

Written brief for House of Commons

My name is Dr. Angela L. Rasmussen and I am a Principal Research Scientist (Scientist III—equivalent in academic rank to Associate Professor) at the Vaccine and Infectious Disease Organization (VIDO) at the University of Saskatchewan in Saskatoon. I also hold Adjunct Professorships in the Department of Biochemistry, Microbiology, and Immunology at the University of Saskatchewan in Saskatoon, and the Department of Ecology and Evolution at Stony Brook University in Stony Brook, New York. I have a bachelor of arts (2000) degree in biological sciences from Smith College in Northampton, Massachusetts and a master of arts (2005), a master of philosophy (2006), and a doctor of philosophy (2009) from the department of Microbiology and Immunology at Columbia University in New York, New York. I completed a postdoctoral fellowship at the University of Washington in Seattle in 2012 and previously held Assistant Professor-level faculty positions at the University of Washington and the Columbia Mailman School of Public Health prior to joining VIDO in 2021. I am a US citizen and a permanent resident of Canada and I have conducted virology research in both countries for nearly 20 years.

Viruses like H5N1 influenza A virus are obligate parasites, thus infecting compatible hosts is essential for viruses to replicate and cause disease. These virus-host interactions determine whether or not a virus can infect, replicate, or cause disease in a given species or individual. My expertise is in understanding how viral pathogens emerge from their natural reservoirs to “spill over” into new species and the role of the host in determining susceptibility and disease severity. My laboratory applies diverse experimental approaches and modern computational analysis methods to study interactions between different host species (including both cattle and humans) and a broad range of emerging viruses, including Ebola virus, dengue virus, MERS-CoV, SARS-CoV-2 (the virus that causes COVID-19), and highly pathogenic influenza viruses, including the 1918 pandemic virus and avian viruses such as H5N1 and H7N9. For the last month, I have worked closely with colleagues in Canada, the US, and abroad to investigate the origins, spread, and scope of the US H5N1 cattle outbreak, including work to assess whether this has impacted Canadian dairy or beef cattle.

Scientific Background

The current H5N1 panzootic, or pandemic occurring in non-human animals, has been ongoing since 2021. The H5N1 2.3.3.4.b clade viruses that are causing the current outbreak in cattle was introduced to Atlantic Canada by wild migratory birds in 2021 and rapidly spread through birds throughout the nation. In addition, other mammalian species, including pets such as dogs and cats, livestock such as goats and pigs, marine mammals such as seals, and wild animals such as red foxes, raccoons, and skunks, in Canada and abroad. in the US in 2022. The panzootic has had devastating consequences for some bird species, as well as a profoundly negative economic impact on poultry production and food security, with millions of birds dying from infection or being culled. However, animal losses and health have not been limited to avian species; multiple species of mammals have become infected with H5N1, including seals, sea lions, cats, dogs, foxes, skunks, mink,

and raccoon dogs. In addition to sporadic infections caused by exposure to infected wild birds or bird carcasses, several large “die-offs” have occurred, as well as spread through fur farms.

H5N1 presents a major risk to humans, as well. Since 2021, there have been 26 human cases reported to WHO (four occurring in the Americas), of which 7 were fatal. Since 2003, there have been 887 human cases, resulting in 462 deaths. Historically, H5N1 has not been efficiently transmitted from human to human. This is thought to be due in part to the virus being better adapted to transmit between and infect avian hosts than mammalian hosts. However, the current panzootic has been characterized by increasing frequencies of outbreaks in mammals where mammal-to-mammal transmission has occurred. This is a significant concern, as with sufficient opportunity to adapt to mammalian hosts, variants may emerge that are capable of efficient human-to-human transmission. The risk of human infections and the emergence of human-adapted variants increases with increased transmission between mammals that are numerous and have frequent contact with humans, such as cows.

Routes of transmission for different susceptible species include inhalation of infectious aerosols, oral exposure or consumption of infected carcasses, as well as direct and indirect contact with infectious virus. Influenza viruses are capable of rapid adaptation when under high evolutionary pressure (such as when adapting to a new host) through two mechanisms: mutation (“genetic drift”) and reassortment (“genetic shift”). Mutation is a more gradual evolutionary process that occurs every time the virus replicates. Mutation results from “mistakes” that occur when the viral genome is copied during replication. Mutations that confer an advantage to the virus in a given host will undergo positive evolutionary selection and will be retained. The US cattle viruses have acquired numerous mutations associated with adaptation to a mammalian host. Reassortment occurs during a co-infection with two different viruses and the different genome segments from these viruses are shuffled together randomly, resulting in new emerging viral progeny. Reassortment can result in rapid, drastic evolutionary shifts and has been a driver of every influenza pandemic in recorded history. The US cattle viruses are themselves reassortants, combining genes from low pathogenicity North American avian H5N1 viruses and the high pathogenicity Eurasian avian H5N1 virus. Further spread in mammalian hosts or in a variety of mammalian and avian hosts increases mutation and creates opportunities for reassortment, increasing the likelihood that novel variants with unknown pathogenicity and transmissibility will emerge that are adapted to both.

H5N1 presents two major categories of risk to Canadian agriculture and public health.

1. Agricultural, ecological, and environmental risk
 - a. Introduction into additional susceptible species, including livestock, poultry, companion animals, or wildlife with frequent human contact
 - b. Widespread infection of domestic or companion animals may result in the emergence of new variants or reassortants with unknown virulence or transmission potential

- c. H5N1 causes severe disease in many species including cats, dogs, birds, and marine mammals and is a substantial risk to food security, the economy, ecosystems, and human and animal health
2. Pandemic/epidemic risk
 - a. Adaptation to new mammalian species or repeated infections across multiple species could lead to the emergence of variants that are capable of efficient human-to-human transmission
 - b. Infection of cattle and other species that are both numerous and have frequent contact with humans provides the virus with more opportunities to adapt to humans

Current Situation in the US

The extent of the outbreak is currently at 54 herds affected in 9 states, although the full scale of the outbreak is presently unknown. Phylogenetic analysis shows that the virus has spread among dairy cattle for three to four months prior to being detected. Data from both the USDA and an independent group of international scientists has determined that the outbreak began via a single introduction into cattle (likely in Texas) in late 2023 based on currently available sequence data, although large gaps exist in the available sequences to analyze. The estimate of a single introduction and the timing of emergence may change as new sequence data and associated metadata become available.

Undetected Spread. The initial introduction was not detected, as cattle were not thought to be very susceptible to infection and did not shed large amounts of virus in experimental studies. H5N1 infection does not appear to cause severe disease in many cows and was identified only after there were observable losses in milk production by infected herds, as well as multiple reports of infected animals and thick, discoloured milk that failed to meet quality standards for processing and retail sale. Because the initial infections were not detected, spread occurred undetected for several months, allowing infected cattle to be transported to other states and resulting in additional infected herds. The number of infected herds in the US is currently unknown due to gaps in testing and reporting, which is sporadic and varies by state and county. There is also evidence that the virus has “spilled back” from cattle to birds and other species, based on sequences obtained from birds, cats, and raccoons found dead on site at affected farms.

There is evidence that some cows are infected asymptotically, which further complicates efforts to define the scale of the outbreak. The FDA and independent academic researchers have identified widespread regional positivity in US commercial milk. This suggests that infected cows are shedding virus with no effect on milk quality or evidence of disease in the animals, since clearly milk from infected cows is meeting quality standards for retail sales. In addition, USDA identified a positive lung sample from a culled cow that had no observable clinical signs of disease.

One human case in the US has been linked to transmission from cattle in a dairy worker in Texas who reported extensive contact with cattle and no contact with birds or other

species. No sequence data was collected from cattle on the farm where the patient worked. The virus sequenced from the human case contained additional mutations associated with mammalian adaptation and it remains unclear if those mutations were acquired in cattle from the farm where the patient worked. This human case presented atypically and was associated with conjunctivitis. Notably, the patient did not have pneumonia or respiratory symptoms, in contrast to poultry-associated cases, possibly indicating a different transmission route.

Delayed availability of data associated with US cases has slowed the ability of stakeholders in the US and abroad to assess the situation and respond rapidly. A lack of available centralized testing data makes it challenging to ascertain what herds have been tested, running the risk of duplicating some efforts as well as failing to identify infected herds. Sequences released without associated metadata such as date and specific sampling location have complicated efforts to understand the evolutionary history of H5N1's emergence into cattle, the current scale and scope of the outbreak, and its trajectory in the future. Epidemic containment depends on rapid identification of infected herds and individuals, thus, delays in data availability have resulted in the inability to contain the virus.

Food Safety. Evidence so far suggests that the virus is heat inactivated similar to other influenza A viruses. Although retail milk contains genetic evidence of infected cows, all tests conducted to date do not demonstrate the presence of infectious virus in retail milk. Ground beef to date shows no evidence of virus at all. Both milk pasteurization and cooking beef to temperatures of at least 140° F (medium) inactivates the virus, although tests are ongoing. Cooking beef to lower temperatures results in several orders of magnitude reductions in virus titer, although it does not inactivate the virus completely. Currently there is no evidence that shows that retail dairy products are unsafe provided they undergo pasteurization, although the risk associated with consuming “raw milk” or other unpasteurized dairy products is unknown. Multiple animal species, including cats, dogs, foxes, and skunks, are suspected to have been infected by chewing on or consuming dead birds. As infection by ingestion is a possible transmission route, it is strongly inadvisable to consume unpasteurized milk or undercooked beef. However, as the virus is inactivated by heat treatment, pasteurized dairy products and properly cooked beef are considered safe to consume.

Current Situation in Canada

To date, no cows or milk products in Canada have tested positive for H5N1. However, Canadian cattle remain at risk of having currently infected herds of beef or dairy cattle or infection in the future, due to incomplete surveillance and the nature of influenza A cross-species transmission.

There are two potential routes of introduction for H5N1 into Canadian dairy or beef cattle.

1. Imported cows from the US.
2. Independent introduction from birds or other susceptible species.

Cattle importation. Canada is the second largest importer of cattle from the US (after Mexico). Although new USDA requirements for testing prior to transportation and CFIA regulations imposed in April 2024 should greatly reduce the risk of importing infected animals, cows with undetected infections may have been transported between December 2023 and April 2024. Records of cattle imported from the US between December 2023 and April 2024 may provide a mechanism for directing surveillance efforts most effectively via USDA export documentation disclosing state of origin. Testing could be targeted to animals imported from states with known infected herds, and the animals could be located based on traceability/tag data from CFIA and the Canadian Cattle Identification Agency.

Spillover from avian reservoir. Canada is central to numerous North American “flyways”, or routes taken by migratory birds, which is how H5N1 was initially introduced to Canada in 2021. Because the outbreak in the US began with a single cross-species spillover from an avian host to cattle, there is a strong possibility that this could occur in Canada independent from the outbreak in the US. A separate, independent cross-species transmission event from birds to cows could have occurred in the past and could occur again in the future. A past or future independent introduction in Canadian dairy or beef cattle from birds remains a concern and ongoing surveillance (including of asymptomatic animals) is critical for rapid containment.

Critical unknowns

Many unknowns remain and addressing these knowledge gaps is essential to safeguard the health of Canadian cattle and wildlife, as well as take appropriate measures for prevention. Both the extent of the outbreak and of testing activities so far in the US needs to be ascertained to determine the scale and scope of the outbreak and ensure that Canada is currently free of H5N1 in cattle. The route of transmission between cows is also unknown, although hypotheses regarding ingestion of contaminated feed or water, inadequately disinfected milking equipment, conjunctival exposure, and aerosol inhalation have been proposed and are currently being tested. The extent of viral shedding in cattle, including the amount of virus shed and by what tissues or cell types, is also unknown, but is important to understand to put effective containment measures and worker protections in place. Although there is no evidence of infection in beef cattle, this population needs to undergo thorough surveillance, particularly since observational or indirect measures such as milk production are more difficult to obtain for these animals. In addition, epidemiological and serological studies are needed to assess the number of cows that have been exposed, to better quantify spread and rapidly identify infected herds. The number of dairy workers that have been exposed also should be assessed, to identify humans who are most at risk and rapidly diagnose any human infections. Influenza antiviral drugs are most effective when provided early in infection, and thus time is paramount in minimizing risks to human health. The impact of route of transmission on disease severity in humans and other species will also be essential to implementing effective biosecurity measures to protect dairy workers. A key long-term research objective is better understanding the role of cattle and other mammalian hosts in driving evolution of variants that may be better adapted for

transmission or cause more severe disease. This will be essential for sustained containment and control of the epidemic, as well as for preventing the emergence of variants that might be efficiently transmitted from person-to-person. Finally, H5N1 vaccination needs to be explored as a possible countermeasure, both to protect the cattle population and food supply as well as to protect workers with a high risk of exposure.

Conclusion

Sustained investment in surveillance, research, and producer support is needed to both rule out the possibility of undetected spread in Canadian cattle, fully utilize national response capacity, and mitigate economic harms or risks to the food supply. Delays in data sharing have made it more difficult to maximize response capacity and develop meaningful collaborations between government, veterinarians, academics, and producers and have enhanced public distrust in the US. To prevent H5N1 from having a similar impact in Canada, more collaboration between stakeholders across multiple sectors will leverage full response capacity in a more cohesive manner. I strongly encourage the committee to take preemptive action in this regard to

At VIDO, our National Pandemic Research Centre is contributing to these efforts. We are planning a study to challenge calves with bovine isolates of H5N1 in our large animal containment laboratory to address some of the unknown questions about virus shedding transmission, and disease. We are also planning studies to assess tissue-specific susceptibility to infection in cells and investigate the role of the host in virus replication and pathogenesis. We are also engaged in ongoing surveillance and testing of different animal populations and products in Canada. These efforts are made possible by fruitful collaborations with government and academic partners in Canada, the US, the UK, and Germany. Although currently known to be impacting the US, it's clear that this could have a severe detrimental impact on Canada in the future. These impacts would be broad-ranging, causing great harm to human and animal health as well as the environment, disrupting the food supply, and damaging the economy. For H5N1, the outbreak in the US is a warning that we must be vigilant and work to contain it. If no action is taken, Canada may very well face a similar situation as our neighbours to the south. By working together across sectors and expertise with a common goal of containing the US outbreak, we will be more likely to prevent its further spread to other countries, including our own.

References:

Highly Pathogenic Avian Influenza (HPAI) Detections in Livestock (USDA/APHIS update page) <https://www.aphis.usda.gov/livestock-poultry-disease/avian/avian-influenza/hpai-detections/livestock>

Livestock imported from the United States (Agriculture and Agri-Food Canada's compilation of Statistics Canada import data) <https://agriculture.canada.ca/en/sector/animal-industry/red-meat-and-livestock-market-information/trade/livestock-imported-united-states>

Emergence and interstate spread of highly pathogenic avian influenza A(H5N1) in dairy cattle (USDA preprint) <https://www.biorxiv.org/content/10.1101/2024.05.01.591751v1>

Preliminary report on genomic epidemiology of the 2024 H5N1 influenza A virus outbreak in U.S. cattle (Part 1 of 2) <https://virological.org/t/preliminary-report-on-genomic-epidemiology-of-the-2024-h5n1-influenza-a-virus-outbreak-in-u-s-cattle-part-1-of-2/970>

Preliminary report on genomic epidemiology of the 2024 H5N1 influenza A virus outbreak in U.S. cattle (Part 2 of 2) <https://virological.org/t/preliminary-report-on-genomic-epidemiology-of-the-2024-h5n1-influenza-a-virus-outbreak-in-u-s-cattle-part-2-of-2/971>

Note about availability of H5N1 2.3.4.4b consensus sequences from cattle and other species (access to online resources with sequence data and metadata and analysis tools) <https://virological.org/t/note-about-availability-of-h5n1-2-3-4-4b-consensus-sequences-from-cattle-and-other-species/967>

Highly Pathogenic Avian Influenza A(H5N1) Virus Infection in a Dairy Farm Worker. <https://www.nejm.org/doi/full/10.1056/NEJMc2405371>

Cumulative human cases of H5N1 reported to WHO, February 26, 2024. [https://www.who.int/publications/m/item/cumulative-number-of-confirmed-human-cases-for-avian-influenza-a\(h5n1\)-reported-to-who--2003-2024-26-february-2024](https://www.who.int/publications/m/item/cumulative-number-of-confirmed-human-cases-for-avian-influenza-a(h5n1)-reported-to-who--2003-2024-26-february-2024)

Reported human cases of H5N1 reported to PAHO, May 17, 2024. <https://www.paho.org/en/documents/epidemiological-update-outbreaks-avian-influenza-caused-influenza-ah5n1-region-america>