

History of Swine Influenza Viruses in Asia

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Abstract The pig is one of the main hosts of influenza A viruses and plays important roles in shaping the current influenza ecology. The occurrence of the 2009 H1N1 pandemic influenza virus demonstrated that pigs could independently facilitate the genesis of a pandemic influenza strain. Genetic analyses revealed that this virus was derived by reassortment between at least two parent swine influenza viruses (SIV), from the northern American triple reassortant H1N2 (TR) and European avian-like H1N1 (EA) lineages. The movement of live pigs between different continents and subsequent virus establishment are preconditions for such a reassortment event to occur. Asia, especially China, has the largest human and pig populations in the world, and seems to be the only region frequently importing pigs from other continents. Virological surveillance revealed that not only classical swine H1N1 (CS), and human-origin H3N2 viruses circulated, but all of the EA, TR and their reassortant variants were introduced into and co-circulated in pigs in this region. Understanding the long-term evolution and history of SIV in Asia would provide insights into the emergence of influenza viruses with epidemic potential in swine and humans.

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1 Introduction

Asia is home to the world's largest human population. With its rapid growth and increasing wealth, Asia has an escalating need and demand for more and better quality food sources. Farming practices in Asia have been greatly changed by industrialization and globalization in the quest for greater production. Importation of breeding pigs from the USA and Europe and the establishment of intensive pig-breeding farms have caused the population of pigs in Asia to soar. Now, approximately 60% of the world's pigs are in Asia and China alone is home to over 40% of the world's pigs (USDA/FAS).

Greatly increased swine numbers have led to enhanced opportunities for contact between pigs and humans and between pigs and the similarly enlarged poultry flocks and the wild birds of Asia. Interspecies transmission of influenza to and from swine has been frequently observed (Pensaert et al. 1981; Mohan et al. 1981; Claas et al. 1994; Guan et al. 1996) and pigs are regarded as a major intermediate host in the process of adapting avian viruses to mammalian hosts (Scholtissek et al. 1985; Scholtissek 1990). Highly pathogenic H5N1 and low pathogenic H9N2 avian influenza viruses have become enzootic in Asia and transmissions to humans and pigs have occurred (Webster et al. 2006; Peiris et al. 1999; Lin et al. 2000; Claas et al. 1998; Subbarao et al. 1998). The 2009 pandemic virus had its origins in currently circulating swine influenza viruses (Dawood et al. 2009; Garten et al. 2009; Smith et al. 2009b).

Both the economic consequences to food production and the threat to human health emphasize the importance of swine influenza. Monitoring the evolution and ecology of this virus is an essential task for human well-being. This is especially the case in Asia where the largest population of pigs in the world interacts with such a large human population.

2 Prevalence and Detection of Swine Influenza Viruses in Asia

H1N1 and H3N2 influenza viruses occur in pigs in Asia but the clinical picture of infection is less clear. Pig farming in China and much of Asia has been traditionally based on small family holdings and only in the last 20 years or so have large-scale farming operations come onstream. Consequently, relatively little surveillance has occurred and there is limited information about swine influenza in Asia in the wider scientific literature.

2.1 Classical Swine H1N1 Virus

The presence of classical swine H1N1 (CS) influenza in China probably dates back to the 1918–1919 pandemic when, in the wake of human infections, an outbreak of high mortality occurred in pigs in cities along the Chinese coast (Chun 1919; Kilbourne 2006). A similar disease pattern was observed in the USA with humans infected before pigs (Koen 1919; Reid and Taubenberger 2003). Findings from evolutionary studies revealed that classical swine H1N1 and 1918 pandemic H1N1 viruses shared a common ancestor or were highly closely related to each other (Smith et al. 2009a; Kanegae et al. 1994; Gorman et al. 1991). This historic interrelationship between human and porcine H1N1 viruses may be similar to the current situation with H1N1/2009 viruses. Since its emergence, the 2009 human pandemic H1N1 virus has been repeatedly transmitted from humans to pigs (Pereda et al. 2010; Weingartl et al. 2010; Vijaykrishna et al. 2010).

Although the CS virus was isolated and identified as early as 1930 in the USA (Shope 1931), it was first isolated in Asia in 1974 (swine/Hong Kong/1/74). Since the mid-1970s influenza surveillance of pigs conducted in Hong Kong and Japan has revealed that classical H1N1 viruses are widely distributed in many Asian regions and countries. Surveillance in Hong Kong from 1976 to 1980 took samples from pigs grown in Hong Kong and pigs imported from Mainland China, Taiwan and Singapore (Shortridge and Webster 1979). Regular isolation of classical swine viruses showed their continuing presence in apparently healthy pigs (Shortridge and Webster 1979; Yip 1976). During the same period of time, serological studies revealed that classical swine H1N1 viruses were also common in the pig populations of Japan (Arikawa et al. 1979; Nerome et al. 1982; Ogawa et al. 1983; Yamane et al. 1978).

Further surveillance in Hong Kong during 1993–1994 showed that classical H1N1 viruses were apparently the predominant influenza virus infecting pigs (Guan Y, unpublished). A clear epizootic occurred, with large numbers of viruses isolated in February, March and April of 1994. Little surveillance has been conducted in other countries of Asia. Classical H1N1 swine influenza viruses were reported to be isolated in Thailand in 1988 (Kupradinun et al. 1991) and Mainland China in 1991 (Guan et al. 1996), and this virus was also identified from pigs in

Korea (Lee et al. 2008; Song et al. 2007) and India (Das et al. 1981; Chatterjee et al. 1995).

Generally, classical H1N1 viruses were genetically stable and showed minor antigenic drift in Asian countries. However, a reassortant H1N2 virus, with its N2 segment from early human-like H3N2 viruses and its remaining segments from classical H1N1 viruses (Sugimura et al. 1980), caused a major outbreak in southern Japan from winter 1989 to spring 1990. Affected pigs had a typical influenza illness and most swine tested possessed corresponding antibodies (Ouchi et al. 1996). Similar reassortant viruses were also detected in Hong Kong from pigs imported from China during 1999 to 2004 (Vijaykrishna et al. 2011).

Phylogenetic analyses of large data sets of swine influenza viruses reveal that the classical H1N1 viruses isolated in Hong Kong do not form a single monophyletic group. They are interspersed with North American CS viruses, indicating multiple introductions of CS into Asian countries from the USA (Vijaykrishna et al. 2011). However, it is hard to believe that the classical H1N1 viruses from different Asian countries were all introduced from the USA via importation of pigs from there. CS viruses might have evolved from the 1918 pandemic H1N1 virus as it became able to persist in pigs. Supposedly, then, this virus should have existed in all regions where pigs were available. However, the effect of long-term vaccination practices in the USA might induce an evolutionary advantage in CS viruses from that region, allowing them to replace previously existing CS strains. This hypothesis could be possibly tested again as the 2009 pandemic H1N1 virus and its variants become established in pigs.

2.2 H3N2 Human-like Influenza Viruses

H3N2 swine viruses appear to be the result of multiple transmissions of viruses from humans to pigs. They were first isolated in Asia from pigs in Taiwan soon after the Hong Kong pandemic (Kundin 1970). During surveillance in Hong Kong from 1976 to 1982, and from 1998 to the present, contemporary variants of H3N2 human-like viruses and antibodies to them were regularly isolated or detected in pigs from Asian countries (Shortridge and Webster 1979; Vijaykrishna et al. 2011; Shortridge et al. 1977; Webster et al. 1977). Based on our long-term surveillance, almost all of the major human H3N2 variants could be introduced into the pig population (Vijaykrishna et al. 2011). Some of these variants might remain in somewhat genetically dormant states, akin to evolutionary stasis, in pigs even many years after their counterparts had disappeared from humans (Shortridge et al. 1977).

The first two major H3N2 variants were A/Port Chalmers/1/73 (PC) and A/Victoria/3/75 (Vic) (Shortridge and Webster 1979; Shortridge et al. 1977, 1979). Interspecies transmission to pigs of these two viruses occurred in many Asian countries, including China, Korea and Japan (Shortridge and Webster 1979; Shortridge et al. 1977, 1979; Song et al. 2003; Jung and Song 2007; Yamane et al.

1979; Nerome et al. 1981; Arikawa et al. 1982). In Europe, PC-like H3N2 viruses reassorted with European avian (EA)-like H1N1 viruses to generate an H3N2 virus with PC-like surface genes and EA H1N1 internal genes (Campitelli et al. 1997; Castrucci et al. 1993). This H3N2 reassortant has been maintained in European countries since then and was introduced into Asian countries in the late 1990s (Gregory et al. 2001) (see below). The third major human H3N2 variant to cause zoonotic outbreaks in pigs was A/Sydney/05/97 (Syd). Introduction of this variant into pigs occurred, at least, in China and the USA (Peiris et al. 2001; Yu et al. 2008; Zhou et al. 1999). In China, the virus kept the entire human-like particle, while in the North America it further reassorted with CS and avian viruses to generate double and triple reassortant viruses (TR, H3N2, H1N2 and H1N1 subtypes) (Zhou et al. 1999; Karasin et al. 2006).

Since 2005, although H3N2 viruses have failed to be detected in the pig population under our surveillance program in Hong Kong (Vijaykrishna et al. 2011), contemporary and early human H3N2 variants were still isolated from pigs in the wider region (Hause et al. 2010; Lekcharoensuk et al. 2010; Kyriakis et al. 2011). Except for the major variants mentioned above, most human-like H3N2 variants seem to be transient and to have difficulty in becoming established in pigs as none have formed an independent group or sublineage in the evolutionary trees. Thus, it is likely that human H3N2 variants were regularly introduced into pigs, but most were prevalent at a low level within a small geographic location, and failed to become established.

2.3 European H3N2 Reassortant Viruses

In 1999, an H3N2 reassortant swine virus (represented by swine/Hong Kong/5212/99) was isolated in Hong Kong from pigs imported from southern China. This virus was antigenically and genetically distinct from the human-like H3N2 viruses then circulating in pigs. Genetic analyses revealed that this virus had PC-like surface genes and EA-like internal genes (Vijaykrishna et al. 2011). It was closely related phylogenetically to the European H3N2 reassortant viruses that were generated in the mid-1980s and have circulated in Europe since then (Claas et al. 1994; Campitelli et al. 1997; Castrucci et al. 1993). This virus caused a human infection case in Hong Kong (Gregory et al. 2001).

These findings provide a typical example of the direct introduction of swine influenza virus from Europe to Asia, very likely via pig movement. To largely increase its pig population and production, China started to import breeding pigs from European countries, such as Denmark (e.g. the DanBred organization) and set up breeding pig farms in the Zhujiang delta region in Guangdong since the mid-1990s. Unfortunately, the swine influenza virus was not included on Chinese warrant agent lists before 2009. This European H3N2 reassortant virus seemed to only circulate in Guangdong province in southern China and has not been reported from any other places in Asia.

2.4 European Avian-like H1N1

The first detection of EA viruses outside European countries occurred in early 2001 in Hong Kong. The virus (swine/Hong Kong/8512/01) (Smith et al. 2009; Vijaykrishna et al. 2011) was isolated from pigs imported from southern China. Since then, this virus has co-circulated with other swine influenza viruses, including CS, H3N2 and, later, American triple reassortant H1N2 (see below) viruses in this region and gradually became predominant from 2006. The replacement of CS viruses with EA viruses in pigs in the field took 4 to 5 years, similar to what happened in Europe after the EA lineage became established in pigs in the mid 1980s (Brown 2000). Phylogenetic analyses showed that the EA viruses isolated from pigs in China form a monophyletic group, suggesting a single introduction of this virus (Vijaykrishna et al. 2011).

H1N1 reassortants between CS and EA viruses were also detected in 2001 (Fig. 1), very likely occurring at the beginning of the introduction of EA viruses. Genetic analyses based on publicly available data showed that the EA virus was also introduced into pigs in Thailand around 2000 (Takemae et al. 2008). This virus also reassorted with CS viruses in pigs in this country (Takemae et al. 2008). Currently, EA viruses or its variants have become a major swine influenza lineage prevailing in the region. Whether the predominance of EA H1N1 viruses in the field is directly affecting the prevalence of H3N2 viruses is still unknown.

2.5 American Triple Reassortant Virus

In the reassortment event of 1998, both H3N2 and H1N2 triple reassortant viruses were generated in North America (Zhou et al. 1999; Karasin et al. 2006). Since 2002 American triple reassortant H1N2 viruses were regularly isolated from pigs in our surveillance program in China (Fig. 1). This virus has prevailed since then at generally low levels in pigs but was more prevalent during 2004 (Vijaykrishna et al. 2011). Our surveillance program suggests that triple reassortant viruses were introduced to China on several occasions (Vijaykrishna et al. 2011). From 2004, both H1N2 and H3N2 triple reassortant viruses have been isolated from pigs in Korea (Jung and Chae 2004; Pascua et al. 2008). Given that different subtypes with gene segments falling into polyphyletic groups were found in these two countries, separate introductions of the virus from the USA appear to have occurred.

2.6 Reassortant Viruses Between EA and TR

The 2009 pandemic H1N1 virus was derived by reassortment from several swine influenza viruses, which might include EA viruses (for the NA and M segments), European H3N2 reassortant viruses (for the M segment) and TR viruses (for the

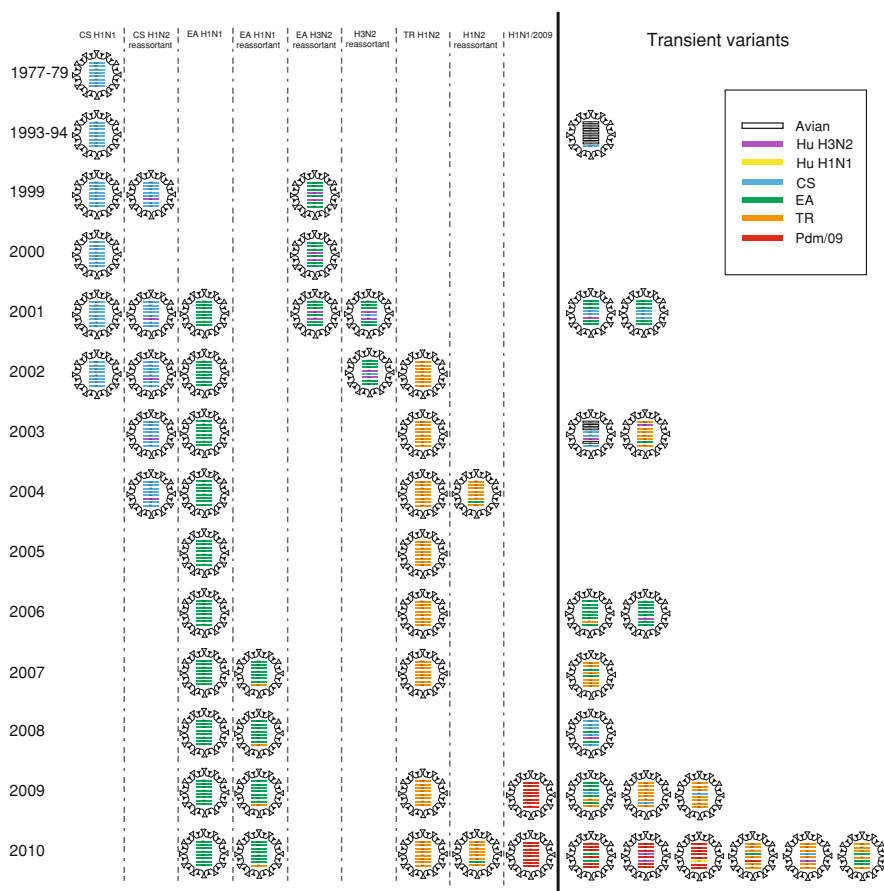


Fig. 1 Timeline of the genotype of viruses identified in surveillance program in China. Genotypes observed over at least two years are shown to the left. Segments are ordered by size from top to bottom for each genotype. The lineage of origin of each segment is indicated by color: white avian origin, purple human seasonal H3N2, yellow human seasonal H1N1, blue classical swine (CS), green European avian-like (EA), orange American triple reassortant (TR), red pandemic H1N1 2009 (Pdm/09)

remaining six segments) (Garten et al. 2009; Smith et al. 2009b). Thus, co-circulation of EA and TR viruses would appear to be essential for the genesis of this pandemic virus. Based on our surveillance findings and publicly available data, co-circulation of EA and TR viruses were observed in China from 2003 onwards (Fig. 1). However, EA-like viruses were never reported from America and TR-like viruses were also not reported from European countries. It is plausible, therefore, that the 2009 pandemic H1N1 virus could have been generated within the pigs of an Asian country (most likely China). Indeed, reassortment

events between EA and TR viruses are not rare, and reassortant swine viruses with differing genotypes have been recognized in the field (Fig. 1). Reassortants between EA and TR viruses, which are the most closely related to the 2009 H1N1 pandemic virus (by having seven gene segments from the same lineages), were isolated in southern China on four sampling occasions (two before and two after the pandemic). However, all these reassortants had different evolutionary pathways, and almost all reassortants between EA and TR viruses appear to be transient. The only exception was a reassortant which had seven segments from the EA lineage and the NS segment from the TR lineage and has become established in the field and may eventually predominant in pigs in China (Vijaykrishna et al. 2011) (Fig. 1).

2.7 Pandemic/2009-like H1N1 and its Variants

From the time of the peak of the human pandemic, the pandemic H1N1/09-like virus has been repeatedly isolated from pigs in many Asian countries (Vijaykrishna et al. 2010; Song et al. 2010). Most of these pdm/09-like swine isolates resulted from different direct introductions from humans to pigs. However, the detection of multiple reassortant viruses between pdm/09 and other swine viruses (Vijaykrishna et al. 2010; Starick et al. 2011; Moreno et al. 2010), along with the high seroconversion rate to the pandemic virus in pigs (unpublished data), suggest that this virus might gradually become established in this host. Questions remaining to be answered are when that will occur, what kind of genetic composition the established virus will have and what its long-term impact will be.

2.8 Avian-like Influenza Viruses

In the last two decades avian influenza viruses have frequently been isolated or detected from pigs in Asian countries, likely due to increased farming activity and interaction between pigs and birds. However, none of these interspecies transmission events caused severe consequences or the establishment of avian origin viruses or virus genes in pigs. The most frequently detected avian viruses in pigs in Asian countries belong to the virus lineages that are long-term enzootic in poultry, such as H9N2 and H5N1 viruses. H9N2 avian-like viruses were detected in China and Korea, and H5N1 avian-like viruses were reported from China, Vietnam and Indonesia (Nguyen et al. 2005; Nidom et al. 2010; Yu et al. 2011). All H9N2 and H5N1 swine virus isolates were from different sublineages and variants, highlighting the long-term potential threat from these viruses.

Other subtypes of avian influenza viruses detected in pigs in Asian countries include H1N1, H3N2, H5N2, H11N6 and H6N6 (Guan et al. 1996; Zhang et al. 2011; Lee et al. 2009; Kim et al. 2010; Kida et al. 1988). Genetic analyses revealed that these viruses were likely derived from those residential in aquatic birds. Almost all were detected only on a single sampling occasion, but some were from disease surveillance in pigs and low seroconversion rates were observed (Zhang et al. 2011; Lee et al. 2009). This shows that pigs are susceptible to most subtypes of avian influenza viruses. A major concern is that should highly pathogenic H5N1 Asian lineage viruses recruit mammalian-adapted virus genes from pigs, a human-to-human transmissible virus might be generated. Systematic surveillance in different countries would be greatly helpful to counteract such an event.

3 Summary

The findings presented here suggest that almost all major swine influenza virus lineages from different continents are co-circulating in pigs in Asian countries. The movement of live pigs between different continents is probably responsible for this. Co-circulation of these different virus lineages will naturally increase virus interaction and reassortment, and the genetic diversity in swine influenza viruses. The emergence of the 2009 pandemic H1N1 virus provided the clearest example of the potential consequences of co-circulating viruses even though we lack evidence to show that this pandemic virus was initially generated in Asian countries. Given that all current swine virus lineages and their constituent segments have been prevalent for more than a decade in pigs (i.e. they are fully mammalian-adapted) and H9N2 and H5N1 avian influenza viruses are widely enzootic in poultry in the region, generation of a novel virus with efficient transmissibility in pigs or even in humans is possible.

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