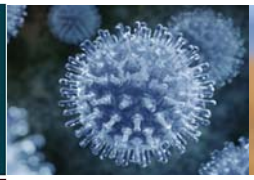
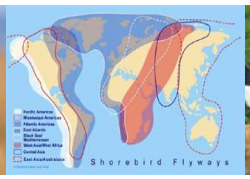
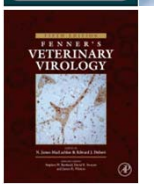
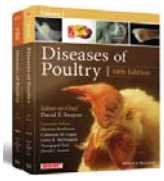




Vaccine usage to control highly pathogenic avian influenza in poultry and other domestic birds: Setting the scene



David E Swayne

Southeast Poultry Research Laboratory, U.S. National Poultry Research Center, Agricultural Research Service, U.S. Department of Agriculture, Athens, Georgia, USA

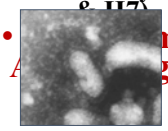
Disclaimer: This presentation is based on current scientific data and is not an endorsement of any specific product or company

1

High Pathogenicity Avian Influenza

1. 1959: Scotland, H5N1	22. 2004: USA, H5N2	• Orthomyxovirus with protein projections on the surface:
2. 1961: S. Africa, H5N3	23. 2004: Canada, H7N3	• 16 hemagglutinin subtypes (i.e., H1-H16) - MUTATIONS
3. 1963: England, H7N3	24. 2004: S. Africa, H5N2 (ostriches)	• 9 neuraminidase subtypes (i.e., N1-N9)
4. 1966: Canada, H5N9	25. 2006: S. Africa, H5N2 (ostriches)	• 8 gene segments: Can REASSORT between different LP & HP AIVs
5. 1975: Australia, H7N7	§ 26. 2005: N. Korea, H7N7	• Vary in pathotype (chickens):
6. 1979: Germany, H7N7	27. 2007: Canada, H7N3	• Low pathogenicity (LPAIV): mild disease (any H1-16)
7. 1979: England, H7N7	28. 2008: England, H7N7	• High pathogenicity (HPAIV): systemic - deadly disease (some H5 & H7)
8. 1983-84: USA, H5N2	29. 2009: Spain, H7N7	• ne Message:
9. 1983: Ireland, H5N8	30. 2011-3: S. Africa, H5N2 (Ostriches)	A ge
10. 1985: Australia, H7N7	31. 2012: Chinese Taipei, H5N2	
11. 1991: England, H5N1	§ 32. 2012-present: Mexico, H7N3	
12. 1992: Australia, H7N3	33. 2012: Australia, H7N7	
13. 1994: Australia, H7N3	34. 2013: Italy, H7N7	
§ 14. 1994-95: Mexico, H5N2	35. 2013: Australia, H7N2	
§ 15. 1995 & 2004: Pakistan, H7N3	36. 2015: England, H7N7	
16. 1997: Australia, H7N4	37. 2015: Germany, H7N7	
17. 1997: Italy, H5N2	38. 2015: France, H5Nx	
§ 18. 1996-present: Eurasia/Afr./N. America, H5Nx (including N1, N2, N3, N5, N6, N8 reassortants) – USA (2014-15 and 2022)	39. 2016: USA (Indiana), H7N8	
19. 1999-2000: Italy, H7N1	40. 2016: Italy, H7N7	
20. 2002: Chile, H7N3	41. 2017: China, H7N9	
21. 2003: Netherlands (BLGM, GRM), H7N7	42. 2017: USA (Tennessee), H7N9	
	43. 2020: USA (S. Carolina), H7N3	
	44. 2020: Australia (Victoria), H7N7	

§ Vaccine used in the control strategy

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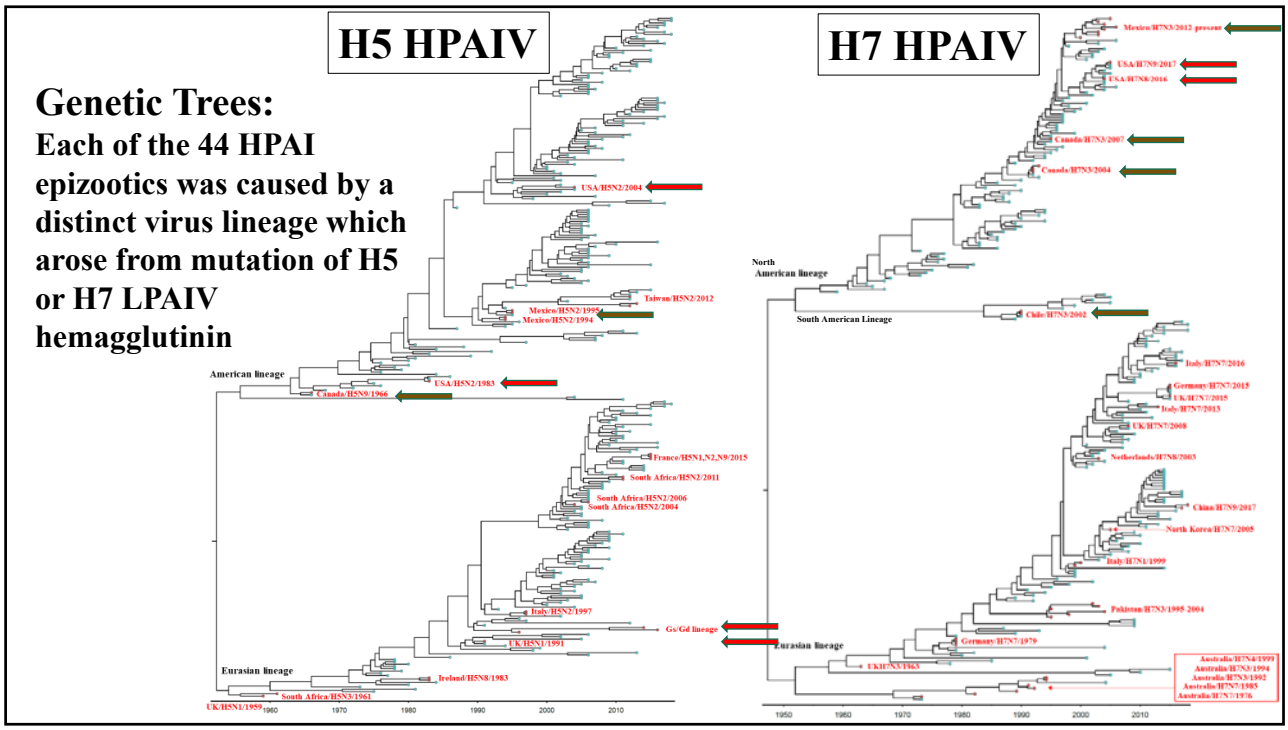
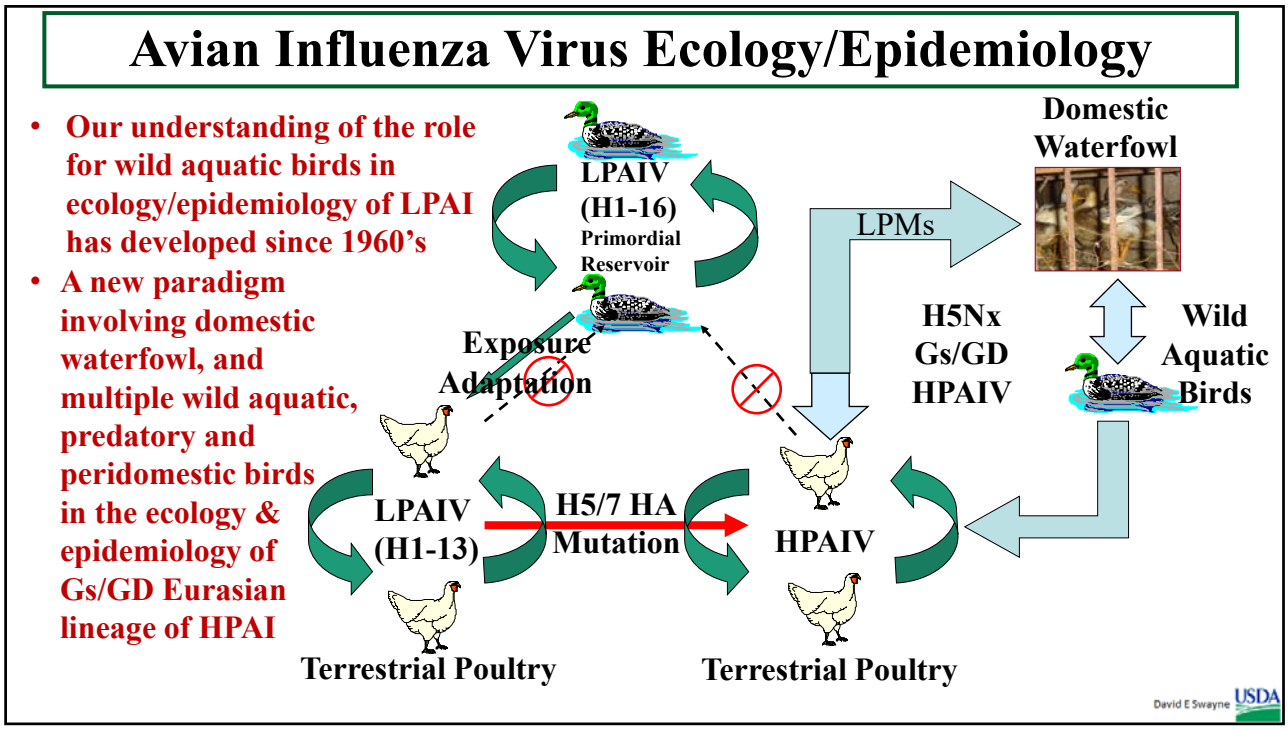

H5 HPAIV
H7 HPAIV
Genetic Trees:
Each of the 44 HPAI epizootics was caused by a distinct virus lineage which arose from mutation of H5 or H7 LPAIV hemagglutinin
American lineage
Eurasian lineage
North American lineage
South American Lineage
Gs/Gd lineage

3


Avian Influenza Virus Ecology/Epidemiology
Our understanding of the role for wild aquatic birds in ecology/epidemiology of LPAI has developed since 1960's
A new paradigm involving domestic waterfowl, and multiple wild aquatic, predatory and peridomestic birds in the ecology & epidemiology of Gs/GD Eurasian lineage of HPAI
LPAIV (H1-16) Primordial Reservoir
Exposure
Adaptation
LPAIV (H1-13)
H5/7 HA Mutation
HPAIV
Terrestrial Poultry
Terrestrial Poultry
LPMs
Domestic Waterfowl
H5Nx Gs/GD HPAIV
Wild Aquatic Birds
David E Swayne
USDA

4

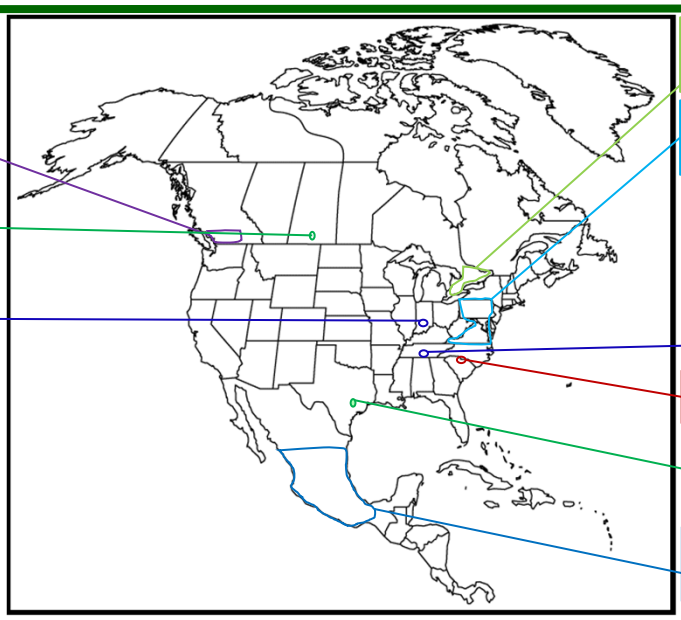
11 HPAI Epizootics in North America by 2022

World Organisation for Animal Health
Founded as OIE

2004: H7N3, B. Columbia
42 comm. farms, 11 backyard premises (1.2m birds)
410 comm. farms & 553 backyard (16m birds), indemnity ($CDN 63.7m), eradicated

2007: H7N3, Saskatchewan
1 comm. farm, (49,000 birds) indemnity, eradicated

2016: H7N8, Indiana
1 comm. Farm, indemnity, eradicated



1966: H5N9 Ontario
2 turkey farms (8100 birds), eradicated

1983-84: H5N2; PA, MD, VA
452 flocks (17m birds) ($142m)
Indemnity ($92m), eradicated

2017: H7N9 HPAI, Tennessee, 2 Br. breeder flocks, indemnity, eradicated

2020: H7N3 HPAI, S. Carolina, 1 turkey flock, indemnity, eradicated

2004: H5N2, Texas
1 LPM farm (6608 chickens) and 5 markets, Indemnity, eradicated

1994-95: H5N2, C. Mexico, 360 flocks "depopulated", no indemnity, LPAI control w/vaccine

5

1 HPAI & 1 H7N6 LPAI in South America by 2022

World Organisation for Animal Health
Founded as OIE

2002: H7N3 HPAI, San Antonio, Valparaiso, Chile
2 comm. farms, (broiler breeders 615,500; 18,500 turkey breeders, 116,000 hatching eggs)

2017: H7N6 LPAI, Marga Marga and Quillota, Valparaiso, Chile
3 premises: 2 comm. farms, (Meat turkeys – 380,012), 1 backyard (chickens, ducks, geese, turkeys – 425)

Various hemagglutinin subtypes LPAI virus identified across South America in wild waterfowl and aquatic birds: Argentina, Bolivia, Brazil, Chile, Columbia, Peru

6

11 HPAI Epizootics in North America by 2022

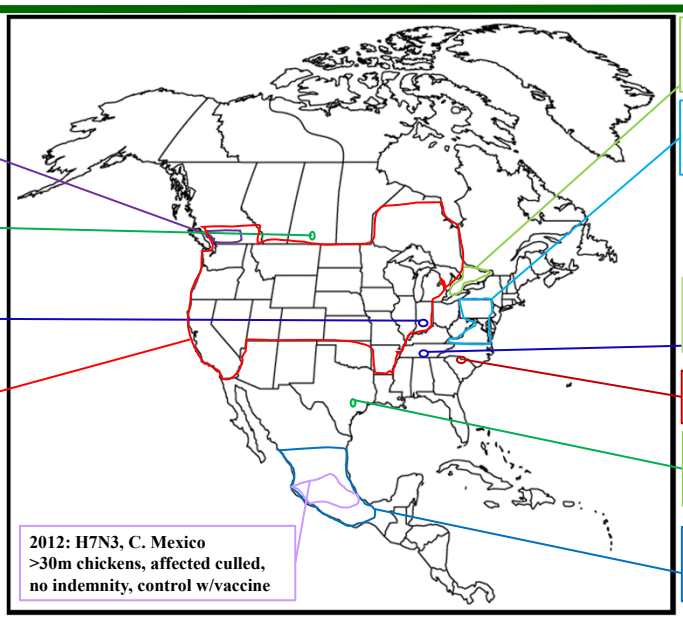
World Organisation for Animal Health
Founded as OIE

2004: H7N3, B. Columbia
42 comm. farms, 11 backyard premises (1.2m birds)
410 comm. farms & 553 backyard (16m birds), indemnity ($CDN 63.7m), eradicated

2007: H7N3, Saskatchewan
1 comm. farm, (49,000 birds) indemnity, eradicated

2016: H7N8, Indiana
1 comm. Farm, indemnity, eradicated

2014-15: H5Nx (clade 2.3.4.4c Gs/GD Eurasian lineage), BC, ON, 21 USA West/Midwest states
Wild birds, backyard & comm. poultry (>$1b), indemnity, eradicated



2012: H7N3, C. Mexico
>30m chickens, affected culled, no indemnity, control w/vaccine

1966: H5N9 Ontario
2 turkey farms (8100 birds), eradicated

1983-84: H5N2; PA, MD, VA
452 flocks (17m birds) ($142m)
Indemnity ($92m), eradicated

2017: H7N9 HPAI, Tennessee, 2 Br. breeder flocks, indemnity, eradicated

2020: H7N3 HPAI, S. Carolina, 1 turkey flock, indemnity, eradicated

2004: H5N2, Texas
1 LPM farm (6608 chickens) and 5 markets, Indemnity, eradicated

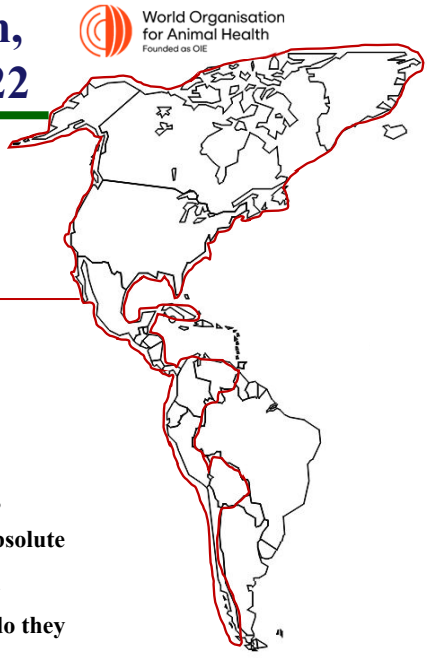
1994-95: H5N2, C. Mexico, 360 flocks "depopulated", no indemnity, LPAI control w/vaccine

7

2.3.4.4b HPAI Epizootics in North, Central and South America in 2022

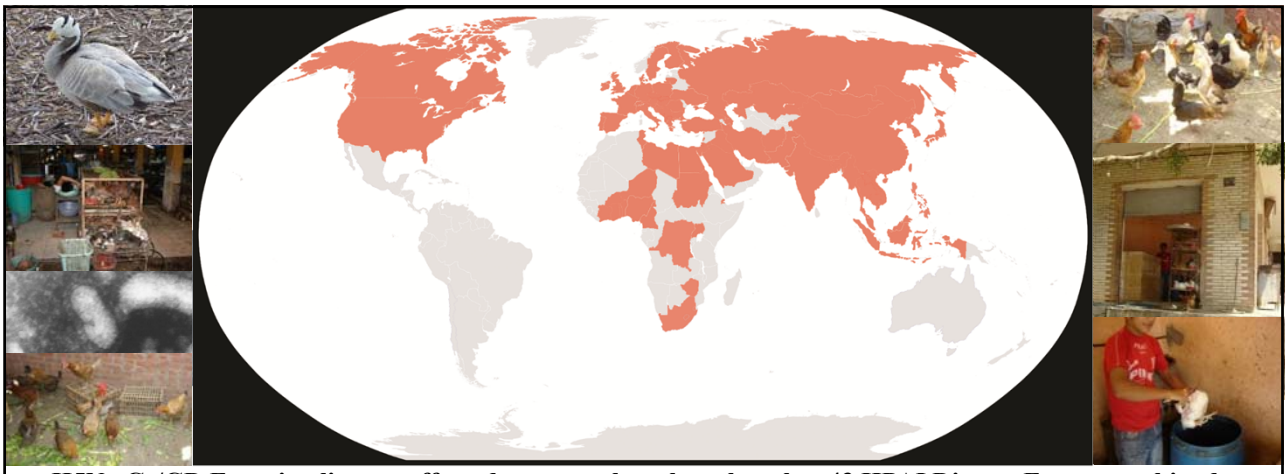
World Organisation for Animal Health
Founded as OIE

2021-23: H5N1 (clade 2.3.4.4b Gs/GD Eurasian lineage)
- Geography: North (including Greenland and Central America) and South America
- Affected: Wild birds, backyard & commercial poultry, wild and captive mammals, and human
- Actions: Indemnity (USA & Canada), eradication vs control



Questions:
- Will 2.3.4.4b HPAI virus crossover to eastern South America? Barrier of Andes Mountains and Amazon basin may not be absolute
- Will it become endemic in wild birds and/or poultry?
- Can each country through biosecurity keep the HPAIV out of commercial farms and backyard production, and if it enters do they have the resources for eradication via stamping-out?

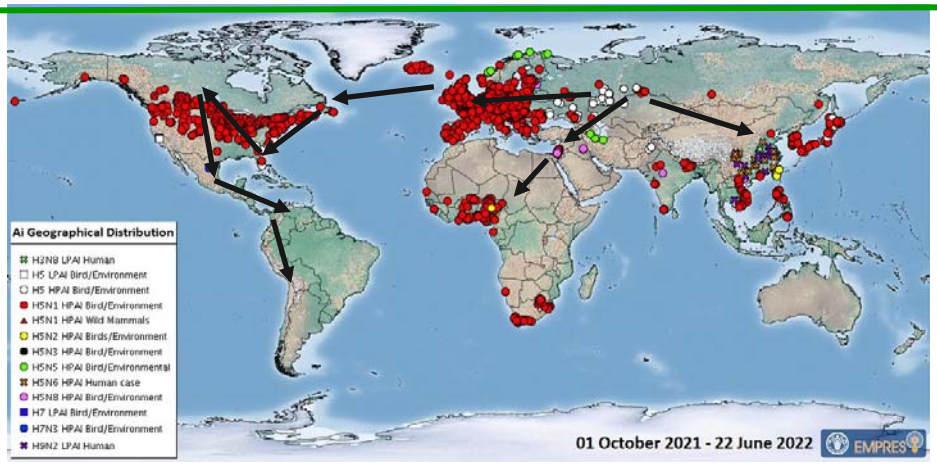
8



- **H5Nx Gs/GD Eurasian lineage affected more poultry than the other 43 HPAI Disease Events combined**
- **>110 countries in poultry, wild birds, wild and captive mammals, and/or humans since 1996**
- **Largest & longest HPAI Outbreak since early 1900's when Fowl Plague spread across Europe, Asia, Africa, and North and South America**
- **Extensive drift in the hemagglutinin and reassortment of the other 7 gene segments has impacted the ecology and epidemiology of the epizootic – e.g. HA clades and subclades and genotypes**
- **Evidence of establishment in some wild birds – ecological change (varies from asymptomatic infection to mass die-offs)**

9

H5Nx Gs/GD Eurasian-lineage HPAIV

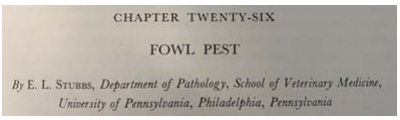


- **Fall 2020, 2.3.4.4b moved from Central Asia to Europe, Eastern Asia, Middle East, and Africa with evidence of bi-directional movement within fall and spring migrations**
- **Fall 2021, 2.3.4.4b moved to N. America and down east coast**
- **Fall 2022, 2.3.4.4b moved to Central and South America**
- **Global (July 2020 to January 2023): 7515 cases, 14million poultry deaths and 254million poultry culled**

10

What did we do in 1924 for Fowl Plague (HPAI): USA 1924-25 outbreak

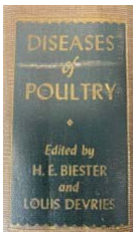
- E.L. Stubbs - "Capable of causing such destruction of the poultry population as to be of economic importance in diminishing the food supply"


CHAPTER TWENTY-SIX

FOWL PEST

By E. L. Stubbs, *Department of Pathology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pennsylvania*

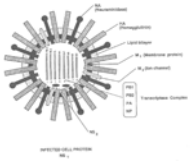
- E.L. Stubbs - "Dangerous character of the disease warranted the radical methods for complete eradication within a few months"
  - Clinical diagnosis: Acute, plaguelike disease with cyanosis and edema of head and systemic hemorrhages
  - Quarantines imposed, embargos placed and poultry shipping on railroads restricted in USA
  - Diligently clean and disinfect premises, coops, crates and carriers
  - Sanitation and disinfection of poultry markets
  - Cessation of traffic in live poultry
  - Destruction of sick poultry and burn or bury carcasses
  - Preventative: isolate newly purchase poultry until proven healthy

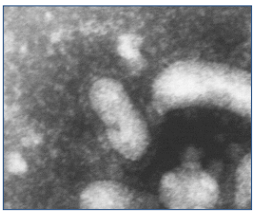


11

High Pathogenicity Avian Influenza Control

- Control since 1920's: Stamping-out programs
  - Infected flocks
  - Dangerous contacts
  - Contiguous properties
  - Zones (1-3 km)





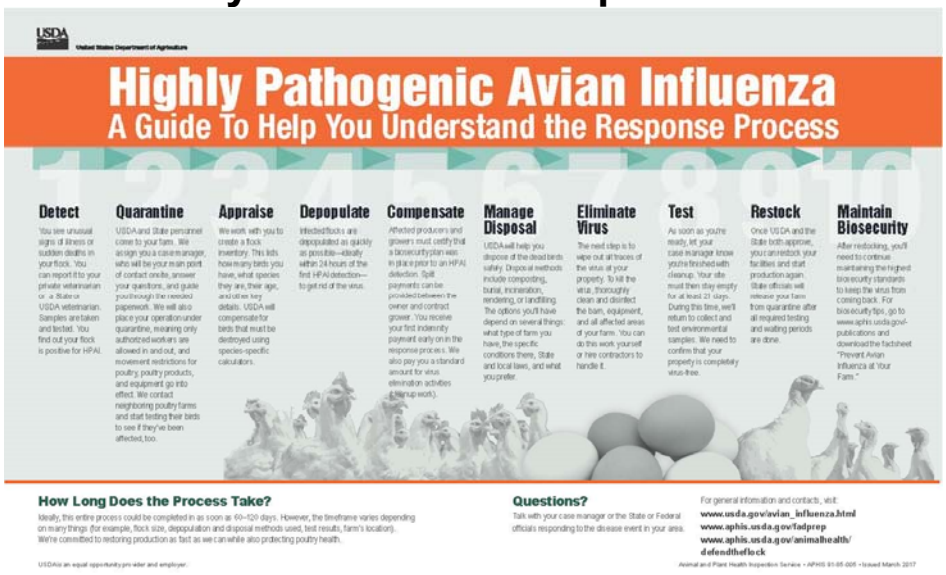
- What has changed?
  - Geometric increase in poultry production with specialization, integration, and increase in size of farms and decrease in number of farms
  - Eradication Programs are expensive: facing political and consumer burn-out from financial support; e.g. 1924-25 fowl plaque cost $14.2M (2017 cost), and 2014-2015 H5N2 outbreak cost $850 million to eradicate
  - Animal Welfare issues: destruction of non-affected poultry and elimination of high-quality protein source
  - Reactive nature of stamping-out – can be too late because of transmission off the farm before diagnosed and depopulated

12

USDA United States Department of Agriculture

https://www.aphis.usda.gov/publications/animal_health/2015/poster-hpai-guide-to-understanding-the-process.pdf

Summary of U.S. HPAI Response Process



USDA United States Department of Agriculture

Highly Pathogenic Avian Influenza

A Guide To Help You Understand the Response Process

Detect

You see unusual signs of illness or sudden deaths in your flock. You can report it to your private veterinarian or a State or USDA veterinarian. Samples are taken and tested. You find out your flock is positive for HPAI.

Quarantine

USDA and State personnel come to your farm. We assign you a case manager, who will be your main point of contact onsite, answer your questions, and guide you through the needed paperwork. We will also place your operation under quarantine, meaning only authorized workers are allowed in and out, and movement restrictions for poultry, poultry products, and equipment go into effect. We contact neighboring poultry farms and start testing their birds to see if they've been affected, too.

Appraise

We work with you to create a flock inventory. This tells how many birds you have, what species they are, their age, and other key details. USDA will compensate for birds that must be destroyed using species-specific calculators.

Depopulate

Infected flocks are depopulated as quickly as possible—ideally within 24 hours of the first HPAI detection—to get rid of the virus.

Compensate

Affected producers and growers must certify that a biosecurity plan was in place prior to an HPAI detection. Split payments can be provided between the owner and contract grower. You receive your first indemnity payment early on in the response process. We also pay you a standard amount for virus elimination activities (clean-up work).

Manage Disposal

USDA will help you dispose of the dead birds safely. Disposal methods include composting, burial, incineration, rendering, or landfilling. The options you'll have depend on several things: what type of farm you have, the specific conditions there, State and local laws, and what you prefer.

Eliminate Virus

The next step is to wipe out all traces of the virus at your property. To kill the virus, thoroughly clean and disinfect the barn, equipment, and all affected areas of your farm. You can do this work yourself or hire contractors to handle it.

Test

As soon as you're ready, let your case manager know you're finished with cleanup. Your site must then stay empty for at least 21 days. During this time, we'll return to collect and test environmental samples. We need to confirm that your property is completely virus-free.

Restock

Once USDA and the State both approve, you can restock your facilities and start production again. State officials will release your farm from quarantine after all required testing and waiting periods are done.

Maintain Biosecurity

After restocking, you'll need to continue maintaining the highest biosecurity standards to keep the virus from coming back. For biosecurity tips, go to www.aphis.usda.gov/publications and download the factsheet "Prevent Avian Influenza at Your Farm."

How Long Does the Process Take?

Ideally, this entire process could be completed in as soon as 60–120 days. However, the timeframe varies depending on many things (for example, flock size, depopulation and disposal methods used, test results, farm's location). We're committed to restoring production as fast as we can while also protecting poultry health.

USDA is an equal opportunity provider and employer.

Questions?

Talk with your case manager or the State or Federal officials responding to the disease event in your area.

For general information and contacts, visit:
www.usda.gov/avian_influenza.html
www.aphis.usda.gov/tadprep
www.aphis.usda.gov/animalhealth/defendtheflock

Animal and Plant Health Inspection Service • APHIS 91-65-005 • Issued March 2017

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What has changed in past 25 years in HPAI Management/Control/Eradication in USA?

- **Incident Command Emergency Response System - logistics and communication timelines are instantaneous**
- **Federal/State/Private partnership for response and eradication: Federal leadership and State and Private workforce**
- **Emergency response activities are exercised at state level**
- **Rapid assessment and indemnity – incentive for early reporting**
- **RRT-PCR for rapid detection of avian influenza viruses for diagnostics and surveillance programs (24 hour goal) – overnight courier sample movement**
- **Molecular definition of HPAI so rapid declaration of HPAI and start destruction process**
- **Improved methods for depopulation (24 hour goal)**
- **Improved methods for disposal: composting and landfill > incineration**
- **Virus elimination – better disinfectants**

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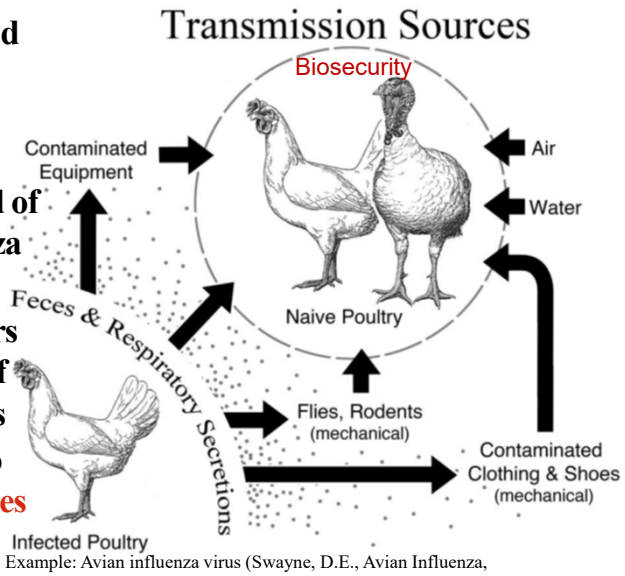
Biosecurity for Poultry: Frontline Defense

- **In simple terms, biosecurity is informed common sense:**
  - Keep pathogens away from poultry and
  - Poultry away from pathogens
- **Goal: Prevent the introduction and spread of an "invisible" pathogen, the avian influenza virus**
- **Components: total of all structural barriers and procedures that keep pathogens out of naive flocks or from leaving infected flocks**
- **But why in modern poultry production do we still have outbreaks? Biosecurity reduces but does not eliminate risks**



Example: Avian influenza virus (Swayne, D.E., Avian Influenza, Blackwell, 2008)

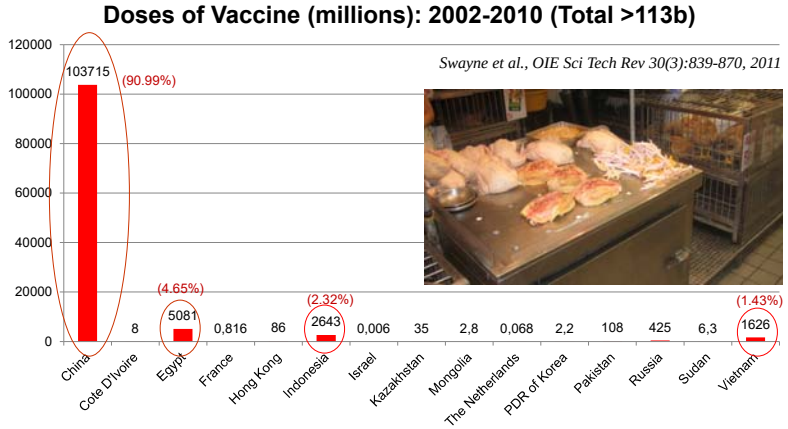
15

General Control of HPAI

- **Control Strategies - Subtype/Pathotype & Country Specific**
- **General:**
  - **HPAI: Consensus - Eradication by stamping-out is preferred strategy; but resource limitations may necessitate the addition of vaccination to reduce poultry susceptibility with a result to decrease transmission and protected livelihoods.**
  - **H5Nx Gs/GD Eurasian lineage HPAI virus. Outcomes vary with each country**
    - **Immediate introduction – eradication through stamping-out program- many countries, but delays in eradication are associated with limited veterinary services, restricted financial resources, lack of logistic development, etc.**
    - **Endemic in poultry or reintroduction – vaccination has been undertaken by about 14 countries as preventative, emergency or routine (endemic) control measure for food security reasons**
    - **2.3.4.4b has seen ecological change with "endemic" in some wild aquatic bird species which makes the threat of introduction into poultry continual**

16

History: H5/H7 HPAI Vaccination Programs



14 countries vaccinated poultry against HPAI (2002-2010)

- **Preventive (<0.2%): Mongolia, Kazakhstan, France, The Netherlands**
- **Emergency (<0.8%): Cote d' Ivoire, Sudan, N. Korea, Israel, Russia, Pakistan**
- **Endemic/routine (>99%): China (including HK), Egypt, Indonesia and Vietnam, plus added Bangladesh (H5N1, 2011-), Mexico (H7N3, 2012-) and China (H7N9, 2017-)**
- **Estimates 2002-2020: >425b; approximately 25b per year, mostly inactivated vaccine but vectored ↑↑**

17

Why Vaccinate?

Increase resistance to AIV infection

Reduce AIV replication in respiratory & GI tract which reduces shedding

Prevent disease and death in poultry

↓

Reduced environmental contamination

Reduce spread between premises

Reduced transmission to birds

Improves animal welfare

Conclusion: Adds an additional layer of protection on top of other biosecurity measures, but does not replace biosecurity measures

18

Globally, additional changes in past 25 years in HPAI vaccines and vaccination?

- Reverse genetic inactivated vaccine strains for antigenic matching to field viruses – e.g. China and Mexico
- Laboratory & surveillance methods to assess vaccine & field virus for updating – RRT-PCR methods and followed by virus isolation and characterization
- Cassette concept to rapidly update non-replicating registered vaccines (used in USA poultry for AI vaccine bank in 2015, USA)
- Recombinant vectored vaccines produce cell-mediate and mucosal immunity as well a humoral immunity – rFPV, rHVT, rNDV, rDEV
- Hemagglutinin-only based vaccines which support serological DIVA strategies
- Improved adjuvants for enhanced immune responses

19

Critical Questions for 2023 H5N1 2.3.4.4b in the Americas:

- Will vaccines and vaccination gain wider acceptance as a control tool?
  - Use of vaccines does not alter avian influenza status from a trade perspective (WOAH Terrestrial Code Article 10.4.1. Provision 6) if an appropriate surveillance system is in place

  - Additional measures are needed to prevent 2.3.4.4b HPAI, given the extent of infection in wild birds, the evidence of increased outbreaks and the large number of poultry that have been destroyed as a result of this disease
  - Vaccination can provide an extra layer of protection, reduce the quantities of circulating virus and the number of farms on which stamping out is required
  - Stamping-out programs are complex, expensive and labor intensive. Can you country implement such programs?

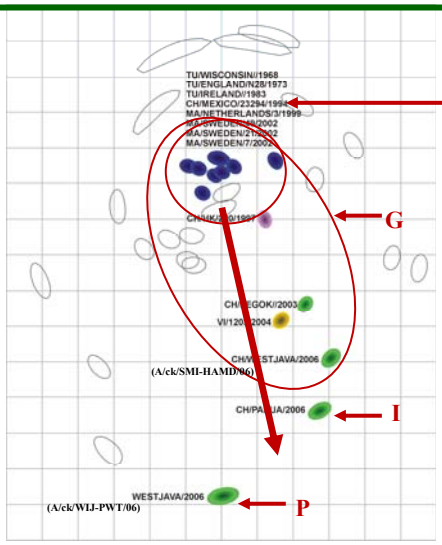
20

2. Special Features of HPAI Vaccines: Antigenically Relevant Seed Strains

Close Antigenic Match to Field Viruses
Inactivated Vaccine Seeds - Indonesia

- Historical H5 Vaccines – Similar antigenicity
- Drifting of HA away from root
  - Good protection: Ck/HK/220/97, Ck/Legok/03, VN/1203/04, Ck/WJ/HAMD/06
  - Intermediate protection: Ck/Papua/06
  - Poor protection: PWT/06

Today: Emergence of resistant field viruses continues necessitating updated inactivated seed strains to antigenically match national field strains



Swayne et al. J. Virol 2015

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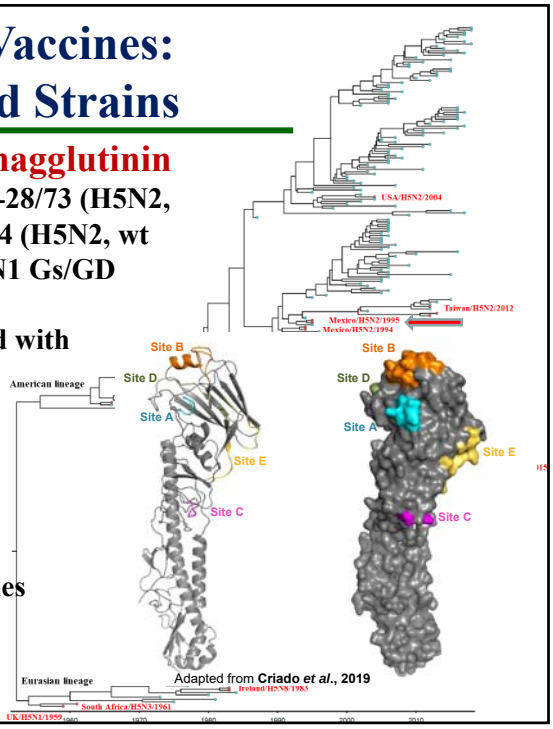
Special Features of HPAI Vaccines: Antigenically Relevant Seed Strains

Changing Vaccine Needs with Drift of Hemagglutinin

- 2002, All H5 were protective: A/turkey/England/N-28/73 (H5N2, *wt* LPAIV) (China) and A/chicken/Mexico/232/1994 (H5N2, wt LPAIV) (Indonesia) as vaccine strains against H5N1 Gs/GD HPAIV. Recommended HA1 homology of >90%
- 2004-2006: Vaccine resistance appeared in the field with elimination of old *wt* LPAIV seed strains
- Use of "custom" strains: reverse genetic (*rg*) LPAIV to match field HPAIV, or HPAIV in BSL-3 vaccine manufacturing facilities (Russia and Indonesia)
- Rapid replacement *rg* strains in China & Mexico, including use of bivalent & trivalent H5/H7 vaccines
- Genetic distance between N. American and Eurasian H5N2 *wt* LPAIV and 2.3.4.4b clade HPAIV is tremendous!!



Adapted from Criado *et al.*, 2019

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Conclusions:

- **From 2020 to 2023, the H5N1 2.3.4.4b clade of Gs/GD Eurasian lineage of HPAIV has unprecedented biological impact on poultry and wild birds with transcontinental movements involving Asia, Europe, Africa, and North and South America**
- **The H5N1 2.3.4.4b virus appears to have become endemic in some wild aquatic bird populations, causing major die-offs in some species, sporadic infections of wild mammals and rare human infections**
- **Global reconsideration and re-evaluation of vaccination as a complementary tool when used with stamping-out programs:**
  - **The limitations of veterinary services in Central and South America may suggest stamping-out will not be immediately successful and may require poultry vaccination to maintain food security and rural livelihoods**
  - **The vaccines will need antigenically relevant strains to match field virus for consistent and predictable protection. Poorly matched vaccines will not provide predicted protection**
  - **There is potential for spread of 2.3.4.4b HPAI to eastern South America and Antartica via migratory aquatic birds**

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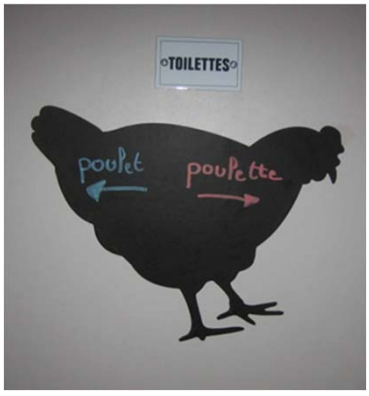
Thank you for your attention!



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