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Emergence of a novel swine-origin influenza A virus (S-OIV) H1N1 virus in humans

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ABSTRACT

A recently emerged novel influenza A H1N1 virus continues to spread globally. The virus contains a novel constellation of gene segments, the nearest known precursors being viruses found in swine and it likely arose through reassortment of two or more viruses of swine origin. H1N1, H1N2 and H3N2 subtype swine influenza viruses have occasionally infected humans before but such zoonotic transmission events did not lead to sustained human-to-human transmission in the manner this swine-origin influenza virus (S-OIV) has done. Its transmission among humans appears to be higher than that observed with seasonal influenza. Children and young adults appear to those most affected and also those who appear to maintain transmission. Clinical disease generally appears mild but complications leading to hospitalization can occur, especially in those with underlying lung or cardiac disease, diabetes or those on immunosuppresive therapies. There are concerns that the virus may reassort with existing human influenza virus giving rise to more transmissible or more pathogenic viruses. The virus appears to retain the potential to transmit back to swine and thus continued reassortment with swine viruses is a cause for concern.

1. Introduction

The one predictable aspect of influenza is its unpredictability. While attention was focused on the threat of an avian influenza H5N1 pandemic emerging from Asia, a novel influenza virus of swine origin emerged in North America, and is now spreading worldwide. The virus appears to confound us even in its nomenclature[1] and the semantics of what constitutes a pandemic.[2]

During April 2009, a novel H1N1 virus was detected in epidemiologically unrelated cases of influenza-like illness in California and was subsequently recognized to be the cause of a major outbreak of respiratory disease in Mexico that had been ongoing for some weeks previously. The virus was found to be an H1N1 virus that was antigenically and genetically unrelated to human seasonal influenza viruses and genetically related to viruses known to circulate in swine. In the ensuing weeks (as of 1st June 2009) this swine-origin influenza virus (S-OIV) H1N1 virus caused 17,410 virologically confirmed human cases and 115 deaths in 62 countries in the Americas, Europe, Asia and Australasia. The majority of the cases so far have been in Mexico (5029 with 97 deaths), USA (8975 with 15 deaths) and Canada (1336 with 2 deaths).

Influenza A viruses are single stranded RNA viruses of negative sense with an eight segmented genome that belongs to the family Orthomyxoviridae. The viral haemagglutinin (HA) and neuraminidase (NA) proteins are envelope glycoproteins and are the key antigens against which humoral immune responses are directed. They are used for the subtyping of influenza A viruses into 16 HA and 9 NA subtypes. Aquatic birds are the natural reservoir of all influenza virus subtypes but some subtypes have become established in other species; H1 and H3 in pigs, H3 and H7 in horses and recently equine H3 subtype viruses have become established in dogs in North America. Pandemics are believed to arise when a novel avian influenza HA and/or NA (together with the PB1 gene segment in the pandemics of 1957 and 1968) is picked up through reassortment by pre-existing human influenza viruses (reviewed in Ref. [3]), or by a purely avian virus adapting to efficient human transmission.[4] Pigs have been proposed to serve as intermediate hosts where such adaptation and reassortment of avian precursors may occur (reviewed in Ref. [5]).

Highly pathogenic avian influenza (H5N1) is entrenched in poultry flocks worldwide and continues to transmit zoonotically to humans, causing a disease with overall mortality of over 60%. The argument for the preparations for a possible H5N1 pandemic was not its inevitability or even that it was the most likely pandemic candidate, but the severity of such a rare outcome.[6] This threat spurred global influenza pandemic preparedness in relation to options for containment, logistics of health care, non-pharmaceutical inter-

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ventions, antivirals and vaccines. All of these, with the possible exception of vaccines, are equally applicable in the current global efforts to confront the novel S-OIV H1N1 virus.

2. Influenza viruses in swine

The H1N1 pandemic of 1918 is believed to have also affected swine in 1918.[7] Its descendents have remained endemic in swine up to now. The first influenza viruses to be isolated in culture were swine H1N1 influenza viruses[8] and they are antigenically very similar to the recently reconstructed 1918 pandemic virus.[9] These swine H1N1 viruses, called the "classical swine" H1N1 viruses, continued to circulate in pigs in Asia, the America's and until the 1980s also in Europe. Until relatively recently, they remained antigenically stable.[10] The emergence in 1979 of a novel H1N1 virus of avian origin in pigs in Europe (avian-like swine H1N1 viruses) led to the replacement of classical swine H1N1 viruses from pigs in Europe but the classical swine viruses continue to circulate in Asia and America up to now. Human H3N2 viruses have repeatedly established themselves in swine at different times in Europe and in Asia, and more recently in USA. In Europe, the avian-like swine H1N1 viruses reassorted in swine with human origin H3N2 viruses, to give rise to the European swine H3N2 lineage which have avian-like swine H1N1 internal genes and human origin H3 and N2. Separately, the European avian-like swine H1N1 viruses picked up human N2 genes to generate H1N2 viruses (reviewed in Refs. [11,12]).

In Asia, classical swine H1N1 continues to be endemic in pigs. In addition, different lineages of human H3N2 viruses have repeatedly become established in swine.[13–15] Interestingly, each H3N2 lineage undergoes less antigenic drift in swine than in humans, leading Shortridge et al. to presciently note that "persistence of such (human) influenza viruses in pigs could serve as a reservoir for subsequent infection of man".[14] European swine H3N2 viruses,[16] other avian origin H1N1 viruses[17] and other reassortants have also been reported in Asia (reviewed in Refs. [11]).

Classical swine H1N1 remained the dominant swine virus in North America until the 1998 when "triple reassortant H3N2 viruses began to be isolated in the USA.[18] These viruses had HA, NA and PB1 of human origin, NP, M and NS genes of classical swine and PB2 and PA genes of North American avian virus origin.[19,20] Unlike the classical swine viruses which at most caused mild respiratory disease in pigs, these triple reassortant viruses had unusual pathogenicity being associated with spontaneous abortion and even death of pigs. Furthermore, they continued to acquire H3 HA genes of diverse origin, very likely through repeated acquisition of different human HA genes. The triple reassortant H3N2 viruses also continued to acquire other virus genes via reassortment to generate triple reassortant H1N2 viruses (acquiring a classical swine H1) or H1N1 viruses (acquiring both H1 and N1 from classical swine viruses). These triple reassortant H1N1 and H1N2 viruses have become antigenically very diverse and increasingly more distant from the classical swine H1N1 viruses.[10]

During this time there was also a range of other reassortant swine viruses detected in Europe (e.g. H1N2; H1N7) and Asia (H3N1; H3N2; H1N1; H1N2).[11,15,21–24] Furthermore, avian viruses have been transiently detected in swine in many parts of the world, including H1N1, H9N2, H4N6 and H5N2[13,17,22,25–27] but it is not clear whether these viruses will establish long term transmission in pigs. While highly pathogenic H5N1 viruses have been occasionally detected in pigs,[22,28] experimental studies indicate that pig-to-pig transmission is limited[29,30] and serological studies do not reveal widespread transmission of H5N1 viruses in pigs in areas where this virus remains endemic in poultry.[29,31]

3. Zoonotic transmission of swine viruses to humans and swine as intermediate hosts for inter-species transmission of avian viruses to humans

Human and avian viruses can infect pigs[32] and the respiratory tract of pigs is believed to express both sialic acid (SA) α2,3Gal (bind avian influenza) and SAα2,6Gal (bind human influenza) receptors that will permit infection with both avian and human influenza viruses.[33] There is also ample evidence that avian and human viruses establish long term lineages in pigs and that these viruses reassort in pigs (see above). Reassortment between avian and human viruses implies infection of both viruses in the same host and same cell. Humans are poorly permissive to avian viruses[34] and avian species are poorly permissive to human viruses. Since swine are known to be permissive to both avian and human influenza viruses, they have been proposed as a "mixing vessel" for the generation of pandemic viruses through reassortment.[35] It should be noted however, that there is no direct evidence that pigs played a role in the genesis of any of the three pandemics of the 20th century.

In common with human influenza viruses, swine influenza viruses generally bind to SAα2,6Gal receptors.[36] Swine viruses of subtypes H1N1, H3N2 and H1N2 viruses of diverse lineages have been reported to zoonotically transmit and cause disease in humans causing flu-like illness but was fatal in 17% of cases.[12,37,38] Such transmission has been detected in North America, Europe and Asia, but may be more common than hitherto recognized. In 1976, 13 cases of classical swine H1N1 with one death was reported at Fort Dix, New Jersey and serological testing revealed the evidence of infection in many others at the same military facility.[39] This led to the USA-wide swine-flu vaccine campaign which was later aborted because of occasional side effects (Guillain–Barre syndrome), and even more importantly, because the anticipated swine-flu pandemic failed to materialize.

Since December 2005, the triple reassortant H1 viruses have transmitted to 11 humans in the USA, 10 caused by the triple reassortant H1N1 and one by the triple reassortant H1N2 virus.[40] Another transmission of an European swine H1N1 virus was reported in Europe.[41] Some of these patients had close exposure to pigs. While some of these zoonotic infections let to occasional transmission to other patients, none of them led to sustained human-to-human transmission.

Antibodies to swine influenza viruses (H1N1; H1N2) have been detected in humans with exposure to pigs.[42,43] The true incidence of natural human infection with swine viruses remains unclear.

4. Genetic and antigenic characterization of swine-origin influenza virus H1N1

Phylogenetic analyses of the current novel S-OIV H1N1 revealed that the HA, NP and NS genes arise from the classical swine H1N1 lineage, the NA and M genes from the avian-like Eurasian swine H1N1 lineage while the PB2, PB1 and PA are from the North America H3N2 triple reassortant linage. While it is true that the S-OIV H1N1 virus has virus gene segments of swine, human and avian origin, these genes were already established in the triple reassortant swine in North America and in the Eurasian swine H3N2 or H1N1 viruses for many years. Thus the immediate reassortment event that led to the generation of S-OIV was very probably reassortment between two or more swine viruses, viz. the triple reassortant H1N2 (or H1N1) and the Eurasian H3N2 or H1N1 swine viruses.[43b] The currently available genetic sequence information does not allow identification of the immediate precursor of the S-OIV H1N1 virus or where such a reassortment may have taken place. This reflects the paucity of surveillance of swine influenza viruses worldwide,