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Swine influenza viruses In Europe

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Right from the time of the first human pandemic in 1918—when swine influenza was first recorded[1]—there has been a continual evolution of swine influenza viruses (SIV) in pigs. However, since then there has been no major spread of classic swine influenza viruses in the human population, although there are periodic occurrences in the human population that appear to be self-limiting[2].

There are four major interest areas for veterinarians and virologists with respect to swine influenza viruses:

- epidemiology,
- independent evolution,
- genetic reassortment and
- interspecies transmission.

There are also four major properties that influence pathogenesis:

- antigenic shift,
- antigenic drift,
- haemagglutination of RBCs, and
- enzyme activity.

There is a major difference between avian influenza viruses (AIV)—which has tropism for both respiratory and alimentary tracts—and SIV, which has tropism only for the respiratory tract.

Ian Brown and his team at VLA Weybridge (Central Veterinary Laboratory) have, over the last few years, tried to follow the evolution of swine influenza viruses in pigs in the United Kingdom and the results presented here are the fruit of their efforts.

History

The history of swine influenza is shown in **Table 1**. The most important features in the study of European viruses are shown.

Virus characteristics

In man there are probably two general types of epidemiology. In **cyclical** infections there is a progressive recycling of H1, H2, and H3 infections and in **spiral** there may be a susceptibility to infection with all haemagglutinin (HA) subtypes (currently number 15). The influenza virus has two important proteins that project from the surface called the HA and the Neuraminidase (NA) and these two are the major immunogens of the virus. The HA proteins are responsible for the attachment of the virus to the host cell receptors, fusion of viral envelopes with host cell membranes and internalisation of the viral genes. The NA proteins are thought to aid penetration of the mucus layer covering the respiratory tract and in release of progeny virus[3].

Today

Three major factors help to spread swine influenza and encourage its continual recycling and change. Firstly, there are the methods of pig production where PRRS has introduced an immunosuppressive effect and where modern intensive or extensive (indoor or outdoor) units of thousands of sows encourage the development of subpopulations of pigs of variable resistance and susceptibility. Second, this does not necessarily produce selection pressure for virus mutation but does facilitate easy spread. Finally, increases in stocking density will encourage virus spread and the close proximity of water fowl, other birds, pigs, humans, and possibly horses—all possibly under stress—causes reassortment viruses to appear.

Early weaning (reduced colostral protection), mixing, and moving will facilitate early spread of the virus and will pose an even bigger hazard if there is no single age, all-in—all-out building system to use as a nursery. Multi-sourcing is a nightmare under these conditions. All of these modern systems provide easy pig-to-pig transmission but the high level of new raw recruits for infection produces relatively low immune pressure and therefore reduced antigenic drift with viruses being selected by fitness.

Viruses in the UK and Europe

The list of viruses that are present today in Europe are shown in **Table 2**. A brief discussion of each of these follows.

Table 1. Salient points in the history of SIV with particular reference to Europe

Year	Event and significance
1918	Swine influenza described in north central USA, Hungary, and China. May have been cause of human pandemic[4]. 30–40 million human deaths.
1930	Shope[5,6] isolated influenza virus from pigs.The prototype classic swine influenza strain (A/Swine/Iowa/30) transmitted experimentally to pigs.
1941	Recognised in Europe[7] and disappeared.
1970	Avian-like H3N2 in pigs in Asia. Transmission of human H3N2 virus to pigs.
1976	Classical H1N1 reappears in European pigs[8,9].
1979	Introduction of whole virus from birds to pigs. Distinguishable antigenically from classical strains.
1984	Human-like strains H3N2 viruses associated with respiratory epizootics.
1986	Classical H1N1 reappears in UK[13], similar to Classical H1N1 in continental Europe.
1987	Human-like H3N2 associated with respiratory epizootics in UK[14]. Related to A/Port Chalmers/H3N2[15] [also first PRCV in UK[16]].
1989	Avian-like swine H1N1 is dominant and widespread in Europe[17].
1992–1993	Avian-like strains widespread in UK, prototype strain A/Swine/England/195892/92.
1994	H1N2 first isolated in pigs in UK. Human-avian reassortant virus.
1992–1998	H3N1, H1N7, also occurred in UK but failed to spread.
1998	H9N2 in pigs in Asia - apparently an avian virus that has adapted to pigs.
1998	H3N2 viruses first detected in N. America, which are antigenically and genetically distinct from earlier strains.

Classic H1N1

Over a long period of time there has been limited variation and conserved antigens have been the feature. There has been a recent Canadian isolate which is very different from the usual North American strains. It is distinguishable from both avian and human H1N1 strains, is distributed worldwide and is still the prominent strain in North America and Asia. It is still associated with epizootics. In the UK, the seroprevalence is probably around 25–30% but is falling as it is replaced by the avian-like H1N1 from Europe and H1N2. Classic H1N1 transmits from pigs to poultry quite easily but, fortunately, seem to rarely move to humans and—when it does—causes mild clinical disease.

Avian-like H1N1 viruses in Europe

In 1979, an H1N1 influenza virus of avian origin was transmitted to pigs in northern Europe. This has created a new stable lineage of swine influenza viruses[18], a strain that has progressively become more prevalent since 1981, and is distinguishable antigenically from human and avian H1N1 viruses. There appears to have been at least two independent introductions of whole virus from birds to pigs. These viruses are not widespread in Eurasia.

The virus first appeared in the UK in 1991 and coming directly in the wake of PRRS was very severe. Clinical signs in pigs included anorexia, pyrexia, sneezing, coughing, prostration, and almost 100% morbidity. Mortality may have been as high as 10% depending on the occurrence of PRRS and secondary bacterial infections. In experimental infections in SPF pigs, the agent produced very little clinical disease or pathology but in conventional pigs it was more severe.

The evolutionary rates of both the coding and non-coding changes of these H1N1 viruses were higher than those of human and classic H1N1 influenza viruses[19]. In addition the early H1N1 isolates showed a marked plaque heterogeneity that consistently appears after a few passages. A mutator mutation was proposed[20] but was later withdrawn[21], but since 1992 this lineage of viruses appears to be more stable.

Human-like H3N2 viruses in pigs

These viruses have resulted from multiple introductions of whole viruses from humans. They are distributed worldwide but there are regional variations. They have been associated with epizootics of respiratory disease. They continue to maintain a high prevalence in the population (40%) and are often involved in genetic reassortment. Although infecting pigs in Europe from 1970 they were not shown to be important in the UK until 1987. The genotype is usually dependent on the year of isolation and region of origin.

This group of viruses isolated from pigs in Italy since about 1985 contain genes encoding internal proteins (not the HA or NA) which are entirely of avian origin. Since then they appear to have similar evolutionary rates to the prevailing strains in the human population[22].

Table 2. Current viruses in the UK

Still present but reduced importance

H1N1 classic
H3N2 human-like swine viruses
H1N1 avian-like swine viruses

Increasing importance

H1N2

Unknown importance (only isolated once)

H3N1 (N1 of swine and H3 from H3N2 (human-like) circulating in pigs
H1N7 (N7 from equine virus—largely disappeared in horses—and H1 from human virus largely disappeared in the 1970s)

Not seen in UK

H3N2 avian-like viruses as in Asia
H9N2 (Hong Kong type of situation)

There is sufficient variation between viruses for the mammalian lineage of H3N2 viruses to be grouped as follows[23]: early human, early swine, intermediate, and recent human. The other major feature of H3N2 viruses has been the recent marked antigenic drift in isolations from northern Europe.

H1N2

This virus was first described in the United Kingdom[24]. Now there is an apparently stable lineage in Europe and a different antigenic group described in Japan. This virus was responsible for a severe clinical disease with stridor, coughing and dyspnoea, and severe economic loss (through growth checks and uneven litters in the UK). This virus has been responsible for the most severe microscopic pathology of all the strains of swine influenza seen in the UK.

There is considerable antigenic heterogeneity in the group but their arrival proved beyond doubt that HA genes of previous circulating human H1 viruses could apparently persist in pigs and reappear following genetic reassortment. The H1 comes from a human H1N1 left over from the 1980s (happily living in a pig) and the N2 component comes from a human-like swine H3N2. The remaining six genes are all derived from an avian-like swine H1N1 virus.

At the moment it appears to be replacing the former viruses (classic H1N1, H3N2, and avian-like H1N1) in the British pig population. The antigenic characteristics are shown in **Table 3**, below[25].

The genetic similarity of the HA1 of swine H1N2 to other H1 influenza viruses is: avian-like, 70.6%; classic SIV, 75.6%; and, swine/England/96A, 93.2%.

Other viruses

The other two viruses H3N1 and H1N7 have only occurred sporadically, failed to colonize, and failed to spread, but their occurrence does highlight the possibility of continual emergence of new viruses.

Table 3. Antigenic characteristics of H1N2 influenza, a virus determined in hamagglutination-inhibiton tests

Virus	Antiserum Swine England 94	Swine England 96	Avian Swine	Classic SIV	USSR 77
Sw/England/94	1280	40	<10	<10	20
Sw/England/96	160	1280	<10	<10	20
Avian Swine	10	<10	1280	80	10
Classical H1N1	<10	<10	80	640	<10
USSR	320	320	<10	<10	320

Conclusion

When you sample pigs on a UK farm for the seroprevalence of UK viruses you are likely to find a picture similar to that shown in **Table 4**.

Thus there is in the pig a major reservoir of influenza viruses that are available for potential infection of a human population. This is particularly true for human viruses that have adapted to pigs in the first instance (e.g., H3N2) and the parts of H1N1 viruses that have subsequently reappeared (e.g., as part of the H1N2 virus). There is always considerable scope for recombination with the avian viruses as these are also found in the pig. The pig is the only mammalian species that allows productive replication of both human and avian influenza viruses.

This susceptibility is due to the presence of both (2.3 and (2.6 galactose sialic acid linkages in cells lining the pig trachea that can result in modification of the receptor binding specificities of avian influenza viruses from (2.3 to (2.6 linkage, thereby providing a potential link from birds to humans[26]. The unique coexistence of influenza A viruses within the European swine population may lead to pigs serving as a mixing vessel for a reassortment of viruses from mammalian and avian sources.

A mutator mutation in the polymerase complex induces a number of variants. Natural selection by fitness is installed at the genetic level. Initially the variants replicate poorly and fail to induce detectable antibody response but the fully adapted virus is pathogenic to pigs. Following the transmission of avian H1N1 and human H3N2 viruses there have been "quiescent" phases where there is little association with clinical disease but detection of antibody in infected animals. The adaptation is characterised by increased pathogenesis and this has occurred for all three major groups (human-like H3N2, H1N2, and avian-like H1N1). The transmission of "adapted viruses" to fully susceptible populations can lead to widespread epidemics like the avian-like H1N1 in the UK in 1992.

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Table 4. Serological titres to the endemic strains of SIV in the UK

Pig No.	Viruses H1N2	classic H1N1	H3N2	avian-like H1N1
1	320	<10	40	<10
2	160	<10	<10	<10
3	<10	10	<10	160
4	<10	10	<10	80
5	<10	10	<10	320
6	<10	10	<10	80
7	<10	10	<10	320
8	<10	40	<10	2560
9	<10	10	<10	80
10	<10	<10	<10	<10

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