Q&A: Will H5N1 avian influenza evolve to become more dangerous to humans?

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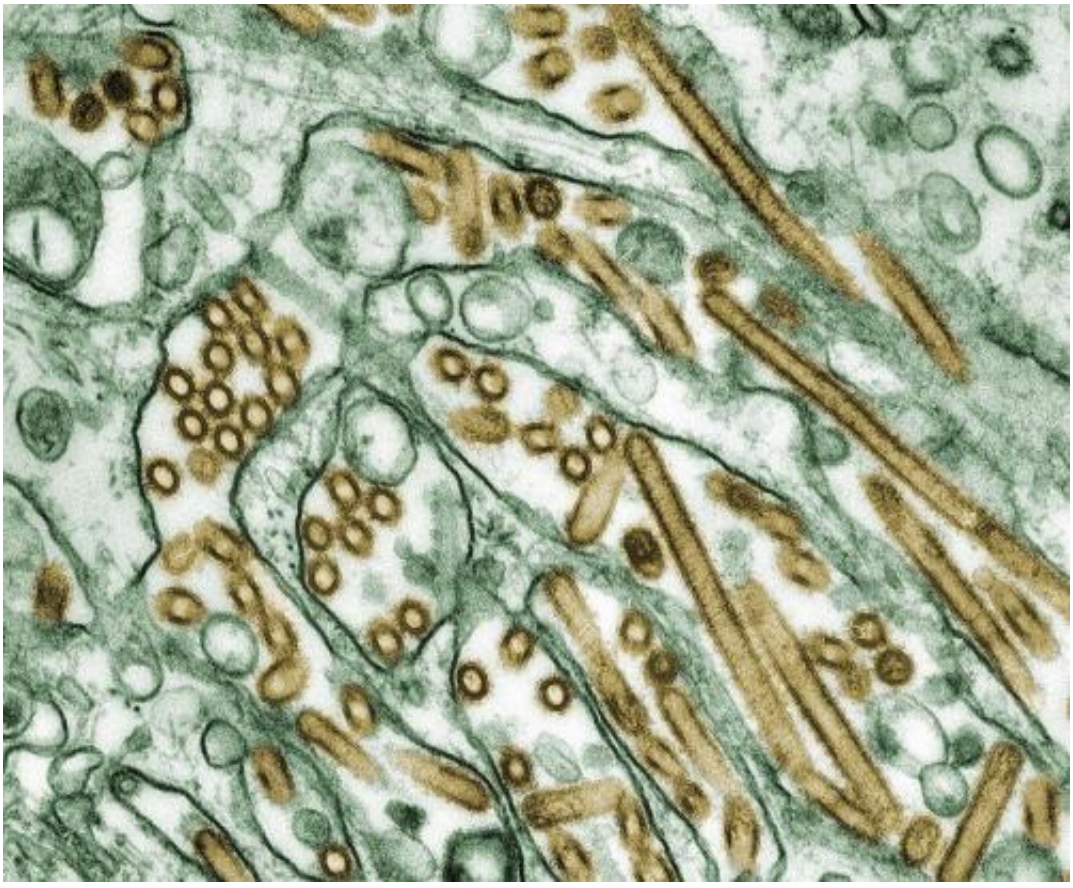

Colorized transmission electron micrograph of Avian influenza A H5N1 viruses. Credit: Public Domain

H5N1 highly pathogenic avian influenza (HPAI) was first detected in dairy cattle in Texas on March 25 and has since spread to several

additional states. The Centers for Disease Control and Prevention (CDC) has confirmed multiple human infections in which the individuals were exposed to infected dairy cattle. The third case, detected in May, was a farm worker who was the only individual so far to exhibit respiratory symptoms. Although the virus has been detected in the commercial milk supply, pasteurization successfully kills the virus, and the CDC said the current risk to the general public from bird flu viruses to be low.

Penn State News spoke with Ruth Nissly, assistant research professor of veterinary and biomedical sciences, to learn more about how scientists are monitoring the H5N1 virus.

Q: How is the H5N1 avian influenza virus related to other influenza viruses?

Nissly: H5N1 avian influenza is a subtype of the influenza A viruses, which also include human influenza virus in people, canine influenza virus in dogs, swine influenza virus in pigs, avian influenza virus in birds and many more. Influenza viruses that are adapted to specific animals have a harder time infecting other animal species than they do infecting another member of the same animal species. For example, while it is possible for a sick human to pass influenza virus to their pet cat, it is more likely that it would spread to their human household members or coworkers. These "types" of influenza virus are somewhat like different breeds of dog—they are all distantly related to one another, but each has distinguishing features in their genomes.

In addition to each organism-specific influenza type, there are multiple combinations of the proteins that are on the outer surface of the virus, which are abbreviated HA and NA, or just H and N. Avian influenza has many combinations of Hs and Ns, most of which only cause mild disease in certain birds. Some of the Hs contain a protein feature that causes

viral infection of birds to be more severe; these are the highly pathogenic viruses.

The H5N1 avian influenza virus responsible for causing disease in dairy cattle earlier this year is the same virus that has been circulating in wild waterfowl, such as ducks and geese, in North America since late 2021. The virus entered North America after having been in migrating birds in Europe for many years before that. Once in North America, the European H5N1 started mixing with low pathogenicity avian influenza viruses that existed naturally in North American birds. This means it has a lot of chances to acquire versions of other viral genes that can impact its ability to infect non-avian species. This has resulted in some H5N1 viruses that infect non-avian species, including foxes and skunks, and can cause severe disease in these mammals. The H5N1 version detected in dairy cows was also found in birds, cats, mice and other wild animals near the dairy farms.

Q: Are there other influenza strains out there that could be dangerous to humans?

Nissly: While it's easy to be concerned about H5N1 HPAI, the seasonal flu strains that people tend to get in the winter months also are dangerous. The CDC estimates an average of over 30,000 people die from seasonal flu, and 10 times more have serious infections that lead to hospitalization.

Q: What are scientists looking for that might indicate that H5N1 is becoming more dangerous to humans?

Nissly: In general, scientists are looking at genome sequences of the viruses that have been found, seeking specific changes in certain viral proteins that are known from years of study to alter the ability of virus to

bind to or enter cells. Fortunately, the U.S. Department of Agriculture (USDA) and other agencies have done a lot of work over the past several years to make it easier and faster to sequence genomes, so a broader range of scientists can explore the impacts of the changes on the virus's ability to infect hosts and replicate.

Q: If the virus does evolve the ability to transmit in humans, who would be most at risk?

Nissly: The people who are most likely to be at risk include those who are unvaccinated against seasonal influenza; those with underlying medical conditions that increase their susceptibility to respiratory infections; and certainly anyone working in close contact with affected animals or individuals and who are not using personal protective equipment like face shields, safety glasses and gloves.

Q: What factors could prevent H5N1 from causing a pandemic?

Nissly: In general, the less a virus is able to multiply in a population, the less likely it will mutate and become better able to infect. For the cow situation, there are state-level and federal-level coordination efforts to set up bulk tank milk monitoring programs that allow farmers to more easily move cows without additional testing and presumably enable early detection of infection in a herd. That's a win-win for the farmers, in my opinion, because it is a huge cost if the animals get sick, including needing to divert many workers to palliative care of the unwell animals. If an infection can be caught early before clinical signs are present, it's more likely to be controllable and not spread throughout the whole herd.

Pennsylvania has its own monitoring program in place, too. If Pennsylvania farmers are interested in participating in this, they can call

717-307-3259 and/or email RA-ahds@pa.gov. They can also just complete the interest form and email it directly to RA-ahds@pa.gov. Similar programs happen in the poultry industry, helping to reduce the overall risk to not only animals but humans, as well.

Q: What research is being done on H5N1?

Nissly: Here at Penn State, several research efforts are underway. Though not H5N1-specific, the Penn State wastewater testing team has been monitoring levels of flu since 2021. My lab is monitoring milk sold in Pennsylvania stores for the presence of viral genetic material and antibodies. Antibodies can indicate that at some time in the past cows were exposed to the virus. We are also conducting infection studies on in vitro models that simulate the respiratory tracts of cattle and the cells from cow udders that produce milk. By studying the existing H5N1 and other strains of flu using these models, we aim to determine whether the newer strains like H5N1 have a different impact in cows than the other strains—and if they do, what it is about those strains that makes them more harmful.

Outside of Penn State, researchers are also examining how well H5N1 remains infectious on different surfaces that are unique to the dairy industry, such as the automatic milking equipment, and how effective heat treatment—which is similar to pasteurization—of milk is at rendering virus noninfectious. Some groups are performing controlled, experimental infections of cows to get a detailed look at what happens. These types of studies complement recently released studies that show which tissues and cell types in the affected cows at impacted farms had virus in them.

Q: Are scientists continuing to monitor wild animals for the virus?

Nissly: The USDA continues to monitor animals around the affected farms. Recently they reported that, in addition to cats, house mice at farms tested positive for avian influenza. These types of investigations at infected premises have historically been extremely challenging from a regulatory standpoint because it required getting federal permission to move material away from the farm. The federal government's pause on select agent [biological agents that have the potential to pose a severe threat to public health and safety] status of HPAI makes such investigations possible—which will go a long way in helping to answer long-standing questions about how the virus gets onto farms in the first place. Even before the outbreak in cows, my lab was planning studies to understand the potential for wild mice to carry avian influenza viruses—those are scheduled to start in late August. We had planned to test mice at non-infected farms, but now we should have the option to pursue testing at infected farms, too.

Others at Penn State are also investigating wild animals. Kurt Vandegrift is working with the USDA to see how he can make use of samples from SARS-CoV-2 surveillance to understand HPAI exposure in wild animals. Justin Brown recently published a study about antibodies in canines, including hunting dogs who retrieve ducks or other birds that might have HPAI.

Provided by Pennsylvania State University

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