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# Highly Pathogenic Avian Influenza A(H5N1) Virus Infections in Humans

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## ABSTRACT

### BACKGROUND
Highly pathogenic avian influenza A(H5N1) viruses have caused widespread infections in dairy cows and poultry in the United States, with sporadic human cases. We describe characteristics of human A(H5N1) cases identified from March through October 2024 in the United States.

### METHODS
We analyzed data from persons with laboratory-confirmed A(H5N1) virus infection using a standardized case-report form linked to laboratory results from the Centers for Disease Control and Prevention influenza A/H5 subtyping kit.

### RESULTS
Of 46 case patients, 20 were exposed to infected poultry, 25 were exposed to infected or presumably infected dairy cows, and 1 had no identified exposure; that patient was hospitalized with nonrespiratory symptoms, and A(H5N1) virus infection was detected through routine surveillance. Among the 45 case patients with animal exposures, the median age was 34 years, and all had mild A(H5N1) illness; none were hospitalized, and none died. A total of 42 patients (93%) had conjunctivitis, 22 (49%) had fever, and 16 (36%) had respiratory symptoms; 15 (33%) had conjunctivitis only. The median duration of illness among 16 patients with available data was 4 days (range, 1 to 8). Most patients (87%) received oseltamivir; oseltamivir was started a median of 2 days after symptom onset. No additional cases were identified among the 97 household contacts of case patients with animal exposures. The types of personal protective equipment (PPE) that were most commonly used by workers exposed to infected animals were gloves (71%), eye protection (60%), and face masks (47%).

### CONCLUSIONS
In the cases identified to date, A(H5N1) viruses generally caused mild illness, mostly conjunctivitis, of short duration, predominantly in U.S. adults exposed to infected animals; most patients received prompt antiviral treatment. No evidence of human-to-human A(H5N1) transmission was identified. PPE use among occupationally exposed persons was suboptimal, which suggests that additional strategies are needed to reduce exposure risk. (Funded by the Centers for Disease Control and Prevention.)

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Highly pathogenic avian influenza A(H5N1) viruses were first recognized to cause human illnesses in Hong Kong in 1997. As of November 1, 2024, more than 900 human cases in 24 countries had been reported globally since November 2003, with a cumulative case fatality of approximately 50%.[1] In the United States, circulating A(H5N1) viruses belonging to clade 2.3.4.4b began a resurgence in 2021.[2] With the exclusion of all U.S. human cases, 11 A(H5N1) cases associated with clade 2.3.4.4b have been reported from 5 countries since January 2022; of these 11 cases, 7 were asymptomatic and 4 were symptomatic with severe or critical illness (resulting in one death).[3] Before 2024, only 1 human A(H5N1) case had been reported in the United States — in a poultry worker from Colorado in 2022 — with fatigue as the only symptom.[4]

Since March 2024, when the first presumed U.S. cow-to-human A(H5N1) virus transmission occurred, additional A(H5N1) cases have been identified in persons exposed to dairy cows and poultry[5,6] and in one person with no identified exposure source. In this report, we summarize information on U.S. human A(H5N1) cases identified from March through October 2024.

## Methods

### Surveillance Methods

State and local public health officials monitored occupationally exposed persons for 10 days after last exposure to animals suspected or known to be infected with A(H5N1) viruses and collected specimens from symptomatic persons.[7] All but one case was identified through symptom monitoring. The one case with no identified exposure source was detected through routine influenza surveillance.[8] All monitored persons with acute respiratory illness or other A(H5N1)-related symptoms were recommended to have a nasopharyngeal swab, a combined nasal–oropharyngeal swab, or both collected, and persons with eye-related symptoms were also recommended to have a conjunctival swab obtained.

A case identified through symptom monitoring was defined as molecular detection of A(H5N1) virus with the use of the Centers for Disease Control and Prevention (CDC) Human Influenza Virus Real-Time RT-PCR (reverse-transcriptase–polymerase-chain-reaction) Diagnostic Panel Influenza A(H5) Subtyping assay in a symptomatic person who had exposure to infected animals.[9] For this assessment, a person exposed to infected poultry or infected or presumably infected dairy cows (hereafter referred to as cows) was considered to have been exposed to the A(H5N1) virus. Specimens that tested presumptive positive at a state or local public health laboratory were sent to the CDC for real-time RT-PCR confirmation and genetic sequencing.[10,11] Here we report on CDC-confirmed A(H5N1) cases with specimens collected between March 28 and October 31, 2024.

Case patients were interviewed with the use of a standardized novel influenza A case-report form. (Additional details are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Case-report forms were submitted to the CDC and combined with laboratory results from the CDC influenza diagnostic laboratory.

This activity was reviewed by the CDC, was deemed to be nonresearch activity, and was conducted in a manner consistent with applicable federal law and CDC policy. Persons providing information and specimens did so on a voluntary basis.

### Reporting of Data

We described characteristics of case patients overall and according to animal exposure. We separately described the characteristics of one case patient with an undetermined exposure source. Values were suppressed for select variables or stratifications to protect participants' privacy. A list of U.S. A(H5N1) cases is detailed in Table S1 in the Supplementary Appendix. Laboratory results were reported according to specimen type and according to the presence of select signs or symptoms. Mean cycle threshold (Ct) values for RT-PCR assay results from positive specimens were also reported; specimens with Ct values of less than 38 with the use of the CDC influenza A/H5 subtyping assay were considered to be positive. Genetic sequencing was performed on available specimens (additional details are provided in the Supplementary Appendix). Although the N1 neuraminidase could not be confirmed for all cases, we refer to all cases as A(H5N1) throughout, given that this is the neuraminidase subtype that has been reported in all cows and poultry flocks described herein.

We produced epidemiologic curves of human cases according to symptom-onset date and stratified according to exposure type, as well as A(H5N1) virus detections in cows and poultry, from March through October 2024 (additional details are provided in the Supplementary Appendix). Data were analyzed with the use of R software (R Core Team, 2023) and SAS software, version 9.4.

## Results

### Overall

Between March 28 and October 31, 2024, a total of 46 human A(H5N1) cases in adults 18 years of age or older were reported from six states. A total of 25 case patients had exposure to infected cows, 20 had exposure to infected poultry, and 1 had no identified exposure to animals or sick persons.

### Case Patients with Animal Exposures

Among the 45 case patients with animal exposures, case patients who were exposed to poultry were interviewed a median of 4.5 days after symptom onset, and those who were exposed to cows were interviewed a median of 2.0 days after symptom onset (Table 1). The median age of the patients was 34 years, and 76% reported no underlying medical conditions. All the case patients who were exposed to infected poultry were involved in depopulation activities. Among dairy workers, 4 (16%) were exposed to cows and 21 (84%) to both cows and raw milk. There were two dairy farms with more than 1 case, but without clear links that would have brought the case patients into direct contact with each other (e.g., cohabitation or overlap of duties). Three poultry farms with depopulation events had multiple cases, but symptoms developed in all the case patients during periods of intense exposure to infected poultry. Gloves (71%) were the most frequently reported type of personal protective equipment (PPE), followed by eye protection (60%) and face masks (47%). Reported use of both eye protection and respirators or face masks was less common (36%). All categories of reported PPE use were higher among poultry workers than among dairy workers.

All 45 case patients reported at least one sign or symptom (Table 2). Conjunctivitis was the most common condition (in 42 patients [93%]) among both poultry and dairy workers, followed by fever or feeling feverish (in 22 [49%]) and respiratory symptoms (in 16 [36%]). Symptoms that were reported more commonly among poultry workers than among dairy workers included fever or feeling feverish (60% vs. 40%), headache (55% vs. 36%), myalgia (55% vs. 32%), and respiratory symptoms (45% vs. 28%). The symptom profile in the overall population of case patients did not change over time.

A total of 15 of 45 case patients (33%) had conjunctivitis only, 14 (31%) had conjunctivitis plus respiratory symptoms, 13 (29%) had conjunctivitis plus nonrespiratory symptoms, and 3 (7%) had only nonconjunctival symptoms; conjunctivitis alone was more common among dairy workers than among poultry workers (44% vs. 20%). Among 16 case patients who had symptom resolution and an available symptom-onset date, the median duration of symptoms was 4 days (range, 1 to 8). Nine case patients were still symptomatic at the time of the interview; these patients were interviewed a median of 4 days earlier than those who had completely recovered by the interview date.

A total of 17 case patients (38%) sought medical care; 4 sought care before specimen collection and 13 on the same day as specimen collection (Table S2). No case patients with animal exposure were hospitalized, and none died. A total of 39 case patients (87%) received oseltamivir treatment, and the median duration of treatment in the 29 patients with available data was 5 days (range, 3 to 10); 1 patient started taking oseltamivir for postexposure prophylaxis, which was converted to a treatment regimen after 1 day owing to symptom development. Among 34 case patients with available data, the median time from symptom onset to oseltamivir treatment was 2 days (range, 0 to 8); 21 of 34 patients (62%) started treatment within 2 days. No additional cases were identified among the 97 household contacts of case patients with animal exposures.

### Patient with Undetermined Exposure Source

An adult with multiple underlying conditions presented to the emergency department in August 2024 with acute chest pain, nausea, vomiting, diarrhea, and weakness, without respiratory symptoms. The patient was hospitalized and treated with oseltamivir on the basis of a positive influenza A test at presentation. The clinical course was uncomplicated, and the patient was discharged home 3 days after admission. As part of routine surveillance, the positive specimen was forwarded

**Table 1. Epidemiologic Characteristics of 45 Case Patients with Highly Pathogenic Avian Influenza A(H5N1) Virus Infection Who Had Exposure to Infected Animals.***

| Characteristic | Exposure to Poultry (N=20) | Exposure to Dairy Cows (N=25) | Overall (N=45) |
|---|---|---|---|
| Median age — yr† | 28 | 39 | 34 |
| Male sex — no. (%) | 11 (55) | 25 (100) | 36 (80) |
| Race and ethnic group — no. (%)‡ | | | |
| Hispanic or Latino, race not reported | — | — | 13 (29) |
| White and Hispanic or Latino | — | — | 27 (60) |
| Other | — | — | 4 (9) |
| State of report — no. (%) | | | |
| Colorado | 9 (45) | 1 (4) | 10 (22) |
| Washington | 11 (55) | 0 | 11 (24) |
| California | 0 | 21 (84) | 21 (47) |
| Michigan | 0 | 2 (8) | 2 (4) |
| Texas | 0 | 1 (4) | 1 (2) |
| Exposure type — no. (%) | | | |
| Poultry depopulation event | 20 (100) | 0 | 20 (44) |
| Direct contact with cows | 0 | 4 (16) | 4 (9) |
| Raw milk and direct contact with cows§ | 0 | 21 (84) | 21 (47) |
| Median time between symptom onset and interview (range) — days¶ | 4.5 (2.0–11.0) | 2.0 (0–12.0) | 3.0 (0–12.0) |
| Median time between symptom onset and specimen collection (range) — days‖ | 1.0 (0–4.0) | 2.0 (0–8.0) | 2.0 (0–8.0) |
| Median no. of persons in household (range)** | 3 (1–7) | 3 (0–5) | 3 (0–7) |
| Seasonal influenza vaccination in past 12 mo — no./total no. (%) | 6/17 (35) | 4/23 (17) | 10/40 (25) |
| PPE use — no. (%)†† | | | |
| Eye protection and respirator or face mask | 13 (65) | 3 (12) | 16 (36) |
| Respirator | 4 (20) | 0 | 4 (9) |
| Face mask | 15 (75) | 6 (24) | 21 (47) |
| Eye protection | 15 (75) | 12 (48) | 27 (60) |
| Gloves | 17 (85) | 15 (60) | 32 (71) |
| Boots | 11 (55) | 7 (28) | 18 (40) |
| Gown | 16 (80) | 4 (16) | 20 (44) |
| Underlying medical conditions — no. (%) | | | |
| No. of conditions | | | |
| None | 15 (75) | 19 (76) | 34 (76) |
| 1 | 4 (20) | 4 (16) | 8 (18) |
| 2 or more | 0 | 1 (4) | 1 (2) |
| Missing or not reported | 1 (5) | 1 (4) | 2 (4) |
| Asthma, reactive airway disease, or other chronic lung disease | — | — | 3 (7) |
| Other chronic diseases‡‡ | 3 (15) | 3 (12) | 6 (13) |

* The table includes 45 U.S. case patients with highly pathogenic avian influenza A(H5N1) virus infection who had occupational exposure to infected poultry or infected or potentially infected dairy cows; cases were identified from March through October 2024. The table excludes the 1 case patient with no identified exposure source. Some data are not presented to protect participants' privacy. Percentages may not total 100 because of rounding.

† All case patients were 18 to 64 years of age.

‡ Race and ethnic group were reported by the case patients. Data on race and ethnic group were unknown for 1 case patient.

§ "Raw milk" refers to raw-milk consumption, raw-milk exposure, or both. We were unable to separate out raw-milk exposure from exposure to infected dairy cows owing to the way that the data were collected.

¶ Data were available for 36 case patients (14 with exposure to poultry and 22 with exposure to dairy cows).

‖ Data were available for 42 case patients (17 with exposure to poultry and 25 with exposure to dairy cows).

** Data were available for 32 case patients (10 with exposure to poultry and 22 with exposure to dairy cows).

†† Listed are components of personal protective equipment (PPE) used during exposure to infected or presumably infected animals.

‡‡ Included are diabetes, hyperlipidemia, hypertension, prediabetes, and chronic allergies.

**Table 2. Clinical Characteristics of and Outcomes in 45 Case Patients with Highly Pathogenic Avian Influenza A(H5N1) Virus Infection Who Had Exposure to Infected Animals.***

| Variable | Exposure to Poultry (N=20) | Exposure to Dairy Cows (N=25) | Overall (N=45) |
|---|---|---|---|
| **Signs and symptoms** | | | |
| Conjunctivitis — no. (%) | 19 (95) | 23 (92) | 42 (93) |
| Measured fever or feeling feverish — no. (%) | 12 (60) | 10 (40) | 22 (49) |
| Respiratory symptoms — no. (%)† | 9 (45) | 7 (28) | 16 (36) |
| Cough | 3 (15) | 5 (20) | 8 (18) |
| Sore throat | 7 (35) | 6 (24) | 13 (29) |
| Shortness of breath | 3 (15) | 4 (16) | 7 (16) |
| Myalgia — no. (%) | 11 (55) | 8 (32) | 19 (42) |
| Headache — no. (%) | 11 (55) | 9 (36) | 20 (44) |
| Fatigue — no. (%) | 6 (30) | 4 (16) | 10 (22) |
| Nausea — no. (%) | 6 (30) | 0 | 6 (13) |
| Vomiting — no. (%) | 1 (5) | 1 (4) | 2 (4) |
| Diarrhea — no. (%) | 2 (10) | 0 | 2 (4) |
| **Clinical constellations** | | | |
| Status with respect to conjunctivitis — no. (%) | | | |
| Conjunctivitis only | 4 (20) | 11 (44) | 15 (33) |
| Conjunctivitis plus any respiratory symptom | 8 (40) | 6 (24) | 14 (31) |
| Conjunctivitis plus any nonrespiratory symptom | 7 (35) | 6 (24) | 13 (29) |
| Only nonconjunctival symptoms | 1 (5) | 2 (8) | 3 (7) |
| Symptoms still present at time of interview — no. (%) | 2 (10) | 7 (28) | 9 (20) |
| Median no. of days with symptoms (range)‡ | 2.0 (1.0–8.0) | 5.0 (2.0–7.0) | 4.0 (1.0–8.0) |
| Oseltamivir treatment — no. (%) | 18 (90) | 21 (84) | 39 (87) |
| Median no. of days between symptom onset and treatment (range)§ | 1.0 (0–8.0) | 2.5 (0–8.0) | 2.0 (0–8.0) |
| Median no. of days of oseltamivir treatment (range)¶ | 5.0 (3.0–10.0) | 5.00 (5.0–10.0) | 5.0 (3.0–10.0) |
| Hospitalization — no. | 0 | 0 | 0 |
| Death — no. | 0 | 0 | 0 |

* The table includes 45 U.S. case patients with highly pathogenic avian influenza A(H5N1) virus infection who had occupational exposure to infected poultry or infected or potentially infected dairy cows; cases were identified from March through October 2024. The table excludes the 1 case patient with no identified exposure source.
† Respiratory symptoms include cough, sore throat, and shortness of breath.
‡ Data are for 16 case patients (9 with exposure to poultry and 7 with exposure to dairy cows) who had symptom resolution and an available symptom-onset date.
§ Data were available for 34 case patients (14 with exposure to poultry and 20 with exposure to dairy cows).
¶ Data were available for 29 case patients (15 with exposure to poultry and 14 with exposure to dairy cows). The longer duration (up to 10 days) of antiviral treatment was implemented in some settings as part of broader control efforts.

to the state public health laboratory, where subtyping revealed influenza A(H5N1).[12,13] A subsequent epidemiologic investigation did not identify a source of A(H5N1) virus exposure. One household contact was ill at the same time as the case patient and had some evidence of exposure to A(H5N1) virus through serologic testing, but the findings were inconsistent.[13]

### EPIDEMIOLOGIC CURVES

Four human cases occurred between March and June 2024 after exposure to cows in three states

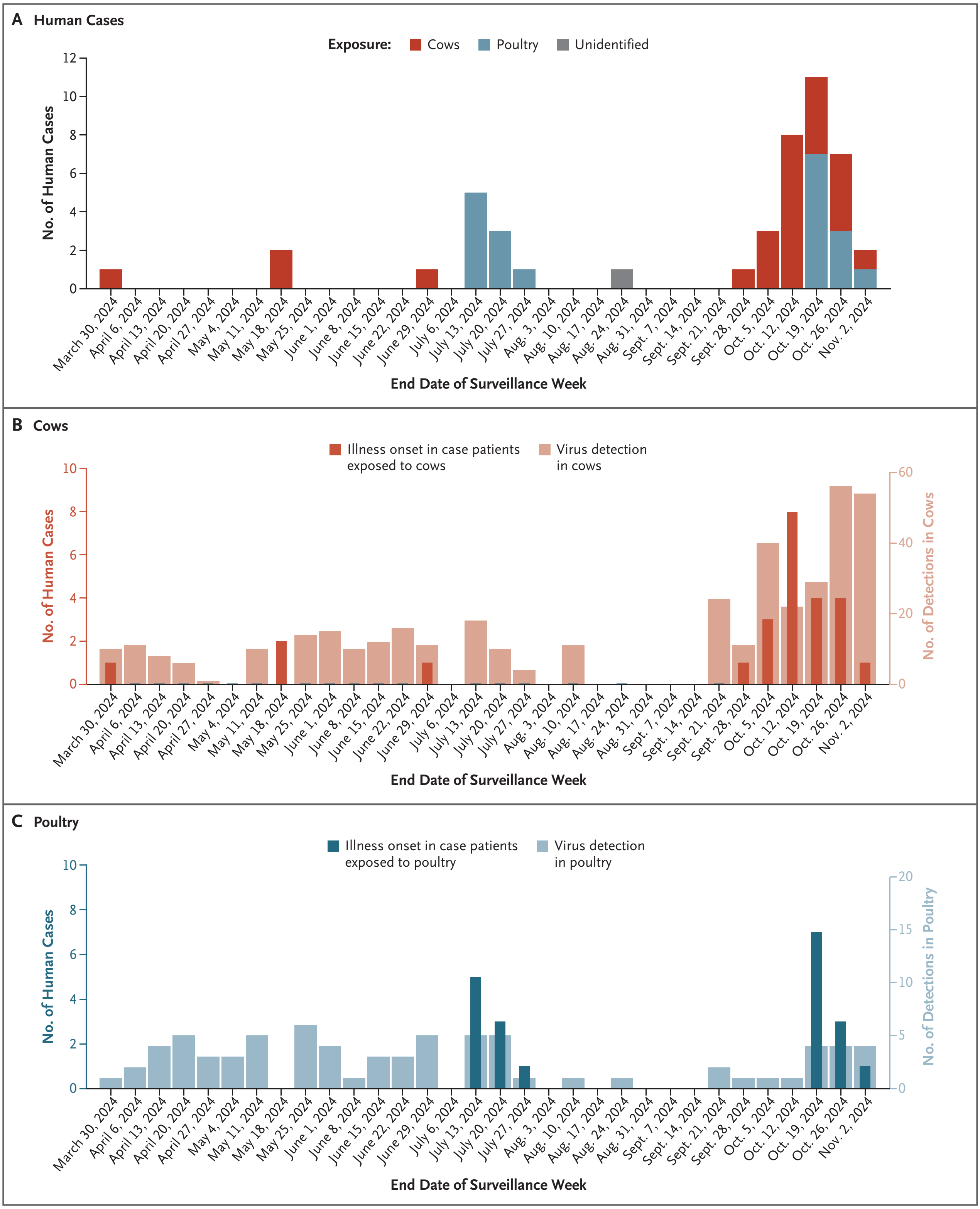
A Human Cases
Exposure: Cows Poultry Unidentified
No. of Human Cases
End Date of Surveillance Week
B Cows
Illness onset in case patients exposed to cows
Virus detection in cows
No. of Human Cases
No. of Detections in Cows
End Date of Surveillance Week
C Poultry
Illness onset in case patients exposed to poultry
Virus detection in poultry
No. of Human Cases
No. of Detections in Poultry
End Date of Surveillance Week

**Figure 1 (facing page). Number of Human Cases of Influenza A(H5N1) Virus Infection According to Date of Illness Onset and Number of A(H5N1) Virus Detections in Dairy Cows and Poultry.**

Panel A shows the number of human cases of highly pathogenic avian influenza A(H5N1) virus infection in the United States according to date of illness onset and exposure type; the 46 cases were identified from March through October 2024. Panels B and C show the number of A(H5N1) virus detections in dairy cows and poultry, respectively, according to epidemiologic week, overlayed by the number of human cases stratified according to exposure type. The case with no identified exposure route was excluded from Panels B and C.

(Colorado, Michigan, and Texas). In July 2024, a cluster of nine human cases was identified in Colorado and was associated with a poultry depopulation event (Fig. 1A).[14] Human cases were not detected again until late September 2024, when A(H5N1) viruses were identified in cows in California with rapid spread across dairy farms, and a poultry depopulation event took place in Washington. From late September through October, 32 additional human cases were identified in parallel with the increase in detections in animals, especially in cows (Fig. 1B and 1C).

### LABORATORY RESULTS

Of 45 case patients with animal exposure, 41 had conjunctival swabs collected, 36 had nasopharyngeal swabs collected, and 22 had combined nasal–oropharyngeal swabs collected (Table 3). Conjunctival swabs were positive for A(H5N1) in 88% of case patients exposed to poultry and 88% of those exposed to cows; nasopharyngeal swabs were positive in 58% and 21%, respectively; and combined nasal–oropharyngeal swabs were positive in 67% and 37%, respectively. Among all 46 case patients, conjunctival swabs were positive in 90% of patients reporting conjunctivitis, and nasopharyngeal swabs and combined nasal–oropharyngeal swabs were positive in 45% and 56% of patients reporting respiratory symptoms, respectively (Table 4). Among case patients who had conjunctivitis only, 13 of 15 conjunctival swabs (87%), 3 of 13 nasopharyngeal swabs (23%), and 1 of 6 combined nasal–oropharyngeal swabs (17%) were positive.

The mean Ct value from the RT-PCR–positive specimens was 31.0 (range, 18.6 to 37.9). Ct values positively correlated with the ability to generate at least partial sequence data from specimens. Partial sequences were successfully generated from 25 of 35 positive conjunctival swabs (71%), 9 of 13 nasopharyngeal swabs (69%), and 6 of 9 combined nasal–oropharyngeal swabs (67%). Genetic sequencing was successful for 87% of specimens with Ct values of less than 34 and 44% of specimens with Ct values of 34 or more. The hemagglutinin (HA) gene was successfully sequenced from specimens obtained from 26 case patients (57%), and phylogenetic analysis revealed that all cases had H5 clade 2.3.4.4b. HA genes of viruses clustered phylogenetically either with other HA genes from B3.13 genotype viruses detected in dairy cattle or poultry or, in four cases from Washington, with D1.1 genotype viruses detected in poultry (Fig. S1). Additional details are provided in the Supplementary Appendix.

## DISCUSSION

A total of 46 U.S. human A(H5N1) cases were identified across six states from March through October 2024; no case patients had critical illness or died. Except for one case patient with an undetermined exposure source, all case patients had occupational exposure to infected animals. PPE use among occupationally exposed workers was suboptimal. More than 90% of occupationally exposed case patients had conjunctivitis, with approximately one third also having respiratory symptoms; all had mild illness of short duration, and none were hospitalized. No additional human cases were identified among 97 close contacts of occupationally exposed workers undergoing monitoring or through national influenza surveillance, which is consistent with a current lack of evidence for human-to-human transmission of A(H5N1) viruses in the United States.

Since A(H5N1) viruses were detected in U.S. dairy cows, public health officials have monitored occupationally exposed workers for illness and prioritized testing and treatment of symptomatic persons[15] to detect infections and prevent onward transmission. This systematic surveillance approach was built on a decade of experience

**Table 3. Laboratory Results According to Specimen Type among 45 Case Patients with Highly Pathogenic Avian Influenza A(H5N1) Virus Infection Who Had Exposure to Infected Animals.***

| Specimen Type | Exposure to Poultry | | Exposure to Dairy Cows | | Overall | |
|---|---|---|---|---|---|---|
| | Specimen Collected | Positive Specimen | Specimen Collected | Positive Specimen | Specimen Collected | Positive Specimen |
| | *no./total no.* | *no./total no. (%)* | *no./total no.* | *no./total no. (%)* | *no./total no.* | *no./total no. (%)* |
| Conjunctival | 16/20 | 14/16 (88) | 25/25 | 22/25 (88) | 41/45 | 36/41 (88) |
| Nasopharyngeal | 12/20 | 7/12 (58) | 24/25 | 5/24 (21) | 36/45 | 12/36 (33) |
| Combined nasal–oropharyngeal | 3/20 | 2/3 (67) | 19/25 | 7/19 (37) | 22/45 | 9/22 (41) |

* The table includes 45 U.S. case patients with highly pathogenic avian influenza A(H5N1) virus infection who had occupational exposure to infected poultry or infected or potentially infected dairy cows; cases were identified from March through October 2024. The table excludes the 1 case patient with no identified exposure source.

working with agricultural partners to monitor exposed workers during poultry depopulations.[16] New challenges with the dairy-cow outbreak have required adapted monitoring approaches. Without knowledge of the natural history of A(H5N1) virus infection in cows, such as duration of infection, how long workers should be monitored is unclear. U.S. Department of Agriculture (USDA) research showed that experimentally infected cows were ill for up to 14 days and took up to 24 days to recover.[17] In addition, high levels of A(H5N1) virus have been found in unpasteurized raw milk, which is probably an important source of transmission from cows to dairy workers.[17,18] Protracted on-farm surveillance identified 4 human A(H5N1) cases among dairy workers from March through June and an additional 21 cases during September and October, which correlated with increasing numbers of infected cows on California dairy farms. On December 6, 2024, the USDA announced a federal order to test raw milk intended for pasteurization, with a goal of eliminating the virus in cows.[19,20]

It is possible that cases could have been missed, and this seems most likely in persons with close exposure to infected animals, as evidenced by a recent serosurvey on dairy farms.[21] Between February 25 and October 31, 2024, the USDA reported A(H5N1) detections in poultry from 21 states and in cattle from 15 states. However, there are no data to suggest a reservoir of undetected A(H5N1) illnesses more broadly in the United States. Between February 25 and October 31, 2024, U.S. public health laboratories tested 59,827 surveillance specimens using a protocol that would have detected A(H5N1) and other novel viruses.[8] Only one case without a known exposure source was detected this way. Nevertheless, ongoing vigilance is warranted.

Conjunctivitis was the most common condition among occupationally exposed workers, and conjunctival swabs were positive in 90% of case patients reporting conjunctivitis. In May 2024, the Food and Drug Administration granted enforcement discretion for the use of conjunctival swabs as an acceptable specimen type to be used with the CDC influenza A/H5 RT-PCR assay when paired with a respiratory specimen. The importance of this decision is underscored by both the high percentage of case patients with conjunctivitis and the high percentage of infections that were detected by conjunctival specimen testing. At least one commercial laboratory now offers an influenza A/H5 diagnostic assay for clinical use that can also be used to test conjunctival swabs.[22]

Globally, human A(H5N1) cases have shown a wide spectrum of clinical disease severity, ranging from asymptomatic illness,[4,23-26] conjunctivitis,[6] and mild upper respiratory tract symptoms[13] to lower respiratory tract disease and critical illness, including death.[27] Why recent U.S. cases have generally been clinically mild remains unclear; early detection and initiation of antiviral treatment may play a role. Other factors that require further exploration include routes of exposure, virologic characteristics, and preexisting immunologic profiles of infected hosts.[28] Although U.S. human cases have generally been mild, animal studies have shown varied results. Ferret inoculations with the A/Texas/37/2024 A(H5N1) virus[6] led to severe infection and death in two studies,[29,30] whereas a study in ferrets that used an A/Michigan/90/2024

**Table 4. Specimen Positivity According to Sign or Symptom Type among 46 Case Patients with Highly Pathogenic Avian Influenza A(H5N1) Virus Infection.***

| Sign or Symptom Type | Conjunctival Swab (N=41) | Nasopharyngeal Swab (N=37) | Combined Nasal–Oropharyngeal Swab (N=22) |
|---|---|---|---|
| | *number/total number (percent)* | | |
| Conjunctivitis | | | |
| Yes | 35/39 (90) | 11/33 (33) | 9/20 (45) |
| No | 1/2 (50) | 2/4 (50) | 0/2 |
| Respiratory† | | | |
| Yes | 11/13 (85) | 5/11 (45) | 5/9 (56) |
| No | 25/28 (89) | 8/26 (31) | 4/13 (31) |
| Clinical syndromes‡ | | | |
| Conjunctivitis only | 13/15 (87) | 3/13 (23) | 1/6 (17) |
| Conjunctivitis plus respiratory | 11/12 (92) | 5/12 (42) | 3/6 (50) |
| Conjunctivitis plus nonrespiratory | 11/12 (92) | 3/8 (38) | 5/8 (62) |
| Nonconjunctival only | 1/2 (50) | 2/4 (50) | 0/2 |
| Fever | | | |
| Yes | 18/20 (90) | 7/18 (39) | 3/10 (30) |
| No | 18/21 (86) | 6/19 (32) | 6/12 (50) |
| Gastrointestinal§ | | | |
| Yes | 6/6 (100) | 3/5 (60) | 1/2 (50) |
| No | 30/35 (86) | 10/32 (31) | 8/20 (40) |
| Other symptoms¶ | | | |
| Yes | 22/25 (88) | 10/23 (43) | 8/16 (50) |
| No | 14/16 (88) | 3/14 (21) | 1/6 (17) |

* The table includes 46 U.S. case patients with highly pathogenic avian influenza A(H5N1) virus infection; cases were identified from March through October 2024. Unless otherwise indicated, signs and symptoms are not mutually exclusive.
† Respiratory symptoms include cough, shortness of breath, and sore throat.
‡ Shown are mutually exclusive clinical syndrome categories.
§ Gastrointestinal symptoms include nausea, vomiting, and diarrhea.
¶ Other symptoms include myalgia, headache, and rash.

A(H5N1) virus showed less severe disease.[31] The Texas virus has two changes in polymerase proteins that may help it to replicate better in mammals and humans.[32] Reassuringly, A(H5N1) viruses that were identified in recent human cases in California are more similar to the Michigan virus. However, the recent report of a critically ill teenager in British Columbia, Canada,[33] followed by a severely ill person in Louisiana, both infected with viruses belonging to the D1.1 genotype,[34] are stark reminders of the illness severity that A(H5N1) viruses can cause.

Given that A(H5N1) viruses can cause severe human disease, public health efforts have focused on protecting workers exposed to potentially infected animals[35] and providing prompt testing and antiviral treatment to symptomatic workers. Low rates of PPE use among dairy workers might reflect real-world challenges with implementation of adequate protection for those with prolonged exposure to infected animals and their environments (e.g., raw milk and fomites) during daily work. Despite the high frequency of conjunctivitis, only 48% of dairy workers reported using eye protection. Suboptimal access and adherence to PPE remain ongoing challenges.[36,37]

Oseltamivir is recommended for treatment of A(H5N1) virus infections on the basis of observational studies.[38,39] On-farm monitoring has led to a shorter time between symptom onset and A(H5N1) virus detections and also facilitated earlier access to treatment. In this analysis, oseltamivir use was high (87%), with most case patients receiving treatment within 48 hours after symptom onset. To date, with the exception of four viruses with mutations conferring minor decreases in susceptibility to neuraminidase inhibitors (three viruses) and baloxavir (one virus), A(H5N1) viruses from U.S. human infections are susceptible to currently available antiviral agents.[40,41]

This study has several limitations. To the extent that on-farm monitoring varied across farms and jurisdictions, there may be some ascertainment bias resulting in underdetection or underreporting of cases. Some data from case-report forms were missing or incomplete. Case data were often collected before symptom resolution, which probably skewed some results to a shortened time frame. Exposure data were unable to identify specific behaviors associated with increased infection risk. For example, owing to the high correlation of exposure to both infected cows and raw milk, we could not differentiate the relative importance of each. Finally, although we did not identify human-to-human transmission among close contacts of case patients, this study was not specifically designed to assess transmission risk.

This case series highlights the risk of A(H5N1) virus infection among workers exposed to infected animals. Although most U.S. cases have been mild, global data and studies in animals have shown that A(H5N1) clade 2.3.4.4b viruses can cause severe disease and death. Sequencing of viruses from U.S. cases has shown no changes in the HA gene associated with increased infectivity or transmissibility, and no mutations have been identified in other genes indicating mammalian adaptation.[41,42] However, it is critical to investigate each human case to monitor for any changes that might suggest increased pathogenicity, virulence, or transmissibility to and among humans, which would warrant a shift in the response to more aggressive control measures to mitigate pandemic risk. Although the risk of the A(H5N1) virus to the U.S. public is currently low, good farm biosecurity is paramount and requires strong coordination between public health and animal sectors through a collaborative One Health approach, which is multisectoral and recognizes that the health of people, animals, plants, and the environment are closely linked and interdependent. Public health efforts should continue to focus on protecting workers exposed to infected animals through implementation of prevention measures on farms, including PPE use, and ongoing monitoring, early testing, and prompt antiviral treatment.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC) or the California Department of Public Health or the California Health and Human Services Agency.

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