ZOONOTIC DISEASES, HUMAN HEALTH AND FARM ANIMAL WELFARE

Swine influenza

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INTRODUCTION

Swine influenza typically causes respiratory disease in pigs with a rapid onset of fever, loss of appetite and coughing. It is rarely a fatal illness; animals may lose a considerable amount of weight, which has economic consequences, but they usually recover within 7 to 10 days[1]. Vaccines against swine influenza are available.

The influenza A virus genes are encoded by RNA rather than DNA, which is encapsulated in the virus as eight segments, each of which encodes one or two proteins. Two of these proteins, the haemagglutinin (HA) and neuraminidase (NA), are each encoded by a separate RNA segment. The HA and NA project from the surface of the virus particle and are responsible for allowing the virus to gain entry into host cells and for newly produced viruses to exit the cell, respectively. As these proteins are exposed on the surface of the virus, they are the major targets of the body's immune defences. The body recognises the HA and NA as foreign proteins and generates antibodies that circulate in the blood stream for a while and neutralise the virus. On re-exposure to the same virus strain, memory cells rapidly respond to ensure that protective antibodies are generated. However, there are different subtypes of HA and NA that are sufficiently antigenically distinct that antibodies raised in response to one subtype will not neutralise another subtype. Until recently, there were 16 known different subtypes of HA (H1 to H16) and nine NA subtypes (N1 to N9), all of which have been found in different combinations in wild aquatic birds (in particular ducks and gulls). As a result, wild aquatic birds are seen as the reservoir for influenza viruses from which certain subtypes would emerge and occasionally become established in mammalian species including people, pigs and horses[2]. When a species becomes infected with a new subtype of influenza A virus, this is referred to as 'antigenic shift'. In 2012, a completely novel influenza virus was isolated from bats in Guatemala, South America[3]. The significance of this discovery is not yet clear.

To date, four main influenza subtypes have been isolated from pigs (H1N1, H1N2, H3N2 and H3N1). Pigs can become infected with human influenza viruses[4] or with avian influenza viruses[5]. Furthermore, in contrast to human influenza virus strains, which tend to spread worldwide throughout the human population, the circulation of different strains in pig populations has historically tended to be more geographically restricted. As a result, the influenza strains circulating in pigs around the world present a complex picture. 'Classical' swine H1N1 viruses have circulated in pigs in North America and elsewhere for decades. In Europe, classical swine H1N1 has been replaced by an avian-like H1N1 that was first detected in Belgium in 1979[6]. The avian-like swine H1N1 also circulates in Asia (hence it is called Eurasian avian-like H1N1) along with human-like H3N2 and North American triple-reassortant virus[7]. The North-American H3N2 triple reassortant virus with genes from classical swine H1N1, an avian-origin virus and human-like H3N2 was first found in pigs in 1998[8]. Further reassortment or shuffling of the gene segments occurred between different pig viruses leading to H1N1 and H1N2 triple reassortant swine viruses[9].

In addition to antigenic shift, influenza viruses also undergo more gradual change in the HA and NA proteins as a result of point mutations in the genes, a process called antigenic drift. Eventually, sufficient mutations accumulate that the HA or NA protein is no longer recognised by antibodies generated to a previous strain and the variant strain 'escapes' immunity. This is of significance for vaccine-induced immunity. If a vaccine contains an earlier influenza strain, the antibodies induced by it may not be fully effective at neutralising a strain that has undergone antigenic drift. A vaccine that is not fully effective may provide protection against clinical signs of disease without completely suppressing viral replication, leading to unseen spread of the virus. In pigs, virus is shed in respiratory secretions and can pass from one pig to another by direct (nose-to-nose) or indirect contact or *via* droplets expelled into the air by coughing.

Risk to human health

It has been proposed that pigs may serve as a 'mixing vessel' for reassortment of influenza viruses because they can be infected with both human and avian strains[10]. If a pig cell is simultaneously infected with both an avian and a human influenza virus, mixing up of the viral gene segments can result in a novel combination of HA and NA genes. Thus, although aquatic birds are considered the main reservoir for the different influenza virus subtypes, pigs can act as an intermediate host in the introduction of novel influenza subtypes into the human population. If a virus emerges with HA and NA proteins not previously encountered by the majority of people and the virus is able to transmit from person-to-person, then a pandemic (i.e. rapid worldwide spread of a virus to which most people have no immunity) can result, with potentially devastating consequences. The most notable pandemic in human history is that of 1918-19, which is estimated to have killed 50 million people[11]. During that pandemic in the US, there were numerous accounts of farmers contracting influenza from their swine and *vice versa*[12] implying the potential involvement of pigs in the onset of the pandemic. Genetic analysis of fragments of the 1918 virus obtained from preserved tissues of victims of the pandemic has suggested that the virus was entirely avian in origin, but whether the virus was introduced into the human population directly from birds or *via* pigs is unknown[13]. A further two pandemics occurred in the twentieth century – one caused by an H2N2 virus in 1957 and one by an H3N2 virus in 1968[14]. These two pandemic viruses appear to have arisen by reassortment between avian and pre-existing human viruses [15].Most introductions of novel influenza A subtypes into the human population have involved swine, but have only resulted in isolated cases or limited outbreaks[16]. These include the transmission of swine influenza to two people involved in a study in which pigs were experimentally infected with the virus[17].

The severity of swine influenza in people can range from mild to severe. There were 36 human cases of swine influenza reported in the US between 2005 and April 2012, none of which were fatal[18]. On the other hand, in 1988, a pregnant woman who had been healthy previously died of pneumonia after visiting a country fair where there were sick pigs[19]. Healthcare workers looking after the woman also became ill and were shown to have contracted the swine influenza virus, but there was no further spread of the infection. Testing of serum samples from others exposed to the ill pigs revealed that 76% had antibody to the virus, whereas other exhibitors at the fair that did not have contact with the pigs had no antibodies. A more severe outbreak of swine influenza in New Jersey, US in 1976 sparked fears that it marked the start of a pandemic because 230 people were known to be infected, 13 of whom were hospitalised and one died[20]. However, the outbreak did not take off.

Serosurveys in which blood samples from various people were collected and tested for antibodies to swine influenza viruses have revealed that people that have contact with pigs through their work (e.g. farmers, veterinarians and abattoir workers) are significantly more likely to have antibodies to swine influenza than members of the general population[21]. The

percentages of farm workers tested that had swine influenza antibodies ranged from 0 to around 20%[22]. Although having antibodies to the virus indicates that a person was exposed, it does not necessarily mean that they had any clinical signs of disease.

In 1993, two viruses that were genetically closely related to viruses circulating in pigs at the time were isolated completely independently from children living in different regions of the Netherlands[23]. The viruses were reassortants with the H3 HA and N2 NA from a human influenza virus and the other proteins from an avian virus that were first detected in Italian pigs in the mid-1980s[24]. Interestingly, neither child had direct contact with pigs but the father of each, one of whom worked on a pig farm, had antibodies to the same virus although they had not been ill. It is likely that the parents were old enough to have resistance to infection due to previous exposure because the viruses were related to H3N2 viruses that circulated in people in the mid-1970s.

When the first infections and deaths caused by the highly pathogenic avian influenza H5N1 subtype occurred in Hong Kong in 1997, it was thought that this virus had the potential to be the cause of the next influenza pandemic. Fortunately, it has not, to date, acquired the capacity to transmit readily from person-to-person. It has, however, been found to circulate in pigs in China and Indonesia[25]. Worryingly, although this virus has a high fatality rate in people, it can infect pigs without causing any clinical signs of disease.

In the meantime, the multiple reassortant events taking place in pigs gave rise to the first pandemic of the 21st Century. Initially termed 'swine-origin' H1N1, the virus that was later declared to be a pandemic H1N1 virus first emerged in Mexico in 2009. The H1 HA and other genes came from the triple-reassortant swine viruses while the N1 NA and a gene coding for two other viral proteins were from the Eurasian avian-like swine influenza virus[26].

Influence of farming practices

The swine industry has changed profoundly in various regions of the world. In the US, the proportion of small herds (i.e. with fewer than 5,000 animals) has fallen from over 70% in 1994 to less than 20% in 2008[27]. The modern large herds are maintained through the frequent introduction of young swine into facilities; these animals are potentially fully susceptible to influenza infection due to lack of prior exposure. A consequence of this is that whereas swine influenza in the US was a seasonal disease, like human influenza, there is now year-round transmission in pigs[28]. This creates a constant opportunity for infection of workers. As herd size has increased in the US, so have the numbers of pigs imported into the country (a fourfold increase from fewer than 2 million before 1996 to more than 8 million since 2004)[29]. This increased globalisation could have consequences for the worldwide spread of swine influenza strains. Indeed, movement of live pigs between Eurasia and North America seems to have facilitated the mixing of swine influenza viruses that led to the multiple reassortments that gave rise to the pandemic H1N1 virus[30].

Intensive farming concentrates large numbers of animals close together. This is expected to facilitate animal-to-animal transmission of viruses as crowding increases the likelihood that an infected animal will be in contact with an uninfected animal for long enough to pass on the virus[31]. Influenza viruses are inactivated by exposure to the ultraviolet rays in sunshine, therefore the virus may survive for longer in the environment indoors[32]. Furthermore, unless there is an extremely efficient ventilation system, there will be a greater accumulation of virus in the environment. Conversely, housing animals indoors may reduce the risk of a new virus being spread on the wind and introduced into a facility from other facilities or wild birds in the vicinity.

Intensive farming units tend to be consolidated in specific geographical areas. They may be close to large cities that they supply or in regions where cereal crops, used for pig feed, are cultivated, as is the trend in the UK. Poultry also have cereal-based diet and are a cheap protein source, which can lead to co-localisation of intensive pig and poultry units, potentially enhancing the risk of transmission of avian influenza to pigs[33]. In Singapore, an intensive pig farming estate was established when farms had to be moved from a water catchment area. Recurrent viral diseases were identified among pigs on the estate, in particular Aujeszky's disease, swine fever and transmissible gastroenteritis, although swine influenza was not found to be a recurring problem[34].

The potential for pig farm workers to act as a 'bridging population' is highlighted by the case of the Dutch child who appeared to have contracted swine influenza from her father described above. The likelihood of this kind of occurrence may be enhanced in intensive farm units where the numbers of workers involved mean that people travel from their homes in larger communities to work on the farm, potentially increasing the interactions between farm workers and other members of the general population[35].

Preventive measures

There are numerous biosecurity procedures that can be adopted to minimise the risk of spread of influenza. Ideally, pigs being introduced onto a farm should be quarantined from other animals for a period to minimise the risk of bringing influenza into the facility. There should be procedures for disinfection when moving equipment and for people moving between buildings and premises. Buildings where pigs are housed should have screens or nets in place to limit the entry of wild birds. The use of lagoons and ponds on pig farms by waterfowl should be discouraged and water from such sources should not be used for washing down pig units etc. without treatment to destroy any potential contaminating viruses[36].

Enhanced awareness of the potential for new strains of influenza to emerge *via* swine among healthcare and veterinary workers and heightened surveillance of people working with swine could enable early detection of an emerging potential pandemic virus in future. Unfortunately, it is all too easy for such rare events to be overlooked. Vaccination of people working on pig farms (including veterinarians) against a potential pandemic influenza (e.g. H5N1), preferably with a killed virus vaccine has been proposed[37]. However, it is difficult to predict exactly what will be the next pandemic virus and vaccinating a farm worker with a strain that only provides partial immunity could lead to infection without any clinical signs. This enhances the risk that they continue with their daily lives and pass on the infection to susceptible contacts. Vaccinating farm workers against regular seasonal human influenza would minimise the risk of people passing influenza to the pigs that could potentially undergo reassortment, and may provide some cross-immunity against people being infected with swine influenza viruses. Farm workers with flu-like symptoms should be advised to stay away from work until their symptoms have cleared[38]; this rule may not be adhered to by workers if missing work entails a penalty such as deduction of wages.

Vaccination of pigs has become increasingly widespread. In the US, regular vaccination of breeding females doubled from 10% of animals in 2000 to around 28% in 2006[39]. Vaccinating sows also gives some protection to piglets as they will pass on some antibody in their milk. However, as for vaccination of people, use of an imperfect vaccine may mean that infection occurs without clinical signs, leading to unseen transmission. Furthermore, influenza experts have been reported to admit that widespread use of vaccination could drive the selection of variant viruses[40].

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