**UK detects first human case of Influenza A(H1N2)V**

In November 2023 the UK notified the World Health Organisation (WHO) of a human case of swine-origin influenza A(H1N2)v clade 1B.11 virus infection. The infection was detected as part of the routine national flu surveillance undertaken by the UK Health Security Agency (UKHSA) and the Royal College of General Practitioners (RCGP) and was the first case of human influenza A (H1N2) infection detected in the UK. The case was an otherwise well person, over 75 years of age who has since fully recovered. What makes the case intriguing is that the case reported no direct contact with pigs, pets or farms; however, pig farms are located within a few miles of where the case resides. As of the 4th December 2023 no virological confirmed transmission has been reported and the source of the infection is still under investigation.

**Influenza viruses**

Influenza viruses are members of the family Orthomyxoviridae, they are enveloped, helical viruses that have a negative-sense, single-stranded segmented RNA genome. There are four genera in the family each of which is a single species of influenza viruses A, B, C and D. Influenza A and B cause the ‘winter’ seasonal flu epidemics in humans. Influenza viruses are subtyped based on the properties of their viral surface proteins, haemagglutinin (H) and neuraminidase (N), there are 18 H and 11 different N subtypes. These subtypes are named based on the combination of N and H; combining the H and N numbers for example influenza A(H3N2). The WHO reports that the influenza A viruses (IAV) currently circulating in humans belong to the subtypes A(H1N1), A(H3N2) and A(H1N1)pdm09

Seasonal epidemics of flu occur every winter, with millions of people infected. These seasonal epidemics occur partly due to the viruses ability to ‘antigenically drift’ meaning that the immune response may only provide partial protection over the following years strain; hence the need for annual flu vaccination.

However more interestingly Influenza A has the ability to form new genetically distinct variants. It does this through a mechanism called ‘antigenic shift’, which involves the re-assortment of whole segments of the RNA genome resulting in new combinations of H or H/N subtypes of the virus. Although the emergence of a new strain is possible by antigenic shift, it is limited by the fact that re-assortment can only occur when at least two different influenza viruses infect and replicate within the same host cell; a simultaneous infection. In 2009 antigenic shift was responsible for the pandemic influenza A (H1N1)pdm09 virus. This novel variant virus contained a re-assorted genome from pig, bird and human influenza viruses and resulted in a IAV subtype dubbed ‘swine flu’ that had never been seen before in the human population. The new combination allowed it to evade any pre-existing immunity, protection from vaccination and rapidly spread from person to person. The result of which was the ‘swine flu’ pandemic that killed an estimated 284,000 people.

Influenza is mainly transmitted via respiratory droplets. For the virus to be successful a chain of transmission needs to occur including a reservoir (source of virus) a portal of exit from the reservoir and a portal of entry into a susceptible host. Therefore, IAV must be able to infect via the respiratory mucosa, replicate and release virions to infect a new host. The main receptor for the virus is sialic acids of the cell surface glycoproteins and glycolipids which are recognised by the viral hemagglutinin. It is the interaction between the virus/ cellular receptor that contributes to the host pathogenesis and allows interspecies transmission of IAV.

Clinically IAV presents with fever, sore throat, myalgia, non-productive ‘dry’ cough, runny or blocked nose, headaches and fatigue after an incubation period of 3 to 7 days. The most frequent complication is from secondary bacterial infections/ bacterial pneumonia.

**Influenza A in animals**

IAV are known to infect many different animals including birds, pigs, horses, cats, dogs, whales and seals. When animal IAV infect their host, they are referred to via their host species for example avian IAV (birds) or swine IAV (pigs). Recent outbreaks of avian IAV have devastated bird populations across the world.

Spillover respiratory virus infections from one species to another are quite common. Respiratory viruses including IAV spread through close contact. Human transmission is usually through close contact with infected animals, so people living or working with animals are at higher risk. However, it should be noted that the majority of these spill over events go undetected, as many are asymptomatic, or the virus does not replicate sufficiently to spread from person to person due to host specificity breaking the chain of transmission.

In avian influenza risk factors for human infection include exposure to infected poultry (both alive and dead) or contact with contaminated environments, such as farms or bird markets. Since 1997 there has been several hundred cases of avian influenza reported in humans including, A(H5N1): mostly in Asia, but also reports from America, Africa and Europe. In 2013 the first cases of human A(H7N9) were reported in China, with over 1500 cases reported to the WHO between 2013 and 2019. More recently there have been reports of outbreaks of A(H5N1) in mammals, including seals in the United States of America, sea lions in Chile and a mink farm in Spain. More concerningly A(H5N1) has been detected in domesticated animals, with an outbreak reported in Poland in July 2023 in household cats.

Swine IAV is common in pig populations in many regions of the world. It can be detected worldwide and is an enzoonotic infection, meaning that it regularly affects animals in a particular district or at a particular season. Three subtypes of swine IAV have been found to circulate in pigs A(H1N1), A(H1N2) and A(H3N2) depending on geographic location. Human infections with swine variant subtypes have been detected sporadically across the globe including Asia, Americas, Europe and Australia mainly after direct or indirect contact with infected pigs or contaminated environments. Swine IAV infections in humans tend to present as mild illness and are similar to those of influenza. Current evidence suggests that these swine IAV have limited pathogenicity amongst humans with most transmissions being epidemiological dead-end events with no onward transmission.

**Swine H1N2**

On the 25th of November 2023 the UK notified the World Health Organisation (WHO) of a human case of swine-origin influenza A(H1N2) virus infection. The case, an otherwise well person over 75 years old reported mild symptoms and presented to their GP on the 9th of November in North Yorkshire. During this visit a swab was analysed as part of the national routine influenza surveillance programme undertaken by UKHSA and RCGP. It subsequently tested positive by reverse transcription polymerase chain reaction for swine influenza A(H1N2) virus deemed A(H1N2)v. Genome sequencing conducted at the Worldwide Influenza Centre at the Francis Crick Institute (a WHO Collaborating Centre) and the World Organization for Animal Health (WOAH) avian and swine influenza reference laboratory at the Animal and Plant Health Agency, indicated the virus belonged to the distinct genetic clade 1B.1.1. which is different to recent human cases, but is similar to viruses circulating in UK pigs. This was the first time a virus from this swine genetic clade has been detected in a human in the UK.

Sporadic cases of human infections with swine H1N2 have been reported globally since the 1950s, there have been a total of 50 human cases of swine A(H1N2) reported since 2005, however, none of which were genetically related to the UK variant (according to UKHSA). Including a case reported in August 2023, in Michigan in the USA, investigations by local public health officials identified swine exposure by the patient at an agricultural fair. The UK case lived in a region containing pig farms, but no direct contact between the case and pigs was reported. Neither this case or the UK case were hospitalised and made a full recovery from the illness

After further virological testing (to the 4th of December 2023) no direct link or chain of transmission had been identified in the UK and no human to human transmission had occurred. Two contacts reported resolved symptoms by the time of sampling, however this could not be confirmed to be A(H1N2)v by virological testing. No further cases had been identified through enhanced surveillance, supporting the evidence that these swine IAV have limited pathogenicity amongst humans. Serological assessment is ongoing with results to follow.

Overall, this case highlights the importance of the national routine surveillance of respiratory virus infections and how the data collected through surveillance underpins our knowledge of current infections across the UK. It showcases the virological, genomic and public health response to novel infections of which biomedical scientists play a pivotal role.