

NOVEL "SWINE-ORIGIN" H1N1 INFLUENZA IN PEOPLE: THOUGHTS FROM A SWINE FLU VIROLOGIST

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A novel H1N1 influenza virus emerged in humans in Mexico and North America in March and April 2009 and subsequently spread to Europe and other continents. Phylogenetic analyses showed that the virus is a reassortant of at least two existing swine influenza viruses (SIVs) (Garten et al. 2009⁽³⁾, Smith et al. 2009⁽⁹⁾). Six gene segments were similar to those of triple reassortant SIVs circulating in pigs in North America. The genes encoding the neuraminidase and matrix proteins, on the other hand, were most closely related to those in SIVs circulating in Europe or Asia. Influenza viruses of H1N1, H3N2 and H1N2 subtypes are enzootic in swine populations worldwide, but the antigenic and genetic constellation of the predominant viruses is entirely different in North America versus Europe or Asia (Olsen et al. 2006⁽⁷⁾). In North America, viruses of the "classical" H1N1 lineage were the dominant cause of swine influenza until the late 1990s and H3N2 viruses have only become widespread since 1998. The predominant H3N2 viruses were so-called triple reassortants with genes of classical swine, avian and human origin. These viruses further reassorted with classical swine H1N1 viruses, leading to H1N2 and reassortant H1N1 viruses (Vincent et al. 2008⁽¹¹⁾). In Europe, the predominant H1N1 SIVs have an entirely avian genome and were introduced from wild ducks to pigs in 1979 (Pensaert et al. 1981⁽⁸⁾). These avian-like H1N1 viruses have established a stable lineage and have replaced the classical H1N1 viruses soon after their introduction. They are currently cocirculating with H3N2 and H1N2 SIVs, which also differ from their counterparts in the US. The European swine H3N2 viruses have been derived from the human virus causing the "Hong Kong flu" pandemic in 1968, but their internal genes have been obtained through reassortment with the avian-like H1N1 virus. The dominant H1N2 viruses retained the genotype of these reassortant H3N2

viruses, but they have acquired an H1 gene through reassortment with a human H1N1 virus from the early 1980s (Brown et al. 1998 ⁽²⁾).

While the well-known SIVs cause only sporadic human infections (Myers et al. 2007 ⁽⁶⁾), the novel H1N1 virus transmits efficiently between humans and the World Health Organization declared the first flu pandemic in 41 years in June 2009. The novel H1N1 virus most likely emerged in pigs, though the specific virus had not yet been reported in swine populations anywhere in the world at the time of its discovery in humans. Thereafter, between May and October 2009, the novel H1N1 virus has been isolated from swine farms in Canada, Argentina, Australia, Singapore, (Northern) Ireland, Norway, USA, Japan and Iceland (2). Humans were suspected to be the source of infection in all cases and pigs so far did not contribute to the spread of the novel pandemic virus in humans. Recent experimental infection studies have also confirmed the susceptibility of pigs to the virus and its capacity to transmit between pigs (Brookes et al. 2009 ⁽¹⁾, Lange et al. 2009 ⁽⁵⁾). One crucial question, however, is to what extent pre-existing immunity against SIVs that are enzootic in Europe may protect pigs against the novel H1N1 virus. Interestingly, preliminary investigations of sera from pigs immune through infection or vaccination with European SIVs revealed greater cross-reactivity than one would expect based on antigenic and genetic analyses as such. In the first part of my lecture, I will focus on the origin of the novel H1N1 virus and present my personal viewpoint on its significance for the swine industry as well as for human health.

Pigs have been assigned a role in the generation of pandemic influenza viruses for humans for decades. In theory, such pandemic viruses could emerge following modification of an established swine strain, adaptation of a strain of avian origin to mammals, or reassortment between avian and human influenza viruses (Ito et al. 1998 ⁽⁴⁾). It is a classical theory that pigs are more susceptible to avian influenza viruses than humans, and that they are essential intermediary hosts for the introduction of avian viruses or avian virus genes in the human population. The recent outbreaks of H5N1 avian influenza in Asia, as well as the current novel H1N1 pandemic have started to change our classical viewpoint of the role of the pig in the transmission of influenza viruses to humans. H5N1 and other wholly avian viruses have been able to infect pigs under experimental conditions and in nature, but there is also a strong

barrier to infection of pigs with such viruses (Van Reeth 2007⁽¹⁰⁾). In addition, avian influenza viruses largely lack the capacity to spread between pigs. The human cases of infection with H5N1 were invariably due to direct contact with infected poultry, and the virus still fails to spread efficiently between humans. On the contrary, swine-adapted influenza viruses of various subtypes and genotypes have been shown to transmit to humans on several occasions, but second generation transmission was extremely rare (Myers et al. 2007⁽⁶⁾). The novel H1N1 virus is the first virus of presumed swine origin that resulted in efficient transmission between humans. Unfortunately, we still have a very limited understanding of what is needed for efficient replication in and adaptation of avian influenza viruses to pigs. Similarly, it remains unknown what factors trigger transmission of influenza viruses from pigs to humans at the physiological and molecular level, or what is needed for the further transmission of such viruses between humans. In the second part of my lecture, I will review our current knowledge about these issues.

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