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# Dealing with Highly Pathogenic Avian Influenza: An Impending Crisis

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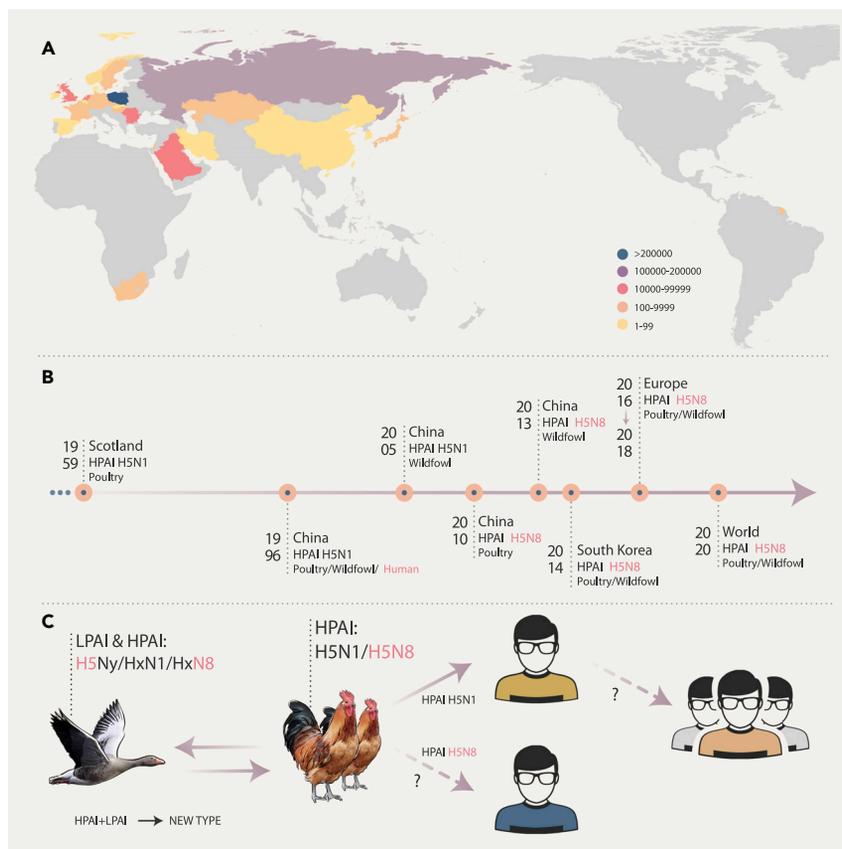
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Humans and other animals have always been battling viruses, especially those that cause emerging and re-emerging infectious diseases. Along with the ongoing COVID-19 pandemic, highly pathogenic avian influenza (HPAI) viruses of the H5 subtype are attacking silently as a re-emerging disease, thus seriously impairing poultry and human health. Recently, there have been outbreaks of the H5N8 subtype of HPAI virus in many regions around the world. According to data available through the Global Animal Disease Information System (<http://empres-i.fao.org/>) of the Food and Agriculture Organization of the United Nations, a total of 412 HPAI H5N8 outbreaks were reported worldwide from August 31 to December 1, 2020, with 353,851 animals confirmed to be infected in 26 countries around the world. Only sporadic cases of this strain were found during the same period in the previous year.

The HPAI H5N8 virus was first isolated in 2010. It belongs to the clade 2.3.4.4 of HPAI H5N1 (Gs/GD lineage), which undergoes reassortment, swapping its neuraminidase and other segments. HPAI H5N8 emerged and then

spread intercontinentally. Multiple HPAI H5N8 outbreaks have occurred worldwide, with large epidemics in 2014/2015<sup>1</sup> and 2016/2017.<sup>2</sup> At the beginning of 2020, H5N8 was again detected in Europe, and two novel strains of HPAI H5N8 were isolated in Germany. In October, a strain with high nucleotide homology to the German samples was isolated from field samples in South Korea, indicating that this strain had been transmitted intercontinentally. At present, it appears that these HPAI H5N8 strains have undergone further reassortments, although identification and analysis of the 2020 strains are still ongoing.

Although no HPAI H5N8 human infections have been reported so far, it still needs to be taken seriously (Figure 1). Strains of the clade 2.3.4.4 have been found to infect cats and pigs, and clade 2.3.4.4 H5N6 has caused infections in humans. Under laboratory conditions, some strains of the H5N8 subtype can seriously infect minks and transmit via direct contact. Whole-genome analyses of HPAI H5N8 have shown the molecular characteristics, including



**Figure 1. Overview of the Emergence, Spread, and Outbreak of Highly Pathogenic Avian Influenza (HPAI) Viruses of H5N8** (A) Chart of H5N8 HPAI cases in various countries from January 1 to December 1, 2020. Different colors indicate case range.

(B) Major events in the history of H5N8 HPAI. Several neuraminidase enzymes, including N8, were obtained by recombination of the H5N1 HPAI with other low-pathogenic avian influenza (LPAI) viruses.

(C) Transmission chain of H5 subtype of influenza A virus. Wildfowl may carry HPAI and LPAI viruses, including H5Ny, HxN1, and HxN8, asymptotically and interact with poultry. HPAI H5N1 in poultry may infect humans, but the possibility of human-to-human transmission is not clear. There is currently no evidence of HPAI H5N8 infection in humans.

PB2-613I and PB2-702R, related to genes found in strains infecting human beings after the 2014 outbreak of HPAI H5N8, indicating that HPAI H5N8 has the potential to infect human beings to a certain extent.

However, we are not helpless against virus outbreaks, as scientists have taken great efforts in virus prevention and control. For virus detection, a method for the detection of HPAI H5N8 using the TaqMan minor groove binder and real-time reverse transcriptase-polymerase chain reaction has been reported, with its sensitivity reaching 10 copies per reaction.<sup>3</sup> In vaccine research and development, several key amino acid mutation sites have been reported to lead to an antigenic drift in the hemagglutinin antigenic determinant B of clade 2.3.4.4. In addition, titers of the strains of clade 2.3.4.4 in chick embryos have been greatly improved through specific gene modification, while the modified virus strain does not infect mammals.<sup>4</sup> These studies lay a solid foundation for the research and development of highly effective HPAI H5N8 vaccines.

Nevertheless, vaccines alone are not a long-term solution for the prevention and control of influenza A virus outbreaks. As we know, it is not practical to vaccinate all the wild birds, which are the ultimate problem in the spread of H5N8 to Europe. Ongoing monitoring has shown that whether the development and application of a vaccine may create significant selective pressure on the evolution of the influenza A virus is also a concern.<sup>5</sup> Furthermore, various public health factors, such as rampant live poultry trading in Asia, imperfect vaccination and elimination programs, and an intercontinental HPAI monitoring network that needs improvement, are considered to be strongly associated with the prevalence of HPAI.

Finally, the explosive population growth in the 21st century has led to increased demands on the global breeding industry, and the challenges of HPAI compel us to face this global difficulty together. To maintain the prev-

alence of HPAI in domestic bird populations, health authorities at all levels of government and international organizations need to coordinate and cooperate to identify ways to minimize the threat posed by these viruses.

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## AUTHOR CONTRIBUTIONS

J.L. and R.S.L. wrote the manuscript and completed its revision. L.L., S.L., and W.J.L. made many suggestions for the manuscript. All authors read and approved the final version.