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Review

April 2009: an outbreak of swine-origin influenza A(H1N1) virus with evidence for human-to-human transmission

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Abstract

A swine-origin influenza A(H1N1) virus is currently responsible for an outbreak of infections in the human population, with laboratory-confirmed cases reported in several countries and clear evidence for human-to-human transmission. We provide a description of the outbreak at the end of April 2009, and a brief review of the zoonotic potential of swine influenza viruses.

Keywords: Swine influenza; Zoonotic potential; Human-to-human transmission; Pandemic preparedness

Human cases of swine influenza A(H1N1) virus infection have been identified recently in several countries [1]. As reported by the World Health Organization (WHO) on April 27, 2009, 26 laboratory-confirmed cases were detected in Mexico including 7 fatal cases; while 40, 6 and 1 confirmed cases were identified in the USA, Canada, and Spain, respectively [2]. These reports led the WHO to activate the Global Alert & Response Network and to declare a «public health emergency of international concern». On the following days, the number of cases in the USA and Canada expanded, and new confirmed cases were reported in several European and Asian countries [3]. The median age of the 47 patients reported to the Centers for Disease Control and Prevention (CDC) with known age was 16 years (range 3–81 years) [4]. The patients showed symptoms of acute respiratory illness, including fever, cough, and headache, associated with diarrhea and vomiting in some cases [4–6]. First epidemiological evidence for human-to-human transmission of the virus and for its ability to cause community-level outbreaks led the WHO to raise the level of influenza pandemic alert from phase 3 to phase 4 on April 28 [7], and to recommend that all countries should enhance their global surveillance and diagnostic capacity for swine influenza A(H1N1) infections [8]. Evidence for human-to-human spread in more than one country led the WHO on April 29, 2009 to declare phase 5 (pandemic imminent) and to recommend that all countries should activate their pandemic preparedness plans [1].

Clinical signs of influenza in swines were first observed in 1918, coinciding with the «Spanish flu» pandemic in humans. The etiological agent, isolated by Shope in 1930, was an influenza A virus of the H1N1 antigenic subtype [9]. At present, influenza A viruses of the H1N1, H3N2 and H1N2 subtypes are endemic in swine populations worldwide, and are responsible for a highly contagious respiratory disease in pigs [10]. Whereas aquatic birds are known to be the reservoir of influenza A viruses, pigs are frequently involved in interspecies transmission events [11] (Fig. 1). Such events are facilitated by swine husbandry practices, which provide frequent opportunities for contact with other species, particularly humans and birds, and because pigs are naturally susceptible to infection with both avian and human influenza A viruses. This broad susceptibility is due to the fact that α2,3-galactose- and α2,6-galactose-linked sialic acids, which serve preferentially as cellular receptors for avian and human influenza

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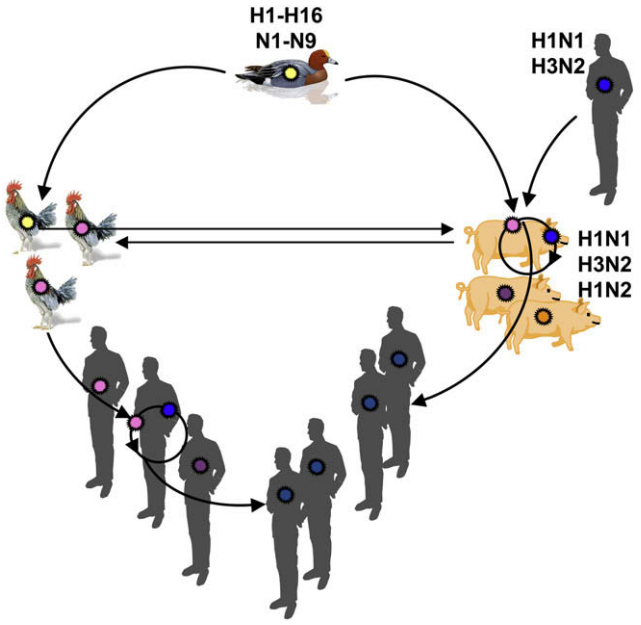

Fig. 1. Models for the role of pigs in interspecies transmission and adaptation of influenza viruses. Pigs serve as reservoirs of H1N1, H3N2 and H1N2 influenza viruses which can be transmitted to humans [10]. They may also serve as intermediate hosts in the process of transmission of avian influenza viruses from the wild birds or poultry to humans [10]. Establishment of new influenza viruses in the human population requires full adaptation and the potential for human-to-human transmission. This may be acquired either progressively through successive inter-human transmissions, or through reassortment in the pig of avian, swine and/or human viruses, as pigs are susceptible to and allow productive replication of avian and human influenza viruses. Only reassortant viruses with a gene constellation that confers efficient replication and transmission in humans can persist in the human population. Along the pathway to adaptation to humans, increased virulence does not seem to be a prerequisite and is likely to involve determinants distinct from those related to species specificity.

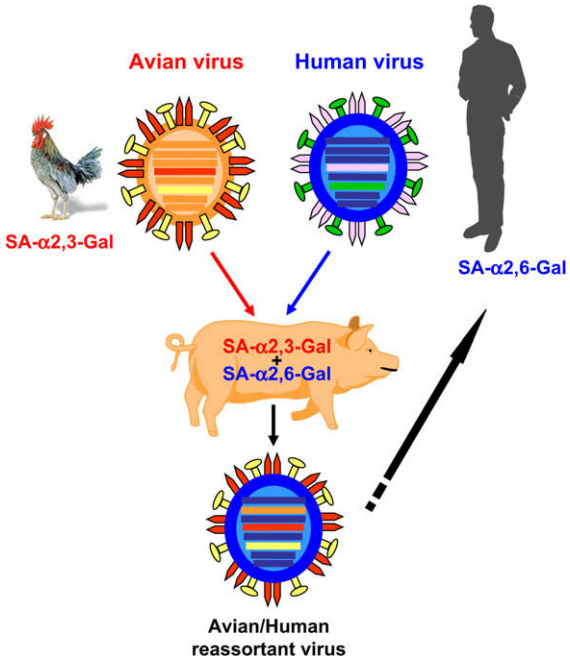

Fig. 2. Schematic representation of a genetic reassortment between an avian and a human influenza virus taking place in the pig. Avian viruses bind preferentially to α2,3-galactose-linked sialic acids (SA-α2,3-Gal), whereas human viruses bind preferentially to SA-α2,6-Gal. This receptor binding specificity correlates with the relative predominance of SA-α2,3-Gal and SA-α2,6-Gal at the sites of viral multiplication in birds and in humans, respectively, and involves specific residues in the receptor binding site of the hemagglutinin (HA) [23]. The susceptibility of pigs to both avian and human viruses is related to the presence of both SA-α2,3-Gal and SA-α2,6-Gal on the tracheal epithelium cells [12]. Co-infection with an avian and a human virus, facilitated by frequent contacts of domesticated pigs with birds and humans, can give rise to progeny reassortant viruses presenting a new combination of genomic segments corresponding to a mixture of the parental genomes [10,15,16]. A specific constellation may confer increased replication potential in pigs and/or increased transmission potential to another species.

viruses, respectively, are both present on the tracheal epithelium surface in pigs [12]. Following transmission to pigs, avian and human influenza viruses undergo diverging evolution and establish new genetic lineages, usually referred to as «avian-like» and «human-like» swine lineages, respectively [10]. The 1918 swine outbreak descriptions, taken together with the recent phylogenetic analyses of the reconstituted 1918 human influenza virus sequences [13,14], support the hypothesis that the virus most probably spread from humans to pigs. Although the exact origin of the 1918 human virus is unknown, phylogenetic analysis suggests that the virus came from an avian reservoir and entered the human population either directly or through an intermediate host [13,14]. Co-infection of pigs with two viruses of different origins or lineages can give rise to progeny reassortant viruses presenting a new constellation of the eight genomic segments [10,15,16] (Fig. 2). A specific constellation may confer increased replication potential in pigs and/or increased transmission potential to another species. The pig has been proposed as an intermediate host for the emergence of the avian–human reassortant viruses responsible for the 1957 and 1968 pandemics, but there is no direct evidence for this hypothesis.

As a result of multiple introductions of avian and human viruses, reassortment events, and/or geographical separation, there are distinct lineages existing within each of the three antigenic subtypes of swine influenza A viruses. In particular, the H1N1, H3N2 and H1N2 influenza viruses circulating in European and in North-American populations of pigs are genetically and antigenically distinct [10,11]. Full or partial sequences are available for each of the eight genomic segments of swine influenza A(H1N1) viruses associated with two recent human cases in California [5]. Sequence data indicate that both viruses are genetically similar and present a unique combination of genomic segments that had not been reported previously among swine or human influenza viruses [5]. The NA and M segments are most closely related to corresponding segments from influenza viruses isolated from pigs in Eurasia, whereas the six remaining segments derive from influenza viruses isolated from pigs in North-America [17]. Where and how this reassortant virus emerged is still unknown. Given the relatively low number of laboratory-confirmed cases to date (148 cases on April 29, 2009) [3], it is difficult to predict the transmissibility and pathogenicity that