



UK Health  
Security  
Agency

# **Influenza A(H5N1) 2.3.4.4b B3.13: US cattle outbreak update**

Human health evidence review and  
situational assessment 17 July

**UKHSA, APHA, FSA, and Defra**

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## Overview

The UK Health Security Agency (UKHSA) is working with the Animal and Plant Health Agency (APHA), the Department for Environment, Food and Rural Affairs (Defra), Food Standards Agency (FSA), and the public health agencies of the 4 nations to monitor the risk to human health from emerging influenza viruses.

A [previous assessment](#) of this situation was published in May 2024.

## Current evidence review

### 1. Animal outbreak

There is ongoing transmission of influenza A(H5N1) in the US, primarily through dairy cattle but with multispecies involvement including poultry, wild birds, other mammals (cats, rodents, wild mammals) and humans ([1](#), [2](#)). There is high uncertainty regarding the trajectory of the outbreak and there is no apparent reduction in transmission in response to the biosecurity measures that have been introduced to date. There is ongoing debate about whether the current outbreak should be described as sustained transmission given that transmission is likely to be facilitated by animal farming activities ([3](#)). However, given that this is a permanent context, the majority of the group considered this outbreak as sustained transmission with the associated risks.

The available genomic data show a single expanding clade, genotype B3.13, consistent with ongoing transmission through dairy cattle and spillover into other mammals and birds.

### 2. Human cases

There is evidence of zoonotic transmission (human cases acquired from animals). There is likely to be under-ascertainment of mild zoonotic cases ([4](#)). There have been ten human cases detected associated with the current US outbreak, 4 in dairy workers at separate farms and 6 in poultry workers exposed during a single depopulation event at which a large number of workers were symptomatic ([1](#)). Environmental factors may have contributed to increased viral exposure at this site ([5](#)). Human case genomes where available are within the cattle outbreak clade although the first human case in Texas is distinct ([3](#)). The sequence from this case (EPI\_ISL\_19027114) does contain the HA L131Q and T211I mutations present in all B3.13 sequences, but not contain the PB2 M631L, PA K497R or the NA N71S mutations observed in the main cattle outbreak clade. It contains PB2 E627K and D441N mutations, K142E in PA, and S7L and Q40R in NS1 that are not observed in other B3.13 sequences.

The ongoing cattle outbreak in dairy cattle with spillover to poultry farms means that there could be large numbers of human exposures and increased opportunity for zoonotic cases. However, there are insufficient data to assess whether the rate of zoonotic infection is unusually high.

### 3. Virus profile

In order to inform rapid risk assessments, we consider virus biological properties of receptor binding, polymerase function, pH stability and sensitivity to restriction factors as indicators that may be relevant to adaptation to human infection and transmissibility. This assessment uses genomic data shared by the US, published phenotypic data and unpublished preliminary data supplied by the UK FluTrailMap One Health consortium. It is focused on viruses in the expanding cattle outbreak, although differences to the human case in Texas are noted.

#### Receptor binding

The key change of concern would be alteration in haemagglutinin binding profile towards affinity for  $\alpha$ 2,6 sialic acid receptors which would adapt the virus towards human upper respiratory tract tropism. In referencing haemagglutinin mutations in this evidence we use Met1 H5 numbering. All sequences in the cattle outbreak clade contain HA:L131Q and T211I mutations. Using a deep mutational scanning approach ([6](#)), the L131Q mutation was predicted to increase binding to both  $\alpha$ 2,3 and  $\alpha$ 2,6-linked sialic acid receptors compared to the candidate vaccine virus A/American wigeon/South Carolina/22-000345-001/2021. The T211I mutation was characterized, using glycan microarrays in one preprint, to increase the breadth of binding to different  $\alpha$ 2,3SA containing glycans ([7](#)). This is supported by deep mutational scanning data which shows a preference for  $\alpha$ 2,3SA over  $\alpha$ 2,6SA. One peer reviewed paper reports that the bovine virus displays some binding to  $\alpha$ 2,6SA receptors as well as to  $\alpha$ 2,3SA receptors ([8](#)). However other preprints and unpublished data do not find significant binding to  $\alpha$ 2,6SA receptors ([7](#), [9](#)). The current consensus of the technical group is that the virus that spilled over into dairy cattle (that is, with L131Q and T211I mutations only) binds strongly to  $\alpha$ 2,3SA receptors as is the case for typical avian influenza viruses.

Since the first reported cattle herd infection on 25 March 2024, a small number of mutations have been acquired by some viruses throughout the outbreak clade; of these T143A, Q154L, D171N, A172T, P174Q, I178V and Q234R have been phenotypically tested individually in the background of the bovine H5 HA (EPI\_ISL\_10914383 containing L131Q and T211I). None of these resulted in any detectable  $\alpha$ 2,6SA receptor binding ([10](#)). Overall, there is no evidence of change in HA which is suggestive of human adaptation through these acquired mutations. Although genomic surveillance data are likely to lag behind infections, the lack of evidence of viral adaptation to  $\alpha$ 2,6SA receptors after thousands of dairy cattle infected may suggest that transmission within cows does not strongly predispose to human receptor adaptation. Evidence of which sialic acid receptors are present in cows, which is needed to support this hypothesis, is still preliminary and requires confirmation ([11](#), [12](#), [13](#)).

## Polymerase

One early human case in Texas (EPI\_ISL\_19027114) had the mutation PB2 E627K which is known to enhance viral replication in mammalian cells ([14](#), [15](#)). However, this mutation is not seen in the rest of the dairy cattle outbreak or other associated human cases. Two other polymerase mutations are seen frequently throughout the cattle outbreak: PB2 M631L and PA K497R. Preliminary in vitro evidence suggests that these mutations enhance the virus' ability to replicate in both bovine and human cells to some degree, although this is a smaller effect than is seen with E627K ([10](#)).

## Restriction factors and pH stability

There is no new data on restriction factors or pH stability.

## 4. Evidence relevant to human transmissibility

Despite the increased activity of the bovine virus polymerase with the PB2 M631L and PA K497R mutations in human and other mammalian cells, the lack of human receptor binding supports the virological observations that bovine virus (EPI\_ISL\_19014384), like earlier clade 2.3.4.4b viruses that circulated in the UK, replicates and spreads poorly in human airway epithelium at 33°C (similar to temperatures in human nasal passage) ([10](#)). Preprint data finds respiratory inoculation is possible in experimentally infected heifers and published data suggests inefficient respiratory transmission in the ferret model ([8](#), [16](#), [17](#)).

## 5. Characteristics of genotype B3.13

There are insufficient data to assess whether the genotype B3.13 was already fitter in birds or mammals at the point of spillover (that is, had a predisposition to cause a mammalian outbreak) and therefore it is difficult to assess whether other genotypes seen in Europe could cause similar outbreaks given similar opportunity. In vitro data shows that other influenza A viruses with internal genes derived from avian viruses including those of clade 2.3.4.4b replicate efficiently in bovine cells ([10](#)). Widespread transmission in marine mammals is also noted in South America, involving a slightly different genotype ([18](#)). With the current evidence we should not assume that the risk of a mammalian outbreak is limited to clade B.3.13.

## 6. Risk of reassortment

There is an ongoing elevated risk of reassortment with other influenza viruses given the range of animal and human infections occurring. There is also early in vitro data suggesting that human seasonal influenza viruses can replicate in bovine cells ([10](#)). This implies that reassortment resulting in exchange of genes between the bovine virus, avian influenza viruses and fully human adapted influenza viruses could also occur in cattle, as it does in pigs.

## Current situational assessment

Levels are indicators that a zoonotic influenza virus outbreak may be an increasing human health threat, either because the opportunities for it to evolve are increasing or because there is evidence that it has already begun to evolve. All levels are pre-pandemic events.

The current situational assessment is shown in Table 1 alongside accompanying evidence, updated from the [previously published situational assessment](#) (May 2024).

**Situational assessment: the outbreak is currently at level 4 (MODERATE confidence).**

Confidence levels for this assessment are set using modalities of data supporting the assessment.

If one of epidemiology, genomic, or virological data supports: Low confidence  
 If 2 of 3 categories of data support: Moderate confidence  
 If all 3 categories of data support: High confidence

**Table 1. Situational assessment framework and evidence supporting the assessment (cells highlighted in blue indicate the current level and evidence available)**

Level	Level description	Epidemiology supporting evidence	Genomics supporting evidence	Virology supporting evidence
0	Avian influenza circulating in birds, epidemiology within seasonal norms.			
1	Avian influenza circulating in birds, epidemiology outside seasonal norms.			
2	Evidence of propensity to infect humans and/or other mammals (individual cases without onwards transmission).			
3	Limited or facilitated mammalian transmission			
4	Sustained and/or multispecies mammalian outbreaks; increasing human zoonotic cases or limited person to person spread, linked to zoonotic exposures.	At least 5 months of sustained transmission in cattle in the US with additional mammalian species affected and onwards transmission to poultry. Transmission may relate to farming practices but these are widespread standard practices. Regularly identified human zoonotic infections although rate cannot be assessed. No person to person transmission demonstrated.	Phylogeny supports sustained and multispecies transmission over period of months in the US (tMRCA estimates in range November 23 to January 24) (19, 20). A mutation in the PB2 segment, M631L, was acquired early in the outbreak and is present in all sequences from the outbreak apart from the first human case from Texas. An additional mutation in the PA segment K497R is present in a large proportion of sequences from the outbreak from multiple species, in combination with PB2 M631L. All B3.13 sequences contain two HA mutations (L131A and T211I). These mutations are also present in sequences from other related genotypes and did not emerge in this genotype. Within the outbreak clade a small number of non-synonymous changes in HA have been observed but only one of these (T143A) is present in more than 3% of sequences.	Virological data are preliminary and require confirmation. There is in vitro evidence of polymerase-related adaptation to mammalian cell replication
5	Human outbreaks (larger or without identified zoonotic links).			
6	Sustained human to human transmission.			

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## UKHSA zoonotic influenza technical group

The zoonotic influenza technical group includes expert members from UKHSA, Defra, APHA, FSA, and academic partners with relevant expertise who are willing to share and jointly assess data. The group includes epidemiology, virology, genomics and human and animal health clinical specialists.

## Technical group members

Technical group members undertaking assessment of 17 July 2024:

Ashley Banyard, Wendy Barclay, Ian Brown, Andre Charlett, Meera Chand (chair), John Edmunds, Eileen Gallagher, Daniel Goldhill, Natalie Groves, Ruth Harvey, Joe James, Robert Jordan, Rowland Kao, Nicola Lewis, Sophia Makki, Kimberly Marsh, Paul Millar, Catherine Moore, Richard Myers, Massimo Palmarini, Tom Peacock, Richard Puleston, Oliver Pybus, Steven Riley, Helen Roberts, Sakib Rokadiya, Anika Singanaygam, Richard Vipond, Erik Volz, Nick Watkins, Christopher Williams, Anthony Wilson, James Wood, Maria Zambon.

## Contributing organisations

- UKHSA
- Animal and Plant Health Agency
- Department for Environment, Food and Rural Affairs
- Food Standards Agency
- Health and Social Care Northern Ireland
- Public Health Scotland
- Public Health Wales
- Imperial College London
- Royal Veterinary College
- The London School of Hygiene and Tropical Medicine
- The Pirbright Institute
- University of Cambridge
- University of Edinburgh
- MRC Centre for Virus Research, University of Glasgow
- Worldwide Influenza Centre, Francis Crick Institute

# About the UK Health Security Agency

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