

# IDSE

# Infectious Disease SPECIAL EDITION

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# The Avian Flu Outbreak That Just Won't Die Out

*By MARIE ROSENTHAL, MS*

More than 100 years later, the 1918 influenza pandemic still sends shivers down the spines of flu experts.

The 1918 pandemic, often called the Spanish flu, which resulted in the deaths of an estimated 50 million people worldwide, was the most severe epidemic in recent history, according to the CDC. Almost 700,000 people died in the United States alone, and historians estimate that 500 million people or about one-third of the global population at the time was infected, the agency said.

The 1918 flu was atypical in that mortality was higher in young, healthy adults, rather than the very old and the very young, who typically suffer more with severe influenza. Researchers have suggested the end of World War I helped spread the disease as millions of young adult servicemen and women returned home.

That devastation was caused by a pathogenic avian flu strain called H1N1.

With that historic view in mind, flu experts are monitoring closely an avian influenza outbreak that has been circulating around the world for more than a year.

“Anybody who works in flu is always keeping an eye on these viruses in animals because that is where new viruses in humans come from,” said Lynnette Brammer, MPH, the team lead of the CDC’s Domestic Influenza Surveillance Team.

“The World Health Organization conducts surveillance for new influenza strains around the world 24/7, 365 or 366 days a year,” added William Schaffner, MD, a professor of preventive medicine and health policy at Vanderbilt University, in Nashville, Tenn. “So, avian flu is of great interest because new influenza strains come from these avian flu strains when they pick up the genetic material that permits them to be readily transmitted among humans.”

Fortunately, he said, that is uncommon.

“But you have to watch these avian flu strains constantly, and to be on the alert, because when that switch happens, then you’ve got the material for another pandemic,” he warned.

To say a flu pandemic on the heels of COVID-19 would be a disaster would be an understatement. Just as the 1918 pandemic not only killed millions of people, but was an economic catastrophe that affected every aspect of society, the COVID-19 pandemic touched every aspect of society from business to schools to families.

Hospitals and healthcare workers were also not immune from the COVID effect. Many died and many more became sick, and some are still suffering from Long COVID. The WHO estimated that between 80,000 and 180,000 healthcare workers died from COVID-19 between January 2020 and May 2021.

More than three dozen hospitals entered bankruptcy in one year, according to a November 2020 report by the American Hospital Association (<https://www.aha.org/system/files/media/file/2020/11/fact-sheet-covid-hospital-bankruptcies-1120.pdf>). Many of them closed, and others still sit on the edge of closure

as owners try desperately to keep them open. Most of these facilities are in underserved areas: rural counties or inner-city neighborhoods.

“There is no doubt” that an influenza pandemic would be a difficult blow to an already fragile public health system, just as the world is rebounding from COVID-19, according to Dr. Schaffner.

“Ordinary bad flu seasons strain our healthcare system, and that is true of everywhere in the world,” Dr. Schaffner said. “And a new pandemic you can be absolutely sure would strain public health facilities in every country in the world.”

“We don’t have that much reserve capacity either in terms of bed, emergency rooms, urgent care clinics, and those are just the physical facilities—let alone the personnel. Our chief nursing officer has said: ‘We can open up more beds, but unless we have the trained personnel that can take care of the patients, a bed is just a bed.’”



**Avian flu viruses have been found in U.S. commercial and backyard poultry in 44 states and in wild birds in 46 states this year alone.**

Source: CDC

### Is Avian Flu a Real Threat?

Luckily, many things have to happen before an avian flu strain becomes competent at human-to-human transmission, which would be needed for a pandemic flu strain to take hold. The avian flu strain has to infect another mammal, often a pig, which is simultaneously infected with a human strain of influenza, and they would have to swap genetic material that permits the avian strain to be readily transmitted among people, Dr. Schaffner explained.

Although rare, it can happen. So far, sporadic infections of H5N1, the current circulating avian strain, among mammals, including wild foxes and skunks, have been reported in the United States, Canada and other countries, according to CDC veterinarians, who answered questions by email. According to the Wildlife Society, a conservation group, avian flu also killed



a bottlenose dolphin (*Tursiops truncatus*), which was found in September off the coast of Florida.

And there have been a handful of people infected with H5N1 who had handled sick birds, according to Scott R. Beyer, PhD, MS, an associate professor at Kansas State University, in Manhattan, Kan., who is an expert in poultry nutrition and management. (Although the CDC recommends vaccination for everyone older than 6 months of age, Dr. Beyer said it is important for those in the poultry industry to be vaccinated. No one would want to mistake an avian flu for the circulating human strains.)

But none of these H5N1 infections are unusual, and as of December, the strain is still not effective at human-to-human transmission, they said.

“Avian flu can cause a few human infections,” Dr. Schaffner explained. “These are usually people who are very closely associated with animal populations.

“These viruses on occasion can get deep down into their lungs and establish an infection, but they are unable to establish an infection in the upper airway, so they cannot be transmitted readily,” he explained.

The CDC, WHO and other agencies track the strains looking for cross-species transmission. In fact, the CDC has asked state health departments to report any influenza strains they come across that are not readily typeable, and send them to the CDC “so they can be examined further to see if they have the potential for suddenly spreading to humans,” Dr. Schaffner said.

“The genomic analysis would be done at the CDC, and they have increased their surveillance of these odd influenza strains, as well as the ones we know are circulating—H3N2 and H1N1, and the Bs that we are all familiar with. They are particularly interested in getting strains that are not readily typed by the state health departments because they want to look at those and make sure that they don’t detect something more threatening,” Dr. Schaffner said.

That is a second line of defense. The first line of defense is the veterinary field, farmers, the poultry industry and everyone else who works with chickens, turkeys and other domestic and wild birds.

These are the people who are encountering the avian flu and working to stomp it out, Dr. Beyer explained. Just as their human counterparts do, folks like Dr. Beyer and the Department of Agriculture keep a close eye on avian flu as it passes through other countries, trying to anticipate when and where it will enter the United States.

And various industries test flocks all over the country and respond, usually by culling the flock.

As of Dec. 2, more than 52 million birds in 46 states have been culled during this outbreak, which began more than a year ago. “That sounds like a lot of birds,” Dr. Beyer admitted. “But we deal with flocks of birds that are 300,000 to 1 million in a flock.



**Above: Migratory birds, such as geese, are the source of the avian flu infections being seen on poultry farms, in backyard chickens, zoo animals, etc. Below: Discoloration of chickens’ legs and comb are common symptoms of avian flu.**



“Birds are very small. On a cattle farm, 300 head of cattle is a lot; well 300,000 ‘head’ of broilers to me is normal,” he explained.

The best way to contain a flu virus in domestic animals is to kill the flock and prevent the viruses from spreading to other birds. Just because 52 million birds were destroyed does not mean 52 million birds had the flu, he said.

“The actual number of infections is [much lower],” he explained. “Once we confirm a flock has the virus present, and there is no doubt about that through sampling, the entire flock of birds will be terminated as a precaution,” Dr. Beyer explained. “And then, inspectors will go and visit facilities all around [the infected flock] and do sampling. So, this is bigger than just the flock itself.”

The last time they dealt with a large outbreak of avian flu was in 2015, and luckily, most poultry farms learned better biosecurity systems, so that this time, they are seeing fewer neighboring flocks becoming infected. But still, 52 million birds surpasses the number culled in 2015.

Although there are several poultry flu vaccines available in the United States, they are not used here because U.S. trade would be more difficult with some countries, and it would be more difficult to identify exposed birds. However, the industry and the government are discussing whether the vaccines should be permitted.

If they were used, it could be difficult to differentiate vaccinated from infected birds. Since avian flu strains can be so deadly to humans, surveillance and this differentiation are very important.

The industry is also worried about selling vaccinated birds

if they can't be differentiated from infected ones. The poultry industry is big business: In 2020, the sale of broilers, eggs, turkeys and chickens was \$35.5 billion.

### About Avian Flu

There are two forms of avian influenza: low pathogenic and high. The H5N1 strain currently circulating is considered a highly pathogenic strain.

Avian flu in birds is a pretty devastating disease, causing signs within hours of infection and death shortly after, Dr. Beyer explained. The flu causes weakness, and birds that fly tend not to be able to take off. Chickens and other poultry tend to start slowing down. They get ruffled feathers, which is a sign

of chills, and the bare skin around the eggs and the wattles sometimes start to swell. "As it advances, it turns color," Dr. Beyer said.

Since it is a respiratory disease, the birds have trouble breathing, and they die shortly afterward. It is a highly virulent virus, especially this H5N1 strain from clade 2.3.4.4b.

"It's been devastating, especially with turkeys," Dr. Beyer said. "And less so with the egg layers and broilers, but mortality is a big concern."

But just like any flu, there are mild cases, too.

Avian flu in general is a little harder to control because it starts with wild birds, mostly migratory birds like ducks and

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## Human Flu Activity Still High

As of Dec. 2, influenza activity was still high, according to the CDC, with outpatient visits for a flu-like illness still 7.5% above baseline.

Most are influenza A viruses, but there are pockets of influenza B circulating, too, according to William Schaffner, MD, a professor of preventive medicine and health policy at Vanderbilt University, in Nashville, Tenn. Seventy-nine percent of strains are H3N2 and 21% have been H1N1, according to the CDC's FluView database.

"This season started four to six weeks early, and it was fierce," he said. "By that I mean, cases started and the curve just had an upward rocket-like trajectory."

The virus started in the South, moved up to the East and over to the Southwest, and continued across the country from there.

When asked whether that geographic movement was normal for flu, Lynnette Brammer, MPH, the team lead of the CDC's Domestic Influenza Surveillance Team, laughed. "It's one of the ways that flu moves in the United States," she said. "I've been doing this for a while, and it seems like as soon as you say, 'Oh, yeah, this is the pattern of how flu spreads,' then it totally changes."

Like the virus itself, flu patterns are not very predictable, she admitted.

Although the flu started early and more than 19,000 people were hospitalized from flu in one week, it's hard to say whether the season will be mild or severe, both Dr. Schaffner and Ms. Brammer said. However, Australia had a similar start to its season, and it died out pretty quickly, so there is hope that the United States will see a similar course.

Dr. Schaffner called the season moderately serious. "It all will depend on how sustained the flu is out in the community," he said. "There have been some seasons, such as last year, where flu suddenly dropped down in January, but there have been many other seasons where flu has been out there in the community for three or more months. And those seasons can be bad."

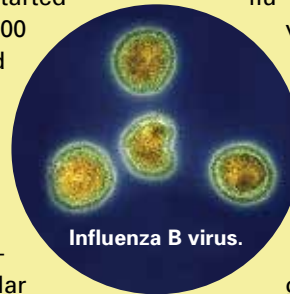
Ms. Brammer said the bottom line is that "we are going to have to wait and see. Activity does seem to be picking up pretty quickly, but again, we need to see what happens over the coming couple of weeks."

One activity that just about everyone can do to keep the flu under control is be vaccinated, they both said. So, physicians and other health-care workers should encourage flu vaccination, even late in the season.

The vaccines are a good match to circulating strains, so vaccination is the best way to protect oneself from serious disease, hospitalizations and death from influenza, they said. As of Nov. 19, 154.10 million doses of flu vaccine have been distributed in the United States, much of that delivered in November.

Dr. Schaffner said there is a general vaccine fatigue after COVID-19, and receipt of both the flu and COVID-19 bivalent vaccines has not been as high as officials would have preferred.

"People are being asked to roll up both sleeves and get vaccinated," he said. "But some people are really quite indifferent. One of my friends has called this 'vaccine ennui.' I call it vaccine fatigue, but her assessment has a little more style to it."



who require PrEP and ensure they offer it to everyone who could benefit.

This is one area where pharmacists can help, because they are a trusted medical health professional and can spend a little more time with patients than a physician who has a 15-minute time slot for each patient.

Education for both providers and patients is essential, he added.

“Many patients who have a negative experience in health-care typically tend not to return,” Dr. Phan said. “We need to provide an affirming environment.”

One simple way to acknowledge people’s gender identity is to ask which pronouns they prefer, according to Dr. Phan, who introduced himself to the audience with his preferred pronouns: he, his and him.

Other ways to overcome barriers is to have community advocates, hire more minority healthcare professionals and provide positive messaging to patients through social networks and social media “to improve knowledge and attitudes and reduce stigma,” Dr. Phan said. “We know there are effective prevention strategies for HIV, and the future continues to provide us with hope.” ■

*The sources reported no relevant financial disclosures.*

## Avian Flu

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geese, which are the natural hosts of avian flu. “Everybody is scratching their heads trying to come up with a reason” why this outbreak appears more difficult to control than others, according to Dr. Beyer.

“It doesn’t seem to be dying down, and I don’t know why that is,” he admitted.

Wild birds spread the virus through saliva, nasal secretions and feces, so when infected ducks or geese, for instance, stop at a pond or on a lawn, their droppings can spread the virus to domestic birds and some other animals.

The important thing to remember, Dr. Beyer said, is the virus starts in wild birds. It is not starting on farms or in backyard poultry. It starts with wild animals. It’s random, and just “dumb luck” for the most part when a flock is contaminated.

“Practice great biosecurity,” he said. “Make sure facilities are clean, your feet are clean [so you don’t carry the virus into the facility], and you don’t contaminate your flock,” Dr. Beyer said.

“But often it feels like you just have to cross your fingers and hope they [wild birds] don’t fly over your facilities.” ■

*The sources reported no relevant financial disclosures.*

## RSV Update

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the mRNA vaccine is anchored to the cell membrane. It has a transmembrane region. So, it’s displayed on the surface of a cell, just like it would be in the context of a viral infection. The protein vaccines introduce soluble protein into the body that can be recognized by the immune system, but it’s never attached to a cell like it will be in the context of a virus,” said Christy Shaw, PhD, the vice president, Portfolio Head of Respiratory Vaccines, at Moderna.

Dr. Shaw also noted that there is an ongoing phase 1 trial for mRNA-1345 in children, as well as development of mRNA-1230 vaccine (a triple-combination vaccine against RSV, seasonal influenza and COVID-19) and mRNA-1365 against RSV and human metapneumovirus.

Pfizer, along with developing vaccines for older adults for RSV, is looking at developing maternal vaccines.

Its phase 3 clinical MATISSE (Maternal Immunization Study for Safety and Efficacy) trial is investigating a bivalent RSV prefusion vaccine candidate, administered to pregnant participants to help protect their infants from RSV disease after birth. MATISSE “met the success criterion for one of two primary end points. The observed efficacy for severe medically attended lower respiratory tract illness (severe MA-LRTI) was 81.8% (CI: 40.6%, 96.3%) through the first 90 days of life. Substantial efficacy of 69.4% (CI: 44.3%, 84.1%) was demonstrated for infants over the six-month follow-up period,” Pfizer said in a statement (<https://bit.ly/3gDq6ud-IDSE>).

“The use of the RSV monoclonal antibody palivizumab [Synagis, Sobi] lends credence to the idea that maternal vaccines would be safe in infants. Palivizumab has proven successful at protecting high-risk very young infants from RSV infection and not been associated with any adverse events. It’s very

costly, though,” Dr. Anderson said.

The cost of palivizumab is not the only factor that limits its current usefulness. Treatment with the drug is not recommended for adult prophylaxis against RSV, further highlighting the need for a safe and effective RSV vaccine.

“The future of monoclonal antibodies is modifying the current treatments so that their epitope, where the monoclonal antibody is binding to the protein, takes longer to clear. This will mean a higher neutralizing effect that lasts longer. Its efficacy should cover RSV season,” Dr. Anderson said. “But in the end, cost concerns are an issue with monoclonal antibodies, and developing a successful vaccine is likely to be able to help more people worldwide.” ■

*Dr. Anderson reported that he is under contract with Pfizer for serological testing studies of RSV infection of adults and transfer of maternal antibodies to infants, and has received consulting fees from Janssen’s scientific advisory board. The other sources reported no relevant financial disclosures other than their employment.*



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