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Epidemiology and evolution of human-origin H10N5 influenza virus

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ABSTRACT

H10 subtype avian influenza viruses were endemic in wild and domestic avian species worldwide. Strikingly, it frequently crossed the species barrier to infect mammalian hosts. Human infection with H10N3 and H10N8 were reported previously. Recently, a 63-year-old woman from Anhui province of China who died from a mixed infection of H3N2 and H10N5 influenza viruses, which have drawn widespread public health attention. Here, we perform the evolutionary dynamics of H10N5 influenza viruses of bird- and human-origin worldwide, and found that wild bird-origin H10N5 influenza viruses from China did not cluster together with human-origin H10N5 influenza viruses, while grouped together with LPAIV gene pools circulating in wild birds that derived from other Eurasian countries. Human-derived H10N5 virus is a novel reassortant, which frequently reassorted with wild bird-derived influenza viruses, and in turn, spillover into humans. Collectively, our results suggested that H10 subtype influenza viruses continuously pose threat to public health.

1. Introduction

Recent study frequently reported that H10Nx avian influenza viruses (AIVs) of wild bird-origin in China pose new threat to mammals [1–4], suggesting that H10 subtype AIV is a new threat to public health. Notably, the emergence of H10N3 avian influenza virus (AIV) had caused human infection [5,6]. Besides, it is also reported that chicken-origin H10N3 influenza virus could be transmitted between guinea pigs via respiratory droplets [7]. In recent decades, H10Nx viruses have become endemic in birds and mammals, and 5 cases of human infection with H10 subtype influenza viruses were frequently reported in China. These results suggest that H10 subtype influenza viruses pose increased threat to public health. Strikingly, on December 16, 2023, a 63-year-old woman from Anhui province who died from a mixed infection of H3N2 and H10N5 influenza viruses according to the National Disease Control and Prevention Administration of the People's Republic of China (https://www.ndcpa.gov.cn/jbkzzx/c100008/common/content/content_1752234546782195712.html). To assess the evolutionary dynamics of H10N5 influenza viruses, we systematically explored the global distribution and genomic evolution of H10N5 influenza viruses in birds and mammals.

2. Methods

All of the genomes of H10N5 influenza virus across the globe were download from GISAID's EpiFlu Database. In addition, we downloaded the reference gene sequences that were genetically closely related to the H10N5 influenza viruses from GISAID's EpiFlu Database. After filtering low quality gene sequences (i.e., large account of the deletion of fragments), a total of 271, 275, 250, 196, 215, 210, 202, and 220 reference sequences in PB2, PB1, PA, HA, NP, NA, M, and NS were obtained, respectively. To perform the evolutionary dynamics of H10N5 influenza viruses, we conducted the phylogenetic analysis of H10N5 influenza viruses across the globe. Firstly, we removed sequences with 100 % nucleotide homology. Then, multiple sequence alignment of these sequences was conducted using MAFFT in PhyloSuite [8], with the alignment mode of normal, export format of auto, and code table of the standard code. Subsequently, IQ-tree (v1.6.12) in PhyloSuite was used to construct a maximum likelihood (ML) tree of eight gene segments of H10 subtype influenza viruses from GISAID's EpiFlu Database [8]. Maximum likelihood (ML) phylogenies for the codon alignment of eight gene segments were estimated using the GTR + G nucleotide substitution model in the IQ-TREE. The State freq is Empirical (from data). Node

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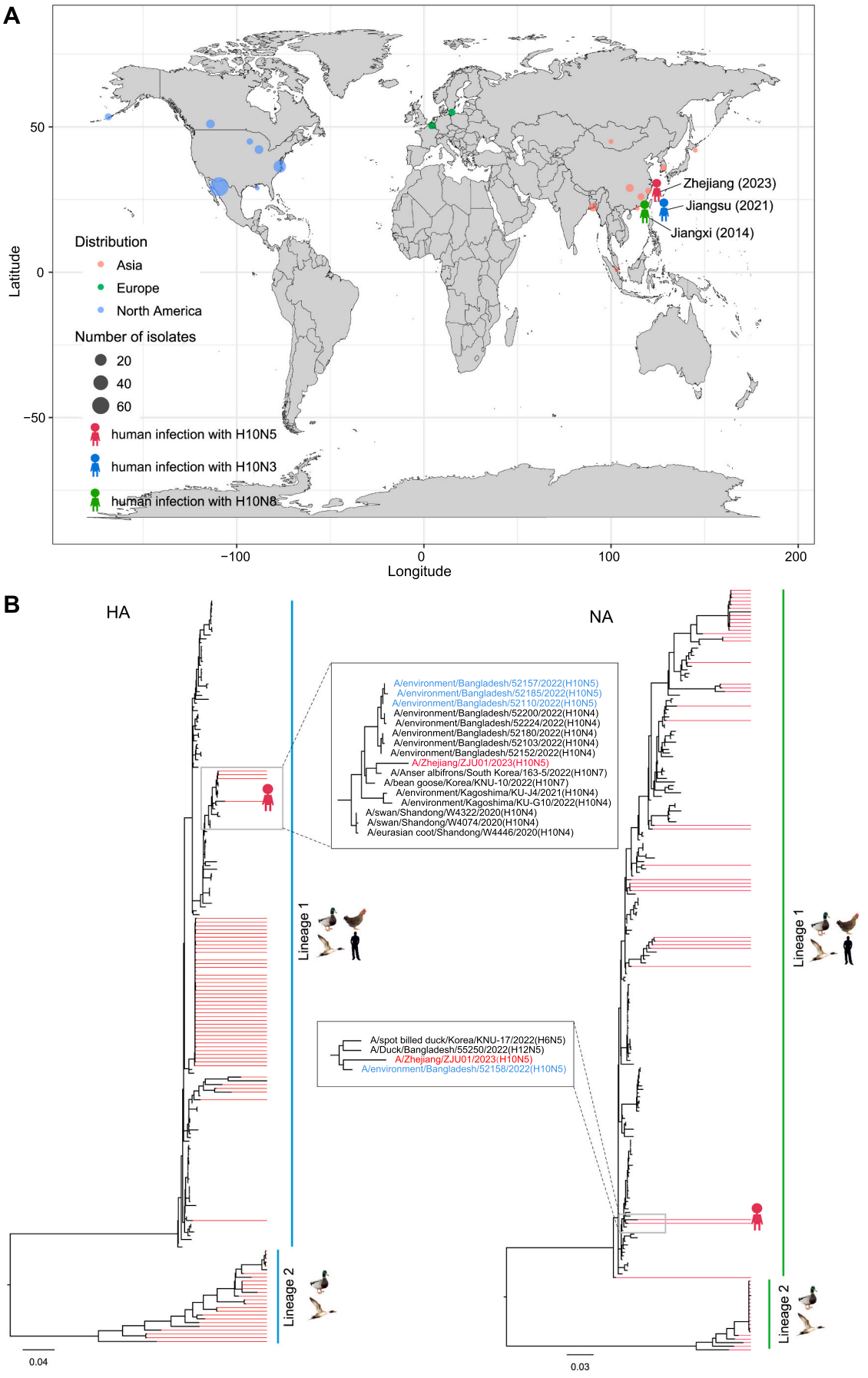

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Fig. 1. Global distribution and phylogenetic trees of H10N5 influenza viruses. (A) Global distribution of bird-origin H10N5 influenza viruses and human infection with H10 subtype influenza viruses. The size of the dot represents the number of H10N5 influenza viruses. The red, blue, and green human cartoon represents human case of H10N5, H10N3, and H10N8 infection. The map was drawn by R software. (B) Phylogenetic trees of surface genes (HA and NA) of H10N5 influenza viruses. The red lines represent H10N5 isolates. All branch lengths were scaled according to the numbers of substitutions per site. Maximum likelihood (ML) phylogenies for the codon alignment of HA gene segments were estimated using the GTR + G nucleotide substitution model in the IQ-TREE. Node support was determined by nonparametric bootstrapping with 1000 replicates. The phylogenetic tree was graphically illustrated in the FigTree (version 1.4.3) program (http://tree.bio.ed.ac.uk/software/figtree/). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

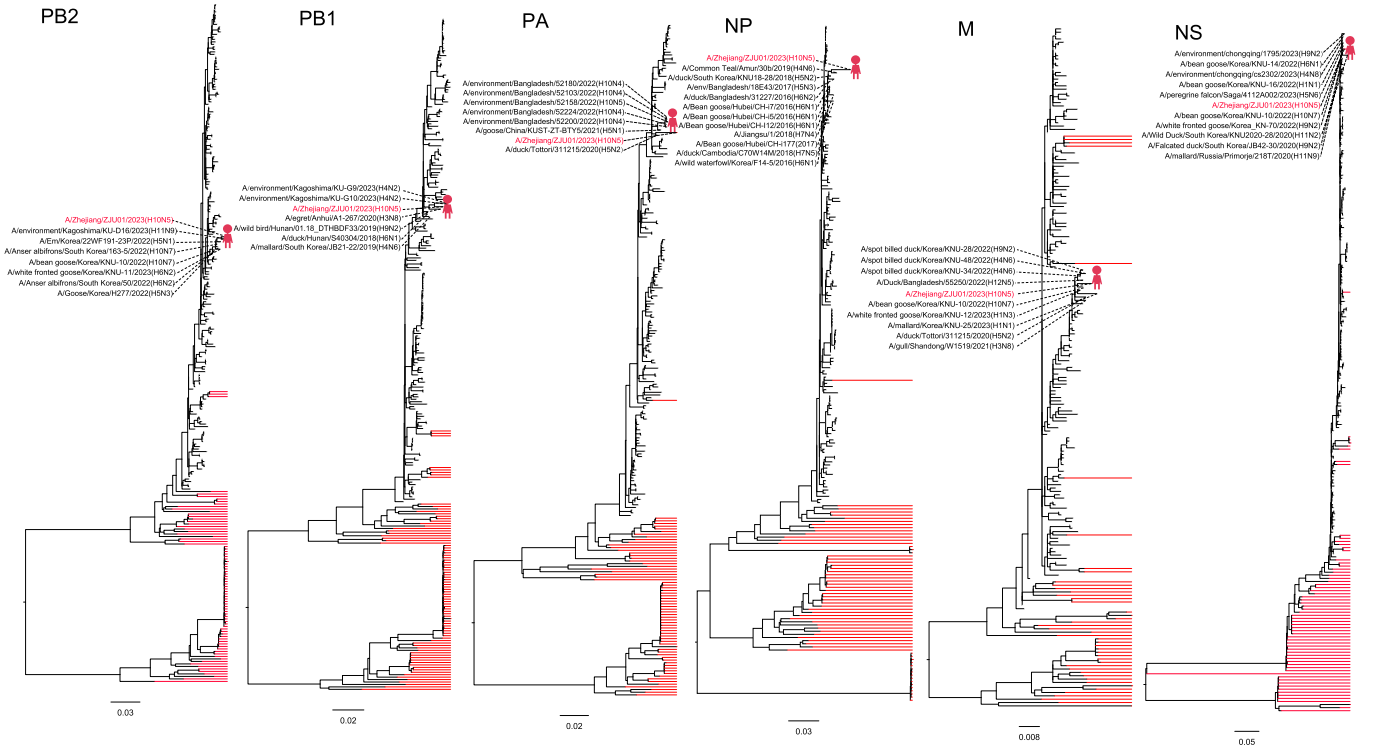

Fig. 2. Phylogenetic trees of internal genes of H10N5 influenza viruses. The red lines represent H10N5 isolates. All branch lengths were scaled according to the numbers of substitutions per site. Maximum likelihood (ML) phylogenies for the codon alignment of HA gene segments were estimated using the GTR + G nucleotide substitution model in the IQ-TREE. Node support was determined by nonparametric bootstrapping with 1000 replicates. The phylogenetic tree was graphically illustrated in the FigTree (version 1.4.3) program (http://tree.bio.ed.ac.uk/software/figtree/). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

support was determined by nonparametric bootstrapping with 1000 replicates. The phylogenetic tree was graphically illustrated in the FigTree (version 1.4.3) program (http://tree.bio.ed.ac.uk/software/figtree/).

3. Results and discussion

According to the GISAID's EpiFlu Database, we found that H10N5 influenza viruses were mainly prevalent in US, and only few wild bird-derived H10N5 viruses were isolated in China (Fig. 1A). The main host species of H10N5 influenza viruses were aquatic birds. We then conducted the phylogenetic analysis of H10N5 influenza viruses of human- and bird-origin. In this study, we found that the HA and NA genes of human-derived H10N5 viruses were genetically closely related to A/*Anser albifrons*/South Korea/163–5/2022(H10N7) and A/environment/Bangladesh/52158/2022(H10N5) isolates, respectively, while the internal genes were derived from varies subtype influenza viruses of wild bird-origin in different regions (Fig. 1B and Fig. 2).

Specifically, the PB2 and PB1 genes of human-origin H10N5 virus were genetically closely related to low pathogenic avian influenza virus (LPAIV) gene pool from Korea and Japan during 2022 to 2023, while PA gene of human-origin H10N5 virus were genetically closely related to environment-origin H10Nx virus from Bangladesh during 2022 (Fig. 1B and Fig. 2). For NP, M, and NS genes, the genome was closely related to LPAIV gene pool of bird-origin from South Korea, and the NP gene of human-origin H10N5 and H7N4 viruses cluster together (Fig. 1B and Fig. 2). These results suggested that the genomes of wild bird-origin H10N5 influenza viruses from China did not cluster together with human-derived H10N5 influenza viruses, while grouped together with LPAIV gene pools circulating in wild birds that derived from Eurasian countries (Supplementary Fig. 1–8), indicating that human-derived H10N5 virus is a novel reassortant, which frequently reassorted with wild bird-derived influenza viruses, and in turn, spillover into humans (Supplementary Fig. 9). Molecular characterization indicated that the HA protein of bird- and human-origin H10N5 influenza viruses across the globe contained Q and G in amino acid residue 226 and 228, respectively, indicating that H10N5 influenza virus preferentially bind to avian-like sialic acid receptor, and human-origin H10N5 influenza viruses did not bear the E627K, A588V, and D701N mammalian adaptive mutations in the PB2 protein. These results suggest that human-origin H10N5 influenza viruses did not acquire increased virulence and transmission ability in mammals.

The dissemination of wild birds accelerates the spread of influenza viruses across the globe. Sustained wild bird-derived influenza epidemic repeatedly spill over and spill back from domestic birds [9]. The recently emerged avian influenza viruses, such as H3N8, H5N6, H10N3, and

H10N5 had frequently reassorted with wild bird-derived influenza viruses [9–11]. Therefore, the prevention and control of poultry-origin influenza virus is not enough. In China, poultry farming occurs in high-density environments and with free-range manner, which promote environments for birds to share common habitats [12]. The frequent contact between wild birds and poultry increases genomic mutation and reassortment of influenza viruses, which generate novel influenza variants that adapt to birds and humans. H10 subtype AIVs have been epidemic in multiple migratory bird flyways. H10 subtype AIVs were frequently isolated from different species of wild and domestic birds across the globe [1,2,13,14], and strikingly, had crossed host barriers to infect mammals, such as harbor seals and swine [15,16], posing significant public concerns.

Human infections with H10 subtype influenza viruses have been reported occasionally. In 2013, the first human case of H10N8 infection resulting in human death was reported in China [17,18], and followed by the reported cases of human infection with H10N3 influenza viruses [19]. These H10 subtype influenza viruses, together with the recently emerged H10N5 influenza viruses, were all novel reassotants that reassorted with wild bird-origin influenza viruses. Recent studies demonstrated that wild bird-origin H10Nx influenza virus replicated efficiently in the respiratory system without preadaptation, and can bind to both human-type α2,6-linked sialic acid receptors and avian-type α2,3-linked sialic acid receptors [1]In addition, other studies had proved that H10N7 influenza viruses had gained aerosol or respiratory droplet transmissibility between ferrets [20], and chicken-origin H10N3 influenza virus could be transmitted between guinea pigs via respiratory droplets [11], which suggested that H10 subtype influenza viruses had acquired the airborne transmission, posing increased public health threat. Therefore, the routine surveillance and prevention of wild bird-derived influenza viruses are needed. Large scale poultry farming instead of free-range style is essential in the future to reduce the contact between wild birds and domestic poultry, which can prevent the generation of novel variants at their origin and reduce human infection.

4. Limitation of the study

This study has several limitations. Firstly, due to the limited sample size of human-origin H10N5 influenza viruses, we cannot performed dynamic evolution of H10N5 influenza viruses in human populations. In addition, sampling bias in the sequence may have affected the results. In most countries, domestic poultry were sampled more intensively than wild birds, and only few sampling sites of wild birds were conducted. Therefore, more comprehensive H10 subtype influenza surveillance of wild bird and human-origin should be enhanced in the future. Secondly, the study have described the evolutionary dynamics of bird and human-origin H10N5 influenza viruses across the globe. However, conducting the biological characteristics of H10N5 influenza viruses *in vitro* is also important to assess the risk to humans. Therefore, complementary experimental approaches will be conducted in future studies.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.onehlt.2024.100893.

Authors contributions

Zhaoxia Yuan and Jiahao Zhang conducted the analysis of influenza viruses. Guangyu Huang collected the genomes of influenza viruses from GISAID. Zhaoxia Yuan, Jiahao Zhang, Danli Jiang, and Wenbao Qi wrote the paper. Jiahao Zhang and Wenbao Qi provided the funding support.

CRediT authorship contribution statement

Zhaoxia Yuan: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jiahao Zhang:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Conceptualization. **Danli Jiang:** Visualization, Methodology, Conceptualization. **Guangyu Huang:** Visualization, Software, Formal analysis, Data curation. **Wenbao Qi:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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References

[1] X. Lv, J. Tian, X. Li, X. Bai, Y. Li, M. Li, et al., H10Nx avian influenza viruses detected in wild birds in China pose potential threat to mammals, One Health 16 (2023) 100515.2.
[2] R. Xie, W. Wang, Y. Gao, W. Liu, B. Yue, S. Liu, et al., Evolution and mammalian adaptation of H3 and H10 subtype avian influenza viruses in wild birds in Yancheng wetland of China, Vet. Microbiol. 279 (2023) 109669.
[3] Y.J. Si, Y.R. Park, Y.G. Baek, M.J. Park, E.K. Lee, K.N. Lee, et al., Pathogenesis and genetic characteristics of low pathogenic avian influenza H10 viruses isolated from migratory birds in South Korea during 2010-2019, Transbound. Emerg. Dis. 69 (2022) 2588–2599.
[4] Y. Wang, M. Wang, H. Zhang, C. Zhao, Y. Zhang, G. He, et al., Emergence, evolution, and biological characteristics of H10N4 and H10N8 avian influenza viruses in migratory wild birds detected in eastern China in 2020, Microbiol. Spectr. 10 (2022) e0080722.
[5] R. Gao, H. Zheng, K. Liu, Z. Ji, M. Cai, M. Gu, et al., Genesis, evolution and host species distribution of influenza a (H10N3) virus in China, J. Inf. Secur. 83 (2021) 607–635.
[6] Z. Wu, J. Liu, S. Chen, H. Zhang, Y.F. Chang, X. Zhang, Q. Xie, The emergence of the novel avian influenza virus (H10N3) in China, 2020-a cause for concern? J. Inf. Secur. 84 (2022) e16–e18.
[7] K. Liu, X. Qi, C. Bao, X. Wang, X. Liu, Novel H10N3 avian influenza viruses: a potential threat to public health, Lancet Microbe 5 (2024) e417.
[8] D. Zhang, F.L. Gao, I. Jakovlic, H. Zou, J. Zhang, W.X. Li, G.T. Wang, PhyloSuite: an integrated and scalable desktop platform for streamlined molecular sequence data management and evolutionary phylogenetics studies, Mol. Ecol. Resour. 20 (2020) 348–355.
[9] J. Zhang, H. Ye, Y. Liu, M. Liao, W. Qi, Resurgence of H5N6 avian influenza virus in 2021 poses new threat to public health, Lancet Microbe 3 (2022) e558.
[10] R. Yang, H. Sun, F. Gao, K. Luo, Z. Huang, Q. Tong, et al., Human infection of avian influenza a H3N8 virus and the viral origins: a descriptive study, Lancet Microbe 3 (2022) e824–e834.
[11] K. Liu, P. Ding, Y. Pei, R. Gao, W. Han, H. Zheng, et al., Emergence of a novel reassortant avian influenza virus (H10N3) in eastern China with high pathogenicity and respiratory droplet transmissibility to mammals, Sci. China Life Sci. 65 (2022) 1024–1035.
[12] Z. Yuan, T. Zhou, J. Zhang, Q. Zeng, D. Jiang, M. Wei, X. Li, The genomic evolution and the transmission dynamics of H6N2 avian influenza a viruses in southern China, Viruses (2022) 14.
[13] H.R. Kim, Y.J. Lee, J.K. Oem, Y.C. Bae, M.S. Kang, H.M. Kang, et al., Characterization of H10 subtype avian influenza viruses isolated from wild birds in South Korea, Vet. Microbiol. 161 (2012) 222–228.
[14] S. Ding, J. Zhou, J. Xiong, X. Du, W. Yang, J. Huang, et al., Continued evolution of H10N3 influenza virus with adaptive mutations poses an increased threat to mammals, Virol. Sin. 39 (2024) 546–555.
[15] J.S. Krog, M.S. Hansen, E. Holm, C.K. Hjulsager, M. Chriel, K. Pedersen, et al., Influenza A(H10N7) virus in dead harbor seals, Denmark, Emerg. Infect. Dis. 21 (2015) 684–687.
[16] N. Wang, W. Zou, Y. Yang, X. Guo, Y. Hua, Q. Zhang, et al., Complete genome sequence of an H10N5 avian influenza virus isolated from pigs in Central China, J. Virol. 86 (2012) 13865–13866.

[17] K.K. To, A.K. Tsang, J.F. Chan, V.C. Cheng, H. Chen, K.Y. Yuen, Emergence in China of human disease due to avian influenza A(H10N8)–cause for concern? J. Inf. Secur. 68 (2014) 205–215.
[18] H. Chen, H. Yuan, R. Gao, J. Zhang, D. Wang, Y. Xiong, et al., Clinical and epidemiological characteristics of a fatal case of avian influenza A H10N8 virus infection: a descriptive study, Lancet 383 (2014) 714–721.
[19] X. Qi, H. Qiu, S. Hao, F. Zhu, Y. Huang, K. Xu, et al., Human infection with an avian-origin influenza a (H10N3) virus, N. Engl. J. Med. 386 (2022) 1087–1088.
[20] S. Herfst, J. Zhang, M. Richard, R. McBride, P. Lexmond, T.M. Bestebroer, et al., Hemagglutinin traits determine transmission of Avian A/H10N7 influenza virus between mammals, Cell Host Microbe 28 (602–613) (2020) e607.