5N1, H5N2, H5N6, and H5N8) and H7N9 subtype, exhibit severe disease phenotype with high morbidity and mortality rates in birds, especially chickens. Although H9N2 AIV only could induce mild or no obvious clinical signs in poultry, the enlarged host species of H9N2 AIV could induce the potential threat to global health.² In late 2019, the novel coronavirus disease (COVID-19) broke out and swept the world population. Drastic mitigation measures were implemented among the international community to stop the COVID-19 crisis, including mass quarantine, physical distancing, and face mask usage. However, the elevated trend of human infections with the emerging AIV during ongoing COVID-19 circulation still highlights the alert of the possible risk for the next human pandemic.³

In H5 lineage viruses, H5N1 extensively spread worldwide and became enzootic. The human H5N1 infection case was firstly reported in 1997. Since 2003, there have been 864 cases identified from 18 countries, with a fatality rate as high as 52.8%. In 2013, the spillover of the H7N9 subtype to human beings occurred in China, causing a total of 1568 human infections and 616 related deaths. Surprisingly, the H7N9 virus primarily showed asymptomatic infection in domestic poultry, reemerged consecutively in live bird markets (LBMs), and evolved into H7N9 HPAIV in early 2017.⁴ The new human H7N9 case was rarely detected during the past seventh epidemic wave since April 2019.⁵ H5N6 was originally defined as a low pathogenic AIV (LPAIV) and reassorted with the internal genes of multiple other LPAIV subtypes to generate the novel H5N6 HPAIV, which was initially confirmed to be responsible for human infection in 2014. The following epidemiological investigation of AIV in LBM demonstrated that H5N6 has gradually become instead of H5N1, a dominant AIV subtype among poultry in southern China.⁶ Accompanied by genetic evolution and close contact with humans, H5N6 could acquire a more robust affinity capacity to bind human-like receptor α -2,6 sialic acid and enhance the virulence in mammals. Up to April 5, 2022, 76 infected patients have been reported, typically preceded by exposure to poultry.⁷ Of these, 75 cases and 1 case were documented in China and Lao People's Democratic Republic, respectively, illustrating that H5N6 displayed a propensity for expanded spread. The reported H5N6 infected human cases in China

were distributed in 15 provinces, and the largest number of positive cases were located in Guangxi ($n = 17$), followed by Guangdong ($n = 13$), Hunan ($n = 13$), and Sichuan ($n = 11$).

Furthermore, an overwhelming proportion of H5N6 was found in southern China with subclade 2.3.4.4 related phylogenetic diversity through hemagglutinin (HA) analysis. This phenomenon may be associated with the higher density of the poultry industry and the preferential consumption of freshly slaughtered poultry in southern China.⁸ It is noteworthy that a significant surge of H5N6 infections in a human was observed after the outbreak of COVID-19. Importantly, 50 cases have been detected worldwide since 2021, indicating the potential arrival of pandemic influenza (Figure 1). A similar pattern existed in current H9N2 in humans with a sharp increase in infection frequency. A total of 16 human H9N2 cases (China, $n = 15$; Cambodia, $n = 1$) and one death were reported in the last 6 months, most of which are also distributed in southern China.

Meanwhile, most H9N2 infected patients were children under 7 years old. H9N2 viruses prevalent in chickens and waterfowl are recognized as donors of the internal genes and contribute to the establishment of novel reassortants of H7N9, H5N6, and H10N8 viruses that were susceptible to humans and caused disproportionate fatalities.⁹ Due to belonging to the same subclade 2.3.4.4 as H5N6 based on HA phylogeny, H5N8 HPAIV has the potential to be transmissible to humans. In February 2021, seven human cases in a poultry farm attributed to H5N8 infections were first reported in Russia.¹⁰ Given the widespread expansion of the H5N8 subtype and the lack of herd immunity among humans against H5N8 viruses, more attention to the risk associated with the influenza pandemic should be addressed. In April 2021, a novel avian-origin H10N3 virus leading to severe illness in a human was first discovered in China's Jiangsu province.¹¹ This reassortant LPAIV contained H9N2 derived gene segments and gained the ability of cross-species transmission, the genetic characteristics of which were also found in the emerged H10N8 isolate responsible for human infection in 2013.¹² Although the zoonotic spread of H10N3 and H10N8 variants seems to be sporadic, continuous surveillance of these LPAIV is important for predicting a future pandemic.

Under the current challenge of the COVID-19 pandemic, strict control practices were carried out to curb this fulminating disease with a substantial decrease in global seasonal influenza transmission. Due to limited laboratory testing capacities and medical resources, human cases infected with AIV may be ignored. However, the frequent outbreaks of AIV in poultry and wild birds and the rapid rise

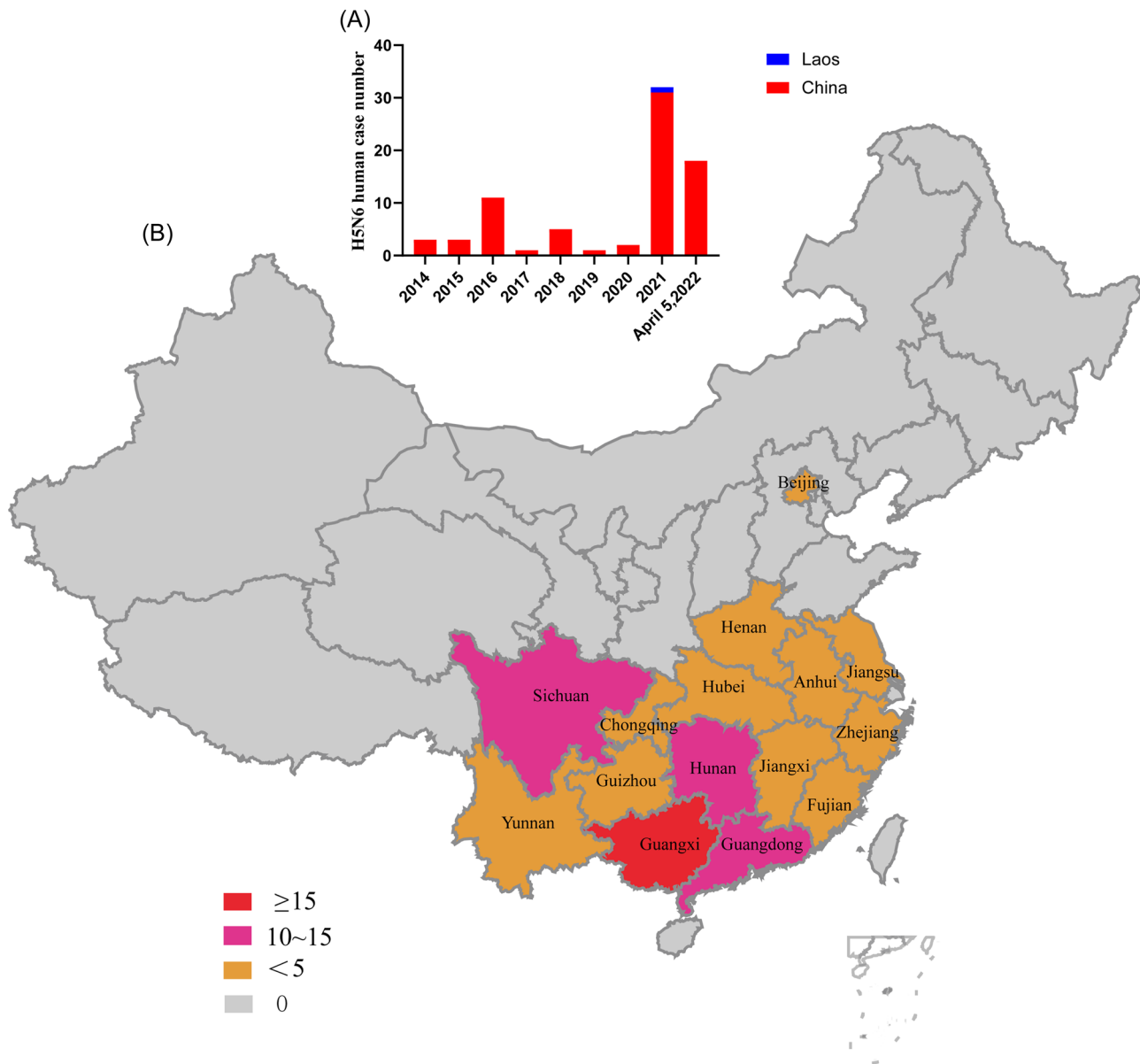


FIGURE 1 Summary of H5N6 human infection cases. (A) Annual H5N6 human infection cases in China and Laos. (B) Geographic distribution of H5N6 human infection cases that were confirmed in China. All data were collected from World Health Organization and the Centre for Health Protection in Hong Kong, China.

in human infections should remind us to monitor and prepare for the latent risk of a disastrous pandemic.

AUTHOR CONTRIBUTIONS

Yu Ye, Zaijiao Ye, Liangyu Yang, and Bin Xiang collected and analyzed the data and Yu Ye, Bin Xiang, and Chunfu Zheng drafted the manuscript and reviewed and approved the paper to be published. All authors read and approved the final manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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