

Pandemic and Avian Influenza A Viruses in Humans

Epidemiology, Virology, Clinical Characteristics, and Treatment Strategy

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KEYWORDS

- Pandemic influenza virus • Avian influenza A viruses • Epidemiology • Virology
- Clinical characteristics • Treatment

KEY POINTS

- Though great progress in the understanding of influenza has been made in the past decades, the incidence, morbidity, and mortality of influenza patients are still high.
- Clinical features of people infected with influenza A virus may range from asymptomatic, to conjunctivitis only, to influenza-like illness, to viral pneumonia complicated with acute respiratory distress syndrome, or shock.
- Severe complications of influenza A virus infection are the orchestrated results of direct viral damage and injury induced by uncontrolled immune response.
- Neuraminidase inhibitors are currently sensitive to most strains of influenza A virus and are widely used worldwide. However, strains that are resistant to clinically used antiviral drugs have emerged.
- As for adjuvant immunomodulators that have been attempted in clinical basis, controversies remain and no concrete conclusion about the efficacy of these drugs can be made based on published data so far. High-level evidence, such as that from randomized controlled trials, is urgently needed to guide clinical practice.

INTRODUCTION

Influenza has raised alarming concern for public health worldwide. From the Spanish flu in 1918 and the Asian flu in 1957 to the 2009 swine flu, millions of people died from influenza pandemics. In the 2009 H1N1 pandemic alone, it

is estimated that, globally, around 201,200 patients died from respiratory diseases caused by influenza A(H1N1)pdm09, and an additional 83,300 patients died from cardiovascular disorders associated with influenza A(H1N1)pdm09 virus infection.¹

Funding Sources: National Science Grant for Distinguished Young Scholars (grant number 81425001/H0104), National Key Technology Support Program from Ministry of Science and Technology (2015BAI12B00) (Dr B. Cao); None (Dr H. Li).

Conflict of Interest: None.

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Clin Chest Med ■ (2016) ■-■

<http://dx.doi.org/10.1016/j.ccm.2016.11.005>

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Normally, the influenza viruses just cause sporadic infection or seasonal epidemics among human beings. However, a pandemic might occur when a novel influenza virus with sufficient transmissibility emerges, to which most people are immune naïve. Recently, more and more novel influenza virus strains have emerged. Though most of the strains reported so far just caused sporadic infections due to the restriction of low transmissibility among human beings, the possibility that accumulative adaptive mutation would confer on a virus the ability to cause a pandemic cannot be excluded. Recent research found that some strains of influenza viruses could gain the ability to spread easily between people by specific mutations.²

During the past decades, great efforts have been put toward exploring new potent antiviral drugs and promoting vaccines worldwide. However, the number of influenza cases did not show any significant decrease during the past decade. Also, the efficacy of most of the current drugs is still under clinical investigation. Meantime, drug resistances have emerged to the antivirals that are commonly used. Also, though antiviral drugs are already available in most areas worldwide, there are still large numbers deaths induced by influenza each year.³

To step up vigilance and improve pandemic preparedness, this article elucidates the virology, epidemiology, pathogenesis, clinical characteristics, and treatment of human infections by influenza A viruses, with an emphasis on the influenza A(H1N1)pdm09, H5N1, and H7N9 subtypes.

EPIDEMIOLOGY

Since 1996, more than 14 subtypes of influenza A viruses have been reported to cause human infections (Fig. 1). Most of the influenza subtypes causing human infections originated from avian strains, whereas only a few strains were from swine, including influenza A(H1N1)pdm09, influenza A(H1N1)v, and influenza A(H3N2)v.^{4–17} In the past 3 years, more subtypes of influenza A virus have crossed the species barrier to cause

human infections than ever before, especially in China, where live poultry markets are popular (see Fig. 1).

Most of the influenza A viruses only caused sporadic or small clusters of infections among human beings. Among all the influenza A viruses reported so far, influenza A(H1N1)pdm09, influenza A(H5N1) and influenza A(H7N9) were documented to have caused large-scale outbreaks in human beings and led to the highest mortality and morbidity rate. Influenza A(H1N1)pdm09, which emerged and caused a worldwide pandemic in 2009, is now established in human population and is circulating seasonally (Fig. 2). Human cases of influenza A(H5N1) was first detected in Hong Kong, China, in 1997 and 18 confirmed cases were reported to the World Health Organization (WHO), including 6 deaths.¹⁸ After 6 years' absence, confirmed influenza A(H5N1) human cases re-emerged in 2003 in Southeast Asia. Since then, the influenza A(H5N1) virus has undergone evolution and generated multiple clades, and gained long-term persistence and geographic migration. As of February 2016, the influenza A(H5N1) virus has migrated to at least 16 countries and more than 846 confirmed cases, including 449 deaths, were reported to WHO.¹⁷ The influenza A(H7N9) virus was first isolated from a human being in March 2013.¹³ Since then, 4 waves of outbreaks among humans have been reported and a total of 722 confirmed cases, including 286 deaths, have been detected. Most of the influenza A(H7N9) cases were from mainland China.¹⁷ Also, similar to the seasonal influenza, most of the influenza A(H7N9) cases emerged in the winter season, except for the first wave (see Fig. 2).

As for transmissibility, it has been confirmed that influenza A(H1N1)pdm09 virus can transmit from person to person efficiently, especially in enclosed environment.¹⁹ By contrast, for most avian originated influenza viruses, including influenza A(H7N9) and influenza A(H5N1), few clustering cases are reported so far and human-to-human transmission is inefficient and unsustainable.^{20–23} However, physicians should be alerted that with the certain mutation and reassortment, some

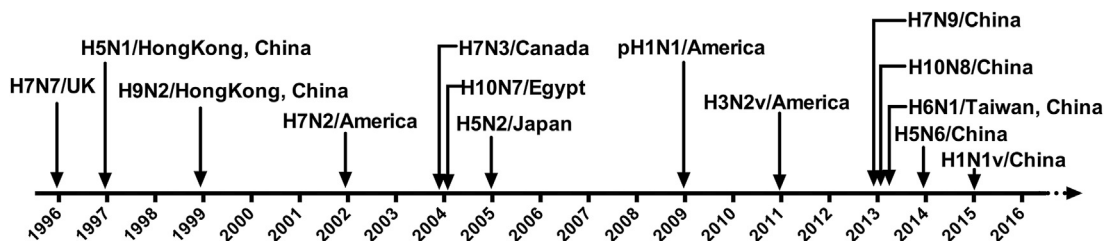


Fig. 1. Year of the first human case infected by specific subtypes of influenza A virus reported worldwide.

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