



03 July 2020

Prevalent Eurasian avian-like H1N1 swine influenza virus with 2009 pandemic viral genes facilitating human infection

<https://www.pnas.org/content/early/2020/06/23/1921186117>

Summary context and global relevance:

The emergence of a dominant subclade (1C.2.3) or 'G4' of swine influenza A(H1N1) viruses in Chinese pigs with evidence of zoonotic transmission has raised questions for pandemic risk and preparedness. OFFLU, working through its open network have assessed the potential implications of the latest research findings. To date there is no evidence that these viruses are present in pigs or humans outside of China but vigilance is strongly advised.

The 'G4' viruses were reported previously by the Harbin Veterinary Research Institute, China in a 2016 publication and have been the dominate genotype in Chinese swine populations since 2016. The viruses in the latest report show a number of characteristics associated with predicted increased affinity for zoonotic transmission, including some genetic markers, replication competence in human airway cells and respiratory droplet transmission in ferrets. Furthermore, a seroprevalence of approximately 10% based on a moderately small sample size in swine industry workers only, indicates some risk of exposure and zoonotic transmission, although such seroprevalence might not be solely attributed to the "new" G4 viruses and to date, only two clinical human influenza A H1 variant (A/H1v) cases have been reported. The WHO Collaborating Centre at China CDC has previously reported human infections by 1C (Eurasian avian-like) A(H1N1) variant viruses, including two recent viruses with the G4 genotype. A candidate vaccine virus (CVV) from a closely related 1C.2.3. (Eurasian avian-like) A(H1N1) virus has been developed by the WHO Collaborating Centre at China CDC.

The implications for swine influenza surveillance worldwide are that we recommend continued vigilance ensuring relevant diagnostic tools used are proven to detect a wide range of viruses including these emergent strains. The clinical effect upon pigs has not been defined. It is important that swine surveillance data derived from national programmes is synthesised rapidly on a global scale in order to be able to track these and other viruses should they spread more widely. The OFFLU open network welcomes and encourages contributions from all stakeholders and is grateful for the support they receive from swine producers and veterinarians conducting surveillance in swine populations globally.

The release of sequence data has allowed both public and animal health specialists to assess areas important in disease emergence, mitigation and pandemic preparedness. We note that a number of countries worldwide (Netherlands, Italy, China) have reported human infections with swine influenza A viruses from the 1C or Eurasian avian-like swine influenza A virus clade. It is critical to assess diagnostic test sensitivity, and the potential for antiviral resistance in any pandemic preparedness planning. The development of influenza candidate vaccine viruses (CVVs), coordinated by WHO, remains an essential component of the overall global strategy for pandemic preparedness. Zoonotic influenza viruses continue to be identified and evolve both genetically and antigenically highlighting the need for continued international surveillance in animal populations. Through international partnership among OIE, FAO, WHO and contributing laboratories, a process to review animal influenza viruses and the potential risk to humans is possible. Within OFFLU, we have active programmes for global monitoring and characterisation of emerging viruses - the outputs of which are rapidly shared amongst the international community.

Background:

Influenza A(H1)v

Influenza A(H1) viruses are enzootic in swine populations in most regions of the world. Depending on geographic location, the genetic and antigenic characteristics of these viruses differ. Human infections with swine influenza A(H1) viruses (designated as A(H1)v viruses) have been documented previously in Asia, Europe and the Americas.

Influenza A(H1)v activity from 24 September 2019 to 24 February 2020 https://www.who.int/influenza/vaccines/virus/202002_zoonotic_vaccinevirusupdate.pdf?ua=1

One human case of an A(H1N1)v virus infection was identified in China in this period. In addition, a previously unreported A(H1N1)v case from China with an onset date of December 2018 was also identified. These A(H1N1)v cases were caused by viruses from the 1C (Eurasian avian-like) swine influenza virus lineage
<https://msphere.asm.org/content/1/6/e00275-16>.

Antigenic and genetic characteristics of the influenza A(H1N1)v virus

The A(H1N1)v virus detected in this period had an HA that differed by 3 amino acids from that of the most similar CVV, A/Hunan/42443/2015. Viruses with similar HA and NAs are known to circulate in swine in the region. No comprehensive antigenic analysis is available that includes these recent swine data alongside other reference swine IAV. Prior analysis of viruses of the 1C HA genetic lineage detected in swine in Europe demonstrated they were genetically and antigenically distinct from the A(H1)v A/Hunan/42443/2015 CVV and thus a second CVV (A/Netherlands/3315/2016) was developed. Additional ferret antisera production and antigenic characterization are underway in order to monitor the antigenic diversity of 1C lineage viruses.

Diagnostics:

From our in-silico analyses, we predict high test sensitivity to detect these Chinese 1C (Eurasian avian-like) viruses using M-gene targeted real-time PCR protocols as recommended by the OIE International Reference Laboratory for Swine Influenza at APHA-Weybridge, UK.

Genetic analyses:

HA gene:

The 77 HA sequences derived from pigs in China all cluster in the 1C.2.3 clade. This clade has only been detected in Chinese pigs. The 1C lineage is very diverse and human infections from other clades in this lineage have been sporadically reported, particularly in Europe. A candidate vaccine virus (CVV) has been developed to a closely related strain (A(H1)v A/Hunan/42443/2015) to those circulating in Chinese pigs and our sequence analyses showed 3 amino acid changes between the candidate vaccine virus and the characterized HA sequence (G4 EA A/swine/Shandong/1207/2016) from Chinese pigs.

Antigenic properties:

The latest research did not assess the antigenic properties of the Chinese viruses against the 1C CVV (A(H1)v A/Hunan/42443/2015) in a hemagglutination inhibition assay and therefore we recommend these phenotypic analyses are carried out urgently by OIE/FAO International Reference Laboratories and WHO Collaborating Centres through the WHO-OIE-FAO tripartite pandemic preparedness framework.

Antiviral mutations associated with sensitivity/resistance:***M2 ion channel inhibitors:***

All G4 1C.2.3 virus sequences reported in the PNAS paper contain the S31N mutation which confers reduced susceptibility to amantadine and rimantadine similar to human M genes derived from the H1N1pdm09 lineage.

A large number of sequences (26/77) contain a V27I mutation. This is not described as conferring resistance, however a similar mutation at this site (V27A) does confer reduced susceptibility to amantadine and rimantadine.

NA inhibitors:

The two strains reported in the PNAS paper (A/swine/Shandong/0334/2017(H1N1) and A/swine/Shandong/0336/2017(H1N1)) contained a I117V mutation which confers increased resistance to oseltamivir. A/swine/Shandong/0336/2017(H1N1) contained an additional mutation (H275Y) which also confers increased resistance to oseltamivir.

Almost all of the strains reported contained additional mutations at sites known to affect susceptibility to NA inhibitors (E119, Q136, V149, R156, D199, I223/H296, E278, H275, S247 and N295) but the exact changes have not been characterised, so have an unknown effect on susceptibility.

References:

https://www.who.int/influenza/vaccines/virus/candidates_reagents/summary_a_h1v_cvv_nh2020_21_20200228.pdf

https://science.vla.gov.uk/fluglobalnet/AI_links.html

Nicola Lewis (APHA/RVC, UK)

Ian Brown (APHA, UK)

Amy Vincent (USDA, USA)

Tavis Anderson (USDA, USA)

OIE/FAO international reference laboratory for Swine Influenza, APHA-Weybridge, UK