

# Eurasian avian-like A(H1N1) swine influenza viruses

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## Event background

The 2009 pandemic was the latest of several pandemics caused by a swine-origin influenza virus [1]. Swine influenza is not a mandatory notifiable disease according to the World Organisation for Animal Health (OIE) criteria for disease notification [2].

A recently published study conducted between 2011 and 2018 in China, and based on surveillance data in pigs, identified an emerging genotype 4 (G4) reassortant Eurasian avian-like (EA) A(H1N1) swine influenza virus that contains internal genes from the human A(H1N1)pdm09 and North American triple-reassortant (TR) lineage-derived internal genes [3]. This virus demonstrated the ability to replicate in human epithelial cells and can spread through respiratory droplets between ferrets [3]. Antisera against seasonal human A(H1N1)pdm09 virus showed poor reactivity with G4 viruses. In the same study, a subsequent serosurvey found that 10% (35/338) of swine farm workers were positive for this G4 EA A(H1N1) virus, with a higher proportion in people between 18 and 35 years of age (21%; 9/44).

These findings raise concern about the pandemic potential of these viruses, which are already able to replicate successfully in human tissue and transmit through droplets between ferrets, being a model for human-to-human transmission.

## The study details

Between 2011 and 2018, 29 918 specimens were collected from nasal swabs of normal pigs in slaughterhouses in ten Chinese Provinces (Anhui, Beijing, Hebei, Heilongjiang, Henan, Jiangsu, Jilin, Liaoning, Shandong, and Tianjin) with high pig-density, mainly in the north-eastern part of the country. In addition, 1 016 specimens were taken from the nose or lungs of pigs with respiratory symptoms at a veterinary school site.

In total, 179 swine influenza viruses were isolated and sequenced for hemagglutinin (HA) and neuraminidase (NA) genes, which showed that the majority of 165 isolates belonged to the Eurasian avian-like (EA) A(H1N1) swine lineage, seven to A(H1N1)pdm09, one to the classical swine (CS) lineage A(H1N1), four A(H3N2), and two were avian influenza A(H9N2) viruses. The full genome of all 77 of the EA A(H1N1) swine lineage was determined and the HA genes belonged to clade 1C.2.3. A high diversity with six internal genes deriving from multiple origins EA A(H1N1) swine lineage, A(H1N1)pdm09, avian, and triple reassortment (TR) lineages was found. Six genotypes (G1–G6) were determined in EA A(H1N1) viruses.

G4 EA A(H1N1) and G1 viruses bound to human-type SAa2,6Gal receptors with high affinity but bound poorly to SAa2,3Gal. Virus of the G4 lineage replicated in human bronchial and alveolar epithelial cells. Similar levels compared to seasonal human influenza A(H1N1)pdm09 viruses were observed.

The virus replicated in high titres in the nasal, trachea and lungs of ferrets, which showed mild respiratory symptoms. G4 caused more-severe lesions in the lungs than G1 or human seasonal A(H1N1)pdm09 viruses. These viruses were also shown to be transmitted through direct contact and respiratory droplets between ferrets.

From 2016 to 2018, a total of 338 serum samples were collected from swine farm workers in 15 pig farms and 230 people in ordinary households in Hebei and Shandong province. Antigens of the G1 and G4 lineages, and A(H1N1)pdm09 were used and showed an overall seropositivity of 39% (131/338) and 32% (73/230) in the swine farm workers group and general population, respectively, for the seasonal A(H1N1)pdm09 virus; 10% (35/338) and 4% (10/230) positivity for the G4 lineage virus and 7% (22/338) of the swine workers and 2% (5/230) of the general population were positive for G1 lineage virus, respectively.

## Related studies and assessments from other organisations

A study published a few days later describes the diversity of swine influenza viruses in China over a comparable time period (2001-2018) and also identified continuous reassortment of different influenza viruses within the pig population, identifying 11 genotypes [4].

In a statement by the Chinese CDC [5], it was underlined that China implemented a dedicated influenza surveillance system in 2010 to identify zoonotic influenza cases early. More than 400 000 specimens are analysed annually on average, and only 13 cases caused by a Eurasian A(H1N1) swine influenza virus were detected; three cases were due to the G4 lineage. Effective human-to-human transmission has not been observed. Still, viruses of the described G4 lineage might have an influenza pandemic potential and the situation in the pig population has been under surveillance. It cannot be predicted when, where, and in what form the new influenza virus could trigger an influenza pandemic, and these findings do not yet constitute an immediate public health threat.

The Chinese Ministry of Agriculture and Rural Affairs also released a statement saying that the infected swine farm workers involved in the study did not show flu symptoms and the test sample is not representative of the pig population in China [6].

The US CDC assessment of the prevalence of G4 virus in the swine farm workers suggests that human infection is 'more common than previously thought,' but underlines that no human-to-human transmission of the G4 viruses has been observed, and no similar viruses are circulating in the US. Several actions are outlined to address this threat [7]:

- coordinating with public health partners in China, including requesting a virus sample for further analysis;
- applying the CDC Influenza Risk Assessment Tool (IRAT) to better assess the risk of the virus causing a pandemic;
- evaluating whether an existing candidate vaccine virus (CVV) against a closely related flu virus (called 'G5') would protect against this virus;
- if needed, developing a new CVV specific to G4 viruses;
- studying whether existing flu antiviral drugs offer any protection against this group of viruses.

The OFFLU (OIE-FAO network of expertise on animal influenza) states that 'to date there is no evidence that these viruses are present in pigs or humans outside of China but vigilance is strongly advised' [8].

Additionally, Dr Mike Ryan of the World Health Organization (WHO) said in a press conference that this virus is not new and has been under surveillance since 2011 by the Global Influenza Surveillance Network (GISRS) [9].

## European situation in the swine population

Swine influenza causes mainly mild disease in pigs and is not a disease that meets the World Organisation for Animal Health (OIE) criteria for disease notification [2]. Although there are no surveillance programmes to monitor swine flu systematically on a global level, a joint OIE-FAO network of expertise on influenza, called OFFLU, supports international efforts to monitor, share biological material and data of animal influenza viruses for the development of human pandemic vaccines.

With more than 700 million slaughtered pigs in 2017, increasing from 518 million in 2000, China is the world's largest pork consumer and producer and accounts for about half of the world's total pig producers [10]. According to the Food and Agriculture Organization of the United Nations (FAO), the number of pigs in China was 474 million (2010) and 447 million in 2018 [11]. Since 2018, African swine fever outbreaks across Asia and in China led to high losses in the pig population and pork production dropped by 21% [12, 13]. In comparison, the pig population in the 28 countries of the EU ranged from 144 to 150 million between 2010 and 2019 [14].

The European Surveillance Network for Influenza in Pigs (ESNIP1-3) conducted surveillance of swine influenza viruses (SIVs) in pigs between 2001-2008 and 2010-2013 [15]. Between 2010-2013, more than 9 000 herds in 17 countries were included in the virological monitoring surveillance programs and 31% of the herds were found to have tested influenza A virus positive. The following European enzootic lineages were described from 1 887 characterised viruses: avian-like swine A(H1avN1) (54%) that emerged in 1979, human-like reassortant swine A(H1huN2) (13%) that emerged in 1994 and human-like reassortant swine A(H3N2) (9%) that emerged in 1984, and the A(H1N1)pdm09 virus (10%).

Viruses of the 1C HA genetic lineage detected in European swine were genetically and antigenically distinct from the A(H1)v A/Hunan/42443/2015 candidate vaccine virus (CVV), so that a second CVV (A/Netherlands/3315/2016) was recommended to be developed [8-16]. Viruses described in the relevant study fall within 1C.2.3 clade, which so far has only been detected in pigs within China.

Following the 2009 pandemic, seasonal human A(H1N1)pdm09 viruses are known to have been transmitted to the pig population (reverse zoonosis) and co-circulation with European enzootic swine A(H1N1), A(H1N2) and A(H3N2) influenza viruses led to multiple reassortment events where more than 15% of the viruses were shown to be reassorted A(H1N1)pdm09-like viruses. Serosurveys in pigs showed a herd prevalence of between 40-50% for A(H1N1)pdm09 in Norway [17]. The wide-spread infection of farms with swine influenza was shown in a serostudy between 2011 and 2015 in a Polish herd, where 89% of the herd showed antibodies to SIV [18] and some lower prevalences in the Netherlands [19]. Serological evidence of transmission of A(H1N1)pdm09 or reassorted swine viruses were also shown in an African setting [20].

## Human cases due to swine A(H1N1) variant viruses

Human infections with swine influenza viruses are named variant virus e.g. A(H1N1)v. Sporadic cases have been observed globally. Human infections due to Eurasian avian-like 1 C lineage have been observed in Europe, however, this lineage covers multiple clades and the viruses identified show high variability including the gene composition. ECDC annual epidemiological reports list human cases due to A(H1N1)v reported between 2014 and 2019, but the list does not reflect the different lineages or clades and might not be comprehensive.

In 2014, the United States reported one human case with previous exposure to swine before onset of symptoms [21]; in 2015 [22] the United States reported three additional human cases including one death. Two severe human cases were reported in 2016 in a school-aged child in the Netherlands and a middle aged man from Italy [23, 24]. An additional mild human infection in Switzerland was also reported [25]. ECDC published a statement [26] on the importance of monitoring swine influenza viruses in Europe in 2016. In Europe, these viruses circulate widely in the pig population [3]. The viruses isolated from the patients were Eurasian avian-like swine influenza A virus clade 1C and differed genetically from each other.

Switzerland reported a mild human case infected with swine-derived influenza A(H1N1)v virus in 2017, which was a male farm worker exposed to pigs infected with the same virus. The US also reported a case infected with A(H1N1)v having had contact with pigs prior to onset of symptoms [27].

In 2018, one human A(H1N1)v case with the Eurasian avian-like swine virus was reported from China [28]. In 2019, the United States reported one human case and China reported one infection with a Eurasian avian-like 1C4 swine influenza virus lineage in a 38-year old man from Hebei, China [16, 29-21].

## Risk assessment questions

- What is the latest information on the G4 EA-H1N1 from primary sources?
- What is known about animal-to-human transmission?
- What is known about its circulation in the general population?
- What is the risk of mutation and human-to-human transmission?

## ECDC risk assessment

### What is the latest information on the G4 EA-H1N1 from primary sources?

Since the pandemic in 2009, reverse zoonotic events with the introduction of human seasonal A(H1N1)pdm09 viruses from humans back into the pig population have been observed. Adaptation of A(H1N1)pdm09 viruses to swine due to reassortment events between different swine isolates and ongoing spread within the pig population has driven this diversification [32]. The occurrence of 55 novel reassorted viruses derived from Eurasian Avian-like and influenza A(H1N1)pdm09 viruses were described in 2016, showing enhanced virulence and transmissibility in mice and guinea pig models [33]. Several other studies described different reassortment events and a large mix of gene segments between the human seasonal A(H1N1)pdm09 virus, the Eurasian swine and triple-reassortant swine lineage [34, 35]. The establishment of viruses containing gene segments from A(H1N1)pdm09 viruses across the European pig population and the increasing diversity of lineages increasing the possibility of the emergence of a genotype with human pandemic potential has been highlighted previously [36]. The circulation of related viruses in Europe has been described and such animal to human transmission events have been observed leading even to severe cases that required admission to intensive care units.

Therefore, the study findings of the circulation and presence of influenza viruses in swine that are able to transmit to humans is not surprising, and this has been described before. The question of how representative a sample of 30 000 specimens over eight years in just 10 provinces for a pig population, with more than 500 million slaughtered pigs each year should also be asked. The massive impact of African swine fever on the pig population in China might have also changed the overall distribution of viruses across the pig population in China.

A few sporadic mostly mild cases infected with related Eurasian avian-like swine influenza viruses were reported from China and Europe. Two severe human cases were reported from Italy and the Netherlands [23, 24] in 2016 and in China in 2015 [37].

### What is known about animal-to-human transmission?

The risk factors described are direct exposure or contact to pig or pig products within farms or at slaughterhouses or markets. In Europe, zoonotic transmission of swine influenza viruses to human cases are a rare event and only sporadically detected, while in the US, human cases due to SIV A(H1N1)v, A(H1N2)v or A(H3N2)v are more frequently observed due to mass pig fair events [38]. At pig fairs in the US, there is direct contact between humans and the animals at the event, which has led to many human cases in the past. However, the tradition of such large fairs that last for several days is not common in Europe.

Human behaviour contributes to the risk of exposure or infection, and modifying certain behaviour can be an effective control against emerging diseases. A recent study in 153 pig farmers, pig traders and pig trade workers in Guangdong, China, showed a lack of awareness of the risk of zoonotic transmission of swine influenza as well as the risk of continuing to work with influenza-like illness [39].

### What is known about its circulation in the general population?

The systematic surveillance of swine flu in Europe has been previously performed within a European network, but this work was discontinued in 2013. The European swine influenza surveillance is currently based on individual initiatives or derives from research projects that might provide only a fragmented view of the overall picture. Systematic surveillance in pig populations in Europe is absent, so data on the circulating SIVs is limited and not regularly performed in a systematic way. The impact of trade-related network and transport structures between pig producers that may contribute to a rapid spread of potentially new influenza viruses across Europe is not known [40]. The assessment of the circulating viruses in the European pig population might therefore be challenging. The circulation of viruses in pigs and their ability to transmit to humans requires monitoring activities to avoid humans serving as sentinels after being in close contact or directly exposed to pigs or pig products..

So far, no human-to-human transmission has been reported. However, the lack of investigations related to human cases and the lack of seroprevalence studies of swine influenza viruses in humans limits this assessment. No information about broad population-based serostudies on swine influenza viruses is available.

The cross-reactivity between different reassorted Eurasian avian-like swine influenza viruses and A(H1N1)pdm09 viruses at a certain level (also with A(H1N1)pdm09 vaccine viruses) is not known. However, the integration of gene segments of human seasonal A(H1N1)pdm09 viruses in Eurasian avian-like swine viruses and the continuous circulation of A(H1N1)pdm09 viruses since 2009 might lead to some immunity in the human population against these viruses.

In the respective study, samples from farmers were only taken between 2016-2018, and from possibly unrelated farms in only two Provinces, so it is not known if virus positive animals were also in the same farms.

The relatively high seropositivity in the general population presented in the study needs to be confirmed and might be due to unspecific cross-reactivity. Seropositive results do not give an indication when the infection or transmission event happened. Therefore, further prospective studies and cohorts with follow-up should be considered to better understand if transmission to the community also occurs.

## What is the risk of mutation and human-to-human transmission?

The emergence of new viruses, as experienced with SARS-CoV-2, or with the emergence of the highly pathogenic avian influenza virus A(H7N9) mutation, new genetic variants, and their epidemiological characteristics in humans and other animals are still unpredictable. The factors that drive the processes are not fully understood as also individual host factors play a strong role.

Surveillance and data collection for diseases with mild clinical signs or which are asymptomatic in domestic animals are limited. This is similarly true for mild diseases in humans and a small cluster of human-to-human transmission associated with mild symptoms might be challenging to be detected through the regular sentinel surveillance systems.

However, human cases with swine influenza variant virus infection are detected sporadically through routine surveillance as has been described recently in Brazil, with the report of a human case of A(H1N2) variant virus. The 22-year-old female slaughterhouse worker presented with influenza-like illness (ILI) on 12 April 2020 and the A(H1N2) variant virus was identified through routine surveillance and sharing of the isolate with the national influenza centre. This underlines the importance to test patients with ILI also for influenza, and in case the virus is untypable, to share with specialised laboratories for further characterisation [41]. A retro- and prospective investigation at the site identified another possible case with similar ILI symptoms during the same time period.

## Options for response

### Diagnosis

In January 2020, WHO updated the recommendations regarding molecular diagnosis for influenza [42]. Influenza A virus isolates or clinical samples that cannot be subtyped should be sent to the national reference laboratory for influenza (National Influenza Centres; NICs), and further to a WHO Collaborating Centre for Reference and Research on Influenza for characterisation.

The human cases detected in 2016 in the Netherlands and Italy were mainly identified through the availability of whole genome sequencing (WGS) in the clinical setting. The availability and increasing use of WGS for routine diagnostics might support the identification of zoonotic transmission events and are highly encouraged to be applied when influenza viruses cannot be typed or subtyped with usual methods.

The awareness of clinicians to test patients with respiratory illnesses for influenza virus infection and perform virus characterisation or whole genome sequencing, at least of severe cases, is of utmost importance to identify clinical cases, initiate follow-up investigations and detect human-to-human transmission. Strains which cannot be subtyped should be sent to national influenza centres and further to WHO Collaborating Centres for further characterisation. ECDC published a statement in 2016 on the importance of monitoring swine influenza viruses in humans in Europe [26].

The monitoring of swine influenza viruses in the pig population together with virus characterisation is needed to better understand the variability of circulating viruses and assess the potential risk for human transmission.

### Reporting

Human infections with novel influenza strains are notifiable under EU legislation and the International Health Regulations (IHR) through the Early Warning and Response System (EWRS) and the IHR notification system [43, 44]. Rapid sharing of such information nationally and internationally is a prerequisite for the ability to early identify new emerging pandemic threats and initiate containment and prevention measures.



## Follow-up

Each human case due to swine influenza infection must be investigated to identify the source and detect any signals of human-to-human transmission.

Infectious disease protocols for case investigations are available from the Consortium for the Standardization of Influenza Sero-Epidemiology (CONSISE) and national authorities [45-47]. Agreed protocols for clinical investigations have been prepared by the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) [48]. Contacts of confirmed cases should be followed-up and tested. International recommendations for the use of post-exposure prophylaxis differ. Evidence of the effectiveness of contact tracing on board airlines in limiting the spread of infection is limited and should only be considered by a risk assessment on a case-by-case basis [49].

## Vaccines

The most important intervention in preparing for the pandemic potential of influenza viruses is the development and use of human vaccines, therefore the situation is constantly monitored and assessed by WHO. Routine vaccination with seasonal influenza vaccine is recommended for workers having contact with pigs to minimise the possibility of co-infection with human and swine influenza viruses thereby reducing the risk of reassortment.

For pandemic preparedness, candidate vaccine viruses (CVV) against zoonotic influenza viruses are recommended and developed. Regarding circulating A(H1N1) viruses in the pig population in China, the Chinese CDC had previously developed a candidate vaccine virus CNIC-1601 (A/Hunan/42443/2015) (H1N1). However, in the most recent WHO report on antigenic and genetic characteristics of zoonotic influenza A viruses and development of candidate vaccine viruses for pandemic preparedness from February 2020, it is mentioned that some mutations were detected in the A(H1N1)v virus reported during this period compared with the A/Hunan/42443/2015 virus. The genome comparison with the currently existing CVV with the G4 virus reveals to be similar, however, no data on antigenic characteristics was available. The report also mentions that European swine viruses of the 1C HA genetic lineage showed a distinct genetic and antigenic profile from viruses where CVVs are developed (A(H1)v A/Hunan/42443/2015 and A/Netherlands/3315/2016) [16].

Research is ongoing to develop vaccines related the CS and EA viruses [50].

Vaccination strategies with optimised vaccines against currently circulating swine influenza viruses in the pig population could counteract the large circulation of different viruses affecting the pig population and also representing a threat to human health. This would result in an overall lower risk of exposure and decreasing risk of transmission to humans.

## Infection prevention and control

Healthcare workers managing symptomatic exposed (or possible) cases should follow standard, contact and respiratory precautions. Current guidelines for COVID-19 in healthcare settings could equally be applied.

Pre- or post-expositional prophylaxis using antiviral treatment for people at risk needs to be considered by the respective authorities based on a situational risk assessment.

## Assessment tools:

The World Health Organization has developed a Tool for Influenza Pandemic Risk Assessment (TIPRA) [51] to assess the risk of influenza viruses with pandemic potential to inform public health preparedness and response actions, which has been used e.g. to assess A(H5) viruses of clade 2.3.4.4 [52].

The US CDC has developed a similar Influenza Risk Assessment Tool (IRAT) [53] to assess influenza A viruses currently not circulating in people regarding their pandemic potential risk and includes one A(H1N2) and two A(H3N2) swine variant viruses, however, no swine A(H1N1)v [54].

The Eurasian avian-like (EA) A(H1N1) swine influenza viruses have not been included in such assessments so far.

## Source and date of request

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## Consulted experts

ECDC expert: Cornelia Adlhoch

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