Highly Pathogenic Avian Influenza Research: A Rapid and Evolving Response

Walter House, May 28, 2024

Summary

On May 28th, 2024, a multidisciplinary, inter-sectoral group of extra- and intra-mural participants convened at Walter House, headquarters of the Royal Society of Canada to collectively discuss the immediate research response to the progressive threat posed by highly pathogenic (HPAI) H5Nx subclade 2.3.4.4b viruses. The inter-continental geographic spread of H5Nx has reached all areas of the globe except for Oceania, and there has also been a substantive and unanticipated alteration of viral ecology in North America. Sustained viral spread between dairy cows through a novel mode of transmission underscored the formidable gaps in our understanding of competent host niches for HPAI. The latency associated with detection of HPAI spread in dairy cows has led to widespread infection among this population, leading to substantive efforts to mitigate further spread. Inter-species spillover to other mammals, including mice, cats and humans, have ensued. Fortunately, there is currently no evidence of HPAI among dairy cows in Canada. We are at an important crossroads in the prevention of HPAI spillover to dairy cows and other species, including humans, in Canadian jurisdictions.

Participants included senior leadership and program leads from the Public Health Agency of Canada (PHAC), the Canadian Food Inspection Agency (CFIA), Environment and Climate Change Canada (ECCC), the Canadian Wildlife Health Cooperative (CWHC), Defense Research DC (DRDC), the Ontario Feather Board, the Office of the ON Chief Medical Officer of Health, the Association of Medical Microbiology and Infectious Diseases (AMMI) Canada, the Office of the Chief Science Advisor of Canada, the Canadian Institutes of Health Research and scientists from 12 academic institutions from 5 provinces.

Meeting objectives

- To consolidate the current state of science, knowledge, and action related to the research response to H5Nx in wildlife and domestic animals, and implications for prevention and preparedness for human health
- To enable multidisciplinary, cross-sectoral efforts to rapidly address research priorities through scientific excellence
- To further integrate a One Health perspective into research planning for an emerging health threat.

Discussion focused around the themes of *Public Health Knowledge Gaps and Research Needs*, specifically H5Nx identification and characterization; methods and tools; and evidence-based interventions.

Meeting key messages

The importance of a One Health approach that integrates all the key aspects of biological, epidemiological and behavioural research across wildlife health, veterinary medicine and human health was made clear. In the near term we should focus on where the virus is active at this time- at the intersection of wildlife, livestock and humans. To do this we need a mechanism for ongoing, cross-sectoral & multidisciplinary research collaboration and coordination through a One Health focal point.

There is a pressing need for integration and harmonization of data with the very clear understanding that the generation of those data requires resources for the people/programs on the ground collecting and processing samples; the importance of these upstream activities cannot be understated, and harmonization in how materials are collected, processed analyzed and rapidly reported to generate meaningful health intelligence requires immediate attention.

Research tools and instruments that could be applied across species are needed for situational awareness and to support decision-making. These include (but are not limited to) molecular diagnostic, genomics (wet and dry lab components), and serological assays and experimental systems (*in vitro, in vivo*), as well as robust research plans of work for the development and advancement of countermeasures, communications, behavioural science and outreach to garner trust across sectors, communities and the public, and inform policy. Existing capacity needs to be leveraged, and additional capabilities advanced and coordinated.

Organizing Committee and support

J. Bowman (Trent University)
F. Maguire (Dalhousie University)
S. Mubareka (University of Toronto)
E. Halajian (University of Toronto; PhD candidate)
Rapporteur Soniya Agarwal (University of Ottawa, courtesy of M. Coté, with thanks)

This meeting was supported by the Royal Society of Canada, the Michael G. Degroote Institute for Infectious Diseases Research (McMaster University), the Emerging and Pandemic Infections Consortium (University of Toronto), the One Health Institute (University of Guelph), and a CIHR-PHAC Applied Public Health Chair (S. Mubareka).

Full Report

Opening of meeting and land acknowledgement, Grandma Karen

Opening Remarks, Dr. S. Viehbeck, Chief Science Advisor (PHAC)

Dr. S. Viebeck underscored the importance greater collaboration and connections across disciplines, and emphasized the need to understand what capacities are in place, where scientific research on H5Nx currently is, where we should go next, and how PHAC can contribute. Collaboration is essential to closing gaps, especially those at One Health interfaces; focus on routine and enhanced surveillance, preparedness, risk at the human-animal interface, and gaps pertinent to different communities. She also underscored the value of scientific excellence to enable timely decision-making.

Panel Discussion: *How do we take the science from here?*
Moderator, Dr. J. Bowman (Trent University & ON Ministry of Natural Resources)

This session aimed to contribute to a shared understanding of the current H5Nx situation and catalyse discussion around how to address research priorities in a rapid and effective manner.

Dr. M. Miller (McMaster University) provided an overview of basic IAV phylogeny, structure and replication. He also provided an overview of influenza antivirals and their mechanisms of action. From a host response perspective, he discussed cross-protection from previous exposure to other influenza viruses earlier in life; antibodies to H1 and H2 confer some degree of cross protection to H5 viral subtype; antibodies to H3 viruses confer some cross-protection to H7 viruses. He emphasized the need to understand viral adaptations, especially in the context of sustained transmission among mammals.

Dr. C. Jardine (University of Guelph & CWHC) described changes in live (active) and sick or dead wildlife surveillance for avian influenza virus (AIV) in Canada including testing in mammals, numbers of cases and range of species. AIV is a multi-species problem and many unknowns around viral ecology, transmission persist despite an interagency surveillance program since 2005. Inconsistent surveillance efforts reflect intermittent funding patterns, particularly for live bird surveillance, noting that dabbling ducks don't succumb to disease and are an important viral reservoir, thus important for surveillance. Migratory bird flyways are overlapping and H5Nx has now been detected in every province and territory. She outlined the well-established chains for diagnostics and reporting, underscoring the value of post-mortem examinations; mammals may be tested for HPAI if encephalitis and other key elements noted on histopathology. There is a clear need to sustain and strengthen all components of wildlife surveillance, including at the wildlife-livestock interface, and where wild mammals have been noted to have severe neurological disease. For this, collaborative, sustained engagement with all stakeholders will be necessary, along with establishing a better understand of domestic animal & wildlife interactions. Targeted surveillance projects for zoonotic risk with integration of different types of wildlife surveillance will be essential.

Dr. F. Maguire (Dalhousie University) outlined how genomics is used retrospectively and can inform response, but could be applied prospectively to identify indicators of outbreaks and adaptation, particularly if linkages between laboratory-confirmed cases and genomic data can be done in as close to real-time as possible. Genomics analyses provide insights into viral virulence, epidemiology and resistance/escape to medical countermeasures. Individual metadata are vital for epidemiological modeling but are prone to sampling challenges. Genomics allows for inference about unobserved cases and can help fill gaps in the data, as well as identify viral reassortment and spillover events, inferring transmission dynamics. He provided an overview of the B3.13 genotype which emerged from dairy cattle, drawing attention to mutational signatures and (weak) signs of selection. Viral genomics also informs follow-on biological work from mutational signatures and signals of adaptation and selection. Issues around data platforms and sharing across sectors, data

& metadata standardization, and a dearth of well-trained individuals persist and are considerable impediments to an effective response. There is a clear need to establish consistent and standardized data models.

Dr. H. Kloeze (Feather Board of ON) provided an industry perspective and spoke to the need to focus on prevention; response in agriculture to IAV outbreaks has devastating consequences economically and to producers, including their mental health and that of all involved in depopulating activities for poultry. He underscored the example of the 2004 outbreak in BC which incurred heavy direct, indirect and societal costs, totalling an estimated $3.6 billion CAD. Canada exports ~50% of beef and pork production and there is substantial financial and human costs to get through surplus depopulation leading to devastating effect on human operators, particularly where euthanasia of animals is required. There are also close/inter-generational relationships between long-time farmers and their animals as well as their healthcare providers from a veterinary perspective. It is important to incorporate key agricultural concepts and considerations (e.g. food safety, biosecurity, quality assurance) into research. He contextualized this approach as “One Welfare”, which balances the welfare of the environment, animals and humans. This requires inter-disciplinary teams and a trusted community to share data and other information, and integrating scientific tools such as genomics. How can scientific research improve diagnostics in the agricultural setting, and who should be fiscally responsible, considering that currently producers must shoulder the burden? Consider establishing frameworks for integrating expertise, allowing for research coordination and sharing of data between scientific & agricultural fields.

Dr. A. McGeer (Sinai Health, University of Toronto) focused on the importance of supporting activities related to prevention and establishing infrastructure for preparedness. What do we need to investigate and understand transmission of AIV into humans and how do we mitigate outbreaks in high-risk populations in the short term? What do we need to build for long-term? There is a dearth of support and infrastructure for virology, modelling and public health research and dissemination; we currently have very limited opportunities for funding laboratory, computing, and data infrastructure, forming a considerable gap in research and training capacity. What research is ongoing into the management of outbreaks in poultry and mass mortality events in wildlife? Investments in public health pale in comparison to those made in other sectors such as biomanufacturing, despite the clear value of prevention.

Open floor discussion included the following questions and comments.

- The likelihood of reassortment between seasonal influenza and H5N1 viruses leading to a pandemic was discussed; although not fully predictable, it is clear that there has been abundant reassortment of internal genes and ongoing viral evolution in mammals through single point mutations, two different mechanisms by which the virus gains in genomic diversity, introducing opportunities for selection and underscoring the importance of ongoing surveillance and biological risk assessments to understand disease and transmission phenotypes for each new genotype. Attention was drawn to the fact that the pH1N1 (2009) pandemic was caused by a reassortment of viral segments of human, avian and swine origins. There are important knowledge gaps in fundamental virology that merit immediate attention.

- Gaps in knowledge around transmission of virus in/between cattle through novel routes (e.g. fomites, semen or intermediates such as small rodents on farms) were underscored, in addition to understanding the potential spillover and spillback of peri-domestic and other wildlife on and around affected premises
- Early warning and changes in risk level were discussed in principle, though there still appears to be gaps in our understanding of what should justify a re-examination of risk and a dearth of accessible data which may serve as signal.
- H5 vaccines development, manufacturing and availability was discussed; there is no stockpile in Canada but contracts are apparently in place in anticipation. Discussion around human vaccinate for H5 viruses revolved around:
    1. Manufacturing capacity; an estimated minimum of 6 months was mentioned to obtain sufficient doses for the general population. This could be reduced but proactively enabling manufacturing capacity and reducing the number required through strategic approaches based on risk. Also, attention was drawn to pitfalls around egg-based manufacturing and the critical need for alternative manufacturing platforms
    2. Vaccination strategy; considerations discussed included vaccine formulation-single, monovalent vs. multivalent (with seasonal influenza), as well as populations to focus on, specifically those at highest risk of exposure
- There was a fulsome discussion around the collection and distribution of data that can be compared across sectors; genomics and traditional modelling can help to predict viral transmission; there is a significant need data infrastructure & content to infer the parameters of these models
- Biosecurity on farms, specifically regarding contact between wildlife and poultry/livestock, needs to be investigated; there is a need to develop specific metrics and indicators of what we should be examining. The ON case-control study underway (OMAFRA, U Guelph) was discussed, as was an initiative to test feral cats by leveraging the existing rabies testing program, however, syndromic surveillance of companion animals remains a substantial gap in knowledge. Also, reinfections on affected premises was discussed; the modes of transmission/mechanisms are unknown.
- We are at a stage where investment in specific policy frameworks to inform prevention, rather than response would be highly beneficial

• H5Nx Public Health Knowledge Gaps & Research Needs

Remarks by Dr. M. Creatore outlining upcoming CIHR funding opportunity underscoring the One Health approach, with a strong focus on animal and human health, followed by moderated open floor discussions under the following themes:

Identification & Characterization of H5Nx viruses

Moderated by E. Halajian and Dr. S. Sharif

This theme focuses on:

- Biology of influenza A(H5Nx) viruses
    - Virology
    - Genomics and viral adaptation, diversity and evolution
    - Innate and adaptive immunity
- Epidemiology of A(H5Nx)
    - Surveillance and testing
    - Factors relating to exposure, susceptibility and transmission
    - Genomic epidemiology
    - Seroprevalence

Discussion:

1. Questions around surveillance - what needs to be done, what can government do to support this across sectors and species in a more consistent, sustainable manner across Canada? Limited funding has led to significant pauses in surveillance activities for some species/jurisdictions. Also, there does not appear to be any active surveillance for humans in place. Similarly, surveillance in all other mammals is a key element for early warning but is largely overlooked, both in terms of wildlife as well as domestic animals (e.g. swine). There was an active discussion also around surveillance through research projects vs. public health initiatives; currently neither approaches are filling the need and there is a very clear indication that this lack of coordination may lead to both gaps and overlaps.

2. There are many outstanding questions around viral biology, including what is known about receptors for avian influenza in cows, humans, and other species, across tissue types. We do have some understanding of innate immunity of avian species; ducks exhibit a robust interferon response are largely asymptomatic whereas this response is absent in chickens, thus they succumb to severe disease. This level of knowledge is absent for species of wild mammals (e.g. foxes develop necrotizing encephalitis but this has not been observed as much in coyotes). We also don't have a fulsome understanding of the clinical and pathological phenotype of this subclade in humans; clinical series/reports have historically involved other H5 subclades (with high mortalities attributed). Understanding host-virus interaction at the molecular scale remains a critical feature of our fundamental understanding of H5 pathobiology upon which countermeasures and other interventions depend.

3. Gaps in knowledge around inter- and intra-species transmission and barriers to spillover were raised. The potential of transmission through raw milk and fomites in cows raises the possibility of vertical transmission through lactation among marine mammals including seals in Canada, which have experience major mortality events. It is critical to understand the biology that drove spillover to, and among cattle; Was it is a stochastic event or were there particular features of the virus that will tell us how to make more reliable risk assessments? An update on plans for experimental dairy cow infections at VIDO were discussed.

4. Given the evolving ecology of H5Nx viruses, there is also relevance to understanding the ecology and population dynamics of other influenza viruses, including those that are endemic in turkeys and swine, as well as low pathogenicity avian influenza viruses circulating in wild birds, since these are donor viruses to reassorted internal genes of H5 viruses.

5. Genomic epidemiology is a critical tool, and substantial capacity for viral whole genome sequencing (WGS) was established across Canada during the pandemic, however this is not being leveraged for influenza viruses

Methods & Tools

Moderated by Dr. D. Joly and Dr. S. Bolotin

This theme focused on:

- Detection and diagnosis
    - Methods and tools for early case detection
    - Enhanced surveillance tools (aggregate/environmental sampling)
    - Testing modalities new molecular and serological methods
- Modelling
    - Modelling to inform risk scenarios for transmission and interventions
    - Forecast capacity for managing cases

Discussion:

1. Methods to determine pre-exisiting and cross-protective immunity across species merit consideration. There is a need for serodiagnostic assay development and comparative validations and standardization antibody responses across methods, with quality assurance. Conversation have begun on current capacity in Canada (led by CIRN), with sharing of protocols and materials. There is a need for formal validation panels for different species; obtaining positive controls remains challenging. While priming of first exposure to H1 influenza viruses may confer some cross-protection, it is unclear how subsequent exposures affect this and the role of NA, which stands to be highly important, particularly since H5N1 and H5N5 viruses are present in Canada.

2. For surveillance, we have the capability to do wastewater testing in more rural areas, though there are issues around agricultural waste and relationships with land owners need be established; it is a different paradigm relative to urban wastewater sampling. There are also issues around 'siloing' of the data and sensitivities around open access.

3. Around preventative measures such as biosafety, biosecurity and vaccination, methods for communication and engagement need to be developed and implemented early, especially in communities at risk. There is a critical role for behavioural sciences in terms of establishing relationships with the private sector and land owners

4. Operational frameworks including animal use protocols, government permits, landowner permissions etc. must be put in place and coordinated for wildlife surveillance; there are a range of stakeholders in this sector, including wildlife biologists, rehabilitators, hunters, trappers and Indigenous communities.

5. At this time, we cannot build either qualitative (e.g. related to interventions) or quantitative (e.g. related to likelihood of reassortment) models for lack of accessible, well curated data and metadata. Sustained bioinformatic storage, sharing and analysis is not possible in the current funding climate. It is also important to note the gaps in incoming data- e.g. most clinical centres do not continue influenza testing outside of influenza season, so cases of HPAI may be missed unless suspicion is high and they are flagged. Conversely, need a scheme to prioritize WGS during influenza season when there are high numbers of cases.

Evidence-based interventions

Moderated by Dr. M. Miller and Dr. S. Hillier

This theme focused on:

- Pharmaceutical- therapeutics
    - Assess safety, effectiveness and relative advantages/disadvantages for chemoprophylaxis, and treatment; development of novel therapeutics
    - Surveillance and mechanisms to reduce the emergence of resistance
- Pharmaceutical- vaccines
    - Effectiveness and safety of human A(H5Nx) vaccines; implementation/intervention strategies
- Non pharmaceutical interventions
    - PPE, ventilation/air filtration, and cleaning/disinfection
- Behavioural and Social Sciences
    - Describe the behavioural factors influencing human-animal interactions
    - Factors affecting adherence to preventative measures
    - Misconceptions and trust

Discussion:

1. Frameworks must be implemented and communicated early to provide transparency and promote public trust in evidence-based interventions; mechanisms to build long-lasting relationships with the public are required, along with ongoing efforts to build understanding around vaccines, pandemics, and animal health. Short-term, catalyst funding does not lead to the relationship-building and behavioural sciences work necessary to establish public trust

2. We must include veterinarians and wildlife health biologists in public health discussions by establishing and maintaining relationships with stakeholders, including the public.

3. Long-term collaborative research is essential to understanding individuals and populations (across species) at risk and assists in building trust between sectors, stakeholders, and the public.

4. There is a need for research into influenza prophylaxis, immune modulators for severe disease and non-pharmaceutical interventions including the use of personal protective equipment.

5. Proactive policies should be considered before knowing potential risk to humans for the subclade 2.3.4.4b virus, which is different from the H5Nx viruses that have historically circulated in Asia and have been attributed high mortality rates in the range of 40-50%. Given the unknowns for reassorted 2.3.4.4b

6. How can we disseminate testing and knowledge into remote communities? We should work with trusted community leaders, nurses and medical staff to promote public health guidance, facilitate testing and enable interventions that focus on prevention (at this time).

7. Access to diagnostic testing that does not require laboratory skills would be valuable for rural areas.

Closing Remarks, Dr. D. Nanang, VP Science (CFIA)

Dr. D. Nanang underscored CFIA's ongoing response to HPAI over the past 3 years, involving approximately 422 infected premises and the depopulation of over 11 million birds. To date, the epizootic has been primarily considered an animal disease, but this has recently shifted and now involves humans. He called upon the need to understand HPAI from a systems perspective, and urged participants to continue this important discussion.

Closing of meeting, Grandma Karen

Meeting key messages

The importance of a One Health approach that integrates all the key aspects of biological, epidemiological and behavioural research across wildlife health, veterinary medicine and human health was made clear. In the near term we should focus on where the virus is active at this time- at the intersection of wildlife, livestock and humans. To do this we need a mechanism for ongoing, cross-sectoral & multidisciplinary research collaboration and coordination through a One Health focal point.

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