

H5 Pandemic Influenza Vaccines: Major Gaps and Priorities



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Potential Research Priorities to Inform Readiness and Response to

Highly Pathogenic Avian Influenza A (H5N1)

National Academies, 10/23/2024

(Outside Interests: Board member, Science Committee, GSK)



GEORGETOWN
UNIVERSITY

Current State

- Licensed Vaccines in US: 2 adjuvanted, 1 not; + several non-US
 - After 2 doses, immunogenicity (anti-HA) correlates w/*moderate* protection assuming consistent with seasonal vaccine experience
 - 1 dose primes an anamnestic response to a 2nd, even years later and vs. a divergent strains - potential for pre-pandemic priming
 - Current US Stockpiled H5 vaccines– limited human and ferret data for cross-protective Abs vs. related clade 2 strains but no published data to confirm dosing or titers vs. most recent isolates
 - Nonadjuvanted vaccine represents most US capacity but impractical dosing, also < response and cross-protection vs. divergent strains
- Investigational vaccines
 - Several mRNA seasonal vaccines in development. No published information but some in larger trials based on positive Phase 1-2 results
 - H5 mRNA vaccine studies underway, no published data but stated that immunogenic

Major Gaps and Priorities I.

- Unclear value of stockpiled filled & finished vaccine:
 - Data on cross-protection vs. current strains and dosing optimization
- Inability to rapidly change strains and produce large quantities:
 - Urgent: speed assessment of cross-protection for emerging strains
 - Enhance modeling/prediction of Ag changes & design of broadly reactive Ags & vaccines
 - Develop more rapidly deployable potency assays for protein vaccines
 - Accelerate mRNA/other platforms through trials and clear pathways to approval/emergency use - global regulatory collaboration and harmonization
- Unknown effectiveness across platforms, need for improved vaccines, unknown performance in pandemics/for new variants:
 - Promote comparative studies; harmonize design, assays, endpoints; include long term outcomes & immunity to assess protection duration
 - Prepare/pre-position large simple trials and RWE platforms/studies

Major Gaps and Priorities II.

- Missed research synergies across human/animal vaccine sectors:
 - Consider establishing One Health Vaccine Group w/ academy, industry, government, regulators
- Deficits in vaccine trust and communication
 - Safety studies and monitoring in special populations (e.g. pregnancy, pediatrics) as needed (e.g. adjuvanted vaccines, mix and match, mRNA vaccines)
 - Studies to inform communication/interventions for diverse groups and circumstances (e.g. occupational, pre-pandemic, pandemic)

Major Gaps and Priorities III.

- Limited data on and consideration of pre-pandemic vaccine strategies
 - Modeling of pre-pandemic vaccine options and outcomes
 - Assessment of population interest/concerns
 - Longer term follow-up of prior and new groups of primed populations to examine consistency/duration of priming and breadth of immunity, including for mRNA vaccines and across platforms (e.g. protein priming for mRNA)
 - Determine immune markers predictive of priming
 - Optimize dosing needed for priming and potentially, for co-administration with seasonal influenza antigens
- *Caveat: closing many gaps depends on resources and financial/regulatory incentives/disincentives, and strong leadership*
- Thanks!



Vaccines, Diagnostics and Treatment Readiness

**Panel Discussion at the Workshop Convened by the National Academies of Sciences,
Engineering and Medicine:**

**Potential Research Priorities to Inform Readiness and Response to Highly Pathogenic Avian
Influenza A(H5N1)**

23 October 2024

Ruben O. Donis, Ph.D.

Influenza and Emerging Infectious Diseases Division (IEIDD)

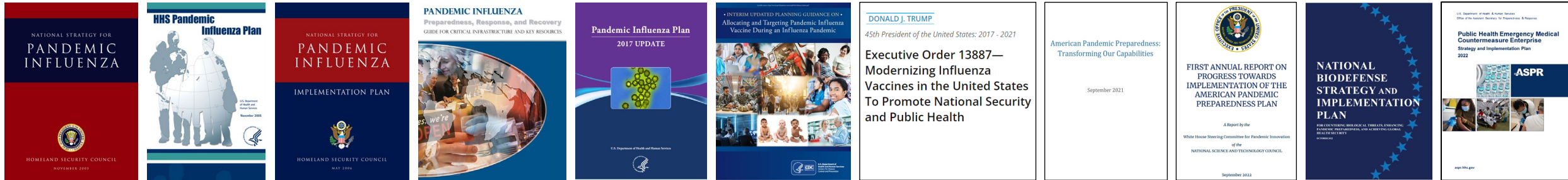
Biomedical Advanced Research and Development Authority (BARDA)

Administration for Strategic Preparedness and Response (ASPR)

U.S. Department of Health and Human Services (HHS)

Pandemic Preparedness Policy

The U.S. government has established several pandemic preparedness goals under plans, such as:



These goals include:

- » Delivery of first finished doses of pandemic vaccine within 3 months of a pandemic declaration;
- » Having a sufficient supply to meet public demand within 4 months of a pandemic declaration; and
- » Manufacture, fill, finish, release, and deliver enough vaccine for the entire U.S. population within 6 months of a Public Health Emergency (PHE) declaration.

To enable rapid response and meet these goals, BARDA continuously maintains influenza virus vaccine seed lots and small quantities of antigen and adjuvant, manufactures clinical trial vaccine lots, and conducts clinical trials to understand the immune response.

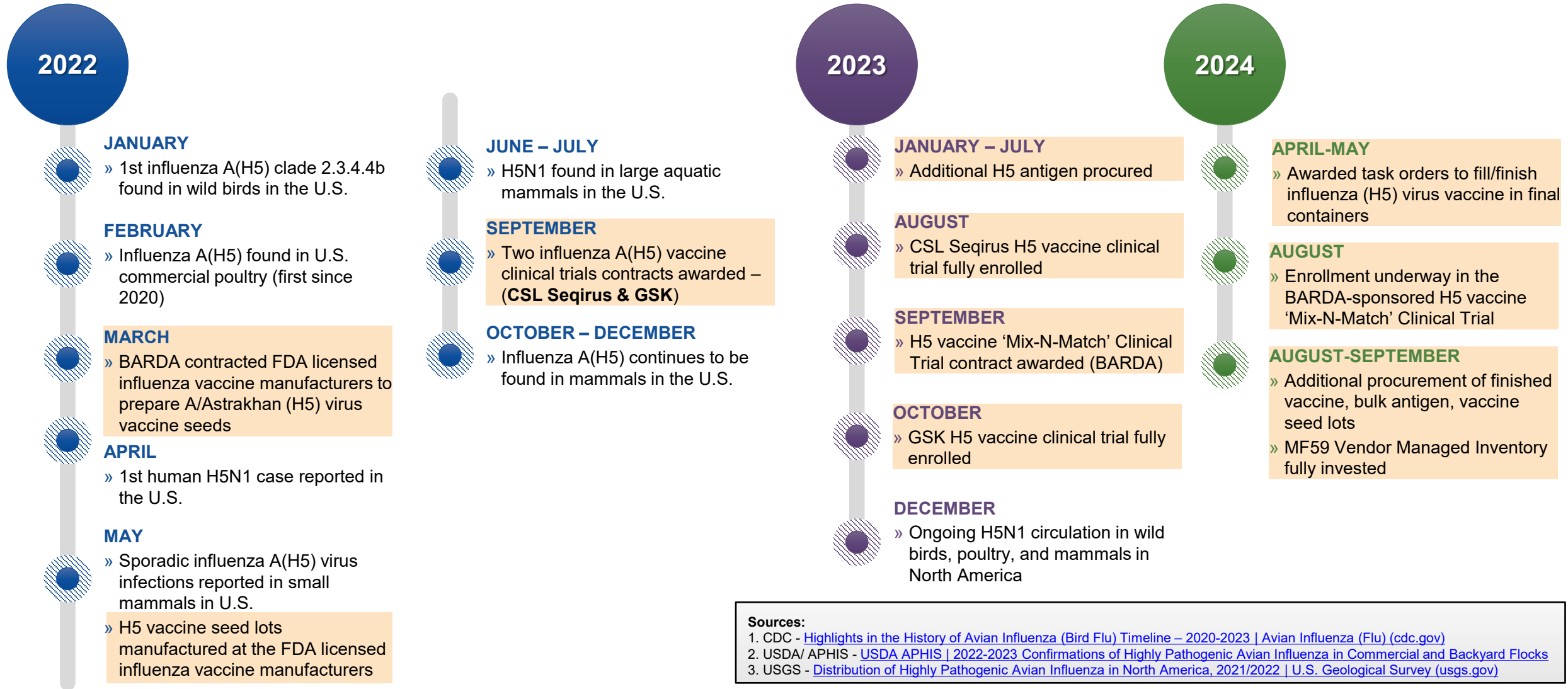


Current Pandemic Influenza Virus Vaccine Response Plan*

- **CSL Seqirus:** cell-based influenza virus vaccine antigen + MF59 adjuvant
 - AUDENZ is approved for use in persons 6 months of age and older
 - Co-formulated antigen and MF59 adjuvant in pre-filled syringes or multidose vials
- **Sanofi, GSK:** Sanofi egg-based influenza virus vaccine antigen + GSK AS03 adjuvant
 - Sanofi is the largest supplier of influenza virus vaccine antigen in the U.S.
 - Sanofi influenza A(H5) virus vaccine (antigen only) is indicated for use in persons 18 to 64 years of age
 - Will require clinical data to support an emergency use authorization (EUA)
- **GSK:** GSK egg-based antigen is not a major part of the response plan in the U.S.
 - Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted is approved for use in persons 6 months of age and older
 - Antigen is manufactured outside the U.S., with pandemic commitments to other markets; however, the U.S. has procured some antigen final containers and bulk antigen.
- mRNA-based vaccines are not a part of the current preparedness activities; however, BARDA is planning for potential future responses.
 - Nucleic acid-based seasonal influenza virus vaccines are not licensed yet in the U.S.
 - If the vaccines become licensed in the U.S., pandemic influenza vaccine response plans will be re-assessed

*subject to funding availability

Influenza A(H5) Virus Clade 2.3.4.4b Preparedness in the U.S.



Pandemic Readiness: Influenza A(H5) Virus Vaccine Clinical Trials, i.

Sponsor: GSK

Protocol Title: A Phase I/II Observer-blind, Randomized, Multi-center Trial to Evaluate the Safety and Immunogenicity of Different Formulations of Monovalent Influenza A/Astrakhan/3212/2020 Like (H5N8) Virus Vaccine With AS03 Adjuvant System (Referred to as Q-Pan H5N8), Given as a Two-dose Series to Adults 18 to 64 Years of Age and 65 Years of Age and Older

Status: Enrollment complete

Study Group (2 doses 21 days apart)	18–64 years*	>65 years*
3.75mcg HA + AS03 _(half dose)	65	65
3.75mcg HA + AS03 _(full dose)	65	65
7.5mcg HA + AS03 _(half dose)	65	65
7.5mcg HA + AS03 _(full dose)	65	65

**Number of Participants*

Outcomes

- Safety: safety and reactogenicity of different formulations adjuvanted with full or half dose of AS03
- Immunogenicity: hemagglutination inhibition (HAI) antibody responses and microneutralization (MN) antibody responses against influenza A/Astrakhan/3212/2020 (H5N8)-like virus at days 1, 22, 43, 6 months following last dose

NCT05975840

Pandemic Readiness: Influenza A(H5) Virus Vaccine Clinical Trials, ii.

Sponsor: CSL Seqirus

Protocol Title: A Phase 2, Multi-Center, Randomized, Observer-Blind Study, to Evaluate Safety and Immunogenicity of Homologous or Heterologous Priming and Booster Vaccinations With H5N8 or H5N6 MF59-adjuvanted, Cell Culture-derived Influenza Vaccine in Healthy Subjects ≥18 Years of Age

Status: Enrollment complete

Study Group	Dose 1 (Day 1)	Dose 2 (Day 22)	Dose 3 (6 months)	18–64 years*	>65 years*
1	aH5N8c	aH5N8c	aH5N8c	120	120
2	aH5N8c	aH5N6c	aH5N8c	60	60
3	aH5N6c	aH5N8c	aH5N8c	60	60

**Number of Participants*

Outcomes

- Safety: safety and reactogenicity of different homologous and heterologous prime boosting regimens adjuvanted with MF59
- Immunogenicity: hemagglutination inhibition (HAI) antibody responses and microneutralization (MN) antibody responses against influenza A/Astrakhan/3212/2020 (H5N8)-like virus and influenza A/Guangdong/18SF020/2018 (H5N6)-like virus at Days 1, 22, 43, 6 months, and days 1 and 21 post dose #3

NCT05874713

Pandemic Readiness: Influenza A(H5) Virus Vaccine Clinical Trials, iii.

Sponsor: Biomedical Advanced Research and Development Authority (BARDA)

Protocol Title: Randomized, Double-Blind, Phase 2 Study to Assess Safety and Immunogenicity of A/H5 Inactivated Monovalent Influenza Vaccines at Different Antigen Dose Levels Adjuvanted with AS03® or MF59®

Status: Recruiting

Sanofi Egg-based Antigen	Adjuvant	Antigen Dose	18–64 years*	≥65 years*
A/Astrakhan/3212/2020 (H5N8)	AS03 Full Dose	3.75 µg	60	0
		7.5 µg	60	60
		15 µg	60	60
A/Astrakhan/3212/2020 (H5N8)	AS03 Half Dose	3.75 µg	60	0
		7.5 µg	60	60
		15 µg	60	60
A/Astrakhan/3212/2020 (H5N8)	MF59	3.75 µg	60	0
		7.5 µg	60	60
		15 µg	60	60
A/bar-headed goose/Qinghai/1A/2005 (H5N1)	AS03 Full Dose	3.75 µg	60	0
		7.5 µg	60	60
		15 µg	0	60
A/bar-headed goose/Qinghai/1A/2005 (H5N1)	MF59	3.75 µg	60	0
		7.5 µg	60	60
		15 µg	0	60

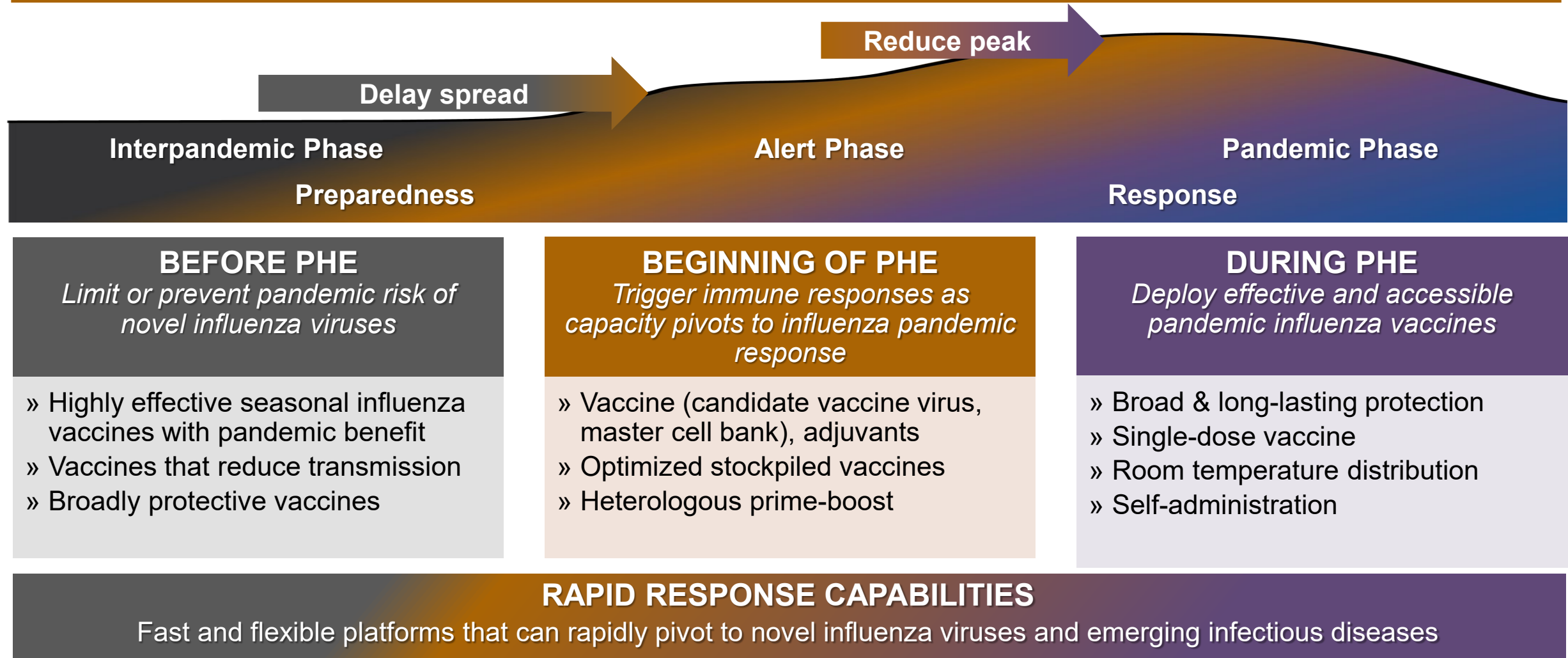
*Number of Participants

Outcomes

- Safety:** safety and reactogenicity following each vaccination of different antigens and antigen doses of vaccine given with AS03 full dose, AS03 half dose, or MF59 adjuvant
- Immunogenicity:** hemagglutination inhibition (HAI) antibody responses and microneutralization (MN) antibody responses against influenza A/Astrakhan/3212/2020 (H5N8)-like virus and influenza A/bar-headed goose/Qinghai/1A/2005 (H5N1)-like virus at days 1, 22, 43, 6 months following last dose

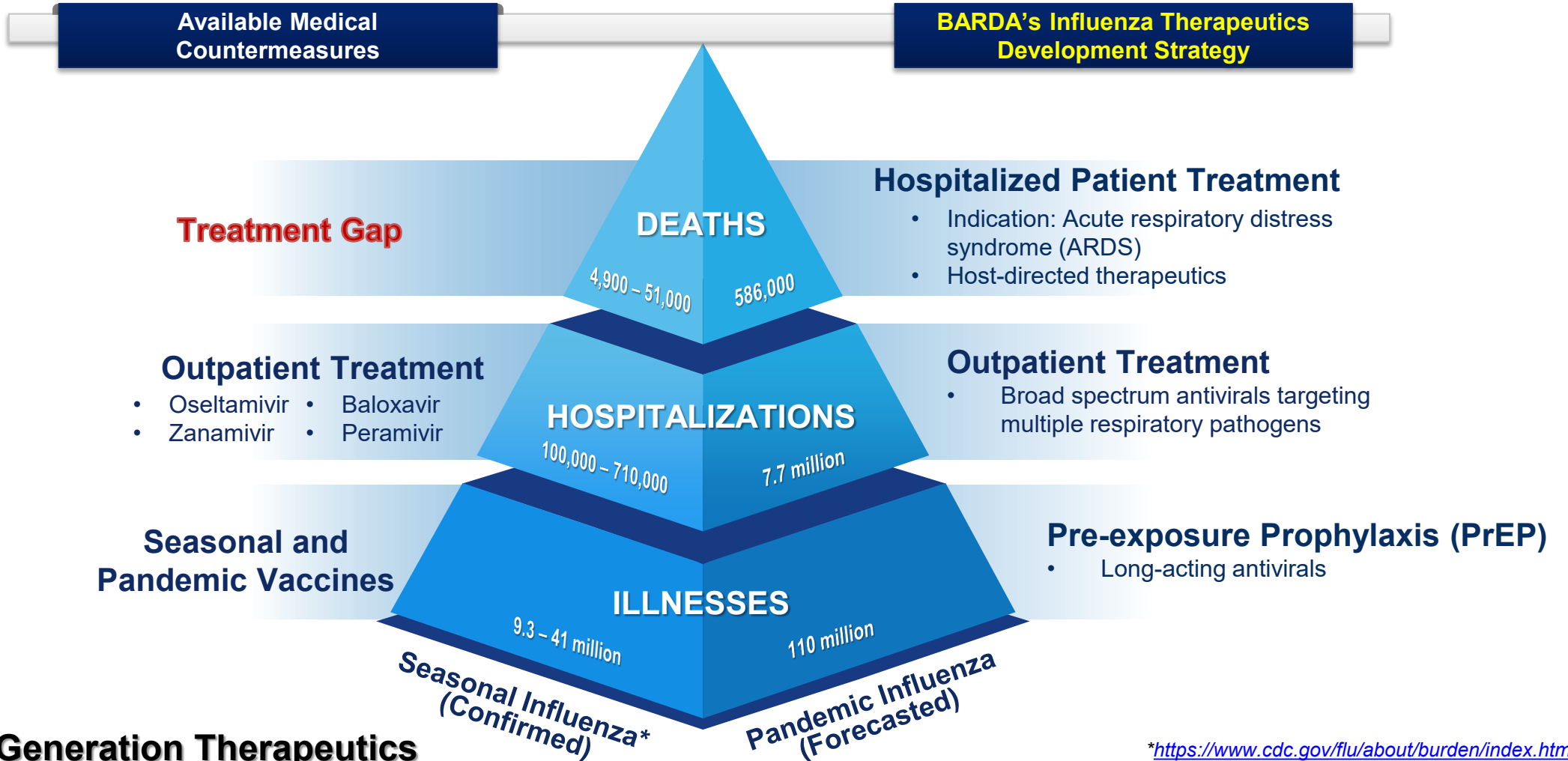
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BARDA Vaccine Development Program Strategic Goals



PHE, public health emergency

Gaps in Pandemic Influenza Therapeutics Preparedness





*Thank
You!!*

Ruben O. Donis, Ph.D.
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Biomedical Advanced Research and Development Authority (BARDA)
Administration for Strategic Preparedness and Response (ASPR)
U.S. Department of Health and Human Services (HHS)

<https://medicalcountermeasures.gov/barda/influenza-and-emerging-infectious-diseases/>



Vaccines, Diagnostics and Treatment Readiness

**Panel Discussion at the Workshop Convened by the
National Academies of Sciences, Engineering and Medicine:
Potential Research Priorities to Inform Readiness and Response to Highly Pathogenic Avian
Influenza A(H5N1)
23 October 2024**

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Unclassified

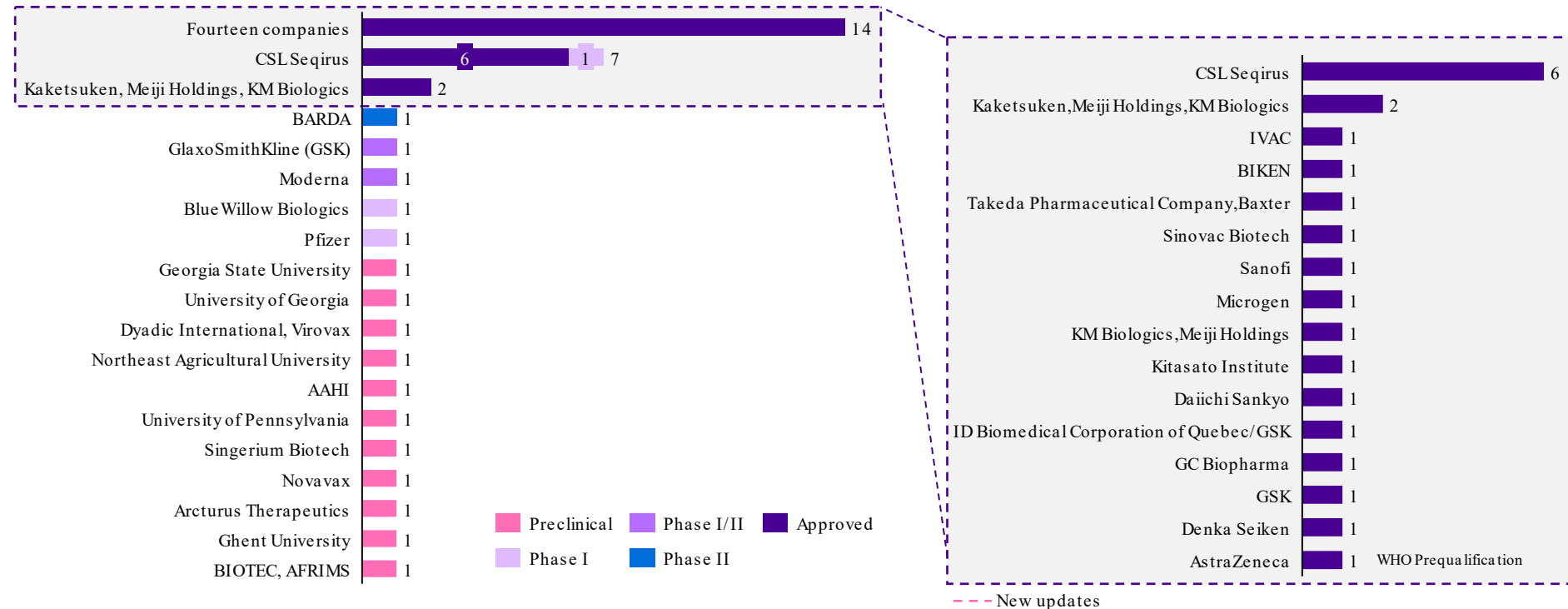
Session 7: Limiting spread in Animals and Humans

Paula Barbosa, IFPMA

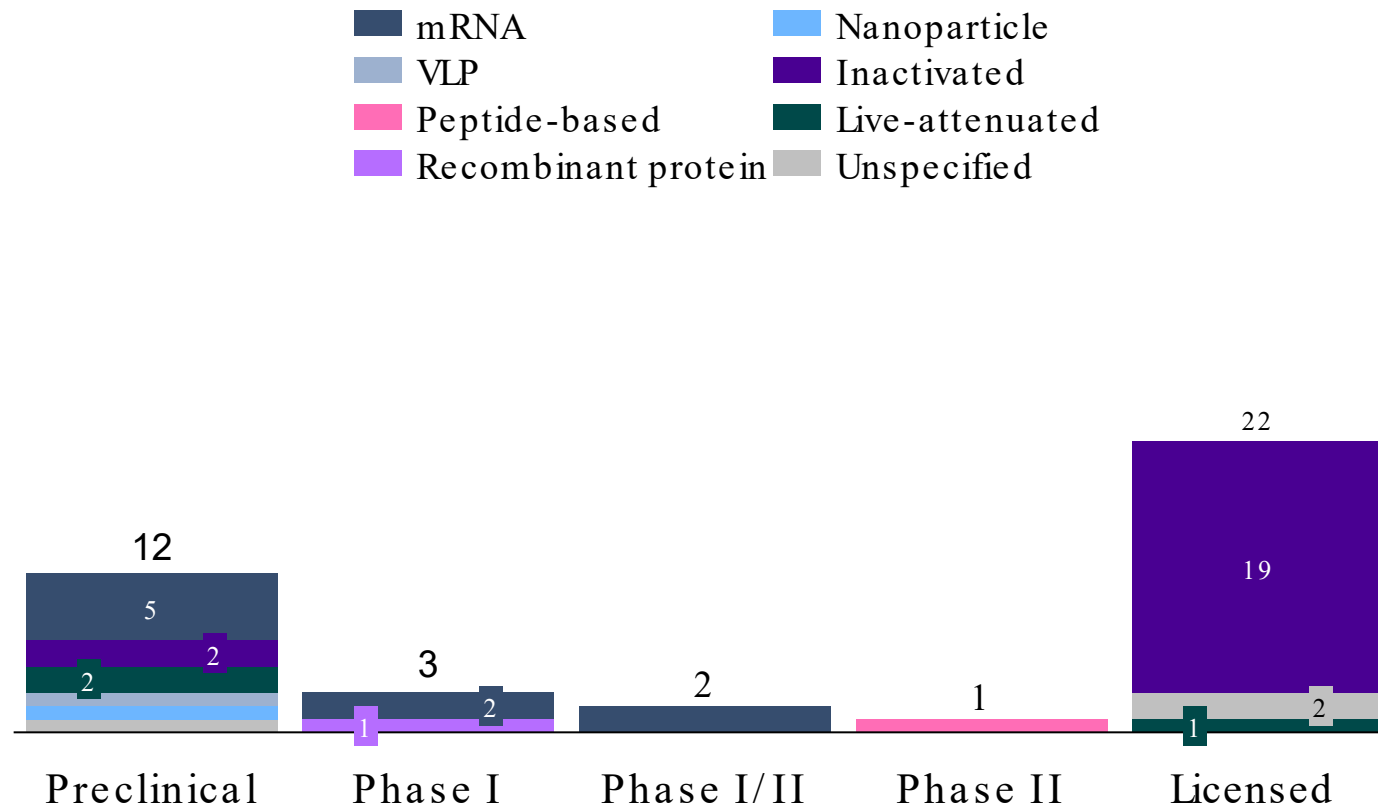
Overview of H5N1 influenza vaccines – approvals & pipeline

There are over 100 pandemic influenza vaccines, including 49 that have been licensed. Of those vaccines, **39 specifically target highly pathogenic avian influenza (HPAI) H5N1**, 22 of which are approved in at least one country.

There are 16 developers with approved H5N1 vaccines
H5N1 pandemic influenza vaccine pipeline overview



Overview of H5N1 influenza vaccines – pipeline by vaccine technology





Other considerations



National Academies H5N1 Webinar

**Therapeutics Research for Influenza Pandemic
Preparedness and Response**

23 October 2024

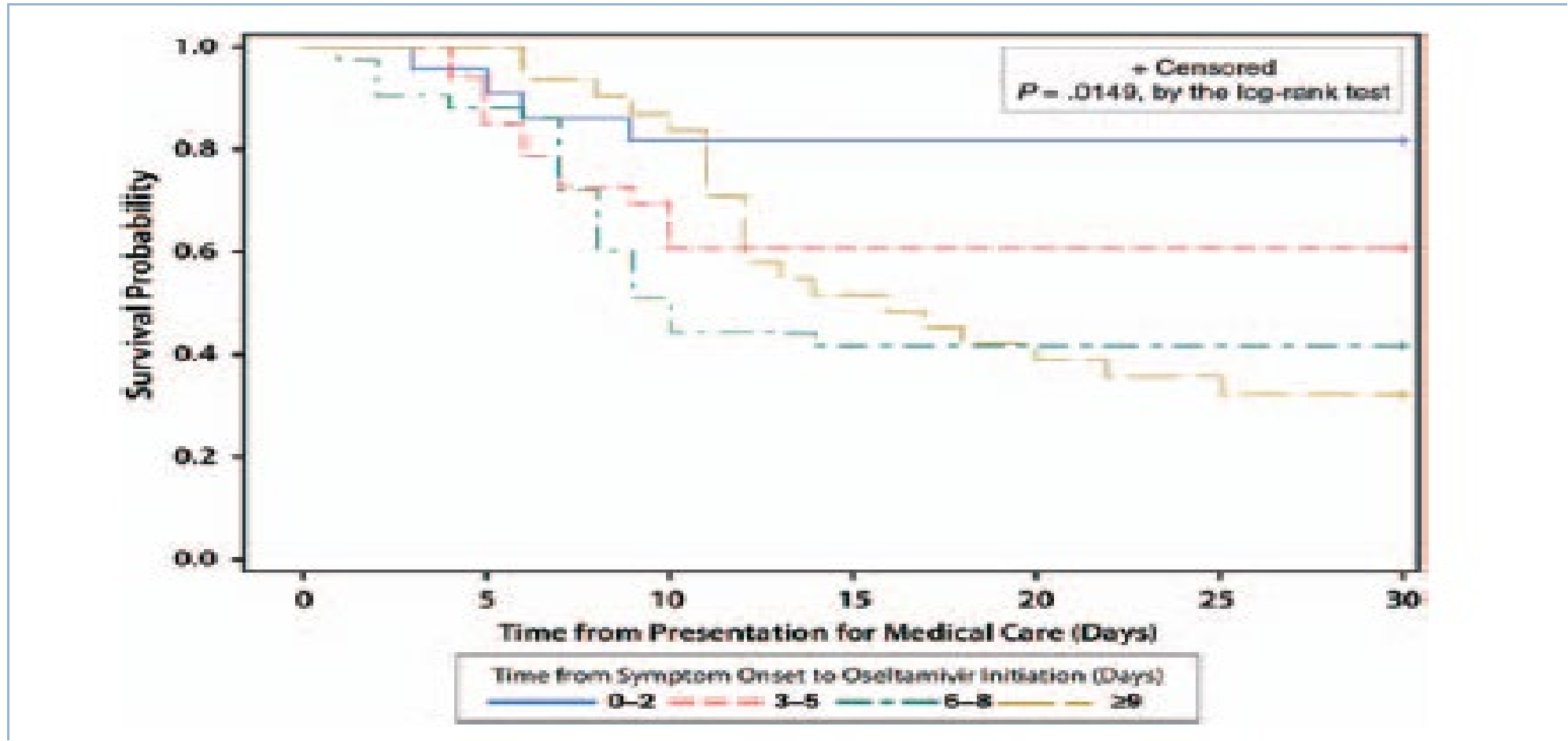
Frederick G. Hayden, M.D.
University of Virginia School of Medicine
Charlottesville, Virginia, USA

Effectiveness of Antiviral Treatment in Human Influenza A(H5N1) Infections: Analysis of a Global Patient Registry

- 308 cases from 12 countries from 1997 to 2009¹
- Crude survival in those given ≥ 1 dose of oseltamivir was 60% (90/150), whereas survival among non-treated patients was 24% (32/134) ($P < 0.001$).
 - Multivariate modeling showed 49% mortality reduction from oseltamivir treatment.
- Lower survival in older patients, those with higher viral loads, hypercytokinemia, and respiratory failure^{2,3}

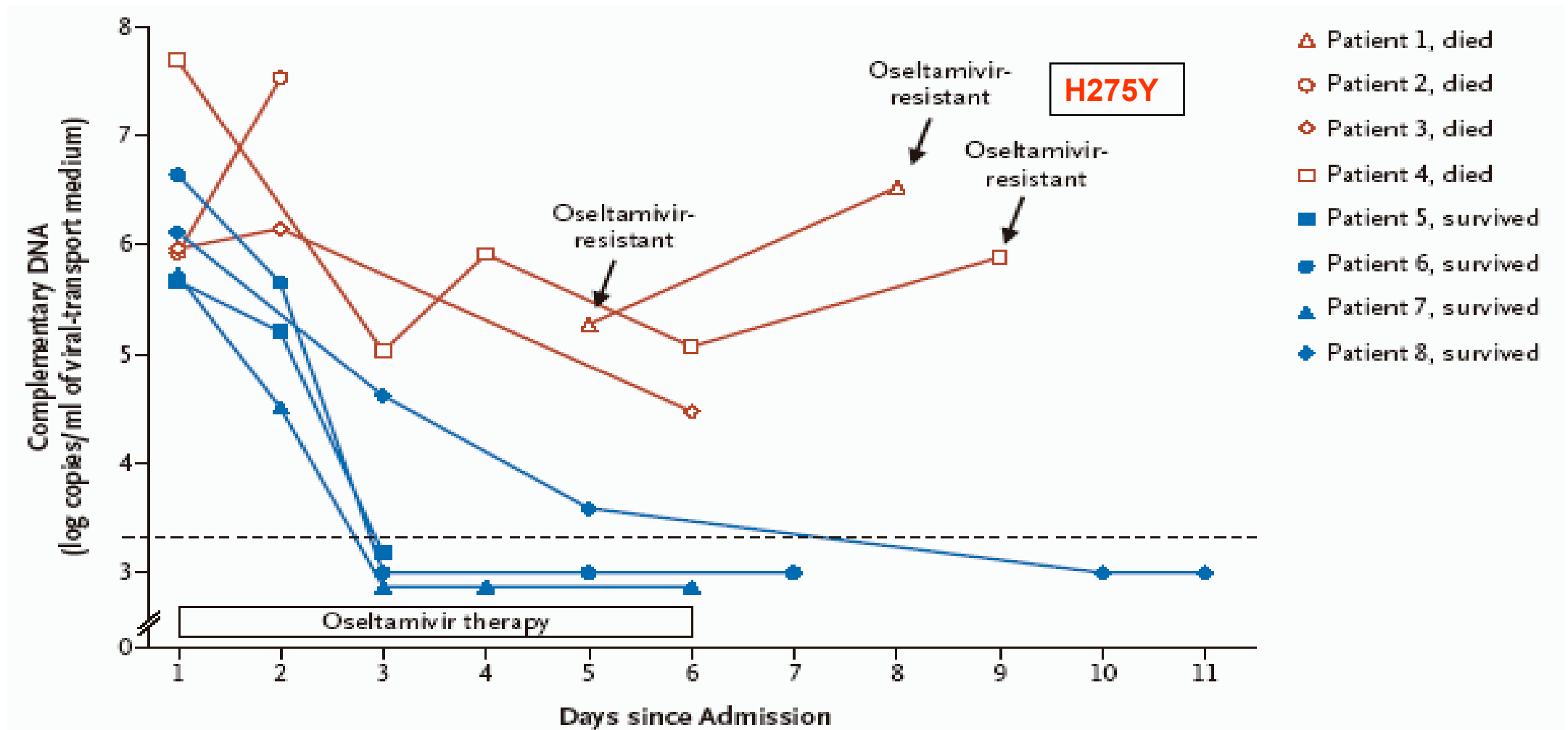
¹Adisasmito et al., J Infect Dis 202:1154, 2010; ²de Jong et al., Nat Med 12:1203, 2006; ³Chan et al., J Infect Dis 206:1359, 2012

Survival in 129 Oseltamivir-Treated H5N1 Cases: *Importance of Time to Treatment*



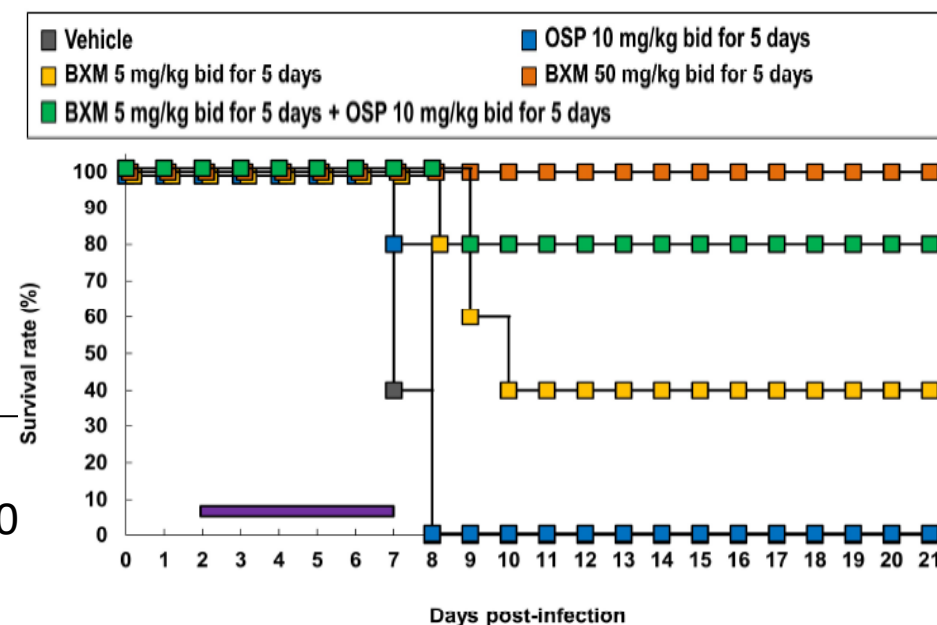
Chan et al., J Infect Dis 206:1359, 2012

Pharyngeal Viral Loads and Resistance Emergence during Oseltamivir Treatment of H5N1



Pre-Clinical Studies of Baloxavir for H5 Viruses

- BXA exhibited similar in vitro inhibition of H5N1 and H5N8 viruses in comparison with seasonal strains.
- At clinically relevant doses, oral baloxavir more effective than oseltamivir for A/Hong Kong/483/1997(H5N1) in lethal murine model.
- In vitro synergy observed with combinations of baloxavir and oseltamivir or peramivir for H5N1.
- Combined baloxavir + oseltamivir in mice are more effective than monotherapies.



Taniguchi et al., Viruses 14, 111, 2022. <https://doi.org/10.3390/v14010>

In Vitro Susceptibility of Human Isolates of H5N1 Clade 2.3.4.4b Viruses to Neuraminidase Inhibitors and Baloxavir

Virus	Median (range) 50% Inhibitory Concentration, nM			
	Oseltamivir	Peramivir	Zanamivir	Baloxavir
Clade 2.3.4.4b (n = 6)	3.66 (2.94-4.38)	0.08 (0.07-0.10)	0.20 (0.18-0.22)	0.83 (0.44-1.06)
Reference viruses				
A(H1N1)pdm09	0.43	0.05	0.16	
A(H1N1)pdm09- NA-H275Y	231.17	16.25	0.25	
A(H1N1)pdm09				1.12
A(H1N1)pdm09- PA-I38T				139.98

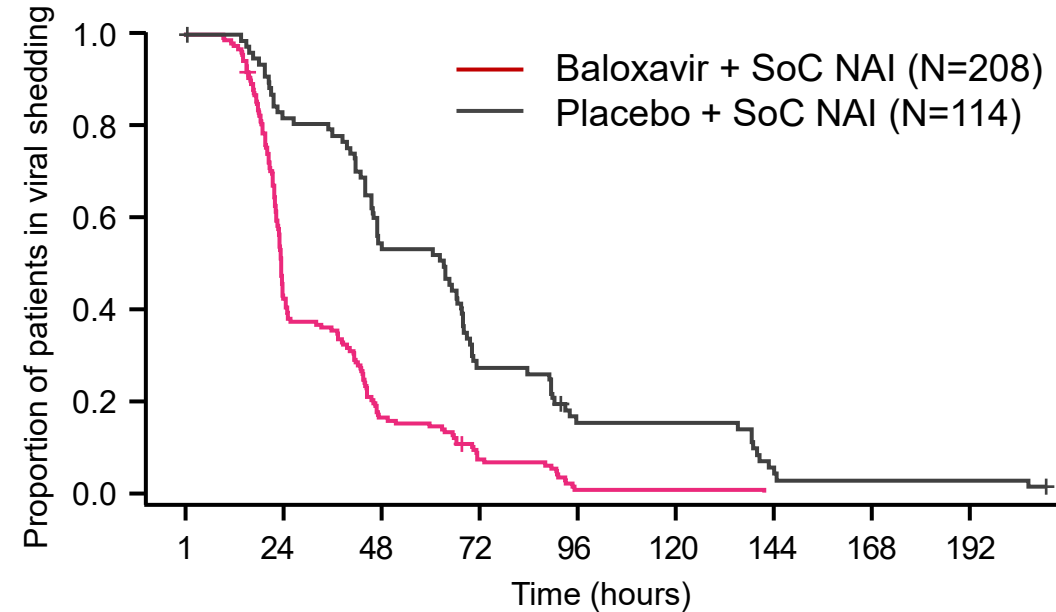
Note: NAI susceptibility by fluorescent NA inhibition assay and baloxavir susceptibility by cell culture assay (Influenza **R**eplication **I**nhibition **N**euraminidase activity-based **A**ssay).

Mean values are listed for reference viruses.

Data generously shared by Dr. Larisa Gubareva, US Centers for Disease Control and Prevention

Flagstone RCT: Combined Baloxavir or Placebo + SoC NAI in Hospitalized Influenza Patients

- Enrolment ≤ 96 hr of Sx onset
- Median time to clinical improvement (TTCI): 97.5 vs 100.2 hr
- 28-day mortality numerically lower (2% vs 6%) with combination
- Median duration of infectious virus detection: 23.9 vs 63.7 hr ($P < 0.001$)



- PA/I38X substitutions in 1%
- NA/H275Y in 1% with combination vs 3% with NAI alone
- PA-I38T + NA-H275Y in 2 IC hosts

Therapeutics in Influenza Pandemic Response: Uncertainties

- Will higher and/or more prolonged dosing be needed with currently approved antivirals for preventing and treating infections by a pandemic virus?
- To what extent will treatment reduce virus transmission?
- How rapidly and how often will antiviral-resistant variants emerge in treated patients?
 - Will such variants retain transmission fitness and virulence for contacts?
- In which patient populations will combination antiviral therapy be needed?
- In seriously ill patients, which immunomodulatory therapies (e.g., corticosteroids, JAK inhibitors, anti-IL-6 and C5a monoclonals) will help and at what stage of illness?

REMAP-CAP Trial in Hospitalized Influenza Patients

(Slide courtesy of Dr. Anthony Gordon, Imperial College, London)

► Influenza antiviral domain

Inclusion criteria

- Hospitalised with moderate or severe influenza
- Laboratory-confirmed influenza
- Aged ≥ 28 days

Response Adaptive-Randomisation



► Other domains: corticosteroids vs not in those on suppl O₂; baricitinib vs tocilizumab vs neither in critically ill

► Primary endpoint:

- All-cause mortality at 90 days post-randomisation

► Secondary endpoints include:

- Hospital + ICU lengths of stay, ICU mortality at 90 days, ventilator-free days, organ failure-free days

Therapeutics for Influenza: Research Priorities

- Large RCTs of combination antiviral therapies and of antivirals plus immunomodulators are required in severe seasonal influenza.
 - Need sustained network in USA to study therapeutics for serious RVIs
 - Intravenous zanamivir warrants further study.
 - Optimization of antiviral dose regimens will require rapid, pre-planned trials early during pandemic response.
- Rapid access is essential for optimal use of antivirals.
 - Demonstration studies needed during seasonal influenza for strategies (e.g., test + treat in pharmacies, mobile units, or households; household delivery or stockpiling; over-the-counter access)
- Antiviral resistance threats highlight needs for
 - Rapid, optimally point-of-care, viral susceptibility tests
 - Diversification and expansion of antiviral stockpiles

Assessment of antiviral susceptibility of US A(H5N1) viruses

- Clade 2.3.4.4b viruses collected from various animal species in US since 2022
- Sequence data generated by USDA, CDC, and other laboratories deposited to GISAID/NCBI
- Sequence data for **~5,200** viruses, including from dairy cattle and humans
- Molecular markers of drug resistance with known clinical relevance:
 - M2 blockers:** **13** viruses with **V27A** (4), **A30S** (4) or **S31N** (5) in M2 protein
 - NAI oseltamivir:** **5** viruses with **NA-H275Y**
 - Not a cluster, all from birds in 2022
 - H275Y may confer cross-resistance to NAI peramivir
 - PA baloxavir:** **3** viruses with **PA-I38T**
 - One from 2022 and two from 2024; none from humans
- Low frequency of resistance detection (<0.5%)
- Other mutations found in NA and PA may also reduce susceptibility to antivirals (e.g., NA-T438I may reduce susceptibility to zanamivir; found in ~1.7% of viruses, mainly from birds in 2022)



Article

Evaluation of Baloxavir Marboxil and Peramivir for the Treatment of High Pathogenicity Avian Influenza in Chickens

Augustin Twabela ^{1,2} , Masatoshi Okamatsu ¹, Keita Matsuno ^{3,4} , Norikazu Isoda ¹ and Yoshihiro Sakoda ^{1,3,*}

DOI: 10.1638/2023-0103

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FOUR-WEEK ORAL ADMINISTRATION OF BALOXAVIR MARBOXIL AS AN ANTI-INFLUENZA VIRUS DRUG SHOWS NO TOXICITY IN CHICKENS

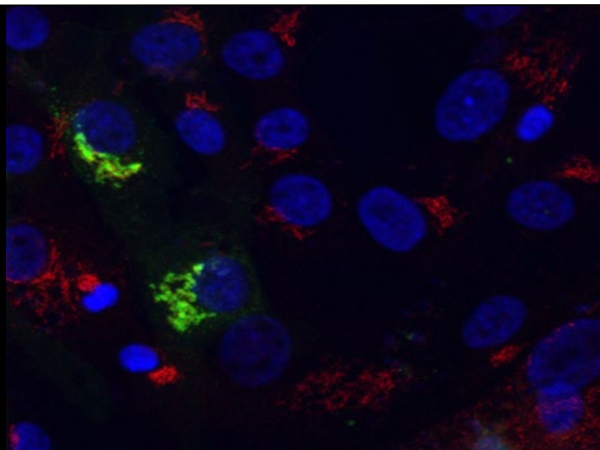
Mariko Miki, DVM, Ryo Daniel Obara, DVM, Kyohei Nishimura, PhD, Takao Shishido, PhD, Yoshinori Ikenaka, PhD, Ryoko Oka, Kenji Sato, MS, Shouta M.M. Nakayama, DVM, PhD, Takashi Kimura, DVM, PhD, Atsushi Kobayashi, DVM, PhD, Keisuke Aoshima, DVM, PhD, Keisuke Saito, DVM, PhD, Takahiro Hiono, DVM, PhD, Norikazu Isoda, DVM, PhD, and Yoshihiro Sakoda, DVM, PhD

- Use of baloxavir and other influenza antivirals in poultry and other animals risks emergence of resistant variants.



Session 7-Limiting Spread in Animals and Humans

Vaccines, Diagnostics, and Treatment Readiness



Darrell R. Kapczynski

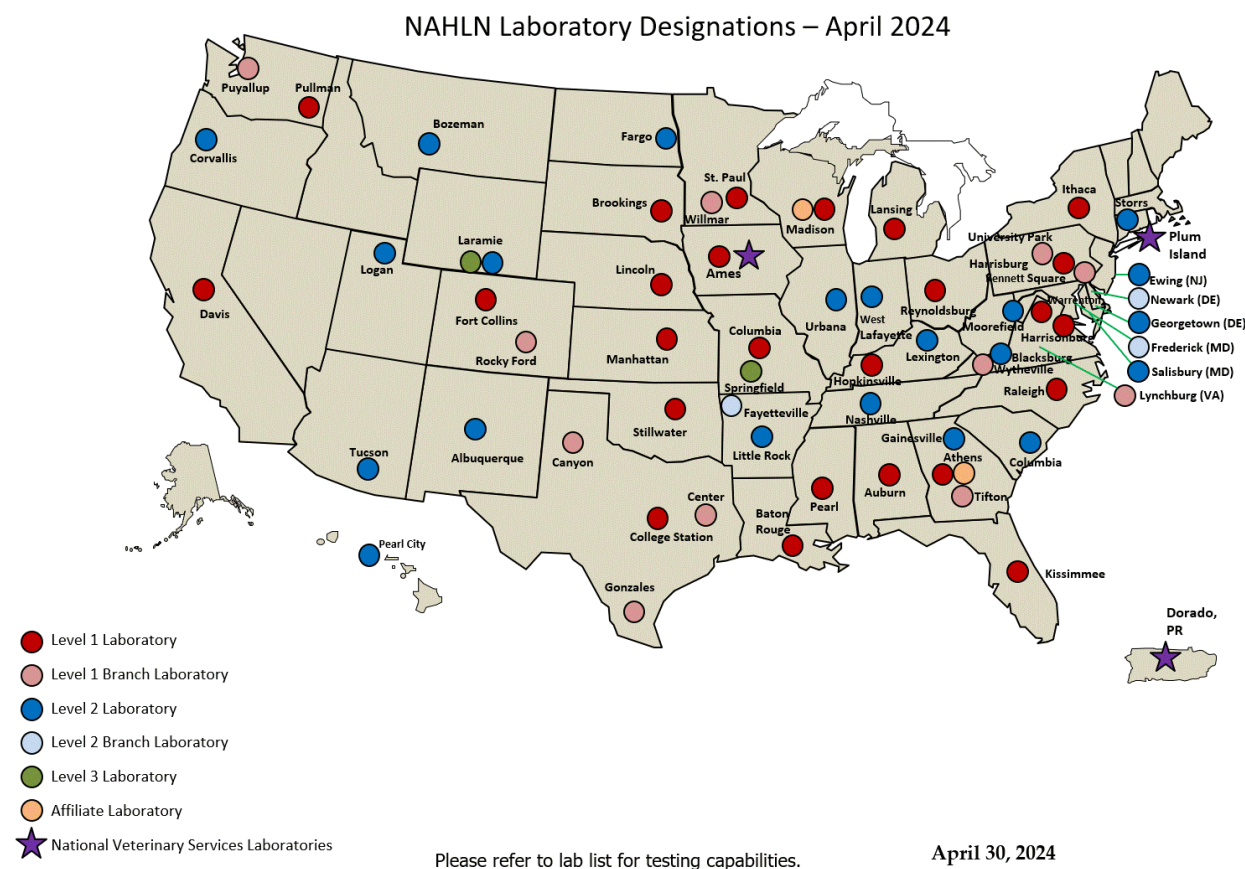
U.S. National Poultry Research Center, ARS, USDA, Athens, Georgia, U.S.A

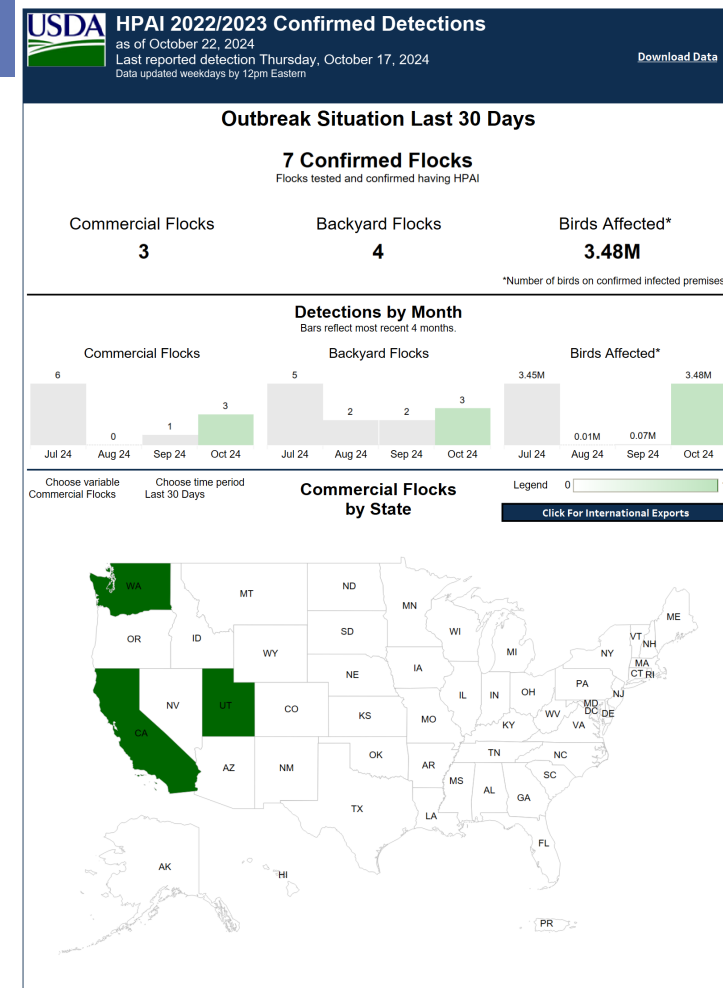
Potential Research Priorities to Inform Readiness and Response to Highly Pathogenic Avian Influenza A (H5N1)

October 22-23, 2024

National Animal Health Laboratory Network

- Created a diagnostic network of labs in 2002 spread throughout the U.S.
- Rapid testing with surge capacity.
- Real-time PCR was one of the targeted technologies that was to be developed.
- Requires labs to use approved tests, provide positives for confirmation to USDA/APHIS, and pass proficiency testing of labs.
- Network has grown to 60 labs





Availability of Rapid Diagnostics

- Quantitative real-time RT-PCR (qRT-PCR) tests for avian influenza were one of first tests used in the NAHLN (2002)
- Validation showed sensitivity and specificity were similar to egg isolation with results in as little as 3 hours
- Use of qRT-PCR have been used successfully in multiple avian influenza (Highly pathogenic and low pathogenic H5 and H7) outbreaks
- Surveillance in wild birds. Genomic sequence data.

Control Options: Depopulation Methods In Outbreak Situations

- Several different methods are approved for mass depopulation of poultry
- Backyard poultry more likely to be euthanized individually
- American Veterinary Medical Association (AVMA) Guidelines for Depopulation of Animals: 2019 Edition
 - Non-binding guidelines, but considered as most important recommendations for approved Euthanasia methods
 - Revised guidelines are currently being prepared and will be open for public comment soon
- Some methods are strongly preferred or other methods
 - Foam
 - Gas-CO₂
 - Ventilation shutdown
 - Individual



Commercial poultry depopulated (as of October 16, 2024)

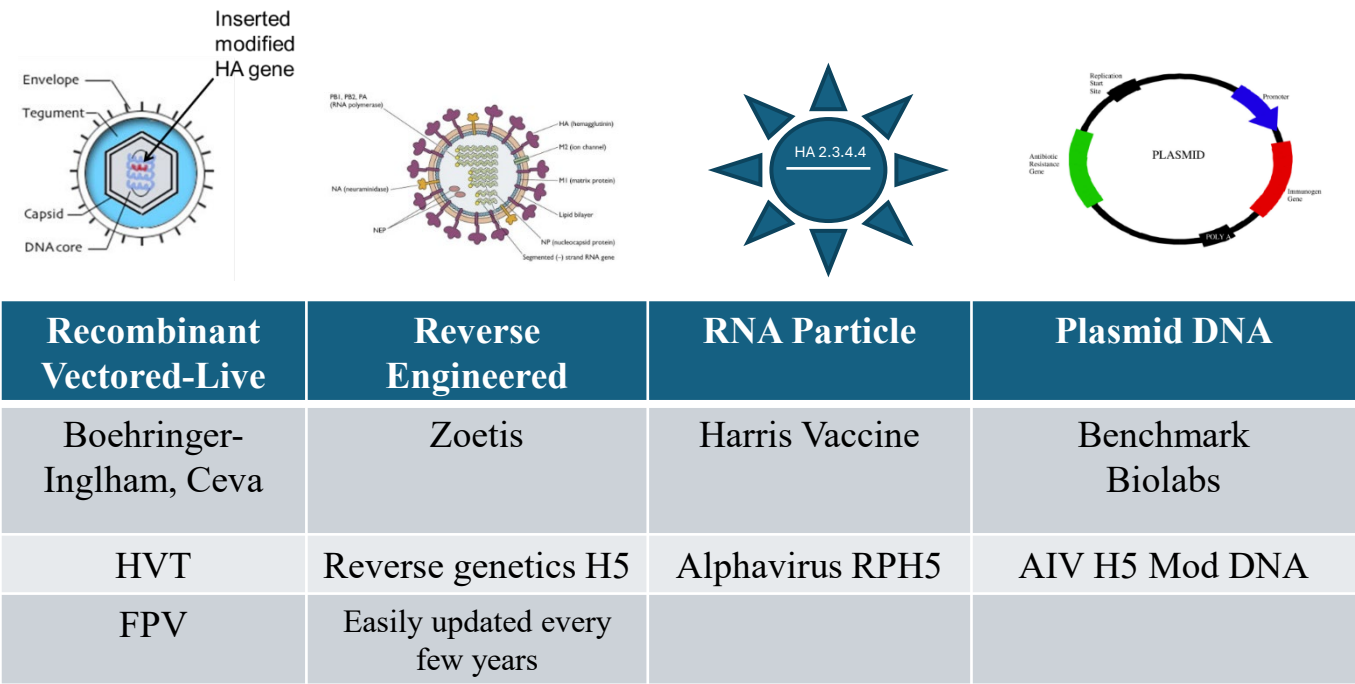
	Commercial
Turkeys	14.8 million
Egg Layers & Pullets	80 million
Broilers	6.1 million
Estimated Total	100.9 million

These depopulation losses represent:

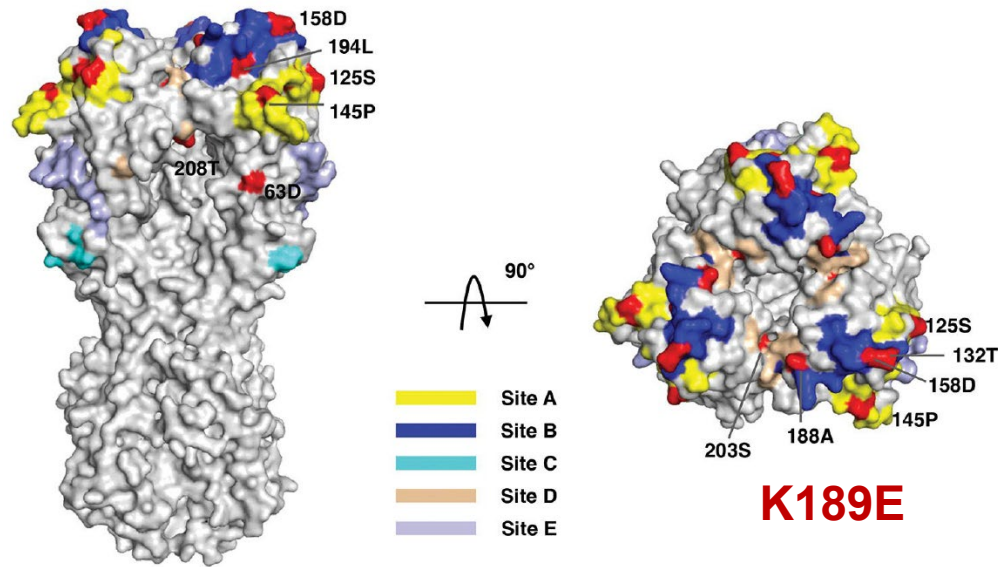
- 6.77% of U.S. annual turkey production
- 19.57% of U.S. annual layer inventory
- 2.72% of U.S. annual pullet inventory
- Less than 0.07% of U.S. broiler inventory (broiler infection has been limited).
- **The largest HPAI outbreak ever recorded in the United States and arguably one of the most significant animal health events in U.S. history.**

Control Options: Vaccines for Poultry

- Don't vaccinate poultry for HPAI in U.S. Biosecurity is #1 option.
- H5-hemagglutinin genetically & antigenically match the outbreak virus.
- Can change hemagglutinin gene to match outbreak virus.
- Rapidly obtain conditional license for non-replicating vaccines.
- Recombinant vectored-live vaccines requires more extensive licensing requirements which delays process and increases costs.



H5N1 HPAIVs mutate quicker than the vaccine update



- There are some **antigenic shifts** between the circulating H5N1 viruses and vaccine strains.
- The **mismatch** between the vaccine and outbreaking H5N1 AIVs: vaccine may couldn't fully protect poultry.

Table 1. HI titers of H5N1 and H5N8 highly pathogenic avian influenza viruses from wild birds in China against antiserum of H5 Re-11, Re-13, and Re-14 vaccines*

Virus	HI titers of chicken antiserum against vaccine strains and H5N1/H5N8 isolates		
	Re-11, clade2.3.4.4h	Re-13, clade2.3.4.4h	Re-14, clade2.3.4.4b
Re-11, Dk/GZ/S4184/2017(H5N6)	256	256–512	128
Re-13, Dk/FJ/S1424/2020(H5N6)	32	256	2–4
Re-14, Ws/SX/4–1/2020(H5N8)	8	16	256
Bs/EC/74-Lg/2021(H5N1)	16	8	128
Ws/NC/AK2-O/2021(H5N1)	2–4	2–4	32
Ws/HN/1-K/2020(H5N8)	8	8	64
Ws/HN/1-G/2020(H5N8)	8	8	64

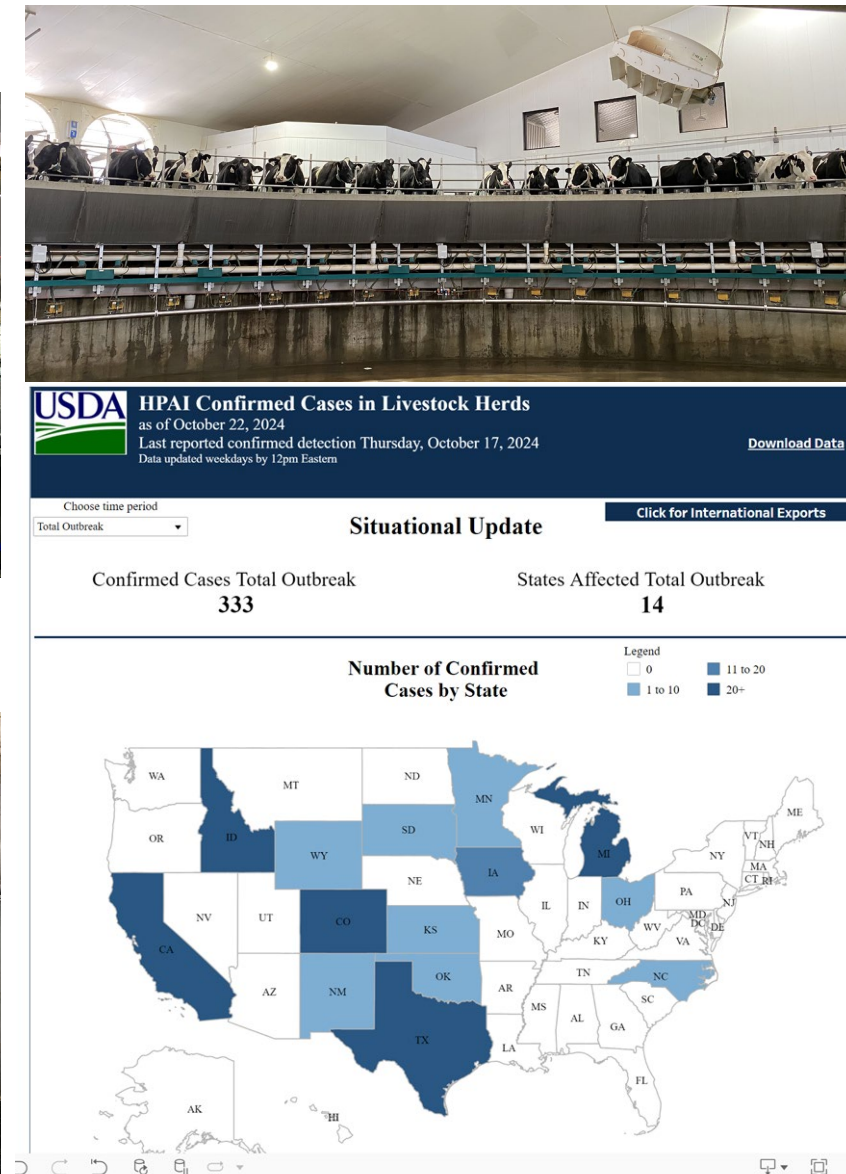
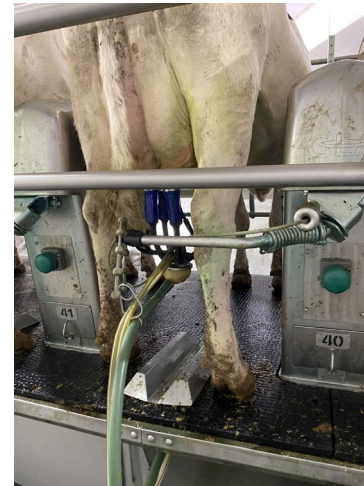
*H5 Re-11 vaccine was used in poultry in mainland China during December 2018–December 2021. H5 Re-13 and Re-14 vaccines have been deployed since January 2022. HI, hemagglutination inhibition.

Issues with Available Vaccines

- Require parenteral vaccination
 - HVT vectored vaccines can be given in ovo or day of age, but use may displace another HVT vectored vaccine in vaccination program
 - More costly to update live-vectored vaccines to allow matched vaccines
- Mass administered vaccines are still unavailable once birds are placed in the field
 - Live virus vectored vaccines potentially could be used, but nothing on the horizon
 - NDV vectored AI vaccines are available, but don't appear to generate a good immunity to poultry previously vaccinated with NDV
- Vaccines matched to field strain provide better protection
 - Will countries accept a DIVA strategy?
- Several technologies are available internationally that are not licensed in U.S.
- Lack of vaccine market in U.S. inhibits innovative solutions

HPAI in livestock

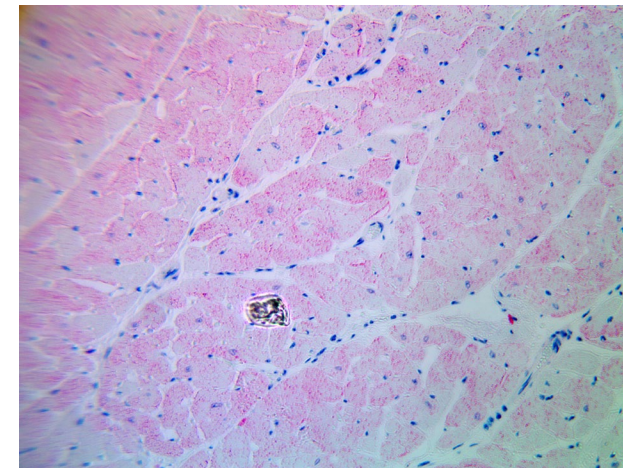
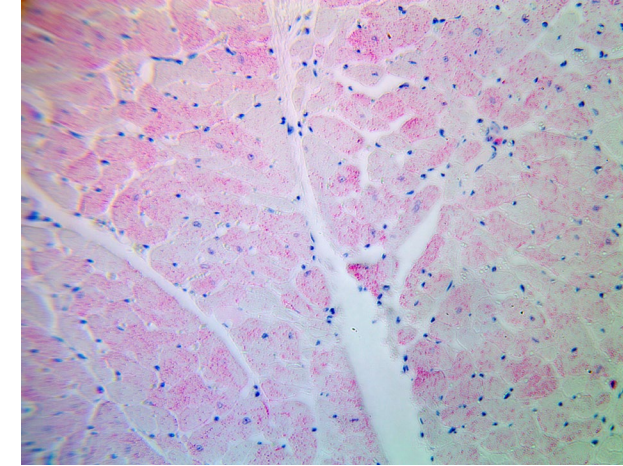
- Dairy Exports are 18% of U.S. production and is valued at 9 billion dollars in 2022
- Little trade restrictions have been realized in dairy products
- No evidence of beef cattle infection
- No evidence of systemic infection, although hamburger may contain lymph nodes
- Culled dairy cattle are 10% of beef supply



Vaccination as a Control Tool in Cattle

- No vaccines available for H5 HPAI in cattle. Prospects of B3.13 vaccines being developed.
- Multiple companies have expressed interest in producing vaccines for cattle.
- Unclear which vaccines would provide protection from viral mastitis and virus shedding.
- Unclear if serum antibodies are reliable marker for protection of the mammary gland.

IHC-Mammary gland



Research Priority Questions-Animals

- Surveillance and detection along with sequencing is critical for control in animals.
 - HPAI reportable FAD in commercial poultry. Not reportable in cattle.
 - Mechanisms for increased speed in detection in agriculture and wild animals.
 - What is needed? LFA for cattle ?
- Vaccines will aid in control but will not eradicate virus. They can protect from disease not infection. Do we need a veterinary stockpile for emergency vaccination of animals?
- We need efficacious vaccines for use in cattle.
- Guidelines for use of vaccines in more susceptible poultry species is a barrier to control. Can we establish vaccine use in different sectors without trade consequences?
- Have a limited capacity to do research, with an ever expanding list of items.
- Need people and infrastructure.
- What is our goal for highly pathogenic avian influenza in animals the U.S. ?