Pandemic Risk Scenario Analysis Update: Influenza A(H5Nx) clade 2.3.4.4b virus and related future novel viruses

Date of this analysis: June 6, 2024; Version: 2.0
Date of previous pandemic risk scenario analysis: March 31, 2023
Reason for the update: Finding of avian influenza A(H5N1) clade 2.3.4.4b in cattle and goats in the United States (US) and associated sporadic human cases.

Purpose

On May 9, 2024, a multi-sectoral expert engagement exercise was conducted to review the Pandemic Risk Scenario Analysis (PRSA) completed in March 2023, and to gather expert opinion and advice related to pandemic risk. It is important to remember that when discussing scenarios, they describe alternative or possible futures around a specific issue and help anticipate future changes to better inform preparedness and planning activities. In the context of the PRSA, the scenarios were used to make judgements about the relative risk of avian influenza unfolding towards a pandemic scenario over a one-year timeframe. Although the scenarios were not intended for use to monitor our current status, the experts were asked to comment on the current situation pertaining to H5N1 findings in US Cattle.

Method

Participants included 93 experts from multiple federal departments in human, animal and environmental health sectors, provincial ministries of public health and agriculture, and academia[i]. The four potential scenarios were reviewed. The participants were asked a series of questions via a whiteboard exercise to determine: what our current situation looks like now compared to last year; what criteria are essential for suggesting that we are in a situation of sustained mammal-to-mammal transmission; and what the situation may look like a year from now. The input provided was summarized and analyzed by a team within the Centre for Surveillance, Integrated Insights and Risk Assessment (SIIRA), PHAC.

Statement Summary

- Avian influenza A(H5N1) clade 2.3.4.4b remains primarily an avian virus, and there have been very few human cases or signs of virus adaptation to mammals. Transmission to and within cattle is new and unexpected. It also represents a new clinical portrait for mammals. This results in new interfaces to consider for biosecurity, including new potential routes of transmission to humans.

- There was agreement between experts that there is cattle-to-cattle transmission occurring, though the mode and extent of transmission is uncertain. The criteria to suggest that we are in a scenario of “sustained mammal-to-mammal transmission” is complex, and not all experts agree on where to place this line. There was disagreement between experts on whether the current situation could be considered one of ‘sustained’ mammal-to-mammal transmission, which was driven by the high uncertainty and different opinions on the extent that ‘sustained’ transmission requires changes to the virus. Suggestions for essential criteria included: respiratory transmission, ongoing outbreaks without human interventions and in groups with minor contact, or genetic changes to the virus favouring mammalian infection.

- Despite disagreement on where to draw the line between scenarios, there was strong agreement between experts that the situation has worsened from last year with continuous transmission in mammals and across species. This may play an important role in the pandemic trajectory as there is an increased opportunity for genetic changes that favour mammalian adaptation. Although no participating

[i] Public Health Agency of Canada, Health Canada, Canadian Food Inspection Agency, Environment and Climate Change Canada, Indigenous Services Canada, Fisheries and Oceans Canada, Parks Canada, Nova Scotia, New Brunswick, Quebec, Ontario, Manitoba, Alberta, British Columbia, and the University of Toronto.

experts indicated that human-to-human transmission would be expected to occur in the next year, concern was raised over the virus's ability to reassort, especially in pigs because they have been identified as mixing vessels.

Question 1: From your perspective, what has stayed the same and what has changed from last year? How sure are we of this?

What has stayed the same?

- Avian influenza A(H5N1) clade 2.3.4.4b remains primarily an avian virus. There continues to be infection in wild and domestic birds, and sporadic detections in wild mammals. There continue to be very few human cases, and no human-to-human transmission. There is a fair amount of certainty about these statements.
- While new genotypes have emerged with certain mutations, there have been no new 'well-recognized' signs of virus adaptation to mammals.
- Genomic analyses also suggest that antivirals remain effective.
- Many uncertainties remain regarding transmission pathways between and within species.

What has changed from last year?

- There have been fewer detections in wild and domestic birds. Although infection is continuing in birds, the severity may be decreasing due to increased immunity.
- There have been findings in new wild mammal species, and in wild mammals in new geographic regions, though this may be due to increased surveillance rather than major changes in the virus.
- Transmission to cattle was new and unexpected, and it represents a new clinical portrait for mammals (e.g., lack of neurological signs). This results in new interfaces to consider for biosecurity (i.e., between different animal species, and animals and humans, and vice versa), including new potential routes of transmission to humans and other animals (e.g., unpasteurized dairy products).
- The case in a dairy cattle worker in the US may represent the first mammal-to-human transmission, but this is still uncertain.
- There was agreement between experts that there is cattle-to-cattle transmission. The mode of transmission is uncertain, with key factors under review including movement of cattle between herds and contaminated milking equipment, but does not appear to be respiratory. There was disagreement between experts on whether the current situation could be considered one of 'sustained' mammal-to-mammal transmission.
- There was strong agreement that the situation has worsened from last year due to more mammalian infections creating a significant opportunity for viral adaptation to mammals. Cattle might also be a new mixing vessel with opportunities for reassortment with influenza viruses of mammalian origin, though this is uncertain.

Question 2: Given our hypothetical pandemic trajectory (i.e., the scenarios leading to a pandemic of respiratory transmission), what criteria are essential to suggest that we are in a scenario of "sustained mammal-to-mammal transmission"?

- Essential criteria indicated by experts were related to transmission and genetic changes to the virus.
- There was agreement among many experts that respiratory mammal-to-mammal transmission was an essential criterion of this scenario. It was highlighted that determining this would require excluding other routes, such as livestock trade, infected farm equipment, or fomites. However, other experts pointed out that even if there is no respiratory transmission, continuous transmission in mammals may play an important role in the pandemic trajectory as there is an increased opportunity for genetic changes that favour mammalian adaptation.
- A few experts indicated that to see sustained mammal-to-mammal transmission we would need to see transmission occurring at sufficient levels to maintain an outbreak without interventions, or ongoing outbreaks in groups that have relatively minor contact with each other.

- Another important criterion discussed was genetic changes to the virus. If new or combined mutations of mammalian adaptations are seen this could be an indicator of sustained mammal-to-mammal transmission.
- While not an essential criterion, experts highlighted that concern would arise if mortality was seen in animals that live on, and around, infected farms.

Question 3: How do you think the situation will progress over the next year in relation to A(H5N1) clade 2.3.4.4b?

- The most frequently discussed themes by the experts were the possibilities of the pathogen genetically evolving and its emergence in new non-human mammal species. Concern was raised over the virus's ability to rapidly reassort, increasing the risk of quickly and frequently adapting to new mammalian species.
- No experts indicated that human-to-human transmission would be expected to occur in the next year. Limited human cases are expected, particularly in occupational settings, as the virus spreads through wild and domestic animal populations.
- Some experts expect the virus to become more widespread among dairy cattle within the next year due to its mild presentation and potential asymptomatic transmission, while others expect the dairy industry will be able to curb the outbreaks.
- Small outbreaks and sporadic cases among wild birds, poultry, and cattle are expected to continue over the next year while natural immunity among these populations develops.
- There is a greater possibility of transmission for domestic and wild animals migrating on and off farm due to the relative openness of cattle operations versus poultry.
- The animal of most concern as the next major mammalian spillover event was pigs. A strain with higher pandemic potential could emerge through recombination between other influenza A viruses (of which pigs are reservoirs) and avian influenza A(H5N1) clade 2.3.4.4b. However, it was also suggested that fewer cases may occur among pigs due to enhanced on-farm biosecurity measures compared to cattle operations.
- Experts also provided comments on impacts that could unfold from economic, agricultural, and environmental perspectives.

In conclusion (see Figure 1), given recent events, experts are identifying that the situation has worsened from last year with continuous transmission in mammals. This may play an important role in the pandemic trajectory as there is an increased opportunity for genetic changes that favour mammalian adaptation. Given the complexities and evidence gaps on transmission, there was disagreement between experts on whether the current situation could be considered one of 'sustained' mammal-to-mammal transmission.

This aligns with the rapid risk assessment (RRA) update recently posted online, which estimates the risk for the immediate situation and describes future risks.

Scenarios are created to explore possible future environments. Experts' insights on the possible progression or not were helpful to identify additional turning points for response and planning by public health authorities. These scenarios continue to be a framework which can be used to investigate longer term risks, as well as for planning and preparedness activities.

Next Steps

- Continue to follow the recommendations and fill knowledge gaps outlined in the recently completed RRA update.
- Monitor triggers for re-evaluation of public health risk and update the RRA as appropriate.

Figure 1. Illustrating the conclusions.