

Scientists call for urgent action on the threat posed by H5N1 bird flu

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Recent testimony by Dr. Robert Califf, Food and Drug Administration (FDA) commissioner, on the spillover of the current strain of the avian influenza virus into US dairy cattle, brings to the fore the wider threat posed by the Highly Pathogenic Avian Influenza H5N1 virus (popularly known as bird flu). Califf appeared May 8 before the Senate Appropriations Committee.

Currently, 42 herds across nine states have been impacted. The states include Texas, where the virus was first detected in cows, as well as Colorado, Idaho, Kansas, Michigan, New Mexico, North Carolina, Ohio and South Dakota. H5N1 genetic material has been found in one out of five test samples of commercial milk sold in the US. At least one person has been infected, which is believed to be the first recorded mammal to human transmission of H5N1.

Califf began his remarks to the Senate panel cautiously by asserting the threat posed by the virus to humans remains low (but higher for animal handlers) and assured senators that milk products are safe for consumption. But he warned, “[We] got to have testing, got to have antivirals, and we need to have a vaccine ready to go. So, we’ve been busy getting prepared for *if* the virus does mutate in a way that jumps into humans on a larger level.” The FDA commissioner specifically noted the potential public health threat posed should the virus become “transmissible through [our] airways, which would be really bad.”

Given the low level of immunity against H5N1 viruses in the human population and the notable disease severity among people infected with H5N1, the remarks by Dr. Califf to senators are chilling. The lethality of COVID, which has killed close to 30 million people, is far lower than that observed with H5N1.

The FDA commissioner then declared, “If we institute the countermeasures now and reduce the spread of the virus now, then we’re much less likely to see a mutation that jumps to humans for which we’re ill-prepared.”

This statement belies the critical fact that the real state of the H5N1 infection among dairy cattle and agricultural livestock remains largely unknown, while the government’s dismantling of the public health infrastructure in response to the COVID pandemic has left the country and the international community less prepared to address future pathogens with pandemic potential.

Addressing this inaction and failure on the part of government and health authorities, virologist Marion Koopmans of the Erasmus Medical Center told *Science*, “The reason why this is not a big human health problem is because the virus is not that transmissible. It’s not because of our actions in response to this new situation.”

Echoing these sentiments, Michael Worobey, an evolutionary biologist at the University of Arizona and lead author of critical studies of the origins of SARS-CoV-2, establishing that it is a zoonotic spillover from the wildlife trade, agreed. “If we’re going to be serious in the US and as a global community about trying to prevent pandemics that we can prevent, then this is not the way to do it,” he told *Science*.

Using molecular techniques for assessing the most recent common ancestor of the HPAI H5N1 clade 2.3.4.4b genotype B3.13 that were obtained from infected cattle, Worobey and colleagues estimated there was a single jump from birds into cattle in Texas in December of 2023, at least four months before the USDA and Centers for Disease Control and Prevention (CDC) first reported the presence of the virus among dairy cows.

These dates were corroborated by observations made in late January 2024 by production veterinarians on dairy cattle displaying unexplained (at the time) reduction in their milk supplies, thickening in the quality of the milk, and decreased feed intake. The members of the National Animal Health Laboratory Network conducted preliminary work sampling milk and nasal passages of the affected animals, identifying influenza A. The samples were then forwarded to the National Veterinary Services Laboratory, which confirmed the presence of the H5N1 virus among the cows.

In conjunction with these observations, recent wastewater data analysis conducted by the WastewaterSCAN network, an affiliation between scientists from Stanford, Emory University and Verily Life Sciences, found traces of the bird flu as early as February 25, 2024, a month before confirmatory tests were done on the sickened animals. This underscores the importance of wastewater as a sentinel warning in the public health domain.

Significantly, in regions where there were high rates of H5N1 infection among cattle, there was a corresponding high concentration of influenza A genetic material in wastewater. Near one treatment facility in Texas, an area with confirmed cases of bird flu in dairy cows, the levels of influenza A material in the wastewater were the highest ever recorded.

The authors concluded, “Our findings demonstrate wastewater monitoring can detect animal-associated influenza contributions and highlight the need to consider industrial and agricultural inputs into wastewater. This work illustrates the value of wastewater monitoring for comprehensive influenza surveillance for diseases with zoonotic potential across human and animal populations.”

However, Dr. Marc Johnson, a virologist at the University of Missouri, who with colleagues developed tests that can specifically track H5N1 in wastewater samples more than a year ago, speaking with Reuters, said that in discussions with the CDC, the agency discouraged the use of such work.

CDC wastewater team lead Amy Kirby told him that although tests on wastewater could identify H5N1 subtypes of influenza A, they do not indicate the source of the virus and therefore could be a drain on resources, although it is the most economical tool available to conduct such sleuth work. The baffled Johnson responded, “I’m not worried about the cows. I’m not worried about the milk. But I’m worried that there are lots of other animals that it can jump to, and eventually it’s going to find a combination that can make it into humans if we’re not careful.”

Denis Nash, distinguished professor of epidemiology and executive

director of City University of New York's Institute for Implementation Science in Population Health, spoke with the *Los Angeles Times* on the CDC's reluctance to deploy wastewater techniques to track H5N1. She said, "It has been consistently demonstrated that wastewater surveillance only enhances traditional surveillance, and often outperforms it when it comes to early/timely outbreak or surge detection. In this case, since traditional surveillance is not systematically occurring, and wastewater surveillance is relatively low-cost and easy to implement, it makes a lot of sense to me to go ahead and deploy it strategically."

Indeed, wastewater testing, if implemented at agricultural outlets, hospitals and community-based facilities, could not only locate where such viral genetic material is being shed into wastewater, it could also track viral evolution in real-time, which is urgently required. Clearly the CDC's reluctance has more to do with the political climate rather than any ambiguity and confusion the deployment of such measures would create. As Johnson said succinctly, "I always think the more information we have, the better."

Perhaps one of the most significant contributions made to understanding the recent spillover of the bird flu into bovines was an international collaboration led by Worobey and colleagues that include Kristian Andersen of the Scripps Institute, a colleague on the SARS-CoV-2 Origin paper, Thomas Peacock from Pirbright Institute at Imperial College London, Angela Rasmussen from University of Saskatchewan and Andrew Rambaut of the Institute of Ecology and Evolution at University of Edinburgh.

Many of these principled scientists were instrumental in providing important truths behind the origins of the COVID pandemic, in opposition to the US government's continuing attempt to use the lab-leak lie as a political and ideological weapon against China.

In a paper published in two parts (Part 1 and Part 2) on the website virological.org, the authors first provide recent historical context for the H5N1 pandemic, underscoring that the *reassortant* genotypes of the virus (produced by mixing segments of RNA from different species to produce a new form) have shown an extraordinary propensity to infect mammals. There is some evidence for sustained mammal-to-mammal transmission, especially outbreaks at mink farms and among sea lions and fur seals in South America.

However, dairy cattle were thought to be resistant to infections with influenza A viruses, which had perplexed scientists. In their analysis of the genomic datasets (See methods section of the paper), the paper concluded:

1. A reassortment event within North American avian H5N1 2.3.4.4b viruses occurred shortly before the start of the cattle outbreak.
2. The cattle outbreak likely had a single origin from the avian H5N1 reservoir.
3. The H5N1 outbreak in cattle likely went undetected and unidentified for an extended period and is now several months old.
4. The cattle outbreak may have originated in Texas.
5. Multiple putatively adaptive substitutions have arisen in the cattle H5N1 clade [strain] ...
6. The original cattle H5N1 virus's hemagglutinin (HA)—a protein that must bind to the host's surface sialic acid residues for the virus to gain entry—was not adapted to a human-like receptor. [See explanation below]
7. H5N1 is transmitting from cattle back into wild birds, poultry, cats, and other species.
8. A virus closely related to, but distinct from, those sampled from cattle was sampled from an individual who was reportedly a

dairy farm worker.

9. Mutational signatures support sustained transmission within cattle.

In their final remarks the scientists warned it was imperative that a "comprehensive genomic and serological surveillance strategy" for this and future outbreaks be established. This would include transparency and timely sharing of data. "Such integrated data," they added, "would help the scientific and animal/public health community best understand the dynamics of these viruses among hosts, and through time and space, and may thereby lead to timely interventions to mitigate its spread, not just among cattle and cattle operations but also more broadly."

Another important paper, a microbiology study of bovine tissue, released in preprint form, attempted to understand why the milk from an infected cow had such high concentrations of virus. In surveying the cow's anatomy, researchers in Denmark made a striking discovery that the mammary glands of dairy cows possessed sialic acid surface receptors like those in humans and ducks.

The influenza A virus (IAV) is an RNA virus. There are two proteins on the surface of the viral particle. HA allows the virus to bind to sialic acid and enter the cell. Sialic acids are widely distributed in animal tissues and are part of glycoproteins and are often important membrane proteins that regulate the cells' functions. A virus's sialic acid receptor type determines the tissue the virus can infect. When different animals have similar surface receptors that a virus can latch on to, it means that it is able to jump into multiple different species.

As described by the authors of a 2021 study published in the journal *Viruses*, "An in-depth understanding of the mechanisms of viral emergence and zoonotic spillover is still lacking. Receptors are major determinants of host susceptibility to viruses. Animal species sharing host cell receptors that support the binding of multiple viruses can play a key role in virus spillover and the emergence of novel viruses and their variants. Sialic acids (SAs), which are linked to glycoproteins and gangliosides serve as receptors for several human and animal viruses. In particular, influenza and coronaviruses, which represent two of the most important zoonotic threats, use SAs as cellular entry receptors."

With regard to infected dairy cattle, the location of their infection is in the alveoli of the upper part of the mammary glands that are located above the udder. Large concentrations of viral material are then shed into the raw milk produced by the infected cows. These specific human and duck receptors were not found in the cow's brains and were only located deep in the respiratory tracts. What the study cannot answer is how the infection got to the mammary glands and how the sustained transmission between animals is taking place.

They wrote:

The transmission route(s) and the pathogenesis of H5N1 in cows remain unclear, and it's not known if the virus enters the mammary gland by an ascending infection or systemically by the blood supply. Interestingly, neither the human-, chicken-, nor the duck receptors were expressed in the ducts of the mammary gland, making an ascending mammary gland infection more challenging. It is not clear to which degree the HPAIV-infected cows develop viremia, however, even a very low degree of viremia may be adequate for the virus to enter the mammary gland and establish infection because the blood flow in the lactation period is around 400 liter per hour.

Perhaps the most concerning conclusions they made were as follows:

The co-expression of both human and avian receptors in the mammary glands indicate susceptibility for viruses of both swine/human and avian origin. This is worrying from a zoonotic perspective, because bovines may act as a mixing vessel for new Influenza A Viruses (IAV) with increased zoonotic potential. Additional research is very much needed to better understand the pathogenesis and epidemiology of IAV infections of cattle and other ruminants to elucidate if these species can act as a mixing vessel for new IAVs.

The implication here is that if the disease becomes endemic in these animals, their proximity to farm workers who do not routinely follow infection control practices nor use personnel protective equipment poses a considerable risk for the virus's evolutionary development into new forms that could directly infect humans or even develop the capacity for airborne human-to-human transmission, as the SARS-CoV-2 virus did.

This would represent a real existential threat for which no government in its present form is prepared to respond. The urgency for action which serious scientists advocate and the dire conclusions they are reaching require an immediate response to avert the potential of a another global calamity.



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