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Novel influenza A viruses and pandemic threats

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A surge in human infections caused by avian influenza A H7N9 virus in China has prompted pandemic concerns and has focused attention on novel influenza A viruses.[1] Since 2013, more than 1400 human beings infected with avian influenza A H7N9 virus, resulting from poultry exposures, have been reported during winter– spring epidemics in China.[2–4] Low pathogenicity avian influenza (LPAI) A H7N9 viruses have spread silently among asymptomatically infected poultry in bird markets and farms. Avian influenza A H7N9 virus infection of human beings can cause severe illness, with high mortality (about 40%) in hospital inpatients.[1–3,5] Since late 2016, more than 600 human infections have been reported from eastern, central, and western provinces, indicating that avian influenza A H7N9 virus circulation among poultry has expanded.[3,6–8] The cumulative number of cases of avian influenza A H7N9 virus infection in human beings now exceeds that of infections caused by highly pathogenic avian influenza A H5N1 virus, which has circulated among poultry and infected people since 1997 (table).[3]

Avian influenza A H7N9 viruses have evolved substantially in the past year. The predominant group of viruses currently circulating among poultry is genetically and antigenically different from previous viruses, meaning that stockpiled pre-pandemic vaccines are unlikely to provide protection. In February, 2017, highly pathogenic avian influenza (HPAI) A H7N9 virus infections were reported in China, indicating that some avian influenza A H7N9 viruses have evolved from LPAI to HPAI.[9,10] HPAI A H7N9 virus can cause high mortality in poultry and possibly even more severe illness in human beings than LPAI A H7N9 virus. Limited human-to-human transmission between family members and between unrelated individuals has been reported.[2,11] Accounting for available virological, epidemiological, and ecological characteristics, avian influenza A H7N9 is considered to present the highest risk among all evaluated novel influenza A viruses in terms of potential to emerge as a pandemic virus and cause substantial human illness (appendix).[12]

Given the pandemic potential of avian influenza A H7N9 and other novel influenza A viruses, it is vitally important to monitor and characterise these viruses. In the past century, all four pandemic influenza viruses were novel influenza A viruses at least partially of avian or swine origin. Several other novel influenza A viruses that are antigenically and

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genetically distinct from seasonal influenza A viruses have also infected human beings (table). In the past two decades, the number of reported infections caused by novel influenza A viruses has steadily increased, partly due to improved surveillance and diagnostic testing, but also due to overcrowding—people, poultry, and pigs have increased opportunities for virus infections.[13] In some cases, avian influenza A H7N9 virus infection has been exported in travellers from mainland China to other countries.[14–16]

Avian influenza A viruses can be either HPAI, occurring only in a subset of H5 and H7 viruses, or LPAI, occurring in all subtypes. HPAI viruses are distinguished from LPAI viruses by molecular and pathogenicity criteria; in general, HPAI virus infection of poultry might cause high mortality rapidly, whereas LPAI virus infection of poultry might be asymptomatic or only cause mild disease. LPAI H5 and H7 viruses can evolve into HPAI viruses, while viruses with new gene constellations can emerge through genetic reassortment. Mild-to-moderate illness, as well as severe and fatal disease, have been reported for human beings with LPAI and HPAI virus infections (table). Thus, disease in poultry infected by LPAI or HPAI viruses might not correlate with disease severity observed in infected human beings.

Pigs are central to the ecology of influenza A viruses because they can be infected with human, avian, and swine influenza A viruses and thus are an important host within which new viruses can arise through genetic reassortment. The swine-origin 2009 H1N1 pandemic virus, now called H1N1pdm09, contained genes from avian, swine, and human influenza A viruses.[17] Sporadic human infections with swine influenza A viruses (so-called variant viruses) can occur through exposure to infected pigs, and outbreaks associated with agricultural fairs have occurred in the USA, including 306 human infections in 2012.[18] Although most variant virus infections have occurred in children and cause mild illness, severe and fatal outcomes have been reported (table), including reports of critical illness in Europe.[19,20]

Because influenza A viruses evolve within their host species, an important public health priority is to strengthen surveillance of influenza A viruses at the animal–human interface, particularly in birds and pigs, and among human beings with mild and severe illness (appendix). Early detection of novel influenza A viruses to reveal their genetic, antigenic, phenotypic, and antiviral resistance characteristics is crucial for pandemic risk assessment and to inform development of candidate vaccine viruses, new therapeutics, and new diagnostic assays. Comprehensive virus characterisation (virological, structural, antigenic, pathogenesis, and transmissibility in animal models) cannot be done only on the basis of genetic data, and such characterisation requires ongoing, timely virus sharing worldwide to inform public health response. Novel influenza A virus detection and characterisation require increased capacity in both animal and public health laboratories worldwide.

The high mortality associated with some avian influenza A virus infections (table) and the emergence of neuraminidase inhibitor resistance during treatment in severely ill patients with avian influenza A H7N9 virus infection highlight the need to improve clinical management of hospital inpatients with influenza virus infections.[1,9,21] Emergence of neuraminidase inhibitor resistance is particularly concerning because neuraminidase

inhibitor antivirals are used to treat patients with influenza virus infections worldwide and are stockpiled for pandemic response. Establishment of ongoing, multisite, regional clinical research platforms can facilitate randomised trials of interventions—including investigational antivirals effective against neuraminidase-inhibitor-resistant viruses, immunomodulators, immunotherapeutics, and different strategies for advanced organ support—for severely ill patients with influenza virus infection. Integrated analyses of prospectively collected clinical and laboratory data (virological monitoring, genetic analyses, antiviral resistance assays, biomarker and immunological measurements) can facilitate understanding of pathogenesis and monitoring of effectiveness of interventions.

Although the evolving landscape of novel influenza A viruses highlights the need for refined public health preparedness and response capabilities, seasonal influenza remains a major challenge. Available influenza vaccines have moderate effectiveness; more effective vaccines and therapies are needed. Efforts to improve the global influenza virus surveillance capacity, rapidly develop high-yielding candidate vaccine viruses and vaccine production processes, and expand vaccine manufacturing capacity and vaccine use worldwide will also strengthen the global response to novel influenza A virus infections and pandemic influenza. Development of next-generation vaccines that stimulate more broadly protective and longer-lasting immunity would greatly improve public health efforts to control both seasonal and pandemic influenza.

Although no evidence exists of sustained human-to-human transmission, avian influenza A H7N9 virus is the greatest pandemic threat to date.[12] It is impossible to know which virus will cause the next influenza pandemic or when or where it will emerge. Nevertheless, ongoing preparedness for avian influenza A H7N9 virus includes the development of candidate vaccine viruses based on recently emerged fifth epidemic wave viruses[9,10] and production of vaccines for evaluation in clinical trials and stockpiling. Continued vigilance is required to monitor changes in the epidemiology or virological characteristics of avian influenza A H7N9 and other novel influenza A viruses that could signal a heightened pandemic risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table:

Subtypes of novel influenza A viruses and clinical syndromes in human infections

	LPAI viruses	HPAI viruses	Variant viruses*
Conjunctivitis	H7N2, H7N3, H7N7, H10N7	H7N3, H7N7	H1N1v, H3N2v
Upper respiratory tract illness	H6N1, H7N2, H7N3, H7N9, H9N2, H10N7	H5N1, H5N6, H7N7	H1N1v, H1N2v, H3N2v
Lower respiratory tract disease, pneumonia	H7N2, H7N9, H9N2, H10N8	H5N1, H5N6, H7N7, H7N9	H1N1v, H3N2v
Respiratory failure, acute respiratory distress syndrome	H7N9, H10N8	H5N1, H5N6, H7N7, H7N9	H1N1v, H3N2v
Multiorgan failure	H7N9, H10N8	H5N1, H5N6, H7N7, H7N9	..
Encephalopathy or encephalitis	H7N9	H5N1	..
Fatal outcomes†	H7N9, H9N2, H10N8	H5N1, H5N6, H7N7, H7N9	H1N1v, H3N2v

A novel influenza A virus is an influenza A virus that has infected humans and is antigenically and genetically distinct from seasonal influenza A viruses circulating among humans. We have included virologically confirmed infections only; laboratory accidents or transmissions from experimentally infected animals were excluded. Data are from published case reports and case series, WHO Disease Outbreak News, and WHO Monthly Risk Assessment Summaries (appendix). LPAI=low pathogenicity avian influenza. HPAI=highly pathogenic avian influenza.

*Variant viruses of swine origin.

†High mortality in reported cases: about 40% for LPAI H7N9, about 50% for HPAI H5N1, and about 70% for HPAI H5N6.