Good afternoon. I'm Captain Ibad Khan, and I'm representing the Clinician Outreach and Communication Activity, COCA, with the Office of Emergency Risk Communication at the Centers for Disease Control and Prevention. I would like to welcome you to today's COCA Call, Clinician Update on Human Cases of H5N1 and Influenza A Virus Surveillance. All participants joining us today are in listen only mode. Free continuing education is offered for this webinar, and instructions on how to earn continuing education will be provided at the end of the COCA Call.

In compliance with continuing education requirements, all planners, presenters, and moderators must disclose all financial relationships in any amount with ineligible companies over the previous 24 months, as well as any use of unlabeled product or products under investigational use. CDC, our planners, presenters, and moderator wish to disclose they have no financial relationships with ineligible companies whose primary business is producing, marketing, selling, reselling, or distributing healthcare products used by or on patients. Content will not include any discussion of the unlabeled use of product, or a product under investigational use, with the exception of Dr. Tim Uyeki's discussion of the use of FDA-approved antivirals for treatment of influenza in outpatients, used in hospitalized patients, and higher dosing for treatment and post-exposure prophylaxis.

CDC did not accept financial or in kind support from ineligible companies for this continuing education activity.

At the conclusion of today's session, participants will be able to accomplish the following: provide an update on human infections are avian influenza A(H5N1) viruses in the United States; discuss CDC's surveillance and monitoring efforts for avian influenza A(H5N1) virus infections in people; outline the public health implications of avian influenza A(H5N1) virus in animals, and the importance of early detection of human infections and control measures; describe expectations for summertime influenza surveillance activities in the United States, including collecting and testing recommended clinical specimens for influenza viruses, subtyping influenza A positive specimens, and submitting influenza A(H5 positive) specimens to CDC.

After the presentation, there will be a Q&A session. You may submit questions at any time during today's presentation. To ask a question, simply click the Q&A button at the bottom of your screen, then type your question in the Q&A box. Please note that we receive many more questions than we can answer during our webinars.

If you're a patient, please refer your questions to your healthcare provider. And if you're a member of the media, please contact CDC Media Relations at 404-639-3286, or send an email to media@cdc.gov.

I would now like to welcome our presenters for today's COCA Call. We are very pleased to have with us Dr. Tim Uyeki, who is the Chief Medical Officer of the Influenza Division in the National Center for Immunization and Respiratory Diseases at the Centers for Disease Control and Prevention. And Miss Alicia Budd, who is the Team Lead of the National Surveillance and Outbreak Response Team in the Epidemiology and Prevention Branch at CDC's National Center for Immunization and Respiratory Diseases. It is now my pleasure to turn it over to Dr. Uyeki. Dr. Uyeki, please proceed.

Dr. Uyeki, we have not had success with your audio yet. Can you please try?

Can you hear me now?

Yes, Dr. Uyeki, we can hear you loud and clear. Thank you. You may proceed.

Sorry about that. Today, I'll speak about highly pathogenic avian influenza A(H5N1) virus and human infections. And I will try to give a brief overview of the virology, the epidemiology, and then focus on some of the key clinical issues. Next slide, please.

So, as background, avian influenza A viruses, including highly pathogenic H5N1 viruses, they circulate among wild waterfowl and other wild birds. They infect the respiratory and gastrointestinal tract of birds. And, therefore, they are excreted in respiratory secretions, but more importantly they are shed in the feces. And avian influenza A viruses can evolve through exchange of genes. We call that genetic reassortment. And also through minor genetic mutations. And this is an ongoing process that is unpredictable.

Now, avian influenza A viruses are classified by pathogenicity, and there are specific criteria for this based upon molecular and pathogenetic, sorry, pathogenic characteristics. And these are divided into highly pathogenic or low pathogenic avian influenza A viruses. And then these viruses are further classified into virus clades and subclassified into genotypes.

Now, high path H5N1 viruses typically cause high mortality in infected poultry. There is endemic or enzootic circulation among poultry in some regions of the world. And more importantly, there is spillover from wild birds to cause poultry outbreaks. And then to cause infections in both terrestrial and marine mammals. And by terrestrial mammals, that may be wild, that may be domesticated, or farmed mammals. Next slide, please.

So, this particular clade of, that's referred to as 2. 3. 4. 4b of viruses, these viruses emerged in 2020 in wild birds, and they've been spread to many, many regions of the world. It's very unprecedented.

There's a wide range of bird species that have been infected in many poultry outbreaks. There's also been a huge range of terrestrial and marine mammals infected, typically causing high mortality. Now, in the U. S., these clade 2.3.4.4b viruses were first detected in wild birds in North America at the very end of 2021. And this was followed in early 2022 with poultry outbreaks in ongoing wild bird detections. And to date, there have been more than 169 million commercial poultry or backyard bird flocks that have been affected in all 50 states, in one U.S. territory. Wild birds have been detected with this virus in 50 states or territories. And then since the early spring of last year, there have been more than 1,000 dairy cattle herds in 17 states that have been confirmed with H5N1 clade 2.3.4.4b viruses. Next slide.

So, the first time we heard about dairy cattle that were infected was in late March of 2024. There have been at least three independent introductions that the U.S. Department of Agriculture has documented from wild birds dairy cattle with the genotype B3. 13. And then this particular genotype is the most, has been the most prevalent genotype of virus that's spread, been spreading among dairy cattle in the U.S.

More recently, genotype D1. 1 virus has been documented in dairy cattle. USDA has documented dairy cattle farm to dairy cattle farm spread, and also dairy cattle farm to poultry farm spread has been documented in some states. Notably, very high levels of H5N1 virus can be detected in the raw milk of acutely infected cows. And in experimental studies, we know that from aerosol

inoculation, so that's really just exposure to the upper respiratory tract of dairy cattle, only mild illness occurs. And virus can only be detected for a short periods of time.

In contrast, experimental inoculation of mammary tissue of dairy cows and result in virus being isolated for these two weeks. Now, we know from several studies that the high levels of H5N1 virus in raw cow milk can be inactivated by pasteurization, although you may still be able to detect some viral RNA fragments. Pasteurized milk is completely safe and free from viable H5N1 virus. Now, viral RNA has been detected in raw milk products such as cheese. And there is a recent preprint not published, not peer reviewed, that has reported detection of viable virus in raw milk cheese reported up to 60 days of aging. Next slide.

So, CDC recommendations on raw milk. Because pasteurization kills H5N1 viruses, pasteurized milk is safe to drink. However, people should not drink raw milk or consume products made from raw milk, because of not only the health risk from other microorganisms, including bacterial infections and other viruses, but for the theoretical risk that one might be exposed to H5N1 viruses present in raw milk, and there might be a risk of human infection.

To date, we have had no confirmed cases of attributed to raw milk consumption, or consuming products made from raw milk, but it is a theoretical risk. And, therefore, we do not recommend consumption of raw milk or products made from raw milk. And because we've had some anecdotal reports, CDC recommends against consuming raw milk that is potentially contaminated or known to be contaminated with live A(H5N1) virus, as a way to develop immunity, to develop antibodies against H5N1 virus, to protect against future disease. Please do not consume raw milk. Next slide, please.

So, H5N1 viruses, they lack the ability to bind well to receptors that are most prevalent in the human upper respiratory tract. Now, in contrast, these H5N1 viruses, they do bind preferentially to receptors that are most prevalent in the human lower respiratory tract. And these receptors are also found on conjunctival tissue. In contrast, seasonal influenza viruses, they bind well to receptors that are most prevalent in the human upper respiratory tract. And, therefore, we're always on the lookout monitoring H5N1 viruses circulating in animals, and that have infected people, to see if these viruses have changed to be able to bind better to receptors that are prevalent in the human upper respiratory tract.

To date, we have not seen this. The first human infections with high path H5N1 viruses were identified in Hong Kong in 1997. There were 18 virologically confirmed cases, with 6 deaths. The median age was 17. And this involved both children and adults. And there was a wide clinical spectrum of illness, including mild upper respiratory tract illness to severe and critical illness with pneumonia.

Since 1997, to date, there have been nearly 1,000 sporadic human cases reported from 25 countries, with approximately 50% mortality. A little bit less. Cumulative case fatality proportion. Most surveillance around the world since 1997 has been hospital based.

And so that is case finding that's focused on severe pneumonia patients. I just want to highlight in calendar year 2025, there have been 10 human H5N1 cases reported from 6 different countries.

That includes Cambodia, India, Mexico, the U. K., the U.S., and Vietnam. And some of those cases have resulted in critical illness and death. Next slide.

This is an epidemic curve of human cases of A(H5N1) by illness, onset, or report date since 1997 to date, 994 cases to date reported by 25 countries. And what you see, starting from the Hong Kong outbreak in 1997, and sort of the middle of the epi curve, you can see some periodic outbreaks in many different countries. And then in 2015, there was a large outbreak in Egypt. But since 2015, a very small number and hardly any human cases until the last few years. And a number of those cases in the last few years have been reported in the United States. Next slide, please.

So, we had our first human H5N1 case in the United States that was identified in April of 2023. But since then, we have had 70 confirmed H5N1 cases since March, late March, of 2024, to date. Sorry, the first case was confirmed in 2022 in the U. S. And of the 70 cases that have been confirmed in the U.S. since March, late March of last year, there have been 13 states that have reported cases. This includes 41 cases in 5 states associated with dairy cow exposures. These have all been mild illness, mainly conjunctivitis.

There have been other cases of conjunctivitis and acute respiratory illness. And a very small number of cases with just acute respiratory illness. There have been 24 cases associated with commercial poultry exposures in 6 states. These have been mostly mild illness. Again, mostly conjunctivitis, or conjunctivitis and acute respiratory illness or small numbers of cases with just acute respiratory illness. There have been two cases associated with backyard poultry exposure in two different states that have resulted in severe or critical illness.

There have been three cases with unknown exposures after a detailed field epidemiological investigations, the sources of exposure and infection could not be identified. This has been reported in two states. And in these two of the cases had mild illness and one had moderate illness. To date, we've had four hospitalized cases in four states. Three had pneumonia. One death occurred. And importantly, there has been no human to human transmission of high path H5N1 virus identified in the U. S. to date. We've also had seven probable causes that are not included in the confirmed case count. These were cases identified in states, but these were not confirmed at CDC. Next slide, please.

So, globally, since 1997, we know that the primary risk factor for human infection with H5N1 viruses is unprotected exposure to poultry. By unprotected, I refer to not using respiratory or eye protection that's recommended. And these kinds of poultry exposures include direct or close contact with sick or dead poultry. And in some cases, visiting a live poultry market.

Now, in the U. S., I mentioned there have been exposures, primarily to commercial poultry, that were sick or dead, but also to backyard poultry in two cases. More recently, particularly in the U. S., exposure to other infected animals has been identified as a risk factor, because of the ongoing transmission among dairy cattle in the United States. Some of these occupational exposed individuals working with dairy cattle had direct contact with the raw milk of these acutely infected cows.

As I mentioned before, we've had no cases attributed to consumption of raw milk or to consumption of products made from raw milk, but it remains a theoretical concern. I would also

say that any animal anywhere in the world that is infected with highly pathogenic avian influenza A(H5N1) virus, poses a transmission risk to a person who is in direct and close contact with that animal.

Then there have been historically a small number of cases that probably were acquired through limited non sustained human to human transmission. And this has occurred through prolonged exposure to a symptomatic H5N1 patient without any protection. So, for example, a family member taking care of a very sick patient at home before that patient was admitted to the hospital, this has also occurred in some hospital settings through unprotected prolonged exposure. This is not through very short casual contact, but this is through many hours of very close prolonged exposure to a symptomatic patient who's coughing. And the last known event of non-sustained limited human- to-human transmission was last reported in 2007. But it is always a concern. And that is why every single human case of H5N1 virus infection needs to be investigated epidemiologically, virologically, to see if there are any changes that it may have occurred that suggest an increase in transmission to humans and among people. Next slide.

So, let me just summarize clinical findings in H5N1 cases worldwide. There is a wide range of clinical illness in patients who have mild illness. The incubation period, so the time from exposure to onset of symptoms, is a mean of about three days, with a range of two to seven days. There have been some outliers that have been reported with a longer incubation period, but seven days will capture the vast majority of the incubation period in symptomatic human cases. And onset, most patients will develop fever or experience feverishness. They will have a non-productive cough, muscle aches, malaise, headache, sore throat, and myalgia. Some patients may complain of abdominal pain, and may manifest vomiting and diarrhea.

In patients who develop conjunctivitis, they may experience eye discomfort, redness, eye discharge approximately one to two days after exposure. Up until 2024, this had been very rarely ever reported. But now there are reports of conjunctivitis, not only in the U. S. cases, but in some other cases, in other countries.

Now, in those who progress to severe or lower respiratory tract disease, they typically progress about five to seven days after symptom onset, where they complain of difficulty breathing, they experience shortness of breath, chest pain, or tachypnea. And in hospital admission typically around five to seven days, again, after symptom onset. There are the typical findings of pneumonia. So, with hypoxia. Laboratory findings, the classic findings are leukopenia, lymphopenia, and mild to moderate thrombocytopenia.

But these findings are not present in all patients. And then radiographically, typically it's a bilateral pneumonia, and there can be a range of findings including patchy interstitial lobar diffuse infiltrates, opacities, consolidation, and sometimes pleural effusions. Next slide, please.

In terms of clinical complications in hospitalized patients, pneumonia is clearly the most common complication, with progression to respiratory failure, and the acute respiratory distress syndrome. I'd like to mention that community-acquired bacterial co-infection is rare, and that is in contrast to seasonal influenza.

However, patients who are on invasive mechanical ventilation for prolonged periods, they may experience ventilator associated pneumonia. Other complications that have been reported in hospitalized H5N1 patients include acute kidney injury, sepsis, shock, disseminated intravascular coagulation, multi organ failure. That is respiratory and renal failure, cardiac failure. And then some atypical complications that have been rarely reported include encephalitis and meningoencephalitis, Reye syndrome with salicylate exposure, and spontaneous abortion. I'll just mention that there have been some cases in recent years of encephalitis in young children with H5N1. Next slide, please.

So, let me cover influenza testing issues. So, if H5N1 virus infection is suspected in outpatient who is clinically stable, definitely we want to use recommended personal protective equipment, which includes gown, gloves, a NIOSH approved N95 filtering facepiece respirator and eye protection with goggles or face mask. And if the patient has acute respiratory symptoms, you should collect a nasopharyngeal swab and a combined nasal and throat swab specimen. So, put the nasal swab and the throat swab in the same tube, put the nasopharyngeal swab in a different tube, a viral transport media, and those specimens should be tested separately.

If the patient has conjunctivitis, collect a conjunctival swab and a nasopharyngeal swab, put each of those specimens into separate tubes of viral transport media. If the patient has bilateral conjunctivitis, collect a conjunctival swab from both conjunctivi separately.

Now, influenza A virus subtyping and H5 virus testing should be done at a public health laboratory. Just to make an important point that nearly all influenza tests that are commercially available in clinical settings for seasonal influenza, they cannot specifically identify an H5N1 virus. They can't differentiate H5N1 virus from seasonal influenza A(H3N2), or A(H1N1)pdm09 viruses, and specific subtyping is needed, especially at public health laboratories.

I'll just mention that there are three companies that have commercial RTPCR assays to detect A(H5N1) virus. Those are Quest, ARUP, and LabCorp. And there are different respiratory specimens or some conjunctival swabs can be used for the ARUP assay. But just to say that there may be some delay. There may be differences in the time from when the specimen is collected and shipped to the laboratory to when a result is available. Next slide, please.

Now, again, for hospitalized patients, just a reminder, the patient should be placed in an airborne infection isolation room with negative pressure. And the recommended PPE should be worn. And, again, it's gown, gloves, NIOSH approved N95 filtering facepiece respirator and eye protection with goggles, or a face shield. Patients with lower respiratory tract disease signs and symptoms, you should, or evidenced by chest x-ray or other chest imaging, you should collect upper respiratory tract specimens, the same specimens that I've just gone over for patients who have mild clinical illness.

If the patient is not intubated, but is able to produce sputum, sputum should be collected as well. Also placed in a separate tube of viral transport media. And that can be tested. If the patient is intubated, then collect endotracheal aspirate specimens. And if a bronchoalveolar lavage has been performed, then the BAL fluid can also be tested.

I will just say that in some countries, the diagnosis of H5N1 in a hospitalized patient who is intubated was made by testing lower respiratory tract specimens, when testing of the upper respiratory tract was net, yielded negative results. So, if there is high clinical suspicion, and also a history that is suspicious of animal exposures, you should collect multiple respiratory specimens from different sites on multiple days for patient, these patients, to maximize the potential for detecting H5N1 virus. Next slide, please.

So, let me move over to talking about antiviral use. So, for antiviral treatment, we do recommend Oseltamivir treatment as soon as possible for patients who are suspected, probable, or confirmed cases of A(H5N1).

Currently circulating clade 2.3.4.4b viruses are generally susceptible to Oseltamivir. And most other FDA-approved antivirals that are approved for seasonal influenza, we do not have any randomized control trials of any antivirals for any antivirals for patients with high path H5N1 virus infection.

However, there are some older observational data that suggests survival benefit with early initiation of Oseltamivir treatment, compared to either no treatment or later initiation of treatment. And that's the basis for recommending Oseltamivir treatment as soon as possible. We have no data for Baloxavir treatment of A(H5N1) patients. And so we don't know the optimal dosing and duration. And, therefore, we don't recommend a Baloxavir monotherapy for antiviral treatment of H5N1 patients. Next slide.

So, if the patient has clinically mild illness, does not require hospitalization, we do recommend starting empiric antiviral treatment with Oseltamivir as soon as possible. While awaiting testing results, don't wait for influenza A and H5N1 test results. Just start the patient as soon as possible on Oseltamivir. We do recommend home isolation for patients with mild illness. And local and state public health should be notified immediately for testing, monitoring, and follow up.

Now, if H5N1 virus is confirmed, the patient needs to be kept on home isolation, or it's recommended. And they need to be monitored for worsening of symptoms, clinical progression. And they should be isolated at least until clinically improved or repeat respiratory specimens are negative for influenza. Next slide.

Now, antiviral treatment for hospitalized H5N1 patients. So, in patients with more severe disease, particularly pneumonia, combination antiviral treatment can be considered. Similarly, for outpatients who do not require hospitalization, but who are immunocompromised, combination antiviral treatment should be considered. Higher dosing of Oseltamivir can also be considered. And because Oseltamivir resistance has been reported in patients in Vietnam during 2004 and 2005, with fatal outcomes, combination antiviral treatment with different, with antivirals of different mechanisms of action should be considered.

And in the graph there, in the figure, what you see in the blue are patients with susceptible, Oseltamivir susceptible H5N1 virus infection. And over time, with treatment, their viral levels decrease. Whereas in the red, those are patients are Oseltamivir resistant virus. Their levels remained high. And there were two patients in which Oseltamivir resistant virus was identified, and they died.

I'll say that there have been some patients, a small number of patients in the U. S. and in Canada, who have received a combination antiviral treatment, including with Oseltamivir, Baloxavir, and either Amantadine or Rimantadine. These represent three different classes of antivirals with different mechanisms of action. Clinicians are reminded that they can contact the CDC Emergency Operations Center and request to speak to clinicians from the Influenza Division at CDC for guidance on antiviral treatment, including combination antiviral treatment.

But if Oseltamivir and either Amantadine or Rimantadine are used, and the patient has acute kidney injury, or renal failure, dosing needs to be adjusted for those drugs. Now, a big gap is that there is very limited human data on combination antiviral treatment of A(H5N1) patients to inform recommendations. We really don't know the optimal duration, the optimal dosing, the optimal frequency of dosing.

There is one case report of a patient who was a critically ill adolescent in British Columbia last year who received combination antiviral treatment. But we can't conclude, we can't make any inferences about the effectiveness of that combination therapy in that patient. Particularly, it's uncontrolled, it's N equals 1, and that there were other interventions that were given. But we do think that it may have had some clinical benefit. Next slide.

Just to say briefly about antiviral post- exposure prophylaxis, if H5N1 virus infection is confirmed in a patient, we do recommend that household and other close contacts should receive Oseltamivir at treatment dosing as soon as possible. So, that means Oseltamivir given twice daily for five days.

If there is ongoing exposure, such as in a household, and the confirmed case patient cannot be sufficiently isolated, then longer duration of Oseltamivir, again, at treatment dosing, should be given for ongoing exposures twice daily. All of these individuals should be monitored for any signs or symptoms of illness. If they do, they should be tested, they should be isolated up to 10 days after the last known exposure to the confirmed case patient. And then post-exposure antiviral prophylaxis should also be offered to persons with high risk, high-risk exposures to infected animals. Next slide.

So, just to kind of summarize clinical management for hospitalized patients, patients should be placed in an airborne infection isolation room. Personal protective equipment is recommended. Disposable gloves, gown, eye protection, either goggles or face mask, and respiratory protection, at least as protective as an, that should be N95 filtering facepiece respirator. Oseltamivir treatment should be started as soon as possible. Combination antiviral treatment can be considered.

But most clinical management is supportive care of complications, including advanced organ support, respiratory support, possible renal replacement therapy, and very good critical care. In terms of the immunomodulators, avoid moderate to high dose corticosteroids, because they are associated with prolonged viral shedding, and may increase the risk for ventilator-associated pneumonia and death. Unfortunately, we don't have any data for any other immunomodulators. For example, the IL 6 receptor blocker, such as Tocilizumab, the Janus kinase inhibitors, has been well used and well studied for severe COVID-19. So, we really can't make any recommendations on the use of any other immunomodulators for severe or critically ill H5N1 patients. Next slide.

And I'll just conclude with a self-knowledge check. What are risk factors for highly pathogenic avian influenza A(H5N1) virus infection in humans in the United States to date? A, consumption of unpasteurized or raw cow milk. B, direct or close unprotected contact with sick pigs. C, direct or close unprotected contact with sick or dead poultry. D, consumption of raw or undercooked beef. E, direct or close unprotected contact with dairy cattle or raw milk. F, A and E. G, C and E. Or H, A, C, and E. Next slide.

The answer is G, C and E. The rationale is direct or close unprotected exposure to sick or dead poultry, or dairy cattle or raw cow milk have been reported for cases of influenza A(H5N1) in the United States. Next slide, please.

So, here are some testing and treatment resources from CDC, including testing and specimen collection, antiviral treatment, infection prevention and control measures, and the use of antiviral post exposure prophylaxis.

And thank you very much. And with that, I'd like to turn it over to my colleague Alicia Budd. Thank you.

Thank you, Tim. And good afternoon, everyone. So, for the next few minutes, I'm going to talk about surveillance and monitoring for human infections with highly pathogenic avian influenza A(H5N1) in particular. Though some of this also applies to surveillance for novel influenza A viruses in general. And I'll point those, those areas out. And when I mention novel influenza A viruses, what I mean by that is any influenza A virus subtype that is different from the H1 and H3 viruses that are currently circulating in people. Next slide, please.

So, to reiterate what Tim mentioned earlier, the current H5 outbreak in animals in the U. S. poses a low risk for most people. However, we know that people who have close, prolonged, or unprotected exposure to infected animals or their environments have a greater risk of infection than people without those exposures. This is true of H5 infection. And it's also true for infection with other novel flu A viruses. And people with these exposures need to be monitored for symptoms, from the time of their first exposure, through 10 days after their last exposure. Next slide.

So, the recommendation to monitor people exposed to infected animals with their environments has been in place for several years. Looking back to February of 2022, which was when we had the first H5 human case in the U. S., looking back until that point, there have been about 26,000 people who have been monitored after H5-related exposures. We're monitoring them for development of symptoms. And if symptoms develop, they would need to be tested for influenza. And almost 1,200 of those, 26,000 have been tested. Now, if we look at the most, at the current situation with H5, which really we look at the time period from March of last year onward, that's when the vast majority of the monitoring and testing has occurred. And that March 2024 period was when the virus was first identified in dairy cattle. So, during that time, more than half of the people being monitored were people who were exposed to dairy cattle.

And the remainder were exposed to either poultry or occasionally other animals. And then more than 880 of those being monitored went on to develop symptoms and were tested for influenza. About a quarter of those tested had had exposure to cows. And about three quarters of those were exposed to other animals. Next slide, please.

So, of the more than 880 exposed people that were tested for H5 as part of this targeted monitoring, 64 of the 70 confirmed human cases of H5 were detected in this manner. Next slide.

So, monitoring of exposed individuals is not only, is not the only H5 monitoring that we do in this country. Certainly the greatest risk for infection is in those with direct exposure. But we also want to cast a wider net and make sure that we are not missing cases or that things are not happening in individuals with, that don't have a known exposure.

So, to do this, we rely on our existing influenza surveillance system that was set up to track seasonal virus epidemics. But it's also set up in a way that allows us to identify novel viruses, were they to be occurring out in the general public. And this happens through subtyping of influenza A positive specimens. So, influenza subtyping for H5 can happen when you use a test that specifically detects H5. And Tim mentioned that earlier in his presentation.

But in the current situation where we're seeing low levels of H5 in humans, usually the first step when you're testing someone is to test for influenza A first, and then subtype, attempt subtyping for seasonal viruses, the H1 and the H3 viruses. And if you don't get a positive result for those human seasonal viruses, we call that an unsubtypable virus. And they need to go on for additional testing as Tim mentioned, usually at a public health lab, and then get sent on to CDC for additional testing. So, 6 of the 70 confirmed human cases of H5 in the U. S. since March of 2024 were identified this way. The specimens were received at public health labs for this additional testing through routine specimen submission networks, or because the provider identified that their patient had a relative, relevant exposure, and notified public health to arrange for additional testing. And I'll talk a little bit more about that in just a minute. Next slide.

So, as Tim mentioned earlier, 67 of the 70 confirmed human cases had animal exposures identified. The graphics on this slide overlay animal infections with H5 and human infections with H5. And you can see this data by state when you look at the map, and also over time, and by type of animal exposure on the graphs on the right. There's a lot to look at here. And in the interest of time, I just want to highlight one particular piece of information. But these graphs are available on the CDC website, and they're updated every week, so you can certainly go in and look at them in more detail on your own.

But what I wanted to point out here is that on the graphs, the three graphs on the right, the animal detections are in the area highlighted in light blue. The human cases are in the bars that are yellow to orange. And you can see that both the animal detections have declined recently, as have the human cases detected. Because as we've heard, most of our human cases are known to be associated with animal exposures. So, fewer infections in the animals leads to fewer infections in the people.

It is certainly great to see these declines in both animal and human cases. But it's also critical that we maintain the monitoring, the targeted monitoring and our general surveillance, so if this situation changes, we'd be able to identify that quickly. Next slide, please.

So, that brings me to what you in the clinical community can do to help us all maintain visibility on what's happening with both seasonal and novel influenza viruses. So, we track information about influenza viruses and their impact year round.

We all know that there are seasonal flu epidemics every winter. But flu viruses are also circulating in the summer, albeit at much lower levels. But during the summer, we have seen flu cause outbreaks at camps, on cruise ships, during sorority rush, just to name a few circumstances. But the other thing that goes on in the summer is it's agricultural fair season. And so that's a perfect environment for animals and people to interact with each other, and potentially share flu viruses.

So, we always want to be thinking about novel flu viruses in the summer. We always want to be thinking about just, you know, these sort of combined living environments, like summer camps, cruise ships, things like that. That's our routine summer. And then on top of that, we continue to have this ongoing situation of H5 infections in animals. So, now more than ever we really need your help to make sure that flu testing occurs throughout the summer, especially important for symptomatic people who have a recent history of relevant exposures, who have participated in communal activities and settings like camps, and people who are severely ill.

So, what you can do to help with this is, you know, be aware and think flu, even though it's summer, and make sure you're evaluating your patients accordingly. Talk to patients about their exposures and their risk. Collect specimens when it's warranted. And facilitate subtyping of flu A positive specimens, either in the clinical setting, if it's possible, or by notifying your state or local public health department if you have a patient is one of these categories, either that you've tried to subtype the virus and it wouldn't subtype as a human, H1 or H3, or if you have a patient who's flu A positive and has one of these relevant exposures, or is severely ill. Any of these situations needs to be investigated further to determine what virus might be causing the illness. And, if warranted, you know, dig deeper, do investigation into particular exposures and contacts so that public health action can be taken quickly. Next slide, please.

So, as I mentioned earlier, the flu surveillance system is set up to address a number of needs, including the detection of novel viruses like H5. And lab testing is really the backbone of that work. Now, this is certainly a very overly simplistic diagram that shows how specimens flow through that system.

But I just wanted to point out it starts with the clinical community, outpatient providers, hospitals, et cetera, collecting specimens from patients. A subset of those patients will get tested, or excuse me, a subset of the patients tested in a clinical setting will go on and get sent to public health labs, as will specimens that there is some sort of clinical suspicion of something else going on. And it's at the public health labs where the subtyping happens, and where a novel virus could be identified. Next slide.

So, again, where we can use your help is at this very top of this diagram, by thinking about flu and collecting specimens. Next slide.

And then, you know, making sure that the subtyping is happening either in the clinical setting or by looping in public health counterparts to help in that regard. Next slide, please.

So, in addition to the virologic surveillance, at CDC, we're also closely monitoring data that's reported to us about outpatient and emergency department visits, hospitalizations and deaths due to flu. And if we notice anything unusual in any of those metrics, we'll reach out to our public health partners at the state and local level, and we'll work together to assess the situation.

We were doing this throughout the H5 activity to date, and continue to do that. And if not, identify any unusual indicators that might be indicative of H5 transmitting among people. And this type of data exploration is certainly not unique to CDC. We know our partners in the state and local level are doing the same thing with the data that they have available to them. And, again, no indicators of any H5 transmission among people. Next slide.

And so the last H5 related surveillance system I wanted to touch on briefly is wastewater surveillance. So, wastewater surveillance gained popularity during the COVID pandemic. And since that time, wastewater surveillance for other pathogens, including influenza, has been explored. So, for flu, we found that wastewater data may complement other existing human surveillance systems, but that it can't really be used effectively in isolation, because, as always, I think flu is complicated.

Flu viruses, as we've been talking about, infect animals, as well as people. And wastewater testing can't determine whether the source of what's in the wastewater is from an animal or a person. And so we saw this play out with wastewater testing for H5, and wastewater testing for flu A in general. So, anytime H5 was detected in a wastewater sample during this past year, the jurisdictions would investigate, everyone would review available data, and none of those detections were determined to be associated with human infections. Instead, it was usually found that an infected dairy premises, poultry facility, or infected wild birds, were in the area of that sewer shed.

And then on the other side of things, flu A, in general, those levels are also being tested for in wastewater as a way to track human seasonal flu activity. But there was a period of time this season when flu A wastewater values in California were high. But other human surveillance systems were not indicating elevated levels of flu activity in people. And it turned out that the flu A levels in wastewater were high, due to the high amount of influenza A(H5) activity in dairy cattle, not because of anything going on in people. So, those two examples just serve as a reminder that while wastewater surveillance or flu can serve a purpose, that it's really important to look at those data in conjunction with other information to make sure that everything is being interpreted correctly. Next slide.

So, here, just a couple of the many monitoring and surveillance resources that are available in the CDC website. This includes what we call our current situation page, which has high level updates. There's also an H5 surveillance and monitoring page that contains more details for situational awareness, as well as guidance for reducing exposures in various people, and carrying out investigations. Next slide, please.

So, lastly here is an additional self-knowledge check. The question is, clinicians can perform which of the following activities to help detect novel influenza viruses this summer? A, think flu, even though it's not respiratory virus season. B, ask patients about any relevant exposures. For example, dairy cattle, raw milk, wild birds, poultry, and agricultural fair attendance. C, collect a specimen for flu testing from symptomatic patients, especially if they have a recent relevant exposure. Or D, all of the above. Next slide, please.

And so the answer is D, all of the above, because all of these are important activities tomorrow detecting novel influenza viruses.

Thank you for your attention, and I will now turn it back over to Captain Khan.

Presenters, thank you so much for providing this timely information to our audience. We are pleased to welcome Dr. Todd Davis and Dr. Marie Kirby, who are joining the presenters for the Q&A session. Dr. Davis is Branch Chief of the Virology, Surveillance and Diagnosis Branch. And Dr. Kirby is Team Lead of the Genomics and Diagnostics Team, both in the Influenza Division at CDC's National Center for Immunization Respiratory Diseases. So, we will now go into our Q&A session.

Our first question asks, is there seasonality to H5N1 similar to seasonal flu?

Hi, this is Todd Davis. I'm happy to field that first one. So, the seasonality that's been noted in H5 and other countries primarily corresponds to migratory bird patterns. So, it's quite different from seasonality for human influenza viruses, and that distribution of the virus among wild birds tends to follow migratory patterns, so we expect to see more circulation of H5N1 of wild birds in the fall and early winters, birds are migrating south from wintering grounds. And that's when poultry flocks tend to be exposed to those wild birds, and then the scenario over the past year where dairy cattle have also been exposed likely to wild birds harboring the virus.

And then subsequently, the chances of human exposure corresponding where those viruses are circulating, while they're in poultry flocks or in dairy cows, so it tends to be more related to migratory bird patterns.

Thank you very much. Our next question asks, how do you recommend clinicians differentiate between conjunctivitis caused by H5N1 versus other common conjunctivis ideologies during flu season and off season?

This is Tim Uyeki. I'll take that one and see if others may want to add. Just to say that, you know, conjunctivis is a very common condition. This can be caused by various infectious pathogens. It can also be caused by irritation. There is allergic conjunctivis. And so there can be increases in allergic conjunctivitis in the spring, and in the fall as well. So, there are many etiologies. The real key to suspecting conjunctivitis associated with H5N1 virus infection is to elicit a history of recent direct exposure or close exposure to infected animals. And it's typically been in occupationally exposed workers, so dairy cattle workers, as well as poultry workers, or people culling birds and poultry outbreaks.

It's probably occurring through contact transmission, either direct inoculation of virus onto conjunctivi surfaces, such as has been reported for some dairy cattle workers who were splashed with raw milk in the milking parlor directly to the eye, resulting in conjunctivitis. It's likely that there's also been transmission, contact transmission from an individual who's either got virus contamination on their hands or on their gloves and they're touching their eyes. And so the real key is going to be to eliciting that history of recent exposure to infected animals, particularly among occupationally exposed people. But another is, you know, that some of these patients have complained of so-called red eyes, which are subconjunctival hemorrhages. And that's been observed a fair amount with the bilateral conjunctivitis associated with H5N1 virus infection.

But the real way to know is if you suspect it is to actually collect conjunctival swabs. And as I mentioned, if the patient only has conjunctivis, you should also collect the nasopharyngeal swab. If the patient has other acute respiratory symptoms, you should collect a combined nasal swab and a

throat swab. And so what that means is you collect a nasal swab and you collect a throat swab separately, but you put them both in the same tube of viral transport media. So, that's really the way to do it.

It's tested then for influenza A, and then subtyped and tested for H5. But let me just see if my colleagues wanted to add anything to that over.

Okay, thank you so much, Dr. Uyeki. So, follow up question that's popped up a couple of times. And this is a fine one to follow up your response regarding the conjunctivitis. Should Oseltamivir treatment be initiated in a patient that presents with conjunctivitis and has known exposure to infected animals or potential, potentially exposed to the infected raw milk?

Yeah, thanks for that question. So, the answer is if you suspect a patient has H5N1 virus associated conjunctivitis, you should certainly offer the patient Oseltamivir treatment as soon as possible. You should also collect conjunctival swab specimens and nasopharyngeal swab specimens for influenza A testing and subtyping. And then for H5 testing. But you should offer the patient Oseltamivir treatment as soon as possible without waiting for any influenza testing.

And just to say that one of the reasons why conjunctivitis is thought to have been prevalent among many of these cases who have been exposed to either H5N1 virus through poultry exposure or through dairy cattle exposure is because conjunctival tissue have abundant receptors for this particular virus on conjunctiva. And that is different than seasonal influenza viruses, for which with seasonal influenza, conjunctivitis has been reported, but it's quite rare. Thank you.

Thank you very much. And as we were at time, we have time for just one last question. And the question asks, what are your recommendations for isolation for patients that are confirmed H5N1, but are exhibiting mild illness?

Right, thank you for that question. So, if the patient is mild, has mild illness, does not require hospital admission, we do recommend isolation at home, so that would be ideally it depends on the characteristics of the home, but ideally in a separate room with a separate caregiver who when they have contact, both the patient is wearing a face mask for source control, and the caregiver is wearing a recommended face mask. We do recommend N95 for respirator or equal. And then ideally gloves and with frequent hand hygiene for both the patient as well as the caregiver. So, in those situations, both the patient needs to be monitored closely for potential worsening clinical progression, and the household members are recommended to receive Oseltamivir post exposure prophylaxis.

So, that's a treatment dosing twice daily for five days, but ongoing exposures, you would extend the Oseltamivir dosing. And then there are situations where it may not be possible, practically possible to isolate that mildly ill person in a separate room. And so I think that you have to do as much as possible, given the situation, social distancing as much as possible, hand hygiene, source control by the patient with a face mask and respirator by the household members, if possible, when they have to be in somewhat close contact. But everybody should be monitored for potential symptoms in those who have been exposed, and then worsening of symptoms in the patient. Over.

Great, great, thank you so much. I want to thank everyone for joining us today, with a special thanks to our presenters and our subject matter experts for sharing their time and expertise with us.

CDC has fully transitioned from the Training and Continuing Education Online system that provides access to CDC educational activities for continuing education to CDC TRAIN. If you do not already have a TRAIN account, please create one at www.train.org/cdctrain. All new activities that offer continuing education from CDC will only be listed in CDC TRAIN. CDC TRAIN is a gateway into the TRAIN learning network, the most comprehensive catalog of shared public health training opportunities. This transition will allow you to access non credit and for credit educational activities, track your learning, including CE, in one place. Many CDC accredited activities are already listed in CDC TRAIN.

The move to one system improves efficiency and makes it easier for learners, CDC staff, and partners to offer and earn CE in one place. You can access and download CE transcripts and certificates in TCEO through the end of 2025. Instructions will be available on both platforms, and a learner support team will be available to answer your questions. All continuing education for COCA Calls is issued online through CDC TRAIN.

Those who participate in today's live COCA Call and wish to receive continuing education, please complete the online evaluation and post test by June 9, 2025, with the course code WC4520R-050625. The registration code is COCA050625.

And those who will participate in the on demand activity and wish to receive continuing education should complete the online evaluation between June 10, 2025 and June 10, 2027, and use course code WD4520R-050625.

The fully closed captioned video and transcript of today's COCA Call will be available on demand next week at www.cdc.gov/coca.

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Again, thank you for joining us for today's COCA Call, and have a great day.