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H7N9 avian influenza A virus in China: A short report on its circulation, drug resistant mutants and novel antiviral drugs.

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Abstract

Introduction: The first human H7N9 avian influenza virus case was reported in Shanghai in 2013. Shortly thereafter, this virus spread to other regions in China. Molecular analysis indicated that the H7N9 virus is a reassortant virus containing internal genes from the H9N2 virus and previously described mammalian adaption markers, which could allow the virus to adapt efficiently to a mammalian host. Fortunately, there is no evidence of sustained person-to-person spread. Most of the human H7N9 cases have a history of exposure to live poultry markets (LPMs). The circulating H7N9 were low pathogenic viruses, however highly pathogenic H7N9 viruses were recently identified in human cases.

Areas covered: In the present article, the circulation of H7N9 in LPMs of China, the five waves of H7N9 infection in humans, recently identified drug resistant mutants and potential antiviral drugs against H7N9 are discussed; this may provide further understanding of the evolution and pandemic potential of the H7N9 influenza viruses.

Expert commentary: All the data reveal that the major source of H7N9 viruses is LPMs and the H7N9 virus is still circulating widely in China. It is concerning that the recent emergence of highly pathogenic H7N9 viruses may result in highly transmissible viruses in mammalian species.

Keywords

H7N9; drug resistant; highly pathogenic influenza virus; live poultry markets

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Declaration of interest

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1 Introduction

1.1 H7N9 avian influenza virus and live poultry markets

A new avian influenza A virus H7N9 was isolated from patients in China in March 2013; 1223 human cases have been reported to date (March 2017) with 339 fatalities in China [1]. Up to now, H7N9 infections of humans have been reported in China, Malaysia, and Canada [2–4]. Further genomic analysis showed that the novel H7N9 virus is a reassortant virus containing internal genes from the endemic avian H9N2 virus, and the surface genes from H7Nx and HxN9 viruses[5]. Most of the H7N9 viruses isolated from human cases carry mammalian adaptation signatures (e.g., PB2 with the 627K mutation and HA with the 226L mutation), which allows the virus to replicate more efficiently in mammalian cells [4–7]. The circulating H7N9 viruses were low pathogenic viruses carrying the KGR/G motif at the hemagglutinin cleavage site. Recently, a molecular change occurred and highly pathogenic H7N9 viruses are now being identified in human cases; these highly pathogenic viruses had insertions of multiple basic amino acids resulting in the KRKRTAR/G or KGKRIAR/G motifs [8]. It is a concern that continuous circulation of highly pathogenic H7N9 may generate highly transmissible virus in mammalian species.

Most of human H7N9 cases have been associated with previous exposure to birds, poultry, and/or to live poultry markets (LPMs)[9,10]. A majority of households in Southern China have a habit of purchasing live poultry in order to eat fresh poultry meat. This habit is the reason for the high numbers of poultry being sold in LPMs, allowing for a high contact frequency between people and poultry, and making LPMs an ideal place for influenza virus to jump across different avian and mammalian species[11]. Epidemiological surveillance revealed that H7N9 viruses can be isolated from pigeons, chicken, geese, and ducks sold in LPMs and therefore these birds are considered the major source of the H7N9 infection of humans[7,9,12–14].

From March 2013 to early 2014, the H7N9 virus was detected in LPMs in different provinces of China. It has been reported that 1.5% (131/8,900) of bird swabs and environmental samples were positive for H7N9 in Guangzhou, and 44.4% to 50 % of the surveilled LPMs were positive for H7N9 in the same province [15]. Also, 6,740 environmental samples collected and tested from LPMs in Zhejiang showed that 10.09% (680/6740) of the samples were H7N9-positive [16]. In April of 2013, 15 H7N9 viruses were isolated from 422 oral-pharyngeal and cloacal swabs collected from birds and environmental surfaces at five LPMs in Jiangsu [17]. In 2014, 6% (16/283; 4 chickens, 7 ducks, 1 goose, and 4 pigeons) of tracheal, cloacal, and fecal samples, collected from a variety of birds in poultry markets and farms in Jiangsu province, were positive for H7N9 viruses[18]. Additional surveillance data revealed that 1.47 % of samples collected in LPMs in Shanghai were positive for H7N9 markers by real-time RT-PCR [19]. Overall it was concluded, that LPMs are critical places where bird to human transmission of H7N9 viruses occurs. In order to control H7N9 virus spread in China, most of the LPMs in Southern China (Shanghai, Guangzhou, Zhejiang, and Jiangsu) were closed thus hopefully providing a control mechanisms for this epizootic and reduce the burden for human infections [20–22]. However, although 464 LPMs in Shanghai were closed on April 6, 2013, 4 additional human

cases were found that year in Shanghai; nonetheless, in early 2014, Shanghai's LPMs were reopened and subsequently, another 8 human cases were reported shortly thereafter [21]. This illustrates how culturally important LPMs in Southern China are and that besides closure of these markets, transmission of H7N9 to humans cannot be totally stopped.

To date (March 2017), partial or full genomic information on 1,356 strains of H7N9 virus are deposited in the GenBank database. Seven hundred twenty one H7N9 virus strains were isolated from humans so far, and molecular analysis showed that most of the H7N9 virus strains contain the mammalian adaptation markers PB2–627K (581/799) and HA-226L (721/799), while only a small number of these viruses contain neuraminidase inhibitor (NAI) resistant mutations (e.g., 18 strains NA292K, 1 strain NA222K, 4 strains NA119V). However, none of the 557 H7N9 strains isolated from poultry (535 from chicken, 13 from duck, 2 from goose and 7 from pigeon) contain known NAI resistant mutations, and only a few isolates (three out of 557 strains) contain the mammalian adaptation marker PB2–627K.

1.2 Five major waves of outbreaks of Human H7N9 infections since 2013

Outbreaks of the H7N9 virus generally follow a seasonal trend. Since the first H7N9 detection in humans in 2013, there were five major waves of outbreaks occurring which caused a continued public health threat in South-Eastern China. The first wave of human H7N9 infection took place from March 30th, 2013 to September 30th, 2013. At least 130 cases were confirmed in China with fatality rate of approximately 30%. The second wave happened in mainland China, Hong Kong, and Malaysia from October 1st, 2013 to September 30th, 2014. Over 260 additional cases were detected. The third wave was recorded from October 2014 to July 2015. A total of over 220 cases were reported in China, Hong Kong, and Canada. Human-to-human transmission has not been detected. All three waves embody similarity in disease symptoms, severity, and mortality rate, and no clear antigenic drift or shift was detected during wave 1 to 3 from 2013 to 2015 [23]. During the fourth wave of H7N9 infection (September 2015–August 2016[24]), 126 laboratory-confirmed human cases of influenza A (H7N9) virus infection have been reported, 35 of which were fatal. The rate of human infections dropped significantly when compared with the third wave (220 cases); however, the fifth wave of H7N9 virus infection of humans is occurring in China since October 2016; 315 cases have been reported in China during October, 2016 to February 14, 2017[25,26]. Notably, the number of reported cases in January to February of 2017 (305 cases) is higher than the number during the same time in the wave 1 to 4, suggesting that the H7N9 virus is still circulating widely in China; Moreover, the human cases reported during the fifth wave happened in multiple provinces in China, suggested that the H7N9 virus is circulating in an even larger geographic area in China (Figure 1).

These data warrants continuous surveillance of LPMs and humans for the presence of H7N9 viruses and increased public health concerns regarding the extended geographical distribution of H7N9 viruses in China.

1.3 Novel drug-resistant substitutions in the NA protein of H7N9

Neuraminidase inhibitors (NAIs) have been used for the treatment of H7N9 virus infections, however, the NAI resistant substitution NA-R292K emerged soon after initial use of the drug[27]. Further laboratory studies showed that NA-R292K conferred resistance to NAIs such as oseltamivir, zanamivir and peramivir [27–30]. NA-R292K H7N9 virus shows compromised fitness in the ferret model as shown by Marjuki et al. [31,32]. Based on the available gene sequences of H7N9 isolates from humans, a limited number of viruses (13/651) contain the NA292K substitution, however no NA292K substitution was observed in any of the H7N9 viruses isolated from birds.

In addition to NA-R292K, additional NAI resistant substitutions, namely NA-E119V and NA-I222K/R, were found in patients after receiving oseltamivir treatment [31]. In vitro NAI assay indicated that the NA-E119V and NA-I222K/R substitutions conferred resistant to oseltamivir, zanamivir and peramivir to a different extent. NAI treatment of wild-type H7N9 infected ferrets resulted in a modest dose-dependent reduction of viral titers in nasal washes, while only a small reduction of viral titers was detected in nasal washes of ferrets infected with the NA-I222K virus [31]. However, NAI treatment failed to inhibit the replication of H7N9 viruses with the NA-R292K or NA-E119V substitutions [33,34]. Recent studies using NAIs and H7N9 virus infections were performed in ducks [28,35]. After treatment of H7N9 infected mallard ducks for 2 days with a low concentration (2.5ug/L) of oseltamivir carboxylate treatment in water, a NA-I222T variant could be isolated [35]. In the cynomolgus macaque model, a NA-I222T H7N9 variant was found in experimentally H7N9-infected macaques after treatment with NAI; further analysis indicated that the NA-I222T substitution conferred resistance to several NAIs, including oseltamivir and zanamivir[28,35].

Fortunately, so far no NAI resistant H7N9 viruses were isolated from birds, suggesting that the H7N9 viruses circulating in birds are still sensitive to NAIs; however, the repeated emergence of NAI-resistant viruses in humans increases the threat potential of the H7N9 viruses to public and global health.

1.4 Novel drug candidates against H7N9

Currently, two classes of drugs, M2 channel blockers (adamantanes) and neuraminidase inhibitors (zanamivir, oseltamivir, peramivi, and laninamivir) are approved for the treatment of influenza virus infections[36]. Adamantanes are commercial available; among the 4 NAIs, oseltamivir and zanamivir are approved in many countries; peramivir has been approved in USA, Japan, South Korea, and China; and laninamivir is approved only in Japan. However, most influenza A viruses including subtype H7N9 have adamantane-resistant mutations in their respective M2 proteins. NAIs are effective drugs for H7N9 treatment, however, the rapid occurrence of NAI-resistant H7N9 viruses highlights the need for new anti-influenza drugs. Several novel drug candidates were reported to have anti-viral activity against the H7N9 virus.

A novel antiviral drug, Favipiravir (T-705) has recently been approved in Japan for influenza treatment[37,38]. Favipiravir inhibits the RNA-dependent RNA polymerase of influenza

viruses by preventing incorporation of natural ATP and GTP for viral RNA synthesis[39,40]. Both in vitro and in vivo data indicated that Favipiravir has antiviral effect against a broad range of influenza viruses, including highly pathogenic H5N1 and H7N9 viruses[39,41–44]. Watanabe et.al reported that Favipiravir has better therapeutic efficacy against NAI-resistant H7N9 viruses in mice compared to NA inhibitors, suggesting that Favipiravir could be a good treatment option for H7N9 viruses resistant to NAI[44]. Tharakaraman and coworkers found that a broad neutralizing human monoclonal antibody (VIS410), targeting a conserved epitope on the HA protein of influenza A, protected DBA mice from A/Anhui/2013 H7N9 virus infection[45]. Additionally, administration of a combination of VIS410 and oseltamivir significantly decreased virus loads and cytokine levels in the lungs [45]. Another human monoclonal antibody 81.39a was reported to effectively neutralize influenza A viruses with group 1 and 2 hemagglutinins, including the H7N9 virus[46]. A single injection (15 or 45 mg/kg) of 81.39a monoclonal antibody protected mice from a lethal challenge with the H7N9 virus and drastically reduced virus replication in mice lungs[46]. In addition, a murine monoclonal antibody (3c10–3) targeting the NA protein of H7N9 showed antiviral effects against the H7N9 virus in cultured cells and in a mouse model[47]. Other monoclonal antibodies with antiviral effects against the H7N9 were reported by different groups, e.g. HNIgGA6 and HNIgGB5 [48], 1B2 and 1H5 [49], and CR8020 [50]. Notably, Wu et al. reported the first successful treatment of an avian-origin H7N9 infection using convalescent plasma (with a neutralizing antibody titer of 1:80) from a recovered patient[51], which suggested that convalescent plasma or a combination of different monoclonal antibodies could present a potential treatment of H7N9 infections.

Another anti-viral drug candidate, DAS181 recombinant fusion protein with sialidase activity, was shown to inhibit the replication of H7N9 viruses by removing the cellular receptors for influenza viruses, thereby blocking the attachment of the influenza virus to its target cells[52]. In a mouse model, DAS181 protected mice from a lethal wild-type and oseltamivir-resistant H7N9 virus challenge [52]. Notably, DAS181 is now in clinical trials as an inhalation drug to treat seasonal influenza virus infections [52]. Similarly, another anti-viral drug candidate, Sp2CBMTD with sialic acid-binding property, has the ability to mask cellular receptors of influenza viruses and prevents viral attachment [53]. A single dose of 10 or 100 μg drug administration protected 80% or 100% of mice from a lethal H7N9 challenge, respectively. Repetitive Sp2CBMTD administration resulted in 100% survival of the mice even at a very low drug dose (0.1 μg). It could be shown that administration of Sp2CBMTD before challenge induced the expression of IL-6, IL-1, MCP-1, MIP-1 and recruitment of neutrophils to the respiratory tract, which resulted in rapid virus clearance from the mouse lungs [53].

In the face of emerging NAI resistant H7N9 viruses combinations of oseltamivir with other antiviral drugs are the choice for H7N9 treatment. For example, combinations of oseltamivir and fenofibrate inhibited virus replication and prolonged survival time of mice infected with a lethal dose of H7N9, by decreasing pulmonary inflammation and increasing the recruitment of CD4+ and CD8+ T lymphocytes. Thus, the combination of oseltamivir plus fenofibrate improved the outcomes of mice infected with H7N9 virus by simultaneously reducing viral replication and normalizing an aberrant immune response [54]. Similarly, Li et al. [55] reported that co-administration of the non-steroidal anti-inflammatory drug

(celecoxib) in combination with zanamivir improved survival and decreased lung pathology of mice infected with H7N9, since celecoxib ameliorates pulmonary inflammation and thereby increases the chance of survival [55].

2. Expert commentary

Widespread human H7N9 infections in China indicate that this virus is circulating in poultry and LPMs in a wide geographic area of China. Continuous co-circulation with other subtype influenza A viruses may generate novel reassortant viruses with enhanced pathogenicity and mammalian transmissibility; Use of NAIs is critical to treat human H7N9 infections, however, the rapid occurrence of various NAI resistant substitutions in the NA protein makes the control and treatment of human H7N9 infections challenging.

3. Five-year view

Novel anti-viral drug development against influenza A virus in general is urgently needed. Vaccination is the best approach to control a variety of virus infections, however, so far, no commercial H7N9 vaccine is available, neither for birds nor humans. Given the ecology of the H7N9 viruses, it will be difficult to control this virus in poultry and humans without a well-designed and executed vaccination approach.

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3.

Key issues

- The LPMs are critical locations where bird to human transmission of H7N9 viruses occurs.
- The H7N9 virus is still circulating widely in China; recent isolation of highly pathogenic H7N9 viruses warrants continuous surveillance of LPMs and humans for the emergence of H7N9 viruses transmissible in mammalian species.
- Repeated isolation of novel NAI-resistant viruses in humans increases the threat potential of H7N9 viruses to public and global health.
- Several novel drug candidates (e.g., Favipiravir, broad neutralizing monoclonal antibodies, Sp2CBMTD, etc.) were reported to have anti-viral activity against H7N9 viruses.
- Favipiravir (T-705) has been approved for influenza treatment in Japan.

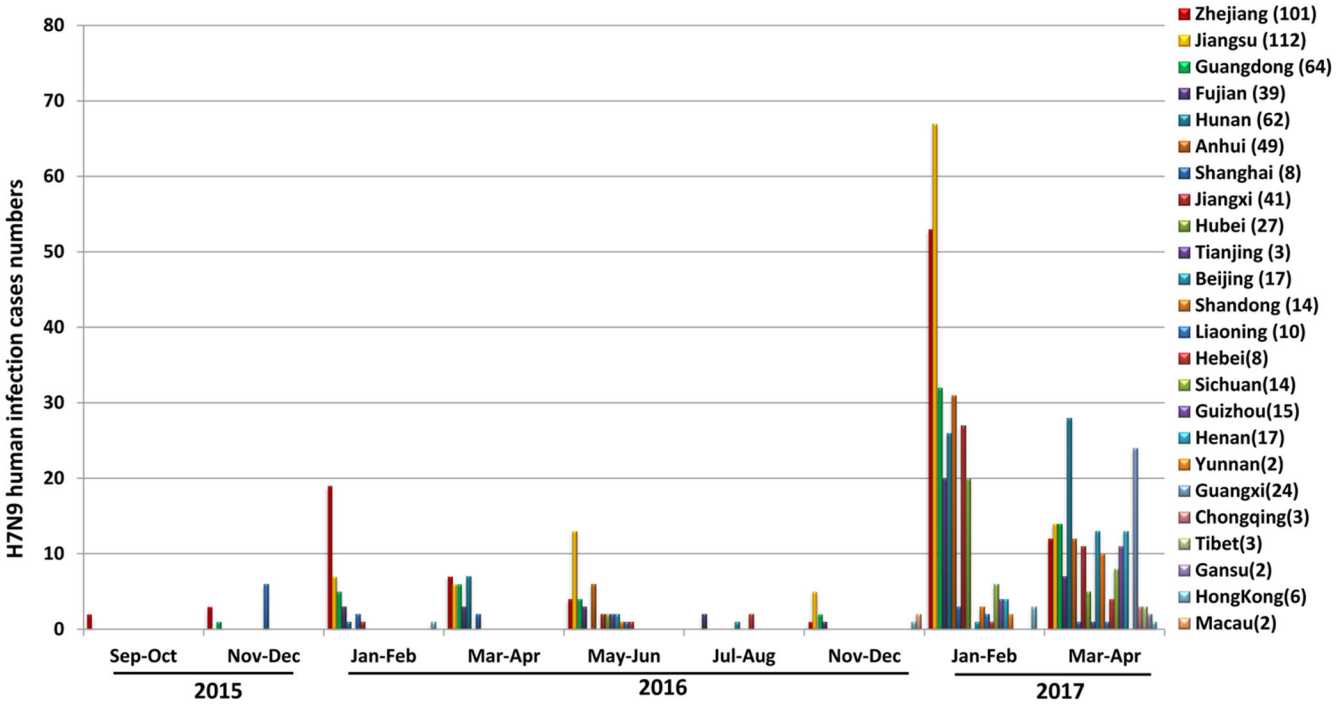

Figure 1.

Numbers of H7N9 Influenza A virus infection in human from September 2015 to April 2017 in China. (No case was reported in September and October of 2016)