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Interspecies transmission of influenza to swine: bird flu or you?

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Swine producers and veterinarians have had to deal with the legacy of the 1918 pandemic and the focus that pigs were responsible for the 1918 pandemic as mixing vessels of influenza. The idea has been that they were the mechanism of adaptation of avian H1N1 influenza virus to mammalian cells. This has historically been thought to be a very difficult task and one that rarely occurred, but the thinking was that if it occurred it would be through pigs. Bird flu, or high pathogenicity avian influenza H5N1 virus that was initially detected in Hong Kong in 1997 has drastically changed that paradigm. Subsequently, Taiwan proved that the reservoir of the virus that killed people as early as 1997 was the mainland of China, which was a provider of live poultry to the Hong Kong markets. Rather than eliminating the virus from the poultry sold to the live markets, the virus continued to circulate in domestic poultry of the mainland until 2003, where the virus continued to increase in virulence through repeated passage through domestic poultry. It is likely that killed vaccine was used in those flocks which enabled the virus to maintain itself with minimal clinical expression while it continued to increase in virulence. By 2005, the virus had become sufficiently virulent that the virus became lethal for its normal host species, free flying waterfowl and shore birds. The May 2005 Lake Qinghai waterfowl die off became the poster child for what is now referred to as bird flu. It is clear that its increase in virulence for domestic poultry and free flying waterfowl paralleled an increase in virulence and ability to infect people. Human mortality data for 2006 through July 4 totaled 55 people from 85 documented cases in 11 countries, or 65% of the people confirmed with bird flu. This is a deceptive statistic, due to poor surveillance in the human population of many of the affected countries of Asia and the Middle East. Pathology of the fatal cases has hallmarks of the 1918 pandemic. Fortunately, as of early July, the virus still has not made the critical adaptive change to be able to be readily transmitted between people.

Although pigs are in abundance in China, the pig has remained in the background throughout most of this story. The pig should have remained there long ago. Over the last 10 years the research laboratory of Jeffrey Taubenberger at the Armed Forces Institute of Pathology in Washington DC has conducted intensive molecular detective work, and has reconstructed the genome of the 1918 pandemic H1N1 virus from fixed tissues at the Institute and from tissues of an Inuit victim that was exhumed from Arctic permafrost. The team's first report in 1999 detailed genetic sequence data for the hemagglutinin of the virus. They continued their work in subsequent years, initially with the neuraminidase sequence data, and ultimately completing sequence analysis of all 8 genes of the 1918 pandemic virus. By 2005, they published data on the polymerase genes and were then able to conclude that the pandemic virus had most likely occurred by direct human infection. Ducks and geese were commonly raised on farms with close contact with farmers at the time of the 1918 pandemic, and may have provided the same scenario as has played out in China, but without the benefit of any vaccines.

Their laboratory has initiated similar studies in a cooperative effort with John Oxford of Queen Mary's School of Medicine at the University of London. Joanna Whitson, a medical student, found more than 200 suspected flu victims fixed tissues from 1915 that had been preserved along with their medical records in the cellars of the Royal London Hospital. Taubenberger's group has examined 12 of the suspected victims and has confirmed that 5 had been infected with influenza virus. Sequence data for the hemagglutinin for 4 of those victims has proven that those influenza victims had been infected with a very different virus containing the H3 hemagglutinin. It appears that the "Hong Kong" flu of the late 1960's, as it relates to increased human disease and mortality, occurred much earlier in the century, as well. If continued examination of the suspected victims confirms these early findings, that will provide further absolution for the pig in the 1918 pandemic.

With that background, let's consider what has occurred in the pig populations of the western and eastern hemispheres in relation to the change that was recognized in the fall of 1998, when H3N2 was initially recognized as a new US type of swine influenza virus that had successfully adapted to our pigs. Serologic sleuthing, through a genetic trial serum bank subsequently revealed that the virus had already adapted to US pigs as early as 1996, which means that the virus successfully entered the swine population as early as late 1994 or 1995. Most introductions of human influenza into pigs are not successful, and the few that have been successful usually require many months, if not a few years to establish themselves in pigs.

So what about the mixing vessel? This is a term coined some decades ago, because it was known that the pig has both mammalian a-2,6 Gal and avian a-2,3 Gal influenza viral receptors. A logical extrapolation was that the pig, due to its proximity to man and poultry in other countries, particularly Asia, would be an ideal host to adapt avian influenza viruses through repeated exposure to a strain of virus that would readily attach to mammalian respiratory epithelial receptors. Bird flu (Eurasian high pathogenicity H5N1 avian influenza) has shown otherwise, despite pigs being a common backyard animal in Asia, as well.

What has occurred on a continuing basis is the introduction of human influenza viruses into pigs. In the case of H3N2, successful introduction was documented as early as 1976 in Europe, and did not occur in this country until the mid 1990's. Both strains of H3N2 have now established themselves as stable lineages of swine influenza viruses, the European strain being an antigenic drift variant of the 1973 Port Chalmers prototypic virus, while the US strain is an antigenic drift variant of 1996-era human H3N2 viruses.

However, there have also been successful fully avian virus introductions into pigs that established themselves as new pathogens of pigs, by crossing the normal species barrier as early as 1979 in European swine. In Japan and Great Britain, H1N2 viruses emerged and established themselves as the predominant swine respiratory pathogen as early as 1980 in Japan and by the early 1990's in Great Britain. In 1999, there was an introduction of H4N6 into Canadian pigs due to use of lake water for washing barns and other uses. It did cause a mild respiratory disease and maintained itself in those hog units for many months. This was an example of a moderately successful adaptation, but to the author's knowledge, it is no longer present in those herds.

More recently, in 2004 and 2005, a human H1N1 virus was introduced into US swine that reassorted with the current swine triple reassortant SIV strains to gain a 2003-era human H1 hemagglutinin. Of significant interest is that this virus is currently displacing the older reassortant H1N1 SIV of the late 1990's in NC swine. The clinical syndrome to date has been very mild and more like what we knew as classical H1N1 before PRRS entered our swine population. Currently, the 2 primary swine pathogens are H1N2-like H1N1 SIV, and MN 2004 contemporary H3N2 SIV strain in NC.

The greatest risk US swine face is the introduction of human strains of SIV that can reassort with our current triple reassortant SIV to create a new pathogen and result in dramatic production losses. The best solution is vaccination of all farm staff with the current human vaccine to minimize ability to transmit, and to encourage staff with influenza-like illness to stay home. With the current molecular research occurring at the Armed Forces Institute, it does appear that the pig will be removed from convicted status for the pandemic of 1918. Bird flu is doing a lot to resolve this long standing inferred guilt.

References

Landolt GA, Karasin AI, Schutten MM, Olsen CW. 2006. Restricted infectivity of human-lineage H3N2 influenza A virus in pigs is hemagglutinin and neuraminidase gene dependent. *J. Clin. Micro.* 44:297-301.

Taubenberger JK, Reid AH, Lourens RM, Wang R, Jin G, Fanning TG. 2005. Characterization of the 1918 influenza virus polymerase genes. *Nature* 437:889-893.

Sharp PA. 2005. 1918 flu and responsible science. *Science* editorial 310:17.

Enserink M. 2006. Influenza-What came before 1918? Archaeovirologist offers a first glimpse. *Science Focus* 312:1725.

Castrucci MR, Donatelli I, Sidoli L, Barigazzi G, Kawoaka Y, Webster RG. 1993. Genetic reassortment between avian and human influenza A viruses in Italian pigs. *Virology* 193:503-506.

Gramer M. Emergence of reassortant influenza viruses: Academic folly or clinically relevant? 2005. *Proc. Allen D. Leman Conf.* pp. 95-96.

Shinya K, Ebina M, Yamada S, Ono M, Kasai N, Kawaoka Y. 2006. Influenza virus receptors in the human airway. *Nature Brief Communications* 440:435-436.

van Riel D, Munster VJ, de Wit E, Rimmelzwaan GF, Fouchier RAM, Osterhaus ADME, Kuiken Thijs. 2006. H5N1 virus attachment to the lower respiratory tract. *Sciencexpress* 23 March (Science 1125548).

Brown IH. 2000. The epidemiology and evolution of influenza viruses in pigs. *Vet. Micro.* 74:29-46.

Stech J, Xiong X, Schlotissek C, Webster RG. 1999. Independence of evolutionary and mutational rates after transmission of avian influenza viruses to swine. *J. Virol.* 73:1878-1884.

Brown IH, Chakraverty P, Harris PA, Alexander DJ. 1995. Disease outbreaks in pigs in Great Britain due to an influenza A virus of H1N2 subtype. *Vet. Record* 136:328-329.

Karasin AI, Brown IH, Carman S, Olsen CW. 2000. Isolation and characterization of H4N6 avian influenza viruses from pigs with pneumonia in Canada. *J. Virol.* 74:9322-9327.

Choi YK, Nguyen TD, Ozaki H, Webby RJ, Puthavathana P, Buranathal C, Chaisingh A, Auewarakul P, Hanh NTH, Ma SK, Hui PY, Guan Y, Peiris JSM, Webster RG. 2005. Studies of H5N1 Influenza virus infection of pigs by using viruses isolated in Vietnam and Thailand in 2004. *J Virol. Notes* 79:10821-10825.