

Feedback from operational stakeholders who manage or respond to outbreaks is that they are often too busy to review literature or obtain relevant background information to assist them with acute response. Unlike a traditional analytical outbreak investigation report, **Watching Briefs** are intended as a rapid resource for public health or other first responders in the field on topical, serious or current outbreaks, and provide a digest of relevant information including key features of an outbreak, comparison with past outbreaks and a literature review. They can be completed by responders to an outbreak, or by anyone interested in or following an outbreak using public or open source data, including news reports.

## Watching brief

<b>Title</b>	Highly Pathogenic Avian Influenza (H5N1) in humans after the emergence of clade 2.3.4.4b in 2020.
<b>Authors</b>	Haley Stone, Adriana Notaras, Rosalie Chen, Jared Edgeworth, Ashley Quigley
<b>Date of first report of the outbreak</b>	The highly pathogenic avian influenza virus A (HPAI) H5N1 was first identified in a farmed goose in 1996 from China (1). High pathogenic avian influenza viruses cause severe disease in poultry and represent a smaller proportion of avian influenzas (2). In 2008, the H5Nx acquired the function to reassort its neuraminidase (N) and created the 2.3.4.4 H5Nx clade. Initial outbreaks of 2.3.4.4b began in H5N8 and H5N6 in 2016 (3). However, in 2020, whole genome sequencing (WGS) conducted in the Netherlands detected a new H5N1 clade, 2.3.4.4b in wild birds along the Adriatic flyway (4), which reassorted from H5N8 2.3.4.4b clade (3). Currently, the 2.3.4.4b HPAI H5N1 outbreak is the dominant circulating strain in the panzootic outbreak. This clade has been responsible for large outbreaks within avian species and spill over into human cases has occurred (5-7). The earliest reported human case was in 2021 (5-7).
<b>Disease or outbreak</b>	Highly pathogenic avian influenza H5N1 clade 2.3.4.4b
<b>Origin (country, city, region)</b>	The first detected human case of H5N1 clade 2.3.4.4b was within the United Kingdom in 2021 (5-7) following a large epizootic outbreak within the country in both wild and domestic birds.
<b>Suspected Source (specify food source, zoonotic or human origin or other)</b>	Zoonotic: Host species range between domestic and wild avian species, with an increase in wild outbreaks in waterfowl.
<b>Date of outbreak beginning</b>	The first human case was detected in 2021 (5-7) following the detection in birds in 2020 (3).
<b>Date outbreak declared over</b>	Ongoing

<b>Affected countries &amp; regions</b>	<p>H5N1 has been reported throughout the globe in both domestic and wild birds in every continent except Oceania and Antarctica (8). Since the avian (HPAI) H5N1 outbreak in 2020, the reported human cases of this clade have been within the United Kingdom (UK), the United States (US), China, Spain, Vietnam, Ecuador, and Chile (9).</p>
<b>Number of cases (specify at what date if ongoing)</b>	<p>There have been 11 human 2.3.4.4b H5N1 cases since the initial reports in 2021 (10).</p>
<b>Clinical features</b>	<p>No difference in clinical features have been identified between 2.3.4.4b and prior clades in regard to human infection. However, early clinical manifestations of human H5N1 infection can include (11, 12):</p> <ul style="list-style-type: none"> <li>• High fever</li> <li>• Cough</li> <li>• Sore Throat</li> <li>• Myalgia</li> <li>• Headache</li> <li>• Malaise</li> <li>• Abdominal or chest pain</li> <li>• Nausea or vomiting</li> <li>• Diarrhoea</li> <li>• Conjunctivitis (very rarely)</li> </ul>
<b>Mode of transmission (dominant mode and other documented modes)</b>	<p>The estimated incubation period of all clades of H5N1 in humans is typically from two to five days, though longer durations have been recorded (13). The dominant mode of transmission to humans is through the unprotected mucous membrane exposed to saliva, mucus, or faeces from birds infected with the H5N1 virus, or via inhalation or contact with infected surfaces (14). H5N1 can persist on surfaces 2.5 times longer compared to other avian influenzas and is able to survive on plastic surfaces and skin for approximately 26 and 4.5 hours respectively, while also being resistant to ethanol (14, 15).</p>

Demographics of cases	Demographic and disease details for the twelve reported human cases are provided in Table 1.							
	COUNTRY	LOCATION	DATE OF ILLNESS ONSET*	AGE	SEX	DATE OF DEATH	EXPOSURE TO POULTRY	SYMPTOMS/SIGNS
	UNITED KINGDOM (5-7)	Devon, England	5 January 2022	79	M	N/A	Domestic contact <sup>†</sup>	Asymptomatic
	UNITED STATES (7, 16, 17)	Colorado	27 April 2022	<40	M	N/A	Occupational contact <sup>‡</sup>	Fatigue
	CHINA (7, 18)	Qinzhou, Guangxi	22 September 2022	38	F	18 October 2022	Domestic contact <sup>†</sup>	Pneumonia
	SPAIN (7, 19)	Guadalajara	27 September 2022	19	M	N/A	Occupational contact <sup>‡</sup>	Asymptomatic
	VIETNAM (7, 20)	Phu Tho	5 October 2022	5	F	N/A	Consumption of meat from sick poultry	Cough, fever, vomiting, yellowing of skin and eyes, progressing to respiratory failure, septic shock, kidney and liver failure
	SPAIN (7, 19)	Guadalajara	13 October 2022	27	M	N/A	Occupational contact <sup>‡</sup>	Asymptomatic
	ECUADOR (21, 22)	Bolivar	25 December 2022	9	F	N/A	Domestic contact <sup>†</sup>	Conjunctival pruritus, coryza, nausea, vomiting, constipation, progressing to meningitis, pneumonia, septic shock
	CHINA (23)	Jiangsu	31 January 2023	53	F	N/A	Domestic contact <sup>†</sup>	Severe pneumonia
	CHILE (24)	Tocopilla	13 March 2023	53	M	N/A	Occupational Contact <sup>‡</sup>	Severe influenza symptoms
	UNITED KINGDOM (25, 26)	Wales	23 April 2023	Unk now n	Unk now n	N/A	Occupational Contact <sup>‡</sup>	Asymptomatic
UNITED KINGDOM (25, 26)	South Yorkshire	29 April 2023	Unk now n	Unk now n	N/A	Occupational Contact <sup>‡</sup>	Asymptomatic	
Case fatality rate	<p><b>Table 1.</b> Demographic details of human 2.3.4.4b H5N1 cases reported since 2020 (n=11).  *If illness onset is not provided or if the case was asymptomatic, the date of H5N1 confirmation is used as a proxy.  <sup>†</sup>Domestic contact: Exposure occurred within a domestic setting (e.g., contact with infected backyard poultry while at home).  <sup>‡</sup>Occupational contact: Exposure occurred within a work setting (e.g., contact with infected poultry while working on a farm or at a market).</p> <p>The case fatality rate (CFR) for the 2.3.4.4b cases is 9% (n=1) (27). However, the overall CFR since 2003 for all H5N1 human cases, regardless of clade, is 52% (n=458) (27).</p>							

<p><b>Complications</b></p>	<p>Severe cases of H5N1 human infection may present with respiratory complications such as dyspnoea and tachypnoea (11). Infection can progress rapidly to pneumonia, pneumothorax, and acute respiratory distress syndrome (ARDS), which can lead to respiratory failure and death (11, 28, 29). Extrapulmonary complications may also occur, including encephalitis, renal disease, heart failure, multiorgan failure, and disseminated intravascular coagulation (11).</p> <p>A 2006 study of 65 H5N1 human cases found that 41 (63%) cases required advanced organ support, with over half (54%) of such cases developing ARDS (28). However, it should be noted that complication rates in such cases may represent only severe disease, as asymptomatic or mild infections may not be reported (28).</p> <p>The 2.3.4.4b case in Chile exhibited two mutations adaptations of concern, both within the PB2 gene, PB2-D701N and PB2-Q591K. The PB2-D701N substitution has been previously seen in both human H5N1 and H5N6 mutations and has been linked to increased severity (30, 31). The PB2-Q591K mutation has increased viral replication in mammals (32). These adaptations were not seen within local poultry or in the mammalian outbreaks surrounding the region, which left researchers to assume these mutations most likely came from host adaptations after the infection.</p> <p>Most recently, a study(33) was output studying the pathogenicity and transmission on the new lineage in North America using two strains of 2.3.4.4b in a wigeon from 2021 and a bald eagle from 2022. In addition, two animal models were used for virus transmission, ferrets and leghorn chickens. Of the sequenced, they identified four distinct viral genotypes, which displayed variations in their nucleoprotein (NP) and polymerase gene combinations, which originated from either North America or Eurasia(33). Results revealed that reassortants containing increasing numbers of North American gene segments exhibited enhanced virulence with neurological involvement in mammalian models (33) and the lineage has a tendency to reassort and target the brain and spinal cord (33). The findings emphasize the rapid dynamics of a natural system and indicate the growing potential for additional reassortment and phenotypic variations. This risk is amplified by the unprecedented global spread of these viruses.</p>
<p><b>Available prevention</b></p>	<p>For this clade and all other H5N1 clades, the most effective prevention method for humans is to avoid direct contact with birds (34). The United States Center for Disease Control (CDC) (31) and World Organization for Animal Health (WOAH) (35) recommends that birds should be observed from a distance where possible, as infected birds may be asymptomatic. Individuals who have direct contact with birds (e.g., those working or living on a farm, hunters, bird hobbyists, etc.) should use personal protective equipment (PPE), including gloves and a mask (a N95 or a fitted surgical mask is recommended) (34, 35). Bodily fluids such as saliva, mucous, and faeces are often highly contaminated with virus, and thus should be avoided or handled using PPE (34, 35). Individuals who are exposed to infected birds for extended periods of time, in close contact and without protection, are most at risk of infection. If individuals are in direct contact with birds or their bodily fluids, it is very</p>

	<p>important that they wash their hands with soap and water prior to touching their mouth, eyes, or nose (34). Any potentially contaminated clothing should be changed and there should be efforts to prevent infection of healthy domestic birds by wild birds(34, 35).</p> <p>Several H5N1 vaccine candidates for both humans and avians have been approved by the US Food and Drug Administration (FDA) (36). For human vaccination, two candidate vaccine viruses (CVVs) have been created in the United States, which use a strain closely related to clade 2.3.4.4b (A/Astrakhan/3212/2020-like), CDC (i.e., IDCDC-RG71A) and U.S. FDA (CBER-RG8A) (34). Unfortunately, no identical clade-specific vaccines have been created and the manufacturing process is often time-consuming as given vaccines are produced by incubating each dose in an egg, limiting their effectiveness in an emergency situation (36).</p> <p>Lastly, control and prevention for poultry is needed to reduce transmission in avians and to humans. Poultry vaccination is still slowly being accepted globally as a preventative measure but there are concerns that poultry vaccination does not stop transmission but rather masks symptoms (37). Many countries share that concern and have long-standing trade restrictions/bans on poultry who have been vaccinated. The European Union 'harmonised' these laws by allowing vaccinated poultry to be traded (37). The United States, Australia, and a few European countries still do not authorise the use of vaccination and opt for culling techniques (37). Despite these concerns, countries have previously had large success from mass vaccination of poultry (38).</p>
<p><b>Available treatment</b></p>	<p>The treatment for all clades of H5N1 human infection is the same, and the key recommendation is to commence antiviral treatment as soon as possible (34). The current recommendation is to use neuraminidase inhibitors, such as oseltamivir, peramivir, and zanamivir, which are effective against most avian influenzas and have been shown to reduce viral replication and improve patient outcomes (39-41). However, some evidence of antiviral resistance has been found in lineages of H5N1 (29, 42) so continual monitoring for antiviral resistance is imperative. Oseltamivir resistance has also been reported (41).</p> <p>Treatment with antivirals should last at least 5 days and can continue if there has been little clinical response. Corticosteroids should not be administered routinely unless clinically indicated. Recent H5N1 viruses have been shown to be resistant to adamantane antiviral drugs, including amantadine and rimantadine, therefore these should not be administered as the only course of treatment (41).</p>
<p><b>Comparison with past outbreaks</b></p>	<p>Since 2003, a total of 874 human cases of H5N1 has been reported across 23 countries (27). Large human outbreaks have simultaneously occurred with a rise in avian H5N1 cases, such as in Egypt during the winter season of 2014-2015. Similar to the current outbreak, cases in both wild and domestic birds were incredibly high and H5N1 was declared enzootic in 2008 (43). Inadequate control measures led to genetic drift in the hemagglutinin (HA) gene (43). Additional mutations found within the human cases were novel or rare within Egypt (43).</p>

	<p>No human-to-human transmission has been identified but there have been examples of probable non-sustained outbreaks in Thailand in 2004 (44), Indonesia in 2006 (45), China in 2007 (46) and Pakistan in 2007 (47). The most concerning was the 2006 North Sumatra, Indonesia cluster, which consisted of eight cases across an extended family (45, 48). The index case had exposure to poultry and came into contact with 20 extended family members, some from different households (45, 48). Of the eight cases, seven lived in three adjacent houses but one lived approximately 10 kilometres away (45, 48). The secondary attack rate for this outbreak was estimated to be 29% (45), and could have been more detrimental if occurring in a less remote village.</p> <p>Currently, there has not been an outbreak between humans with this clade with all of the 2.3.4.4b cases having linkages to poultry. However, as cases increase in more avian species and more spill over occurs, the likelihood of genetic mutations to adapt to mammals will increase.</p>
<p><b>Unusual features</b></p>	<p>Since the virus attaches to upper respiratory tract receptors that are more prevalent in birds than mammals, H5N1 tends to not affect mammals. However, on this occasion, several mammalian species, such as foxes, cats, ferrets, seals, and dolphins, have contracted 2.3.4.4b, presumably through contact with infected birds. Recently, two outbreaks of concern in mammals have arisen, with potential mammal-to-mammal transmission in minks and sea lions both from the clade of 2.3.4.4b.</p> <p>In October 2022, workers at a mink farm in Spain observed a rise in the mortality rate of the minks from a baseline of 0.25% per week to 0.77%, with minks testing positive for H5N1 (49). In subsequent weeks, the disease seemed to spread from two to four pens, where all the animals became infected and died. Unfortunately, the situation worsened, even with restrictions, and more animals fell sick, forcing the workers to cull all 51,986 minks on the farm. Genetic sequencing revealed a PB2 gene mutation (T217A) (50), which has public health implications as it is present in the avian-like PB2 gene of the 2009 H1N1 pandemic flu virus and has characteristics that enable recognition by human airway receptor cells. However, no humans working in the farm or conducting culling tested positive (49). Human transmission, however, remains a concern.</p> <p>An additional example of potential mammal-to-mammal transmission was recently observed in Peru with infected sea lions. Initial reports arose in November 2022 of deaths in three sea lions and one dolphin which tested positive for H5N1 after reports of a mass outbreak in birds in the region (51). By February 2023, the outbreak had spread to 585 sea lion reported deaths and more than 55,000 wild birds (52). In early March 2023, that number again grew to 3,487 reported sea lion deaths in seven protected regions along the Peruvian coastline (53). By the end of March, the sea lion deaths had spread to Chile with approximately 500 seals reported as dead from 2.3.4.4b (54). In less than two weeks, the death count had increased to 1,535 sea lions and by 14 April 2023 (54), more than 3300 seals had reportedly tested positive for 2.3.4.4b(55). In the month of May the death toll had increased to 5860 sea lion deaths encompassing 11 regions (56) in mid-May and, most recently, more than 8000 sea lions have died in 13 regions with 44 positive samples (57) taken. One region, previously unaffected, Aysén (57), which is incredibly south was registered this past</p>

	<p>week. The true number of affected mammals is said to be higher while Servicio Nacional de Pesca y Acuicultura (SERNAPESCA) are investigating. With a large concentration of mammal cases and a strain lineage that has a tendency to reassort, there is a greater likelihood for mutation of the PB2 gene, which is one of the requirements for human-to-human transmission to occur (58).</p> <p>In order to prevent human cases, countries with large avian outbreaks and robust surveillance systems have begun implementing routine asymptomatic testing of those participating in culling and those exposed to wild bird cases, such as the United States (59) and European countries (60, 61).</p>
<p><b>Critical analysis</b></p>	<p>The number of global avian H5N1 cases, including those affecting both wild and domestic birds, has been rapidly increasing. With large avian H5N1 case numbers, spill over has begun into mammals, including humans. While human-to-human transmission has yet to be identified, there have been probable non-sustained outbreaks that have occurred in areas of high avian transmission.</p> <p>According to genetic analysis conducted on the viruses found in European birds affected during the winter season, H5N1 appears to have a higher affinity for avian receptors (58). However, certain markers have been identified in the PB2 protein of the viruses found in mammals that are associated with increased virulence and replication in these animals (58). These changes were rarely observed before 2020 and likely emerged after transmission to mammals, posing potential public health concerns (58).</p> <p>While most H5N1 cases in mammals are found in animals that hunt or scavenge infected birds or dead animals, there are two above mentioned unusual events in a Spanish mink farm and in Peruvian sea lions. The occurrence of these events, along with mutations that make the virus more adaptable to mammals, and serologic evidence of infection in wild boar and pigs (58), are worrisome and warrant close monitoring. The occurrence of asymptomatic infection is still debated as positive cases may be due to contamination of the nasal mucosa rather than active infection (62). However, with the rise of panzootic outbreaks and their subsequent spill over to mammals, it is important to maintain adequate close monitoring on all potential human exposures to environmental contamination. Early monitoring systems, like EPIWATCH, can identify potential hot spots for earlier control measures to be implemented. Official government reporting is often delayed due to many factors including, validation of notifications, case confirmation and sequencing. With countries experiencing large outbreaks, many report avian cases in aggregate form, which makes identifying individual source outbreaks to be difficult and time consuming. Open-source intelligence, such as EPIWATCH, can aid in timeliness of reporting, which is often times needed for rapid surveillance and prevention methods to be implemented. Birds have been found to be natural hosts for a vast range of avian influenza subtypes (63). Enhanced monitoring and surveillance systems are therefore extremely important given the ability of the virus to reassort, heightening its pandemic potential (63).</p>

	<p>As the global spread increases, countries are looking into new prevention and control methods. Vaccination has been considered as an additional tool to control the spread of the disease. While some countries have been vaccinating flocks for some time, others do not vaccinate due to the potential trade implications (8). Recently, the United States changed their stance and has begun vaccinating endangered species, such as the condor (64). It is essential to recognize the amplified risk posed by the unprecedented global spread of this lineage and the emphasises for continual vigilance and research to mitigate the potential impact of these evolving 2.3.4.4b strains.</p>
<p><b>Key Questions</b></p>	<ul style="list-style-type: none"> <li>• Do countries need to adopt poultry vaccination more widely now to prevent potential outbreaks of H5N1 clade 2.3.4.4b?</li> <li>• What enhanced surveillance is needed urgently that is not already adopted?</li> <li>• What are the implications of the seal and mink outbreaks?</li> <li>• What can be done to increase public awareness/education and reduce transmission risk in communities where backyard flocks are commonplace and constitute an important source of food or income?</li> <li>• Are there potential ways to test the capability of genetic mutations in increasing transmissibility or likelihood to transmit among humans without dual-research-of-concern?</li> <li>• Will enhanced epidemiological data, paired with genetic data, aid in outbreak detection for this H5N1 clade?</li> </ul>
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