Potential Research Priorities to Inform U.S. Readiness and Response to Avian Influenza A (H5N1): Proceedings of a Workshop—in Brief (2024)

DETAILS

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Proceedings of a Workshop—in Brief

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Avian influenza A (H5) viruses have been circulating globally for more than two decades in migratory birds, with recent outbreaks since 2020 driven by the variant clade 2.3.4.4b spreading rapidly among wild bird, non-avian wild and domestic (including companion and farming) terrestrial animals, and marine mammals. The recent emergence of H5N1 virus in dairy cattle, caused by genotype B3.13, in the United States has led to challenges in managing and controlling the spread of H5 viruses between livestock, wildlife, and companion animals, as well as to humans from infected animals. To inform readiness and response to the H5N1 outbreak in the United States, the National Academies of Sciences, Engineering, and Medicine (the National Academies) sponsored a two-day virtual workshop[1] from October 22–23, 2024, to explore potential research gaps and priorities.

In her opening remarks, Nahid Bhadelia, Boston University Center on Emerging Infectious Diseases, summarized the current outbreak situation and described how avian influenza A (H5) viruses have continued a steady march infecting a growing number of mammalian species over the last few years. She emphasized that the scale of the outbreak in the United States is immense, with millions of wild birds and poultry infected since 2022, hundreds of dairy cattle herds affected in the months before the workshop, and now dozens of confirmed human cases, with a majority linked to exposures to infected poultry or dairy cattle.

Underpinning workshop discussions, Bhadelia noted, were central questions about how to better support response goals, such as the current state of knowledge, gaps in knowledge that have implications for health emergency readiness and response, and research that can be undertaken to answer critical questions. The workshop design was informed by presentations from a public listening session[2] and followed an interdisciplinary One Health approach, bringing together experts from across human, veterinary, plant, and environmental health. The workshop built on published federal research priorities for H5N1.[3] Implementation research (e.g., incentives and

[1] The workshop agenda, materials, and speaker presentations are available at https://www.nationalacademies.org/our-work/potential-research-priorities-to-inform-readiness-and-response-to-highly-pathogenic-avian-influenza-a-h5n1-a-workshop (accessed October 28, 2024).

[2] Presentations from the public listening session are available at https://www.nationalacademies.org/event/43724_09-2024_session-on-public-stakeholder-perspectives-for-potential-highly-pathogenic-avian-influenza-a-h5n1-research-priorities (accessed October 28, 2024).

[3] For examples of relevant published federal priorities, see Department of Agriculture, *U.S. Highly Pathogenic Avian Influenza A (H5N1) Research Priorities: October 2024*, https://www.ars.usda.gov/research/us-highly-pathogenic-avian-influenza-h5n1-research-priorities/; Department of Health and Human Services, *U.S. Highly Pathogenic Avian Influenza A (H5N1) Research Priorities: October 2024*, https://www.hhs.gov/programs/public-health-safety/us-highly-pathogenic-avian-influenza-a-h5n1-research-priorities-october-2024/index.html (both accessed October 28, 2024).

barriers on the industry and farmworker side) is a large gap in existing H5N1 research agendas, Bhadelia acknowledged. Therefore, this workshop expanded research inquiries to a larger number of disciplines, including perspectives not only from basic translational clinical sciences, but also social sciences, veterinary health, agricultural economics, and occupational health, among others.

This Proceedings of a Workshop—in Brief summarizes key points raised by workshop participants and is not intended to be comprehensive. It is organized by themes consistent with but not identical to the structure of the workshop agenda and covers topics related to transmission dynamics, surveillance, mitigating risk to animal and human health, and cross-cutting issues, such as incentives, community engagement and trust, communications, and research capacity. The views summarized here reflect the knowledge and opinions of individual workshop participants and should not be construed as consensus or recommendations among workshop participants or the National Academies.

RESPONSE PRIORITIES AND GOALS

"[Globally], we have seen a massive epizootic of avian influenza over the last several years while the world was focusing all of our attention on the COVID-19 pandemic," stated Maria Van Kerkhove, World Health Organization (WHO). Among the concerns over the global spread of avian influenza viruses, Van Kerkhove highlighted the expansion of species being infected, the potential emergence of new virus variants and reassortments that could trigger another pandemic, and the need for resources and focus on surveillance systems to monitor changes in virus effectively. Van Kerkhove highlighted the global response priorities: to leverage the expertise and capabilities WHO and collaborating center surveillance systems to assess pandemic potential; to strengthen surveillance, monitor viruses in circulation, reduce the spread of avian influenza viruses in animals and to humans; to advance vaccine development and equitable distribution via the Pandemic Influenza Preparedness Framework;[4] and to maintain a constant readiness state to improve prevention and response systems by applying lessons from past epidemics and pandemics.

[4] For more information on the Pandemic Influenza Preparedness Framework, see https://www.who.int/initiatives/pandemic-influenza-preparedness-framework (accessed October 28, 2024).

Paul Friedrichs, White House Office of Pandemic Preparedness and Response Policy (OPPR), added that clear, context-based communication is needed for both current and future outbreak risks, as is continued investment in global surveillance and public health infrastructure, despite widespread fatigue and resource challenges. Friedrichs outlined four goals of the U.S. government for the outbreak response that were set since H5N1 virus was first detected in dairy cattle: to protect the health of farm workers and rural communities most at risk of H5N1 exposure, especially those in close contact with infected animals, as well as the general public; to continue to ensure that food safety measures are effective and sufficient; to mitigate risks to livestock and related industries; and to clearly communicate accurate information to both public health experts and the public and address concerns about the outbreak.

UNDERSTANDING TRANSMISSION DYNAMICS

The pandemic potential of influenza viruses has been discussed for more than 20 years, Friedrichs reflected. Yet, understanding the increase in species hosting H5 viruses will be a powerful aid to develop mitigation measures, he added. Response actions cannot minimize human infections without looking to the animal sources themselves, emphasized Van Kerkhove. Speakers discussed H5 virus transmission dynamics, focusing on risks among wildlife, poultry, cattle, humans, and species that bridge the interface between these groups.

Natural History and Virus Spillover from Host Species

Jeffrey Root, United States Department of Agriculture (USDA), stressed that baseline foundational information on species susceptibility, disease outcomes, shedding profiles, and transmission potential are needed. Similarly, Carol Cardona, University of Minnesota, noted there remain significant knowledge gaps in what is known about influenza A viruses in their natural hosts or in the avian host. Speakers also raised the need to understand the presence and prevalence of influenza A viruses in wildlife and potential for viruses to transmit across different species, or spillover. Raina Plowright, Cornell University, emphasized how habitat loss has been observed as a driver of animals' use of agricultural areas, thereby increasing contact with bridging hosts and humans. She provided an example from her work on bat populations where research on the patterns and behaviors

of bat host species informed understanding of potential spillover opportunities, particularly in locations and seasons when bats experienced habitat and food scarcity. Plowright stressed that research on events upstream of a spillover occurrence is essential to spillover prevention. She noted that two important areas of research investment that are currently lacking are long-term, multiscale studies of ecological processes that increase overlap between reservoir host and recipient host species and studies of environmental stressors that lead to more infection and shedding. The United States Geological Survey (USGS) is currently conducting work on avian influenza viruses and looking at how migratory birds are using farming spaces (e.g., cattle facilities) in areas where there were no longer wetlands, she said.

Root called for more research on key wildlife species that live in and or around human habitats, like mice and other rodents, especially those with the capacity and mobility to visit natural areas and agricultural facilities. Carrie Reed and Colin Basler, Centers for Disease Control and Prevention (CDC), discussed H5N1 infection risk from barn cats to humans or other animals and called for more robust surveillance on companion animal data, respectively.

Viral Evolution

Jonathan Sleeman, USGS, stressed the importance of capturing the right signals for viral evolution through wildlife surveillance and evaluating how best to undertake wildlife surveillance research to achieve this. Martha Nelson, National Institutes of Health (NIH), emphasized the value of genomic surveillance in understanding spillover events. She presented genomic data suggesting that the 2024 H5N1 outbreak in the United States was seeded to cattle by one wild bird, introducing the new genotype B3.13 (clade 2.3.4.4b), which has since spread among poultry, among cows, and between cows and poultry. Understanding genetic mutations, the evolution of the virus as it transmits, changing ecology, and reassortment potential is necessary to predict changes in transmission and pathogenicity, Nelson said. She noted that genomic sequencing can answer key questions related to how the virus is introduced and maintained in populations, whether through multiple sources or a single main source responsible for repeated seeding of new outbreaks across the susceptible population. It is important to determine whether a severe pathology in dairy cattle following virus introduction, as seen in California dairy herds, is the result of viral evolution or due to environmental stressors (e.g. heat, dehydration, etc.), added Nelson. Richard Webby, St. Jude Children's Research Hospital, emphasized a focus on examining virological characteristics and linking these to epidemiological patterns.

Transmissibility and Pathogenicity in Dairy Cattle

A major unanswered question is what are the precise modes of H5N1 virus transmission among animals, reflected Eric Deeble, USDA. Maggie Baldwin, Colorado Department of Agriculture, noted that some of the challenges regarding understanding transmission to dairy cattle are the complex connections between dairy and poultry facilities and understanding how H5N1 virus spreads directly and indirectly. Similarly, Nelson noted that understanding how cattle are moved around the country could help in understanding and potentially predicting the movement of H5N1 virus. However, the absence of a national database of dairy cattle movement hinders understanding, she added. This type of national database could help create risk assessment maps to understand states that are highest or lowest risk for future outbreaks, she noted. Nelson said that additional unanswered questions include whether pre-movement testing of cattle herds is effective in reducing H5N1 virus transmission between herds and how cattle in California were infected. Keith Poulsen, University of Wisconsin-Madison, commented that nonlactating animals are not presently recognized as a significant source of H5N1 virus infection, but more information is needed to understand if that is truly the case.

Drew Magstadt, Iowa State University, shared research on how H5N1 virus infection presents in dairy cows and immunological aspects. Better understanding these issues could provide insight on when dairy cows are most infectious, he noted. Magstadt and his team observed significant drops in feed intake, milk production, and rumination in infected cows. In 10 days, 15 percent of the herd became clinically ill, meaning 1,500 cows would need treatment in a 10,000-cow operation. He called for further research on factors influencing disease severity, such as lactation stage, age, and infection route. The long-term effects on dairy cattle, like production and reproduction, remain unclear, and researchers need early access to farms for data. Magstadt also noted the high

H5N1 virus levels in affected cows and the transmission risk, with bulk milk samples showing low virus levels two weeks before clinical symptoms. "The transmission risk to naive cattle from raw milk is very likely low," he said, "but we would like to have some confidence in how much that does vary during an outbreak so these farms can return to normal as quickly as possible."

Magstadt emphasized the need for reinfection studies and tests to assess immunity duration in cattle. He noted that hemagglutinin-specific antibodies can last for about four months in milk. Amy Baker, USDA, presented data from intramammary-inoculated cows showing rapid drops in milk production one to two days after inoculation with H5N1 virus and detectable viral RNA in those milk quarters. By day 24, infected mammary tissues showed immune cell infiltration and although viral clearance is not fully understood, field reports suggest lactating cows and mammary inoculation may be a primary infection route. Baker also highlighted challenges in conducting such studies due to labor intensity and the limited availability of large BSL-3 labs.

Human Pandemic Potential of Avian Influenza A (H5) Viruses

When assessing whether avian influenza A (H5) viruses could cause a pandemic in humans, Jesse Bloom, Fred Hutchinson Cancer Center, proposed that while there is molecular evidence to support that dairy cattle H5N1 viral polymerase functions well in mammalian cells, mutations to hemagglutinin that might lead to increased transmissibility to and within humans have not yet been observed in dairy cattle H5N1. He added that there are other adaptations that could promote human transmissibility that are not well understood. Ferret studies to test hypotheses related to functional gains in transmissibility are time consuming and require high biosafety levels, he added, while alternatives like deep mutational scanning that use nonhuman pathogens can be safely done at lower levels and still assess whether a given mutation could affect receptor binding properties of hemagglutinin.

Van Kerkhove noted that while the current H5N1 outbreak in the United States is due to avian influenza viruses affecting dairy cattle, there are also swine influenza and human influenza viruses, which creates possibilities for viruses to reassort, or recombine, into new variants. Nelson raised that reassortment of animal influenza strains with a human seasonal influenza virus had been the cause of prior influenza pandemics. Of concern, she added, is H5N1 clade 2.3.4.4b, genotype B3.13 virus infecting swine due to many diverse lineages circulating in swine that virus could reassort with.

STRENGTHENING SURVEILLANCE

Animal and Environmental Surveillance

Regarding surveillance, particularly in the animal health dimension, participants spoke of numerous challenges, opportunities, and research questions. Surveillance data—particularly those including viral genetic sequences—can feed back into key action or decision points such as updating risk assessments and developing effective vaccines, according to Bloom. However, Erica Pan, California Department of Public Health, observed that California's agricultural data systems deployed to capture and share data on the outbreak are outdated. Cardona emphasized that risk-based regional surveillance across animal populations is crucial and should be implemented as part of a consistent national strategy designed to reduce spread.[5] Additionally, Gregory C. Gray, University of Texas Medical Branch, noted that there is no effective surveillance for novel pathogen emergence on livestock farms. Passive livestock surveillance is clinically based and chiefly focused on previously recognized pathogens, which does not help detect novel emergent viruses that may spill over to humans, he added. Gray added that if H5 viruses were to spread in industrialized pig farms, it is likely to be missed.

Rachel K. Herlihy, Colorado Department of Public Health and Environment, prompted speakers to consider opportunities for uniform and consistent surveillance at the national level. Poulsen said that a herd-level aggregate sampling via bulk milk testing is the ideal way to identify infected herds. Poulsen also said that antibody testing is valuable and should be used in testing strategies. Nora Wineland, Michigan Department of Agriculture and Rural Development, suggested that, rather than voluntary weekly testing, national surveillance focused on bulk milk tanks would be best. She called for a national surveillance strategy that could be flexibly, efficiently, and effectively deployed across all states.

[5] Cardona cited the recommendations of the American Association of Avian Pathologists, AAAP Statement on H5N1, July 23, 2024, available at https://aaap.memberclicks.net/assets/Positions/FINAL-AAAP%20summary%20position%20on%20H5N1%20in%20cattle%207.12.24%20pdf.pdf (accessed October 28, 2024).

An important overall solution for surveillance is that virus detection modalities being deployed need to include virus genome sequencing, said Anthony Maresso, Baylor College of Medicine. He stated that the presence of high viral loads in raw milk should be leveraged through a national milk testing program that incorporates sequencing to detect genetic changes. He added that sequencing is not only to confirm presence of the pathogen but also to elucidate how it changes over time. Darrell Kapczynski, USDA, agreed that surveillance and sequencing are critical for understanding viral evolution and transmission.

Regarding environmental surveillance, participants discussed the utility of wastewater testing and ways it can provide opportunities for tracking virus levels outside potentially more biased individual-level data sources. Pan remarked that each wastewater shed is unique and that viral levels that would trigger concern need to be better understood. Bethany Boggess Alcauter, National Center for Farmworker Health, proposed harnessing citizen science in rural areas to capture information from private septic tanks and sewers. Dustin Oedekoven, National Pork Board, also suggested researching the survivability of virus in manure (a revenue source for producers) and whether that poses a downstream risk to other areas of production.

Several participants noted the need for trust-building with affected worker communities, producers, and other actor groups to engage around surveillance activities. Alcauter noted the importance of combining surveillance with reciprocity activities (i.e. giving back to actor groups), which may vary based on the target community and workforce (e.g. reciprocity activities might appropriately include training and access to personal protective equipment [PPE] among some worker communities, but, in others, attention to family support measures might be more appropriate).

Animal Food Product Surveillance

As H5N1 virus emerged in dairy cattle in the United States in early 2024, an enormous amount of work was done to confirm that food safety measures were effective and sufficient, as it was the first time H5N1 virus had infected cattle and related dairy products that enter the food supply chain, remarked Friedrichs. Michelle Catlin, USDA Food Safety and Inspection Service (FSIS), described four beef safety studies, including three conducted in partnership with the Animal and Plant Health Inspection Service (APHIS) and USDA's Agricultural Research Service (ARS) to verify the safety of the meat supply, considering what was known about highly pathogenic avian influenza in poultry. While cooking inactivates the virus, Catlin noted the need to study how drying or fermenting affects virus viability in meat. Steve Grube, U.S. Food and Drug Administration (FDA), stated that they are confident pasteurized milk is safe. Poulsen highlighted that roundtable discussions hosted by the National Milk Producers Association and the American Veterinary Medical Association emphasized the need to decouple H5N1 as an animal disease from concerns with safety of commercial animal food products outside of raw products. With consumer food safety concerns rising, Oedekoven said the National Pork Board collaborated with FSIS to show H5N1 does not impact food safety.

Reed also highlighted research needs on risks of raw milk consumption and unrecognized H5N1 virus infection and disease presentation. Ongoing FDA-funded studies are on H5N1 virus inactivation in raw-milk cheese, effects of different pasteurization parameters, and viability tests for consumer products that test positive for H5N1 virus by polymerase chain reaction (PCR), described Grube. Stephen Ostroff, University of Pittsburgh and S Ostroff Consulting, also suggested further study on the risk posed by pets exposed to raw milk or pet foods.

Testing and Surveillance for Human Health

Alcauter and Carlos del Rio, Emory University School of Medicine, emphasized the need to develop a rapid diagnostic test, particularly for farmworkers, and to ready point-of-care testing options for detection and surveillance of H5N1 virus, respectively. Reed shared priorities for public health investigations in humans to understand the risks and spectrum of disease and to monitor those with known exposures to infected or sick animals. In addition to robust surveillance to detect any novel influenza virus that is present in the community and investigating cases and contacts identified through surveillance, she noted that additional epidemiological investigation including more systematic studies of human risk, clinical manifestation, exposure, and risk or preventative factors associated with H5N1 virus infection would be helpful. Rodolphe Barrangou, North Carolina State University, emphasized diagnostics and early detection as critical

starting points to identify issues before they become broadly problematic. Research to develop tools using different technologies and approaches for monitoring early detection in the field and on the farm is preferred, he shared.

Kelly Wroblewski, Association for Public Health Laboratories (APHL), expressed several concerns with the PCR-based tests currently available to confirm influenza A (H5) virus. One challenge is that nearly all human cases detected in the United States so far have had very little virus present in specimens, therefore less sensitive tests may miss truly positive cases. Furthermore, currently available PCR-based tests are not optimal for a long-term surge as they are neither high-throughput nor multiplexed, and influenza A (H5) virus point-of-care tests are not designed for use on conjunctival swabs, she said. Wroblewski highlighted a need to explore alternatives to RT-PCR and improve sensitivity and specificity of tests for specimens with low levels of virus present. She also suggested to develop and pre-position diagnostics and testing capacity in advance of the next potential pandemic.

Serological testing can be even more powerful than looking for virus because the signal lasts longer, emphasized Michael Mina, eMed Digital Healthcare, but there are no commercial or at-home tests for influenza A (H5) virus antibody. Pan-serological testing can look at many pathogens at once and be very cost-beneficial, added Mina. Pan also commented that the role of nasal swabs for people is an open question, especially in the context of self-testing. In addition to nasal swabs, Maresso suggested that stool and urine samples should be considered.

Testing is crucial for determining clinical trial participants, said Lauren Sauer, University of Nebraska Medical Center. Additional research is needed to identify the barriers for at-risk individuals to participate in research and improve decentralized trial designs that engage these communities. Del Rio also suggested exploring artificial intelligence algorithms for testing and telemedicine.

MITIGATING RISKS TO ANIMAL AND HUMAN HEALTH

Biosecurity and Response Practices on Farms

The efficacy of various biosecurity strategies on dairy farms and to what degree these strategies could reduce avian influenza (H5) viral spread remains open question, stressed Cardona, and identifying other biosecurity interventions to prevent infections is critical. For poultry, highly pathogenic avian influenza outbreaks are managed through a depopulation approach to biosecurity—neither infected animals nor their products are expected to reach the market, as guided by the Secure Poultry Supply Plan,[6] she noted. She raised questions about better understanding poultry depopulation control strategies and whether depopulating only infected birds rather than the entire flock was possible. "What [are] the environmental and industry limits on how many poultry flocks can be raised over the course of a year?" she asked. Dairy operations tend to have minimal biosecurity for avian influenza in place, as H5N1 virus is a new pathogen for that industry, noted Baldwin. USDA has started to implement financial and other support options to enhance planning and implementation of biosecurity measures and offset costs and losses for dairy producers, Deeble stated. However, Baldwin noted that states must be ready to respond financially, as it is unclear how long USDA will be able to support these programs. Robert Hagevoort, New Mexico State University, highlighted the labor-intensive work associated with taking care of sick dairy herds and providing supportive treatments with methods that put workers in direct contact with bovine body fluids. He commented that as hundreds of cows needed supportive treatments, many producers hired additional new workers.

Cattle and Poultry Vaccinations

Speakers highlighted technical and trade barriers to vaccinating livestock, especially poultry. Kapczynski noted that, without modified live or live virus vectored vaccines, options for poultry remain limited. Trade-related barriers to vaccination include that many U.S. poultry export markets are predicated on disease-free without the use of vaccines status, commented John Clifford, USA Poultry and Egg Export Council. He also noted that all H5N1 vaccine doses administered must be accounted for, and all vaccinated animals must be identified and tracked, according to current regulations. Although World Organization for Animal Health guidelines call for active surveillance to detect wild type virus in vaccinated poultry flocks, Clifford said, there is no internationally accepted

[6] University of Minnesota, Implementing the Movement of Poultry Industry Products during Disease Outbreaks: Secure Poultry Supply https://securepoultrysupply.umn.edu/ (accessed October 28, 2024).

surveillance system for this purpose. However, producers do not object to vaccination in dairy cattle, Clifford commented, so long as APHIS can guarantee with U.S. trading partners that markets will remain open. In fact, multiple companies have expressed interest in providing a cattle H5N1 vaccine, added Kapczynski. Relevant research questions relate to vaccination-mediated protection from viral mastitis and viral shedding, and whether serum antibodies would be a reliable marker for protection of the mammary gland, he noted.

When asked by David Stiefel, Nuclear Threat Initiative, about the need for a DIVA (Differentiating Infected from Vaccinated Animals) strategy for current avian influenza (H5) virus outbreaks in dairy cattle and poultry populations, Deeble explained that DIVA compliance is crucial for poultry to maintain export market access, since differentiating vaccinated from infected birds is necessary to uphold disease-free trade status. However, H5N1 virus was not anticipated in dairy cattle, therefore trade agreements are not in place with DIVA requirements for cattle, he added.

Farmworker and Health Care Worker Protection

In his opening remarks, Friedrichs posed the following question: "How do we frame research questions to reexamine the protective measures that we offer for workers both in the human health space and in the animal health space?" Anabel Rodriguez, Texas A&M University, said the farmworker population is broad, covering producers, veterinarians, farm staff, and owners. She emphasized, "We want to make sure that we give a face and a voice to these all the workers on the farm—not just your traditional dairy farmworker. And that we are also able to tell a story for them and their occupational exposures." Occupation is a social determinant of health, and these workers spend 10–12 hours a day, 6 days a week on the farm, she continued.

Matthew Nonnenmann, University of Nebraska Medical Center, described the occupational environment on a dairy farm—the pace of the work, proximity to cows, different milking tasks, the wet environment, and often warm temperatures—and how this environment presents challenges to protecting farmworkers. There are also questions about how co-exposures, such as from working in a dust-laden barn, could make workers more susceptible to H5 virus infections.

He presented about the different hierarchies of control to best control hazardous workplace exposures[7] and highlighted the need to understand and evaluate environmental engineering controls as a priority for reducing infection spread from dairy cattle to farmworkers. Options for the dairy farming environment include physical barriers or air curtains, equipment, and procedures and administrative policies related to hygiene, clothing, and food consumption on premises, he added. Jonathan Samet, Colorado School of Public Health, highlighted a previous National Academies framework for respiratory protection for the nation.[8] He highlighted the framework's value in understanding airborne transmission of SARS-CoV-2 but noted it lacked follow-up to implement. Pan emphasized the need for more data on effective PPE and its practical implementation. PPE ensembles[9] carry potential for failure, Nonnenmann commented, and Cherissa Abdul-Hamid, Texas Department of State Health Services, suggested that any new PPE developed to prevent H5 virus transmission should ideally be useful for other pathogens and hazards, like dust.

Understanding how H5 viruses transmit in farms and healthcare facilities is essential, emphasized del Rio. Erica Shenoy, Mass General Brigham, highlighted the need to apply evidence-based administrative and engineering controls in hospital settings to prevent potential H5 virus transmission, as well as creative solutions to ease the cognitive burden on healthcare personnel adapting to new information, protocols, and policies.

Frontline Workforce Well-Being

Meghan Davis, Johns Hopkins Bloomberg School of Public Health, emphasized the mental health challenges farmworkers and producers face due to burnout, burden of testing and response requirements, and depopulation. Michelle Kromm, Food Forward, LLC, noted that mental health for veterinarians is especially hard hit, given established stressors in the occupation. For the poultry sector, veterinarians or others conscripted to cull animals face the additional challenge of killing potentially

[7] Learn more about hierarchy of controls here: https://www.cdc.gov/niosh/hierarchy-of-controls/about/index.html (accessed November 6, 2024).
[8] National Academies of Sciences, Engineering, and Medicine. 2022. *Frameworks for Protecting Workers and the Public from Inhalation Hazards*. Washington, DC: The National Academies Press. https://doi.org/10.17226/26372.
[9] PPE ensembles are a set of PPE components worn together to protect against hazards in the workplace.

disease-negative animals in the name of disease control, she said. Christine Petersen, Ohio State University College of Veterinary Medicine, reflected on how motivated veterinarians are to protect public health and food infrastructure. The large network of veterinarians working across the country will be critical to motivate livestock industries, she added.

Medical Countermeasures to Prevent and Treat H5 Infection in Humans

Clear progress on pandemic influenza has been made in the last two decades from a medical countermeasures perspective, stated Rick Bright, Bright Global Health. Commenting on the improved preparedness posture of the United States, he added that the investment and commitment of the public and private sectors have enabled two new vaccine types, stockpiles of antigens and adjuvants, expanded domestic vaccine production, approval of two new drugs, and maintaining a stockpile of oseltamivir. However, the question of whether there are gaps in real and equitable pandemic readiness and the appropriateness of investment in older technologies, compared to a need to upgrade our readiness posture with more modern and responsive tools and technologies in sufficient quantities to control an outbreak among people and animals has yet to be answered, he said.

Participants spoke at length about vaccine readiness. Jesse Goodman, Georgetown University, emphasized that, despite limited data, useful efforts could include modeling pre-pandemic vaccine strategies, assessing public interest or concerns, and conducting long-term follow-up to understand and characterize immune priming and building immunity in a population.

In terms of currently available human vaccines against H5 viruses, additional data are needed on cross-protectiveness of existing candidate vaccines against circulating H5N1 viruses and dosing optimization, noted Goodman. The value of U.S.-stockpiled, filled and finished vaccine is unclear, he added. However, despite years of research, potency assays remain a preparedness gap, reflected Paula Barbosa, International Federation of Pharmaceutical Manufacturers and Associations. The time to produce and calibrate single-radial immunodiffusion reagents for assays is a great limiter in the production of influenza vaccines and could be a considerable bottleneck during a pandemic, she said. More research exploring alternative assays to such reagents is needed, as is research to accelerate the availability of reference reagents and thus could shorten timeframes to readiness, she suggested. "We need to support vaccines for H5 viruses that provide durable protection against future variants, block transmission, do not require adjuvants or other specialized components, and can be administered in a single dose," emphasized Ruben Donis, Biomedical Advanced Research and Development Authority (BARDA). Scientists and the public will also need to see safety and immunogenicity data on the mixing and matching of adjuvants and nonadjuvanted antigen potentially originating from different manufacturers to ensure that this approach performs as expected, as it will likely be needed in a pandemic emergency, Goodman added. Kromm suggested working to increase our understanding of how seasonal influenza vaccine uptake among dairy farm workers might afford economic benefits to producers through decreased absenteeism and public health benefit through reduced potential for viral reassortment.

A U.S.-based, multicenter, hospital-focused trial platform to answer questions on how to optimally treat seasonal flu, which would provide answers for treatment of pandemic flu, could also be used to address respiratory syncytial virus (RSV) and other pathogens, advocated Frederick Hayden, University of Virginia. Tim Uyeki, CDC, acknowledged the need for a comprehensive national clinical research infrastructure using existing and new clinical networks in the United States for seasonal influenza and other respiratory viruses and including adaptive clinical trials and prospective natural history studies. Another unknown is whether a potential pandemic H5 virus strain might require higher or more prolonged therapeutic dosing, to what extent it might reduce virus transmission, in what patient populations combination treatment would be needed, and the extent to which resistant variants will emerge, Hayden said. Donis said that BARDA is supporting host-directed therapeutics to treat severe influenza in hospitalized patients and drugs with new mechanisms of action that avoid issues with resistance. Diversification and expansion of antiviral stockpiles will also help with this, as will the availability of rapid, point of care antiviral susceptibility tests, according to Hayden.

EXPLORING CROSS-CUTTING ISSUES

Agroeconomics and Behavioral Economics Research to Understand Decision-Making

Numerous workshop participants spoke to a need to identify what is driving decision-making across different stakeholders and sectors, that is, what is incentivizing them to act or not act in certain ways related to the outbreak. For example, Wineland highlighted the need to implement incentives and remove disincentives for reporting to improve passive surveillance. According to Deeble, "Detection of H5N1 virus in dairy cattle, especially the costs associated with treatment, testing, and lost milk volume, has created a great deal of economic uncertainty and anxiety in producers." The fear of losing market access is a principal, existential concern of every dairy farmer, though data and experience do not support evidence of market loss, Grube acknowledged. Grube further clarified, noting that there are already strong disincentives to participation. Collectively, there is a desire to know the answer to many questions related to the virus, but individually, there is a fear of the economic consequences, reflected Hagevoort.

Under a true One Health approach, the well-being of both animals and humans would be prioritized in a response, reflected Van Kerkhove. At present, the incentives and disincentives needed for animal and human health sectors to collaborate is not being addressed, she said. Tom Marsh, Washington State University, offered that the percent of public expenditure on animal health has just been a fraction of human health: "My perspective on this is we do need to take a much better, broader perspective of One Health where we look at balancing those investments between animal health and human health." Marsh raised the question of how the impact of disease burden is redistributed across society. He said that One Health frameworks should be used to measure the distribution of economic burden, to assess the costs and benefits of vaccination for dairy cattle, and to explore how trade issues are impacting decision making. He noted that understanding the effects of improved surveillance and trade issues will give us a much better idea about how vaccines could be used in poultry.

Marsh described a need to have a more complete economic model of the costs of animal disease caused by H5 viruses, including, but not limited to production losses, trade losses, implementation costs associated with biosecurity programs, surveillance programs, human health effects, and indirect economic effects of spillover. Implementing such a model will require improving our collection of public expenditure data, developing accounting systems for animal health akin to those for human health, and help from behavioral analysts and economists to identify the appropriate incentive structures and economic safety nets, he added.

Implementation research could support reasons for understanding noncooperation, distrust, strategies to promote cooperation, and evaluation and refinement of response strategies, stated Ostroff. Furthermore, a systems approach to understanding behavioral drivers is necessary, suggested Sleeman, and mapping the system may help identify possible interventions that were previously hidden.

Engaging High-Risk Communities and Building Trust

Rodriguez highlighted challenges in engaging and supporting the heterogeneous farmworker community, including systemic barriers to health, communication challenges, literacy, lack of public transportation, transient lifestyles, work schedules, and deep mistrust of law and immigration enforcement. Cardona noted the need to learn about ways to communicate with farmworkers independent of their employers.

Many participants stressed the need for community engagement approaches. Research should be tied to best practices for inclusive, participatory, reciprocal, and community-centered outreach to and research with dairy farmworker communities and dairy producers, with capacity to share knowledge with participants as well, Alcauter suggested. She emphasized that participation in research must be made productive and convenient for these communities, and researchers must recognize the context in which many workers participate, amid limited time off, long hours, and lack of overtime pay. Alcauter stressed the need to apply the research ethics principle of reciprocity, such as by providing educational trainings about H5N1 virus or sharing testing information learned from any study with participants. Davis also emphasized the importance of participatory approaches to the success of surveillance activities.

Speakers referenced a trust gap that spanned across areas from surveillance to vaccination to clinical trials. Research on the factors that support trust and collaboration is needed, Pan stated. For example, she suggested studies to understand how potentially infected dairy workers can be enabled to come forward for testing and treatment. Codesigning studies with community leaders and supporting access to participation in clinical trials could help, offered Sauer. A lack of trust in vaccines could be mitigated through incorporating special populations into safety studies and undertaking studies to inform communication strategies for diverse groups and circumstances, commented Goodman.

Communicating Accurate Information Clearly

A cross-cutting issue across the livestock industry, health care workforce, farmworkers, and the public is how what is known and not known is communicated in a way that helps restore trust in response measures, reflected Georges C. Benjamin, American Public Health Association (APHA). This communication also needs to convey the collective commitment to protect the welfare of the public, farmworkers, food supply chain, and livestock industry, he added. Veterinarians may be seen as "trusted messenger[s]" by producers and farmworkers, Abdul-Hamid said, noting anecdotally that some farm employees have trusted veterinarians to take them to urgent care during this outbreak. A related need is to understand the barriers to updating communications practices, suggested Stefanie Friedhoff, Brown University. She said that while information inequities and access challenges for high-risk populations are known, a better understanding of these challenges and how technologies like artificial intelligence are influencing health information consumption and sensemaking is needed to build effective response mechanisms.

Sharing Data Rapidly and Transparently

Numerous participants, including Nelson and Davis, noted that transparency and rapid availability of data, including metadata, are necessary. Stiefel highlighted a key question of what interoperable data are truly needed and at which level of response. Gray said specimens collected by USDA-supported veterinary diagnostic labs are not always available to others outside of that network, a notion with which Cardona agreed.

Baldwin provided some perspectives regarding state-level limitations and reasons for sharing or not sharing data. In Colorado, she explained, the Livestock Information Security Act protects producer and livestock information to build trust and assurance among producers and to allow them to conduct data collection—efforts critical to surveillance efforts. Data are being collected to inform response, but it is not necessarily open access, she said. Nelson noted a critical need for real-time spatiotemporal meta-data linked to specimens subjected to genetic testing to inform evaluation of virus evolution as well as efforts for outbreak mitigation.

Enhancing Research Capacity

Conducting research while detecting and responding to outbreaks is a significant challenge, highlighted Asha M. George, Bipartisan Commission on Biodefense. Gray called for federal funding to support new Centers for One Health Research, Training and Response, like existing NIH Centers of Excellence for Influenza Research and Response (CEIRR) and Centers for Research in Emerging Infectious Diseases (CREID). These new One Health Centers would conduct research and training in partnership with agriculture to solve complex agriculture-related problems such as emerging infectious diseases, antimicrobial resistant organisms, and food security. Kapczynski commented that there is limited capacity to conduct research, and more people and infrastructure are needed to execute research priorities.

Risk and Scenario Modelling

Participants also discussed ways to leverage modeling as a risk and preparedness support tool. Friedrichs highlighted the need to describe risk in the present context and potential future risk to support communication efforts. Bryan Lewis, University of Virginia, offered that while a lot of data that can be used in models to explore hypotheses are already available, simple models using less data can still be useful. Goodman suggested that a real focus should be making use of computational sciences to enhance modeling of antigenic change in the virus and the design of potentially more broadly reactive antigens or vaccines. Modeling could be used to explore the public health benefits of building immunity through pre-pandemic vaccination in a population, such as those exposed in occupational settings, he said. Wroblewski noted that using existing expertise and technologies for

forecasting and modeling can help us better predict when to scale diagnostic testing throughout pandemic intervals and how to responsibly use finite public health resources.

CONCLUDING REMARKS

Several speakers emphasized that research priorities and questions should be grounded with clear links to response goals. If the response goal is elimination of H5N1 virus in dairy cattle, then a long-term strategy should be developed, suggested Baldwin. Oedekoven and Poulsen also highlighted the need for livestock industries and surveillance programs to identify shared goals for response plans and develop agreement on whether virus elimination is possible across cattle, poultry, and swine industry partners. Central to the response is also balancing research to inform human, animal, and environmental health to achieve optimal outcomes, noted Sleeman.

In her concluding remarks, Bhadelia reflected on five key priorities for research that emerged from discussions at the workshop (Box 1):

- Understanding transmission mechanisms and address knowledge gaps around transmission scenarios;
- Locating the virus across species and regions and improve surveillance and diagnostics to achieve this goal;
- Prioritizing research that actively engages stakeholders, promotes understanding of incentives and disincentives for participation, and enables collaboration for a meaningful, balanced public health response to H5N1;
- Determining how to use the current toolbox of medical countermeasures or develop new ones that address novel use cases;
- Defining clear triggers for action at each level of response.

Bhadelia underscored that research is a critical component to readiness and response to emerging pathogens—providing evidence-based approaches to better target response efforts, to protect those most at-risk, and to prepare for future scenarios.

BOX 1

Potential Research Questions Suggested by Individual Workshop Participants to Inform H5N1 Readiness and Response

Understanding Transmission Mechanisms and Scenarios

- How is the virus being maintained, introduced, and reintroduced into animal populations, and what is the potential for adaptive mutations or reassortment with other influenza viruses? (Bloom, Deeble, Nelson)
- Is intra-herd spread among cattle primarily mechanical, aerosol, or direct contact, and what interventions can limit spread within an affected herd? (Magstadt)
- What are the primary exposure routes for humans, and how can knowledge of these routes guide preventative practices? (Reed)
- How effective are treatments that inactivate or decontaminate viruses in meat, and how do they affect viral viability? (Catlin)
- What is the risk from consuming raw cow milk to humans, companion animals, or other livestock, and are there potential unrecognized infections from this transmission route? (Reed)

continued

- How effective are different dairy farm biosecurity practices, and to what extent can they reduce viral spread? (Cardona)
- What environmental and administrative biosecurity measures are most effective in a dairy farm environment, and what PPE is suitable for such settings? Are novel PPE needed for different agricultural settings? (Nonnenmann, Pan)
- Does the lack of hemagglutinin evolution to use human receptors indicate a lower pandemic risk, and what other viral adaptations could enhance human transmissibility? (Bloom)
- What are the optimal administrative or engineering controls for health care facilities, and how can these be implemented to minimize burden on healthcare personnel, impact on access to care for patients; what are the triggers for de-implementation of controls? (Shenoy)

Locating the Virus across Species and Regions, Improving Surveillance and Diagnostics

- How prevalent is the virus among wild birds and mammals, including those species living in and around human habitats? To what degree will disease ecology in some of these species, such as mice, inform surveillance and control efforts? (Root)
- How frequently should testing occur in dairy settings with high movement rates, and how can surveillance detect active virus in herds to prevent transmission? What are the best practice criteria to declare herds 'released' from quarantine? (Wineland)
- What research is necessary to develop multiplexed, high-throughput lab assays to handle a surge in cases? (Wroblewski)
- Can rapid diagnostics be developed for use with conjunctival samples? (Wroblewski)
- How can negative test results be interpreted for dairy animals without clinical signs, and can diagnostic tests shorten quarantine periods effectively? (Poulsen)
- What spatiotemporal factors contribute to differences in disease prevalence at various sites? (Magstadt)

Understanding Incentives and Disincentives, Engaging Stakeholders, and Enabling Communication

- What are the economic costs of animal disease across production, trade, biosecurity, human health, and indirect impacts, and who is responsible for these costs? (Marsh)
- What incentives do dairy farmers need to encourage biosecurity practices? (Deeble)
- How would different poultry vaccination scenarios affect long-term market dynamics? (Marsh, Stiefel)
- What incentives or removal of disincentives could reduce market loss fears for livestock and poultry producers, and how do privacy concerns affect participation in prevention or response? (Grube)
- How can trust building and collaboration among farmworkers and other potential vaccine recipients be improved? (Goodman, Ostroff, Pan)

continued

- What barriers hinder modern communication practices, and how can information access be improved for high-risk populations in the context of artificial intelligence (AI) and widely available health information? (Friedhoff)
- What are the mental health effects of outbreaks on veterinarians, farmworkers, and others, how do these stressors inform decision-making, and how can these effects be mitigated? (Davis, Kromm)
- What challenges do at-risk individuals face in accessing research, and how can decentralized clinical trials be designed to engage these communities? (Sauer)

Updating Mitigation Strategies and Medical Countermeasures to Limit Spread, Minimize Health Harms, and Optimize Treatment

- What mitigation strategies can prevent viral spread among animal populations, and should quarantine apply to animals beyond lactating dairy cattle? Is pre-movement testing of dairy cattle working as a mitigation strategy? (Baldwin, Nelson)
- Why does disease severity vary among individual dairy cows, and how do factors like age, gestation stage, or lactation stage influence infection outcomes? (Magstadt)
- Is the increased pathology in California dairy cattle linked to viral evolution? (Nelson, Pan)
- How much herd immunity is needed to protect a dairy herd, and is reinfection possible? Should previously infected cows be vaccinated if vaccination is initiated? (Magstadt, Ostroff)
- Are serum antibodies reliable markers of mammary gland protection in dairy cattle? (Kapczynski)
- Can vaccines for dairy cattle be developed that prevent mastitis, reduce viral shedding, and meet export requirements? (Kapczynski)
- How can clinical manifestations and associated risk factors in humans be predicted? (Nonnenmann, Reed)
- How can human vaccines be produced to provide long-lasting protection against future variants, block transmission, and require no adjuvants? (Donis)
- What research is needed to develop alternative vaccine potency assays and accelerate access to reference reagents to expedite readiness? (Barbosa)
- What pre-pandemic vaccine strategies for humans are most useful, and when should they be implemented? Is the research approach to mixing adjuvants with nonadjuvanted antigen working? (Goodman)
- Would a pandemic H5 virus strain require higher or longer antiviral doses than seasonal influenza, and in what populations might combination treatment be necessary? (Hayden)
- What clinical research infrastructure would enable adaptive clinical trials and prospective natural history studies that could answer questions about course of disease and mitigation through medical countermeasures? (Hayden, Uyeki)

continued

Defining Triggers and Actions for Response

- Could increasing seasonal influenza vaccine uptake among high-risk workers reduce H5 pandemic risk, and can this be modeled effectively? (Kromm)
- How can surveillance data be compiled across systems to provide useful situational awareness and research insights? (Maresso, Stiefel)
- How can computational modeling inform diagnostic test or vaccine development by predicting antigenic changes? (Goodman, Wroblewski)
- In an escalated situation, who would need testing, and how can artificial intelligence help identify those individuals? (del Rio)

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