



ELSEVIER



INSTITUT PASTEUR

Microbes and Infection xx (2009) 1–4



www.elsevier.com/locate/micinf

Original article

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

Nadia Naffakh*, Sylvie van der Werf

Institut Pasteur, Unité de Génétique Moléculaire des Virus à ARN, URA 3015 CNRS, EA 302 University Paris-Diderot Paris 7, 25 rue du Dr Roux, 75724 Paris Cedex 15, France

Received 28 April 2009; accepted 4 May 2009

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.

© 2009 Published by Elsevier Masson SAS.

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 α 2,3-galactose- and α 2,6-galactose-linked sialic acids, which serve preferentially as cellular receptors for avian and human influenza

* Corresponding author. Tel.: +33 1 45 68 88 11; fax: +33 1 40 61 32 41.
E-mail address: nnaffakh@pasteur.fr (N. Naffakh).

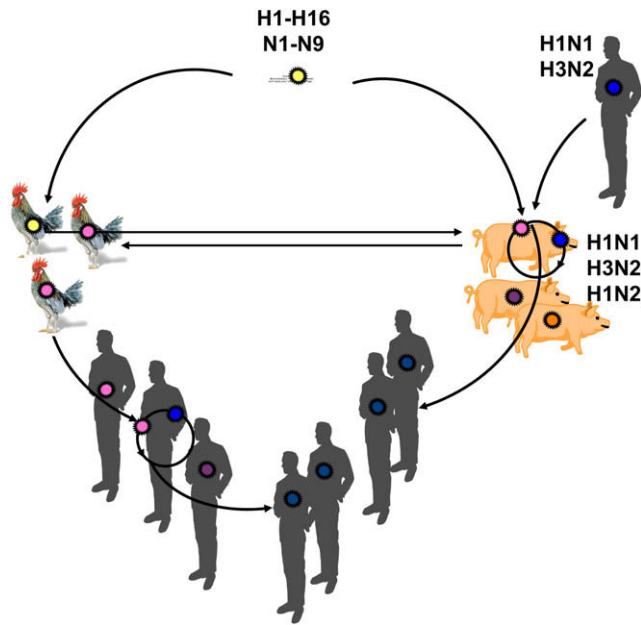


Fig. 1. Models for the role of pigs in interspecies transmission and adaptation of influenza viruses. Pigs serve as reservoirs of H1N1, H3N2 and H1N2 influenza viruses which can be transmitted to humans [10]. They may also serve as intermediate hosts in the process of transmission of avian influenza 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.

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.

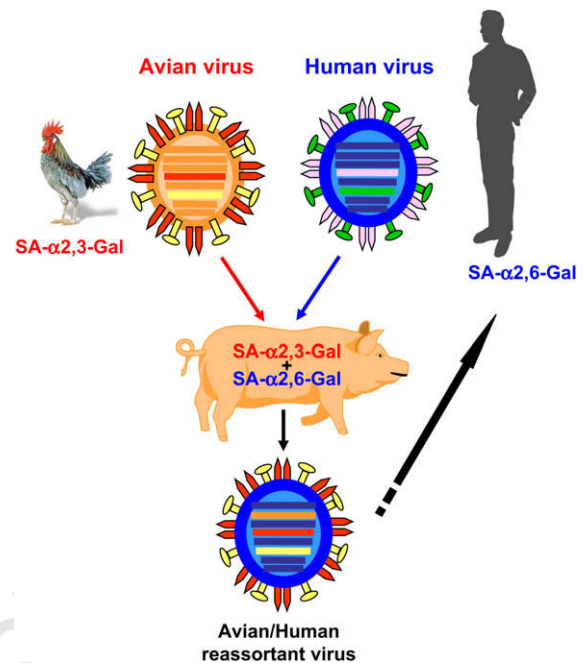


Fig. 2. Schematic representation of a genetic reassortment between an avian and a human influenza virus taking place in the pig. Avian viruses bind preferentially to α 2,3-galactose-linked sialic acids (SA- α 2,3-Gal), whereas human viruses bind preferentially to SA- α 2,6-Gal. This receptor binding specificity correlates with the relative predominance of SA- α 2,3-Gal and SA- α 2,6-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- α 2,3-Gal and SA- α 2,6-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.

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

this specific genotype of swine influenza A(H1N1) virus will have in humans. Its potential for virulence in pigs also remains to be evaluated.

The human seasonal influenza A(H1N1) strain included in the current influenza vaccine is unlikely to provide protection against the new swine A(H1N1) virus. As of April 28, 2009, the WHO recommended that the production of the seasonal vaccine should continue as planned before the outbreak, subject to re-evaluation as the situation evolves [7]. If a decision was made to have a vaccine produced against the swine A(H1N1) virus, the expected production delay would be around 4 months. Meanwhile, specific disease control strategies would rely mostly on prophylactic and therapeutic use of antiviral drugs. The sequence of the swine A(H1N1) virus M2 gene revealed an Ser-31-Asn mutation which is known to confer resistance to the M2 proton channel inhibitors (amantadine and rimantadine). All viruses tested so far (13 out of 64 viruses isolated from patients in the United States) are susceptible to the NA inhibitors (oseltamivir, sold as Tamiflu[®], and zanamivir, sold as Relenza[®], as well as peramivir and A-315675, two investigative inhibitors) [18].

To date, swine influenza viruses are not known to have caused a global outbreak of influenza in humans. Although seroepidemiological studies have documented a high seroprevalence in people with occupational swine exposure [15,19,20], only sporadic cases of swine influenza in humans have been reported (for a review, see [21]). Most patients had had contact with pigs. Fatal cases of human infection with swine influenza A(H1N1) viruses have been occasionally reported but most cases caused a mild influenza-like illness, and evidence for subsequent human-to-human transmission of the virus was very limited [21]. In one instance however, during the 1976 outbreak of swine influenza due to an H1N1 virus in Fort Dix, New Jersey, in the United States, significant human-to-human transmission was observed with up to 230 infection cases resulting in 12 hospitalizations and 1 death [22]. Although it is likely that pigs were the source of the virus, no evidence of exposure to pigs was found.

The successful adaptation and establishment of a swine virus in the human population probably require a multistep evolutionary process, leading to a specific combination of viral factors that confers efficient replication and transmission in humans and the ability to compete with circulating human influenza viruses. Multiple genetic determinants of host-range and pathogenicity have been identified for several proteins of influenza A viruses [23,24]. However our understanding of the multigenic interplay between viral and host factors is still incomplete, and further genomic and functional studies will be required to identify predictors of the pandemic potential of animal influenza A viruses. The current outbreak of swine influenza A(H1N1) virus underscores the necessity for all nations to have effective pandemic preparedness plans and coordinated responses. It also highlights the need for close epidemic surveillance and control of influenza infections in pigs as well as in poultry, and the need for additional antiviral agents that could be used as a first line of defense against zoonotic influenza.

Acknowledgments

We thank David Ojcius for critical reading of the manuscript and helpful suggestions.

References

- [1] World Health Organization, Swine Influenza Statement by WHO Director-General, Dr Margaret Chan, 29 April 2009, World Health Organization, Geneva, 2009, http://www.who.int/mediacentre/news/statements/2009/h1n1_20090429/en/index.html.
- [2] World Health Organization, Swine Influenza Update 3, 27 April 2009, World Health Organization, Geneva, 2009, http://www.who.int/csr/don/2009_04_27/en/index.html.
- [3] World Health Organization, Swine Influenza Update 5, 29 April 2009, World Health Organization, Geneva, 2009, http://www.who.int/csr/don/2009_04_29/en/index.html.
- [4] CDC, Update: infections with a swine-origin influenza A(H1N1) virus – United States and other countries, April 28, 2009, *Morbidity and Mortality Weekly Report* 58 (2009) 431–433. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5816a5.htm>.
- [5] CDC, Swine influenza A(H1N1) infection in two children – Southern California, March–April 2009, *Morbidity and Mortality Weekly Report* 58 (2009) 400–402. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5815a5.htm>.
- [6] CDC, Update: swine influenza A(H1N1) infections – California and Texas. *Morbidity and Mortality Weekly Report* 58, in press. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm58d0424a1.htm>.
- [7] World Health Organization, Swine Influenza Statement by WHO Director-General, Dr Margaret Chan, 27 April 2009, World Health Organization, Geneva, 2009, http://www.who.int/mediacentre/news/statements/2009/h1n1_20090427/en/index.html.
- [8] World Health Organization, Guidance to Influenza Laboratories: Diagnosing Swine Influenza A/H1N1 Infections of Current Concern, World Health Organization, Geneva, 2009. http://www.who.int/csr/resources/publications/swineflu/guidance_laboratories/en/index.html.
- [9] R.E. Shope, The etiology of swine influenza, *Science* (New York, N.Y.) 73 (1931) 214–215.
- [10] I.H. Brown, The epidemiology and evolution of influenza viruses in pigs, *Veterinary Microbiology* 74 (2000) 29–46.
- [11] K. Van Reeth, Avian and swine influenza viruses: our current understanding of the zoonotic risk, *Veterinary Research* 38 (2007) 243–260.
- [12] T. Ito, J.N. Couceiro, S. Kelm, L.G. Baum, S. Krauss, M.R. Castrucci, I. Donatelli, H. Kida, J.C. Paulson, R.G. Webster, Y. Kawaoka, Molecular basis for the generation in pigs of influenza A viruses with pandemic potential, *Journal of Virology* 72 (1998) 7367–7373.
- [13] A.H. Reid, J.K. Taubenberger, T.G. Fanning, Evidence of an absence: the genetic origins of the 1918 pandemic influenza virus, *Nature Reviews* 2 (2004) 909–914.
- [14] G. Vana, K.M. Westover, Origin of the 1918 Spanish influenza virus: a comparative genomic analysis, *Molecular Phylogenetics and Evolution* 47 (2008) 1100–1110.
- [15] L. Campitelli, I. Donatelli, E. Foni, M.R. Castrucci, C. Fabiani, Y. Kawaoka, S. Krauss, R.G. Webster, Continued evolution of H1N1 and H3N2 influenza viruses in pigs in Italy, *Virology* 232 (1997) 310–318.
- [16] I.H. Brown, P.A. Harris, J.W. McCauley, D.J. Alexander, Multiple genetic reassortment of avian and human influenza A viruses in European pigs, resulting in the emergence of an H1N2 virus of novel genotype, *The Journal of General Virology* 79 (Pt 12) (1998) 2947–2955.
- [17] V. Trifonov, H. Khiabaniyan, B. BGreenbaum, R. Rabadan, The origin of the recent swine influenza A(H1N1) virus infecting humans, *Euro-surveillance* 14 (17) (2009). <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19193> [article 3].
- [18] CDC, Update: drug susceptibility of swine-origin influenza A (H1N1) viruses, April 2009. *Morbidity and Mortality Weekly Report* 58, in press. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm58d0428a1.htm>.

- 343 [19] G. Ayora-Talavera, J.M. Cadavieco-Burgos, A.B. Canul-Armas, Sero- 353
344 logic evidence of human and swine influenza in Mayan persons, 354
345 *Emerging Infectious Diseases* 11 (2005) 158–161. 355
- 346 [20] C.W. Olsen, L. Brammer, B.C. Easterday, N. Arden, E. Belay, I. Baker, 356
347 N.J. Cox, Serologic evidence of H1 swine influenza virus infection in 357
348 swine farm residents and employees, *Emerging Infectious Diseases* 8 358
349 (2002) 814–819. 359
- 350 [21] K.P. Myers, C.W. Olsen, G.C. Gray, Cases of swine influenza in humans: 360
351 a review of the literature, *Clinical Infectious Diseases* 44 (2007) 361
352 1084–1088. 362
- [22] R.A. Hodder, J.C. Gaydos, R.G. Allen, F.H. Top Jr., T. Nowosiwsky, 353
P.K. Russell, Swine influenza A at Fort Dix, New Jersey (January– 354
February 1976). III. Extent of spread and duration of the outbreak, *The 355
Journal of Infectious Diseases* 136 (Suppl.) (1977) S369–375. 356
- [23] G. Neumann, Y. Kawaoka, Host range restriction and pathogenicity in 357
the context of influenza pandemic, *Emerging Infectious Diseases* 12 358
(2006) 881–886. 359
- [24] N. Naffakh, A. Tomoiu, M.A. Rameix-Welti, S. van der Werf, Host 360
restriction of avian influenza viruses at the level of the ribonucleopro- 361
teins, *Annual Review of Microbiology* 62 (2008) 403–424. 362

UNCORRECTED PROOF