

Webinar COREB / COCLICO Zoonotic influenza February 07, 2025

Summary of presentations and Q&A

Zoonotic epidemiology: risk and mechanics of species barrier crossing, animal vaccination - Béatrice Grasland, ANSES (French Agency for Food, Environmental and Occupational Health and Safety)

- Influenza A viruses infect a **broad spectrum of hosts**, and can evolve in two ways: through breaks (point mutations) or antigenic shifts (reassortment).
- The reservoir for almost all influenza A viruses is waterfowl (ducks, geese, gulls), with almost all Ha (hemagglutinin) and Na (neuraminidase) subtypes represented. Some viral subtypes of avian influenza viruses can infect mammalian species and then adapt to their new host. All swine influenza viruses can infect humans, and all human influenza viruses can infect pigs.
- Influenza in pigs: the major swine viral subtypes circulate worldwide: H1 and H3 (H3 does not circulate in France). In France, in 2020, the emergence of an A(H1N2) subtype was observed, which has become dominant, with 1 human case described in 2021. A(H1N2) is also circulating in breeding turkeys. There is a policy of vaccinating breeding sows with two types of trivalent H3N2/H1avlike/H1hulike vaccine and a monovalent vaccine with a pandemic H1pdm strain.
- Influenza in birds: H5 and H7 subtypes of avian influenza in poultry can be **low pathogenic** (no clinical signs) or **highly pathogenic** (HPAI) (high mortality, spread of virus in the organs). Highly pathogenic H5 and H7 subtypes are being closely monitored, as they have high zoonotic potential and cause great economic losses in farming.
- Nearly 60 species of marine and terrestrial mammals can be infected by HPAI A(H5N1), with new events of species barrier crossing observed between birds and cattle with the infection of dairy cow farms since March 2024 in the USA. In connection with these outbreaks of HPAI in cattle, cases of infected domestic cats and human cases have been described.
- Since October 2023, **preventive vaccination against HPAI H5N1** has been compulsory in metropolitan France for duck farms producing more than 250 ducks. Two types of vaccine are used: an H5 subunit and an H5 RNA vaccine. This vaccination campaign has drastically reduced the number of HPAI outbreaks in France.
- Communicating and raising public awareness: **avoid all contact with sick or infected animals** (birds, pigs) and, in the United States, avoid drinking raw milk, in which the virus is present in very high quantities.

Surveillance of human cases of zoonotic influenza at international and national levels (update on human cases, case definition and investigations) - Sibylle Bernard-Stoecklin, Santé publique France

- Currently, avian influenza is most often characterized by mild respiratory syndromes and/or conjunctivitis.
- The highest number of human cases observed worldwide is due to two highly pathogenic avian virus subtypes:
 - Subtype A(H5N1) : > 960 cases since the early 2000s (mainly in Asia and Africa), including 80 cases in 2024 in the USA (67 cases, including 1 death) and Southeast Asia (13 cases). Two cases have been described in 2025 (February 07, 1 case in Cambodia and 1 case in the UK);
 - Subtype A(H7N9) : 5 waves during winter in China in the 2010s, with 1 500 confirmed cases. A(H7N9) has not been detected since nearly 7 years, following vaccination campaigns in poultry farms;
- 3 H5 clades are currently causing human cases: 2.3.4.4b (USA, Canada, UK), 2.3.2.1c (emerging with 2.3.4.4b, Cambodia and Vietnam), 2.3.2.1a (India).
- **Focus on human cases in North America: out of 67 cases investigated in 2024**
 - Exposure: dairy/poultry cows or not found for 4 cases
 - Clinical: mostly mild symptoms (mild respiratory symptoms and/or conjunctivitis), 2 severe cases including 1 death in the USA (patients with comorbidities) and 1 case with no exposure found.
 - All due to clade 2.3.4.4b, 2 different genotypes: B3.13 or D1.1
- **Other viral subtypes of avian origin with zoonotic potential are circulating worldwide, mainly:** H5N6 HP in China (93 cases since 2014 including 42 since 2021), H9N2 FP (142 cases since 1998 including 48 between 2021 and February 07 2025).
- **Swine influenza** : > 70 human cases described worldwide, with 3 swine influenza subtypes observed between 2018 and 2023: H1N1, H1N2, H3N2.
- No human-to-human transmission has been detected around recent cases of zoonotic influenza. According to international health organizations, the risk to human health remains low for the general population, and low to moderate for people exposed to animals or a contaminated environment.

Virology: diagnostic and surveillance aspects - Bruno Lina, virologist, head of National Reference Center respiratory infection viruses

- Crossing species barriers: zoonotic viruses are capable of infecting the **lower airways**, but do not find the right receptors to multiply in the upper airways. In theory, therefore, they cannot yet generate human-to-human transmission chains.
- Several serotypes are defined on the basis of surface antigens, hemagglutinin (HA) and neuraminidase (NA). Hemagglutinin allows the fixation of the virus to the host cell. This attachment is made possible by a specific bond between a galactose (Gal) and a

terminal sialic acid of the host cell (SA). In humans, this linkage (SA α 2-6Gal) enables preferential attachment to the ciliated cells of the respiratory epithelium, while in birds it is a linkage (SA α 2-3Gal) that enables virus attachment to the epithelial cells of the intestinal tract. Pigs have both α 2-6 and α 2-3 receptors. A single amino acid change is all it takes to switch from one type of receptor to the other.

The antigenic variation of the influenza virus is explained by the high rate of mutations induced by RNA polymerase replication errors. These mutations give rise to the phenomenon of antigenic drift. Altering the amino acid structure of the hemagglutinin epitope enables the virus to evade the immune system. The viral genome is segmented into eight independent RNA segments. If there is co-infection with two Influenza viruses of different serotypes in the same host, an antigenic reassortment (or shift) can be observed between the genomes of these two viruses. Finally, mutations in the hemagglutinin alone are not sufficient to explain viral genetic variability and to effect a shift, other mutations within the genomic structure are necessary: **the entire genome must therefore be monitored.**

- Milk infection: in contaminated dairy cows, there is a very high viral titer in the milk which is very stable over time, and can be the source of infection via food (high virus concentrations result in a change in the appearance of the milk : milk is “darker”, very dark yellowish in color, with a different texture: thick and lumpy). Pasteurization is effective in inactivating the virus.
- Make the diagnosis with good-quality swabs right **from the start of the infection:** combine swabs from the **upper and lower airways** with non-inactivating swabs (transport suitable for culture). Take a **conjunctival swab** if acute conjunctivitis, and other swab sites depending on clinical signs.
- **Do not use rapid screening tests because they are not suitable for zoonotic viruses.** Most human influenza PCR tests can be used to diagnose type A influenza, with H1, H3 and H5, if possible, subtyping. Some kits may lack sensitivity, so the viral load threshold (Ct for Cycle threshold) must be checked. If Ct in M > 32, the absence of subtyping does not eliminate H1/H3.
- **“Silent” carriage of the virus has been observed:** detection without seroconversion, but important to detect (transcriptomics and serology).
- **Follow-up is essential:** viral load monitoring with iterative sampling, sequencing, serology (seroconversion within 15 days).

Operational, clinical and therapeutic aspects - [Morgane Mailhe, national COREB mission](#)

- **Isolate the patient with protective measures,** hydroalcoholic solution and surgical mask. Healthcare professionals must wear **appropriate PPE (hydroalcoholic solution, FFP2 mask with fit check, goggles, overblouse, non-sterile gloves)** and disinfect the patient's environment with the usual disinfectants (virucide standard EN 14476).

- If a patient presents suspicious clinical and epidemiological characteristics, samples can be taken in city laboratories equipped with influenza A and B RT-PCR. A positive result for influenza A, with negative H1 and H3 subtyping, should raise the suspicion of zoonotic influenza.
- In hospitals, if the room is not equipped with an airlock, dressing will take place outside the room. Undressing will take place inside the room (except for respiratory protective equipment). PPE will be disposed of according to the infectious waste management circuit.
- In addition to symptomatic treatment, specific antiviral treatment with a neuraminidase inhibitor such as **oseltamivir** must be instituted by the first practitioner taking charge of the patient (general practitioner, emergency doctor, infectiologist, etc.) as quickly as possible, at best within the first 48 hours after the onset of symptoms, without this time limit constituting a limit.

Human vaccination - [Brigitte Autran, President of COVARS](#)

- In 2024, COVARS (Committee for monitoring and anticipation of health risks) estimated that respiratory pandemics were the first possible cause of a major exceptional health situation, in particular **zoonotic pandemic influenza**.
- HAS, ANSES, COVARS and EFSA (French and European health institutions) recommend seasonal influenza vaccination for professionals and people exposed to swine and avian viruses during periods of human influenza virus circulation. The aim of this vaccination is to limit the risk of recombination between animal and human viruses, but it does not intend to protect against avian influenza itself.
- **Development of human H5N1 vaccines, some of which are already available and usable.** There is a stockpile of European vaccine cross-reactive with the H5N1 bovine 2.3.4.4.b clade currently circulating in the USA.
- **RNA vaccines are currently being developed** (rapid synthesis, flexibility and production independence from embryonated eggs).
- In countries where the epidemiological situation justifies it, the target populations for these human vaccinations would be those exposed to the virus. The deployment of this vaccine requires parallel research, monitoring and evaluation.

Questions and answers

Epidemiology

Why is the current US epidemic less lethal than the H5N1 epidemics of the 2000s?

The H5N1 subtype viruses of clade 2.3.4.4b currently circulating are not the same as those circulating in the 2000s; they are the result of successive reassortments with different avian viruses. The zoonosis has been extended by the evolution of the 2.3.4.4.b clade, which is more infectious to mammals than the viruses of the 2000s: a very large wild animal reservoir, with exposure of farmed wildlife and mammals in contact with humans. A very significant increase in risk was seen with the infection of dairy cows: no airborne infection in cows (but rather through manu-feeding or milking via the udder). The risk has generally decreased in France with the vaccination of birds: positive effect on both farmed and wild fauna. There has been no change in pathogenicity, only in transmissibility.

The reasons why the frequency of mild forms is higher for viruses of this clade than for other clades of the H5N1 subtype are still poorly understood, and need to be the subject of in-depth epidemiological and virological studies.

What are the implications of the United States' withdrawal from the World Health Organization on the surveillance of zoonotic influenza?

Following this withdrawal, WHO announced that communication with US CDC experts was highly restricted. The absence of US participation in the Vaccine Composition Meetings may have important repercussions in the process of recommending vaccine strains for use in the months and years to come, particularly as regards the sharing of virus strains with WHO collaborating centers.

Regarding surveillance of the situation related to avian and swine influenza viruses currently circulating in the United States, human cases due to these viruses continue at this time to be reported to the WHO in accordance with the International Health Regulations, and this information is then disseminated via the EIS to other member states. In addition, the CDC continues to regularly update the zoonotic influenza pages [on its website](#).

What does the new barrier crossing between birds and cattle in the USA imply?

This crossing of the species barrier from birds to mammals and the circulation within mammal populations increases the likelihood of the virus mutating and adapting to its host, increasing transmission between mammals and thus creating the conditions for a pandemic.

Is there a risk of a pandemic of human cases?

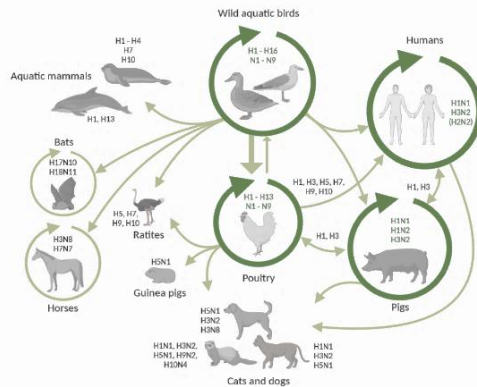
WHO and ECDC consider the risk to be low for the general population and low to moderate for people directly exposed to these viruses. To date, there is a low risk of an epidemic of human cases.

Are there other types of zoonotic influenza besides avian and swine flu?

Yes, all influenza viruses that infect mammals (pigs, cats, dogs, seals, etc.) can infect humans, and vice versa (all human influenza viruses can infect mammalian animals). Some equine, feline and canine influenza viruses have shown zoonotic potential, but to date, influenza viruses of animal origin that pose the most serious risk to human health are of avian and swine origin.

Risk exposure

Which animals are likely to be infected in France and Europe ?



Long, 2019 ; Choi, 2004 et Aymard, 1985

The reservoir for almost all avian influenza viruses is waterfowl (ducks, geese, gulls), with almost all Ha and Na subtypes present. Some avian influenza virus subtypes can infect other species and are species-adapted. All swine influenza viruses can infect humans, and vice versa.

Literature data indicate that at least one H5N1 genotype of clade 2.3.4.4b circulating in Europe (the BB genotype) is capable of infecting dairy cows via the intra-mammary route. The introduction of an H5N1 virus of clade 2.3.4.4b on at least three independent occasions in the USA indicates that such a scenario is not impossible in Europe. Cats and other felids, pigs, and a large number of other mammalian species are also susceptible to infection by H5N1 clade 2.3.4.4b viruses: there are over fifty mammalian species (wild or domestic, terrestrial or marine) in which an H5N1 clade 2.3.4.4b has been found, causing infection of varying severity, from asymptomatic to lethal with respiratory and/or central nervous system involvement.

Is it possible to contract the HPAI H5N1 virus by eating chicken or milk?

To date, no human cases infected in this way have been detected.

In the United States, where the HPAI H5N1 virus is circulating in poultry and dairy farms, it is recommended to cook poultry meat thoroughly at over 63°C for 10 minutes (145.4°F), and to avoid raw milk. Pasteurization of milk can reduce the viral load sufficiently.

In Europe, consumption of poultry meat is risk-free thanks to HPAI surveillance. As the HPAI H5N1 virus does not circulate among ruminants in France, the consumption of raw milk is not affected.

Has contamination via food really been proven?

In the case of H5N1, contamination by the respiratory route has been confirmed in humans. Contamination by the food route via exposure to the airways (aerosolization by drinking contaminated milk) cannot be ruled out.

In the United States, there has been an initial detection of H5N1 in a child who drank raw milk and developed symptoms but the case has not been classified by the CDC (no second detection).

Viral loads are even higher in milk than in birds. There is potentially a fairly long infectious stability of the virus in this matrix: this route cannot be ruled out as a contamination pathway.

Sampling and subtyping :

What does a positive influenza RT-PCR result for a type A influenza virus with a Ct below 32 mean?

A positive influenza RT-PCR result for a type A influenza virus with a Ct below 32 means that infection with this virus is detected with a significant viral load.

- **RT-PCR (Reverse Transcription Polymerase Chain Reaction):** A technique used to detect and quantify the virus' genetic material.
- **Ct (Cycle threshold):** This is the number of cycles required to detect the virus. The lower the Ct value, the higher the viral load.
- **Ct < 32:** Generally, a value below 32 indicates an active infection, with the positivity threshold varying from laboratory to laboratory (often <35).

In summary, a **positive RT-PCR result with Ct < 32 suggests active influenza A infection**, with a viral load high enough to be detected relatively early in the test.

What is the role of rapid antigen tests, frequently used in clinical practice to confirm influenza?

The use of antigen tests targeting human influenza A/B is not recommended in cases of suspected zoonotic influenza.

What does compliant sampling packaging actually mean?

Triple packaging and UN3373 shipment.

Virology

Are NAI resistances virological resistances with clinical impact or just mutations?

NAI resistance mutations are not virulence factors. They lead to a loss of NAI efficacy, making it more difficult to control infection, but they do not increase virus pathogenesis. It should be noted that this resistance is reputed to be associated with a reduction in virus transmissibility, but this is not always true, particularly in the case of the H275Y mutation for N1 neuraminidases.

Can you describe viral kinetics in severe forms of the disease and/or in immunocompromised patients, and what consequences this may have in terms of isolation?

Historically, severe and/or immunocompromised patients show slower viral clearance. They are therefore contagious for longer. Isolation can then be extended beyond 10 days if viral load monitoring on iterative samples is still positive.

Treatment and protection

Is there any point in doubling the dosage of oseltamivir for severe patients? No.

Are pediatric cases of avian flu more severe?

Infants under 6 months of age are more prone to severe forms, according to historical H5N1 data. The currently circulating clade is less pathogenic.

Vaccination

Is there any benefit to vaccinating a farmer infected with zoonotic influenza against seasonal influenza to prevent viral recombination?

If a patient is infected with zoonotic influenza, vaccinating them against seasonal influenza is pointless or even potentially deleterious in terms of immune response.

However, the HAS, ANSES, COVARS and EFSA (HAS, ANSES, COVARS and EFSA (French and European health institutions) recommend seasonal flu vaccination for professionals and people exposed to swine and avian viruses during periods of human influenza virus circulation. It aims to limit the risk of recombination between animal and human viruses. It does not claim to protect against avian influenza itself, nor does it reduce the viral load in cases of proven zoonotic influenza.

Is human vaccination available in France and Europe ?

Zoonotic influenza vaccination of exposed people is not yet considered necessary in France, due to the absence of human cases. Only 2 European countries have decided to do so: Finland and the Netherlands.