附件1

IABS HPAI Meeting - Vaccination Strategies to prevent and control HPAI : Removing unnecessary barriers for usage

October 25-26, 2022

Paris - France

IABS

International Alliance for Biological Standardization

Welcome Comments

- International Alliance for Biological Standardization (IABS)
  Dr. Rick Hill, President
- World Organization for Animal Health (WOAH Founded as OIE)
  Dr. Monique Éloit, Director General
- Food and Agriculture Organization of the United Nations (FAO)
  Dr. Madhur Dhingra, Head of Emergency Prevention system for Animal Health (EMPRES), Animal Production and Health Division, FAO

IABS

World Organisation for Animal Health
Founded as OIE

Food and Agriculture Organization of the United Nations

Genesis of the Conference – HPAI Present

World Organisation for Animal Health
Founded as OIE

TOP STORY

Animal Health SmartBrief
In partnership with the American Veterinary Medical Association
AVMA Our Passion. Our Profession.

Avian Influenza Cases rising again as birds migrate

AVMA Animal Health SmartBrief <avma@smartbrief.com>
Date: Wednesday, October 12, 2022

POULTRY WORLD

Unprecedented number of bird flu cases in Europe this summer

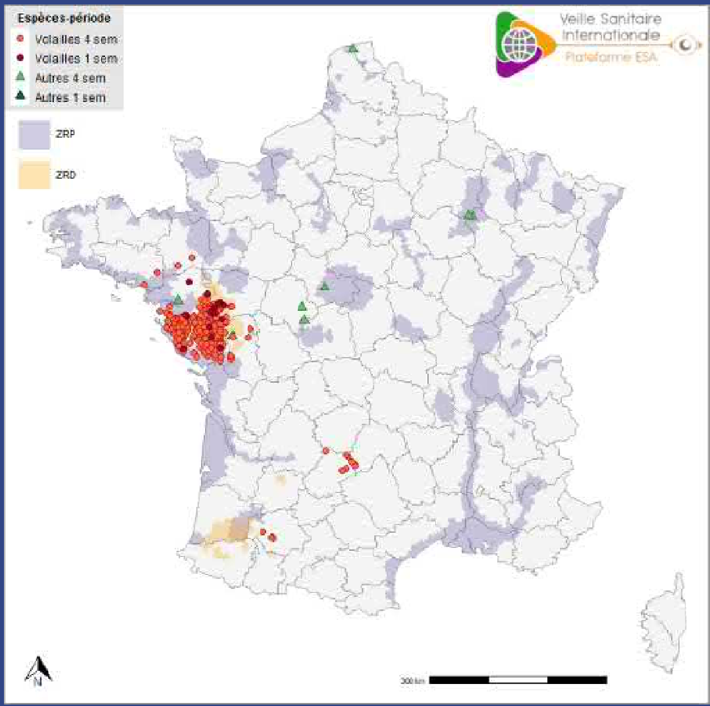
12-10 | Health | News

https://www.poultryworld.net/

HPAI Recent Past

MAGRET DE FRANCE

CANARD À FOIE GRAS DU SUD-OUEST
(CHALOSSE
GASCOGNE
GERS
LANDES
PÉRIGORD
QUERCY)
IGP



- **Figure 3.** Localisation des foyers de « volailles » et cas « autres que volailles » détectés en France sur les quatre dernières semaines et sur la semaine précédant la publication de ce BHVSI-SA. Les définitions de "volailles" et "autre que volailles" sont celles du Règlement 2016/429. Les ZRP et ZRD sont représentées respectivement en violet et jaune sur le fond de carte (source : Commission européenne ADIS le 04/04/2022).

Acknowledgements

The Poultry Veterinary Study Group of the EU

- The Poultry Veterinary Study Group of the EU
- Individuals
  - Léni CORRAND, ABIOPOLE Veterinary Practice
  - Daniel GAUDRY, Advisor to IABS Board
- Scientific Committee – Program Topics and Design
- Sharing meeting results – planned manuscripts:
  - Factors that inhibit usage of preventive vaccination
  - Vaccine availability
  - Epidemiology-driven approaches to surveillance
  - Full Meeting Report; with Conclusions and Recommendations

HPAI Future – Challenges and Questions

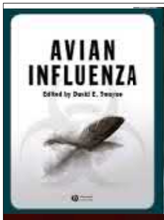
- Recommendations?
- Next steps?
- Need for targeted workshops ?
- Need for a follow-up Meeting or Webinar?

Keynote Speaker

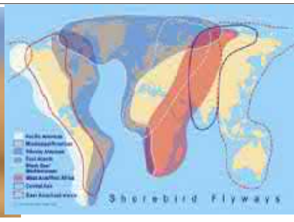
Vaccine usage to control high pathogenicity avian influenza and barriers to more effective usage: Setting the scene

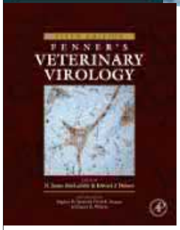
Dr. David Swayne, Department of Agriculture, USA

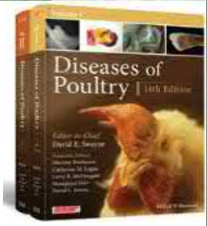
附件2









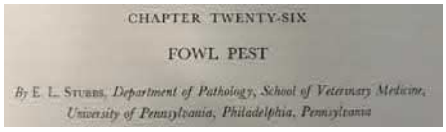
Vaccine Usage to Control High Pathogenicity Avian Influenza and Barriers to More Effective Usage: Setting the Scene

David E Swayne

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

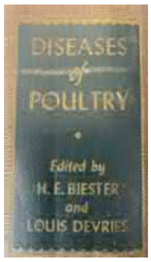
Disclaimer: This presentation is based on current scientific data and is not an endorsement of any specific product or company

What did we do in 1924 for High Pathogenicity Avian Influenza: USA 1924-25 outbreak


CHAPTER TWENTY-SIX

FOWL PEST

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



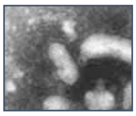
- **Capable of causing such destruction of the poultry population as to be of economic importance in diminishing the food supply**
- **Dangerous character of the disease warranted the radical methods for complete eradication within a few months**
  - **Acute, plaguelike disease with cyanosis and edema of head & systemic hemorrhages; clinical diagnosis**
  - **Quarantines imposed, embargos placed and poultry shipping restricted on domestic railroad movement**
  - **Slaughter, sanitation and disinfection of poultry markets**
  - **Diligently clean and disinfect premises, coops, crates and carriers**
  - **Cessation of traffic in live poultry**
  - **Destroy sick poultry – burn or bury carcasses**
  - **Preventative: isolate newly purchase poultry until proven healthy**

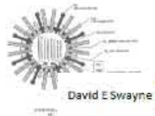
High Pathogenicity Avian Influenza

1. 1959: Scotland, H5N1
2. 1961: S. Africa, H5N3
3. 1963: England, H7N3
4. 1966: Canada, H5N9
5. 1975: Australia, H7N7
6. 1979: Germany, H7N7
7. 1979: England, H7N7
8. 1983-84: USA, H5N2
9. 1983: Ireland, H5N8
10. 1985: Australia, H7N7
11. 1991: England, H5N1
12. 1992: Australia, H7N3
13. 1994: Australia, H7N3
§ 14. 1994-95: Mexico, H5N2
§ 15. 1995 & 2004: Pakistan, H7N3
16. 1997: Australia, H7N4
17. 1997: Italy, H5N2
§ 18. 1996-present: Eurasia/Afr./N. America, H5Nx (including N1, N2, N3, N5, N6, N8 reassortants) –
19. 1999-2000: Italy, H7N1
20. 2002: Chile, H7N3
21. 2003: Netherlands (BLGM, GRM), H7N7
22. 2004: USA, H5N2
23. 2004: Canada, H7N3
24. 2004: S. Africa, H5N2 (ostriches)
25. 2006: S. Africa, H5N2 (ostriches)
§ 26. 2005: N. Korea, H7N7
27. 2007: Canada, H7N3
28. 2008: England, H7N7
29. 2009: Spain, H7N7
30. 2011-3: S. Africa, H5N2 (Ostriches)
31. 2012: Chinese Taipei, H5N2
§ 32. 2012-present: Mexico, H7N3
33. 2012: Australia, H7N7
34. 2013: Italy, H7N7
35. 2013: Australia, H7N2
36. 2015: England, H7N7
37. 2015: Germany, H7N7
38. 2015: France, H5Nx
39. 2016: USA (Indiana), H7N8
40. 2016: Italy, H7N7
41. 2017: China, H7N9
42. 2017: USA (Tennessee), H7N9
43. 2020: USA (S. Carolina), H7N3
44. 2020: Australia (Victoria), H7N7

§ Vaccine used in the control strategy

- Orthomyxovirus with protein projections on the surface:
  - 16 hemagglutinin subtypes (i.e., H1-H16) – MUTATIONS (DRIFT)
  - 9 neuraminidase subtypes (i.e., N1-N9)
- 8 gene segments: Can REASSORT (SHIFT) between AIVs
- Vary in phenotype (chickens):
  - LPAIV: mild disease (any H1-16)
  - HPAIV: systemic - deadly disease (some H5 & H7)
- Distinct virus lineages for different outbreaks and genetic clades for entrenched avian influenza virus





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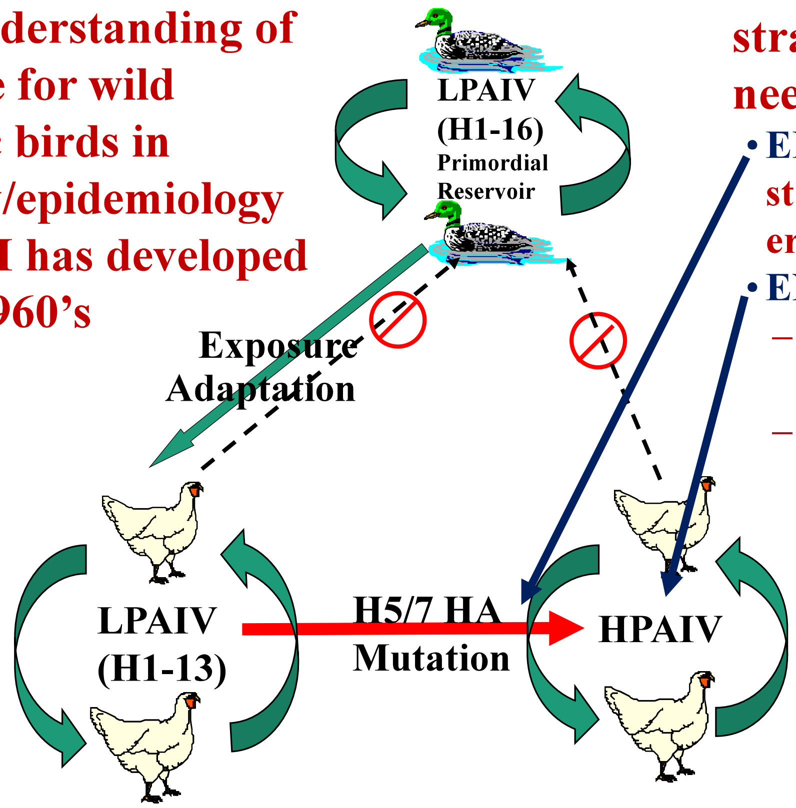
Avian Influenza Virus Ecology/Epidemiology

- Our understanding of the role for wild aquatic birds in ecology/epidemiology of LPAI has developed since 1960's



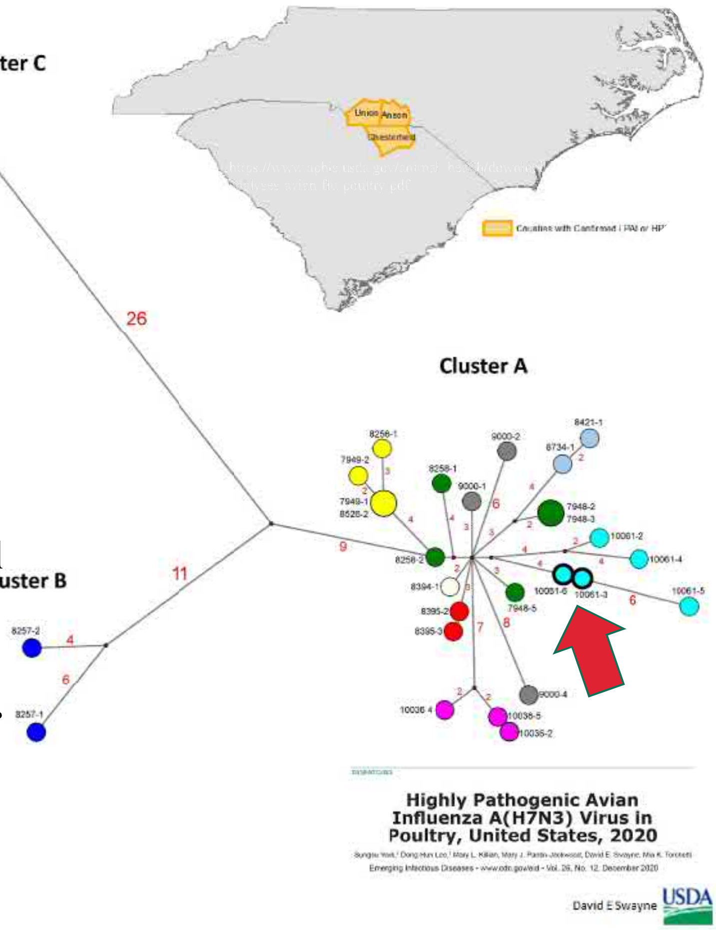
HPAI (H5/H7) control varies with strain and country needs/resources

- EMERGENT strains – stamping-out and eradicated
- ENTRENCHED strains
  - Stamping-out and eradication
  - Managed control (limited stamping-out plus vaccination)

David E Swayne USDA

Ex: EMERGENT AI: 2020 LPAI & HPAI

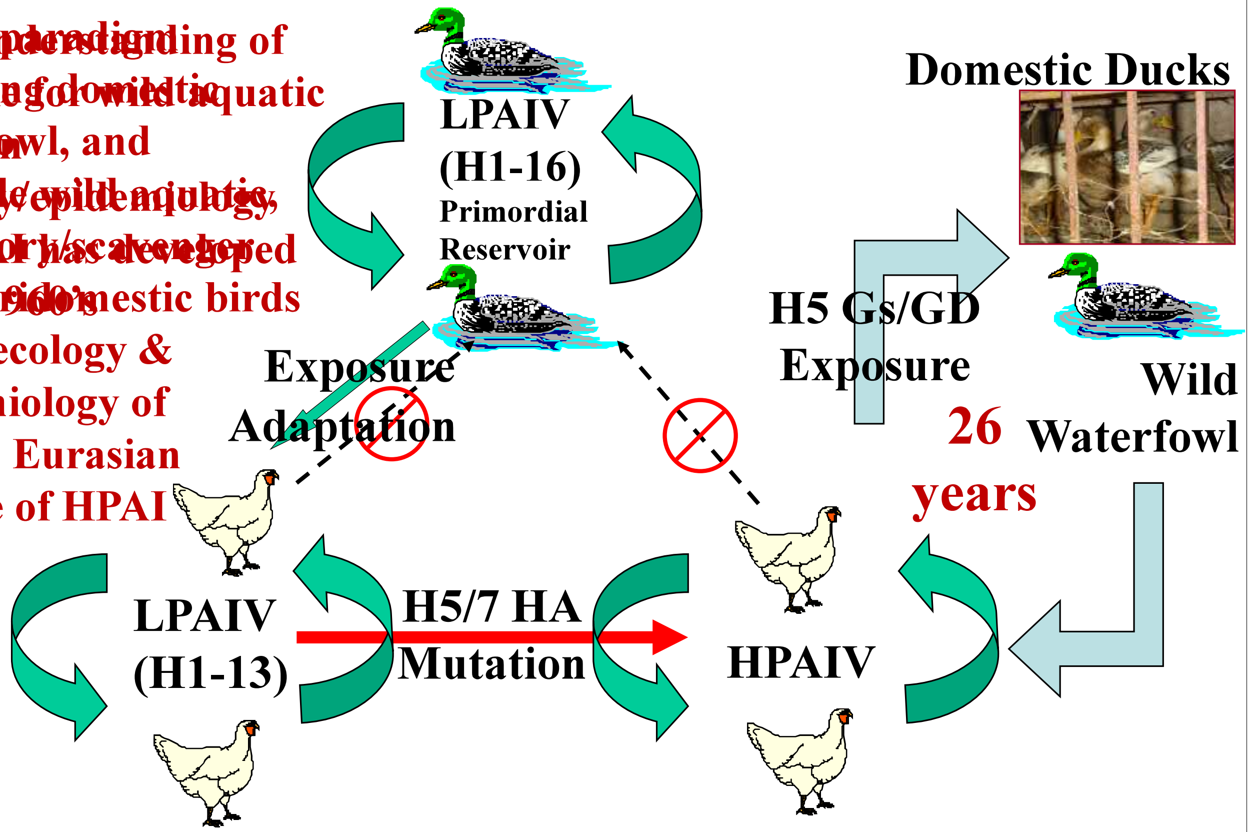
- March 2020, 11 total commercial breeder or meat-type turkey operations detection of H7N3 LPAI virus in N. & S. Carolina
- Single introduction from N. American wild bird reservoir of LPAIV with lateral spread
- Single LPAIV to HPAIV mutational event on South Carolina farm (SC-02) without secondary spread & contained the precursor LPAIV; i.e. HPAI contained & eradicated on the index farm
- Depopulation of 337,362 turkeys on 12 premises with eradication



David E Swayne USDA

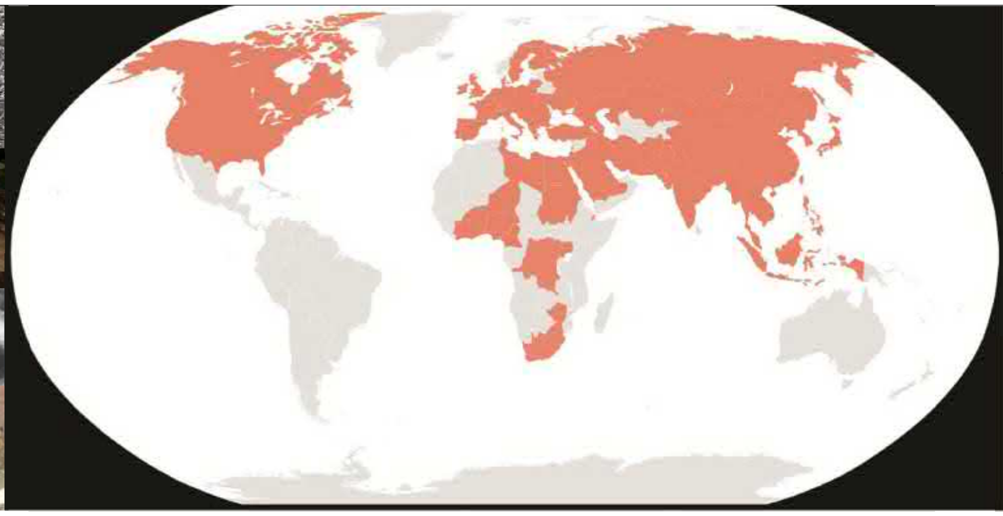
Avian Influenza Virus Ecology and Epidemiology

- Our understanding of the role of wild aquatic birds in ecology/epidemiology of LPAI has developed since 1960's
- A new paradigm involving domestic waterfowl, and multiple wild aquatic, predatory/scavenger and peri-domestic birds in the ecology & epidemiology of Gs/GD Eurasian lineage of HPAI



H5Nx Gs/GD HPAI and wild waterfowl dispersion

David E Swayne USDA



- **Affected more poultry than the other 43 HPAI Disease Events combined**
- **>84 countries in poultry, wild birds or humans**
- **Largest & longest HPAI Outbreak since early 1900's when Fowl Plague spread across Europe, Asia, Africa 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**

Wild Aquatic Bird: Changing Pathogenesis H5Nx GS/GD

- **Variable outcomes depend on virus strain, host and other physiological and/or environmental factors**
- **Outcomes:**
  - **No infections**
  - **Asymptomatic infections**
  - **Sporadic illness with recover**
  - **Sporadic severe illness with death**
  - **Major die-offs**
- **Examples: H5N1 HPAIV, W. swan/Mongolia/2005, 2.2 clade**
  - **2-wk-old mallards: died in <5 days**
  - **10-16-wk-old mallards: no illness or deaths but shed virus oral and cloaca**
  - **12-wk-old geese: 100% illness and 40-75% deaths**
  - **5-6-wk-old swans: 100% illness and 100% deaths**


Journal of Virology

Pathogenicity and Transmission of H5 and H7 Highly Pathogenic Avian Influenza Viruses in Mallards

Journal of Virology 90(21):9967-9982, 2016. http://doi:10.1128/JVI.01165-16
Brown, J, D. Stallknecht, DE Swayne EID 14(1):136-142, 2008
Brown, J, D. Stallknecht, DE Swayne
EID 12(11):1663-70, 2006; J. Wildl Dis, EID, 2008

ID†	Morbidity Rate (days to onset)	Morbidity Duration‡	Mortality Rate (days to death)
Black Swan	5/5 (1-2)	<1 (0-1)	5/5 (2-3)
Trumpeter Swan	5/5 (2)	4 (3-5)	5/5 (4-6)
Whooper Swan	4/4 (2-4)	3 (1-5)	4/4 (4-6)
Mute Swan	5/5 (5-7)	<1 (0-1)	5/5 (5-8)
Canada Goose	4/4 (3-7)	3 (1-9)	3/4 (4-8)
Bar-Headed Goose	5/5 (3-7)	4 (1-8)	2/5 (6-7)

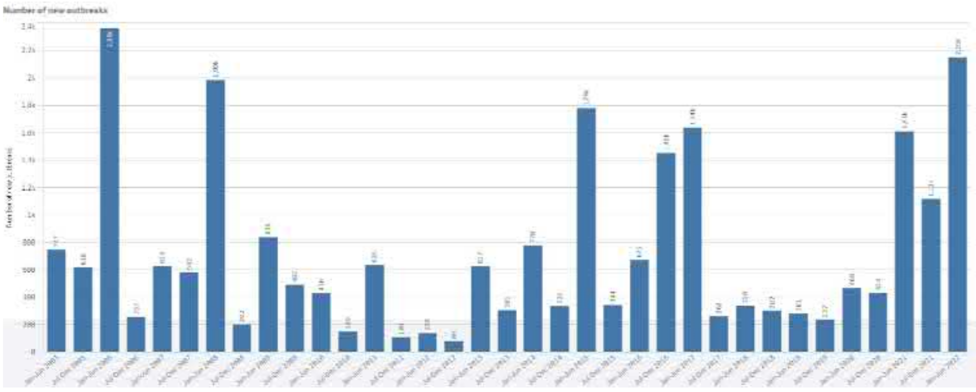
	Morbidity	Mortality	MDT	Oral*	Cloacal*
Wood Ducks	4/6	3/6	7 DPI	4.96 / 5	3.30 / 3
Mallards	0/6	0/6	-	2.57 / 2	0.97 / 1
Redheads	0/6	0/6	-	2.70 / 2	1.23 / 1
Northern Pintails	0/6	0/6	-	3.14 / 2	0.97 / 1
Blue-winged Teal	0/6	0/6	-	1.32 / 3	1.21 / 1

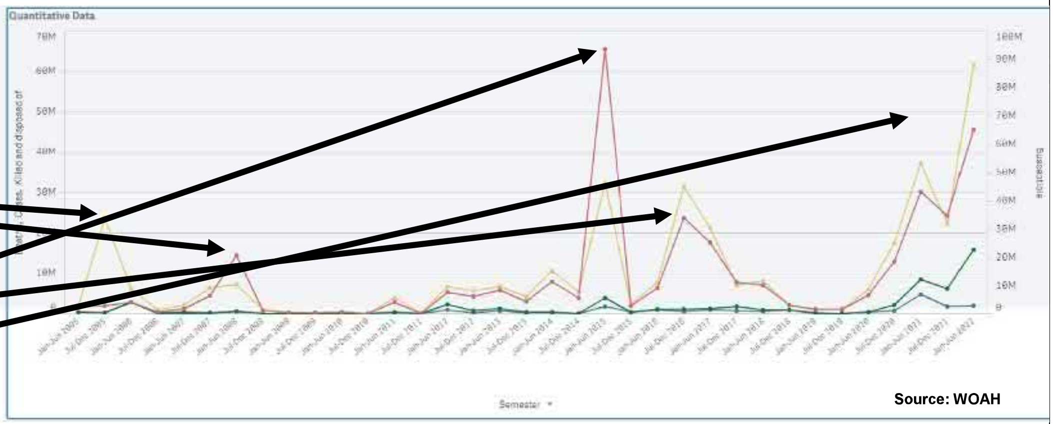
Global High Pathogenicity Avian Influenza: 2005-2022

David E Swayne USDA

Source: WOAH

- **HPAI – internationally controlled disease with entrenched Gs/GD lineage majority of cases >>>>>> H7N9 Eurasian lineage >> H7N3 N. American lineage >>> Emergent H7 > Emergent H5**
- **Number of Outbreaks: 2005-2022- five main H5Nx Gs/GD lineage peaks:**
  - 2005: 2.2 clade
  - 2007-2008: 2.3.2.1 clade
  - 2014-2015: 2.3.4.4c clade
  - 2016-2017: 2.3.4.4b clade
  - 2020-2022: 2.3.4.4b clade





Source: WOAH

H5Nx Clade 2.3.4.4b Gs/GD Eurasian-lineage HPAIV

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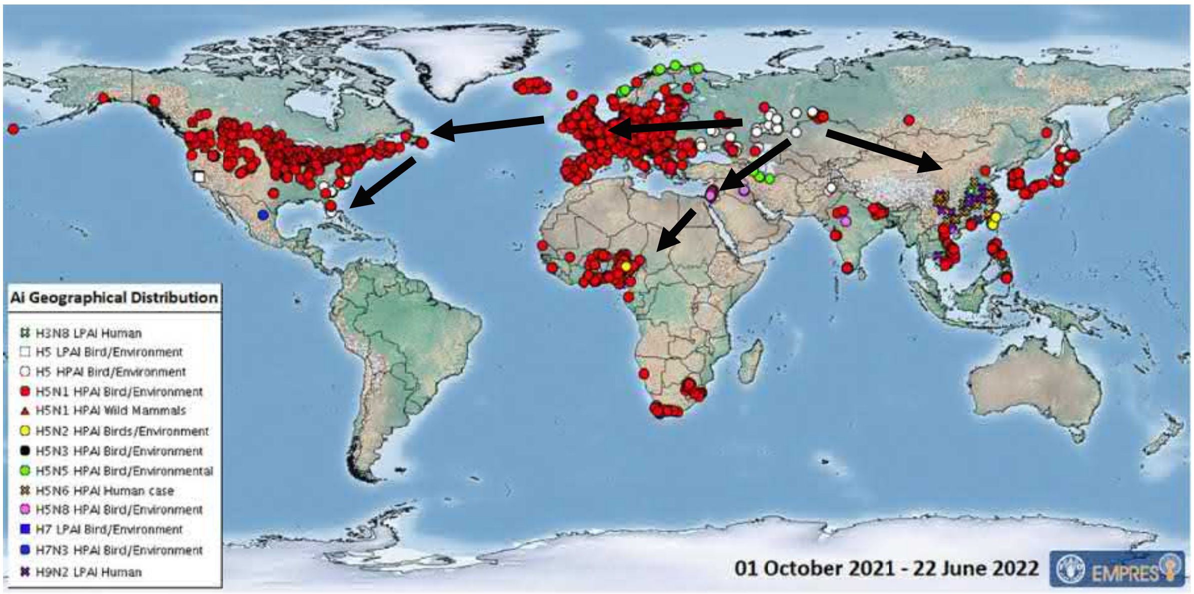
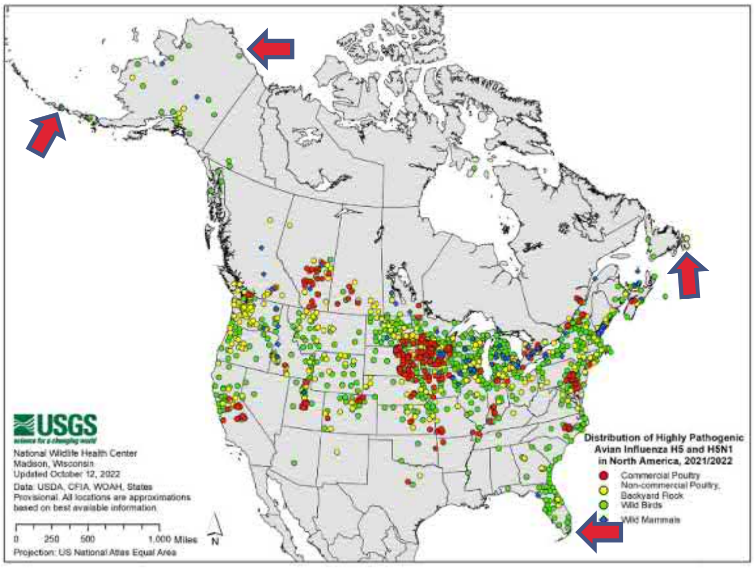


- **Since Fall 2020, 2.3.4.4b has moved from Central Asia to Europe, Eastern Asia, Middle East, Africa and N. America with evidence of bi-directional movement within fall and spring migrations**
- **5771 cases, 154.7 million poultry deaths + culled (6-22-2022)**

Fall 20-Summer 22	Europe	USA
Affected (countries/states)	36	38
Outbreaks (flocks)	2398	395
Culled+deaths	46M	40.1M
Wild birds	2733	1826

H5 Gs/GD Eurasian-lineage HPAIV: North America



10-12-2022

- **N. America (10-14-2022):**
  - **4338 wildlife cases**
  - **706 domestic bird cases (174/532)**
  - **50.57M (3.12M/47.45M)**
- **Broad geographic distribution in 9 months**
  - **East: Avalon Peninsula**
  - **West: Aleutian Islands**
  - **South: Southern Florida**
  - **North: Northern Slope of Alaska**
  - **47 States of USA**
  - **9 Provinces and 3 territories of Canada**

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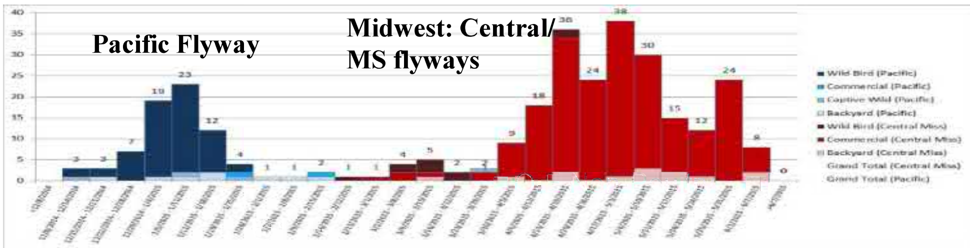
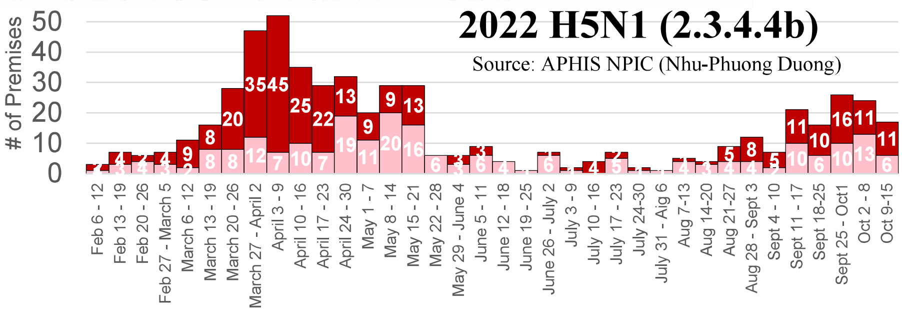
H5 Gs/GD Eurasian-lineage HPAIV: North America 2014-15 vs 2022

2014-15 H5Nx (2.3.4.4c)



Metric	2014-15	2022
States affected: Comm/Backyard	21	42
Cases: Commercial Flocks	211	242
Cases: Backyard Flocks	21	290
Affected birds	50.4M	47.45M
States Affected - Wild Birds	15	45
Wild Bird Cases	98	2930
Flyways Affected	3	4



Comparisons of epidemiological data

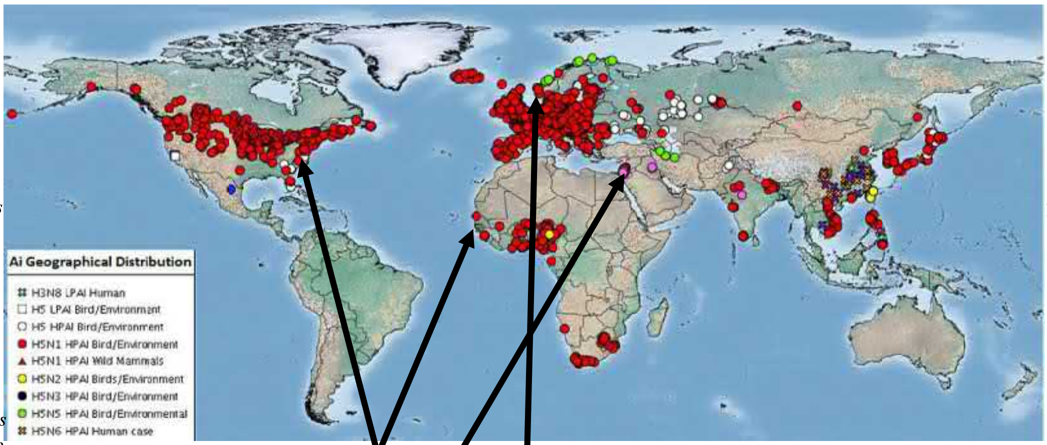
- Commercial/Backyard the epi-curve shifted left on timeline with higher weekly cases peak vs 2014-15
- 2022 commercial outbreak has lasted longer than 2014-15 outbreak, still ongoing
- Higher proportion of backyard to commercial flocks in 2022 vs 2014-15 (52% vs 9%)
- Greater number of wild bird species affected in 2022

David E Swayne USDA

H5Nx Gs/GD Eurasian-lineage HPAIV

Pelecanus onocrotalus
https://www.pinterest.com/pin/298363544067061255/

Thalasseus sandvicensis
Photo source: Wikipedia



Map source: FAO

Grus grus
Photo source: Wikipedia

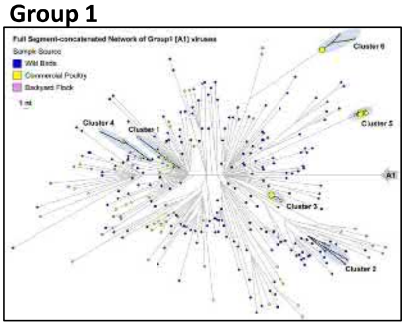
Platalea leucorodia
Photo source: Wikipedia

Unique occurrences of die-offs in wild bird colonies:

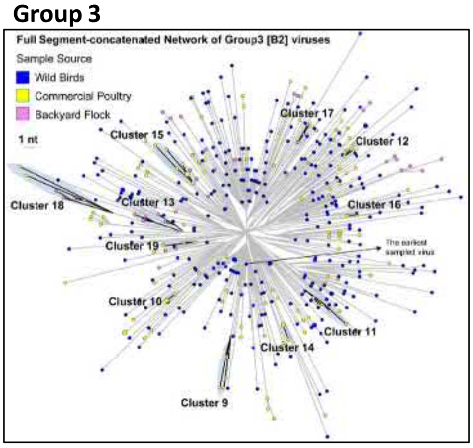
- Senegal: Rose Pelicans
- Israel: Common Cranes
- Europe: Netherlands (Sandwich terns, Eurasian spoonbills, common terns, black-headed gulls), Scotland (northern gannets and great skuas), France (European Herring gulls) and Greece (Dalmatian pelicans)
- USA: Black & Turkey Vultures

Full genome-concatenated network analyses by genetic group

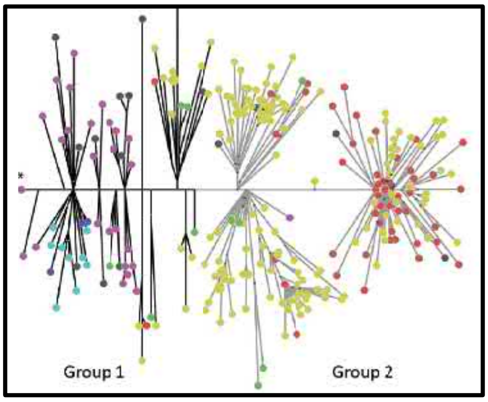
Group 1



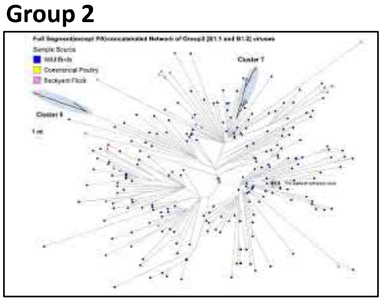
Group 3



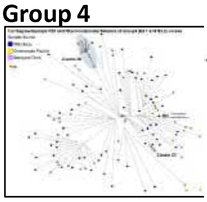
2014-15

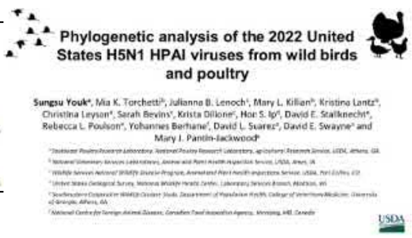


Group 2



Group 4

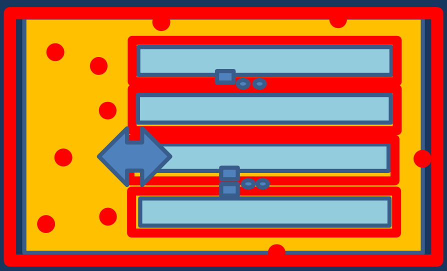




Lee, D.H., Torchetti, M.K., Bahl, J., Killian, M.L., Hicks, J., Pantin-Jackwood, M., Swayne, D.E. Transmission dynamics of Eurasian H5Nx clade 2.3.4.4 highly pathogenic avian influenza in United States, 2014-2015. Emerging Infectious Diseases 24(10):1840-1848, 2018

- 2014-15: Single introduction and initial spread by wild waterfowl; Later primary spread, farm-to-farm spread
- 2022: Evidence for potential lateral (farm-to-farm) or common source transmission was less frequent than 2014-15 outbreak

Biosecurity Principle



- Perimeter Buffer Area:
  fenced human-exclusion zone
- Line of Separation: building/shed walls

Louise Dufour-Zavala

H5 Gs/GD Eurasian-lineage HPAIV: Europe & N. America

David E Swayne USDA

- **Mammalian cases H5N1: sporadic cases**
  - Red foxes (*Vulpes vulpes*) – most frequent (>43) – Europe, Canada and USA
  - Skunks (*Mephitis mephitis*)
  - Harbor seals (*Phoca vitulina*) & Grey seals (*Halichoerus grypus*)
  - Virginia Opossum (*Didelphis virginiana*)
  - Coyote (*Canis latrans*)
  - Common raccoon (*Procyon lotor*)
  - Bobcat (*Lynx rufus*) and Lynx (*Lynx lynx*)
  - Eurasian otter (*Lutra lutra*)
  - European polecat (*Mustela putorius*)
  - European badger (*Meles meles*)
  - Mink (*Neovison vison*)
  - Raccoon dog (*Nyctereutes procyonoides*)
  - Common bottlenose dolphin (*Tursiops truncatus*)
  - Black Bear (*Ursus americanus*)
  - Rare Human Cases

https://en.wikipedia.org/wiki/Red_fox

https://en.wikipedia.org/wiki/Harbor_seal

https://en.wikipedia.org/wiki/Skunk

https://en.wikipedia.org/wiki/Mink

https://en.wikipedia.org/wiki/Bobcat

EFSA Scientific Reports - doi:10.2903/j.efsa.2022.7415
https://www.fao.org/animal-health/situation-updates/global-aiv-with-zoonotic-potential

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

Improved animal welfare

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

David E Swayne USDA

Experiences in Avian Influenza Vaccination

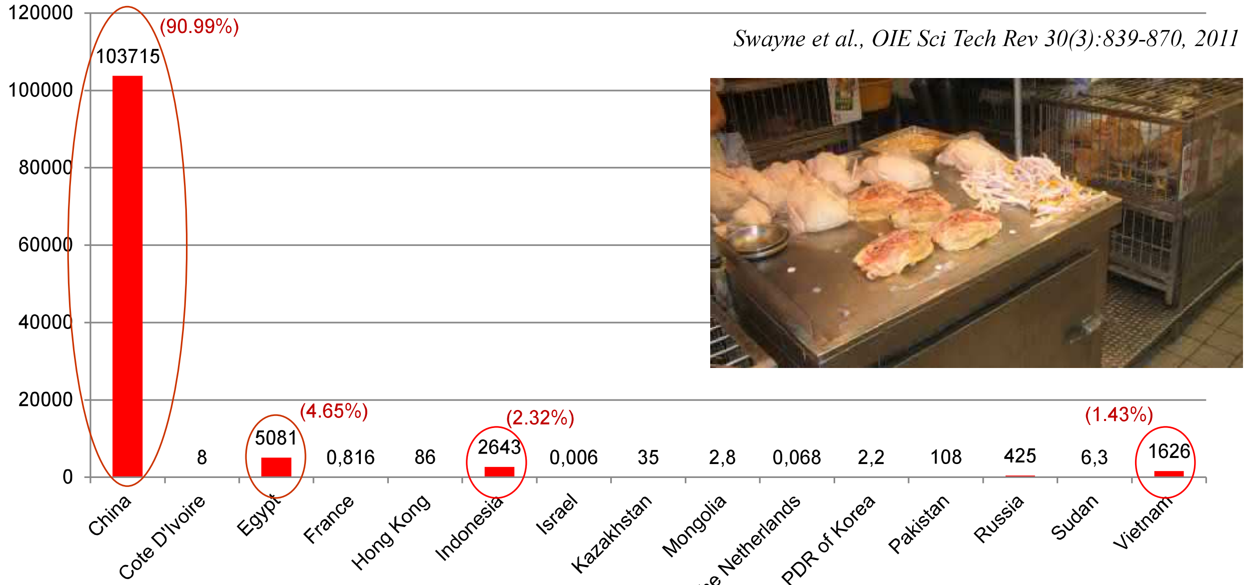
- **One large company in Connecticut, USA: Layers and pullets (1 company, 7 farms, >4.4 million): H7N2 LPAI, 2003-2005**
  - **USDA requested the owner depopulate – no indemnities**
  - **State government and the company developed an alternative control strategy - prevent spread of the infection & eliminate infected birds**
  - **Basic strategy:**
    - **Isolate the farms (biosecurity practices)**
    - **Increase immunity in infected layers (single vaccination H7N2 inactivated oil-emulsified vaccine)**
    - **Replace infected layers with twice vaccinated pullets (H7N3 in pullets)**
    - **Establish a monitoring program - unvaccinated sentinels (serology), screen daily mortalities (virus detection) – monthly testing**
    - **Develop a DIVA strategy using neuraminidase protein**
  - **26 June 2003, last detection of H7N2 LPAI virus (RRT-PCR)**
  - **Declared AI free in mid-2005 and vaccination stopped**

Swayne and Akey, AI Control in USA, In: AI Prevention and Control, Springer:Dordrecht, pp.113-130, 2005

David E Swayne USDA

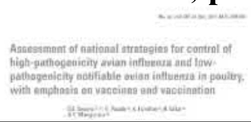
H5/H7 HPAI Vaccination Programs

Doses of Vaccine (millions): 2002-2010 (Total >113b)



14 countries vaccinated poultry against HPAI (2002-2010)

- Preventive (<0.2%): Mongolia, Kazakhstan, France, The Netherlands, Hong Kong SAR
- Emergency (<0.8%): Cote d'Ivoire, Sudan, N. Korea, Israel, Russia, Pakistan
- National/routine (>99%): Mainland China, Egypt, Indonesia and Vietnam, plus added Bangladesh (H5N1, 2011-) and Mexico (H7N3, 2012-)
- Estimates 2002-2022: >475b; approximately 25b per year



David E Swayne USDA

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

- RRT-PCR for rapid detection of avian influenza viruses for diagnostics and surveillance programs
- Molecular definition of highly pathogenic avian influenza
- Improved methods for depopulation and disposal
- Implementation of vaccination programs for HPAI
- Reverse genetic vaccine strains for antigenic matching to field viruses
- Laboratory & surveillance methods to assess vaccine & field virus for updating
- Cassette concept to rapidly update non-replicating registered vaccines
- Recombinant vectored vaccines produce cell-mediated as well a humoral immunity
- Hemagglutinin-only based vaccines which support serological DIVA strategies
- Improved adjuvants for enhanced immune responses

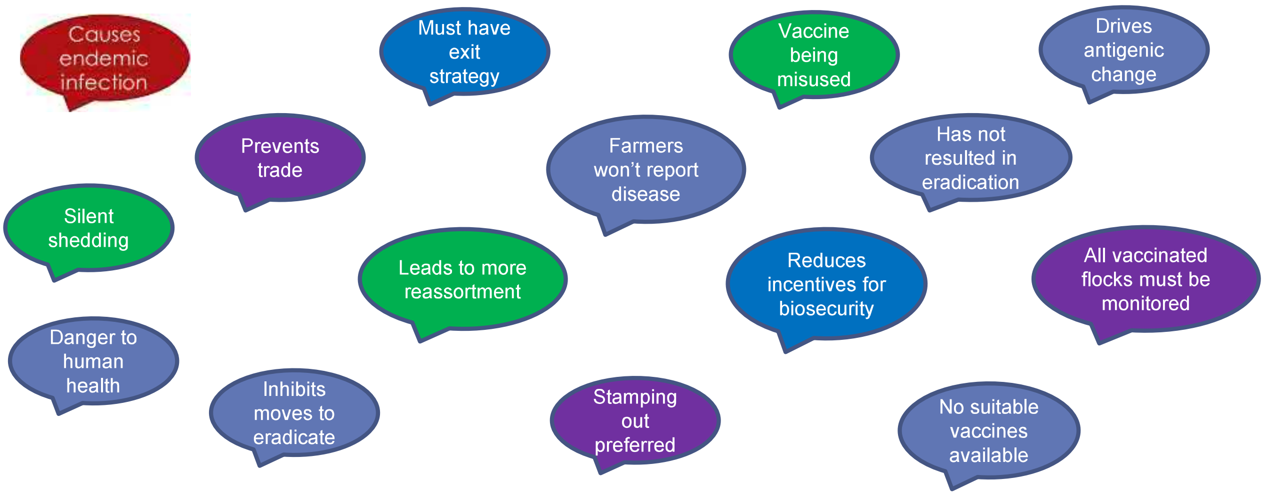
David E Swayne USDA

Why are we having this meeting?

- The change in behavior of the H5Nx Eurasian lineage HPAI viruses
- The effects this is having on production systems (e.g. compulsory housing orders)
- The need to explore options to reduce the massive losses of birds and high cost to industry and government from outbreaks
- Uptake of vaccination has been slow with reliance solely on biosecurity and response to infections
- Recognized that there are several barriers to vaccination that can be overcome
- A change is occurring in thinking towards vaccination especially in places that have experienced repeated wild bird introductions and epidemics in poultry
- Mounting citizen pressure against repeated mass depopulation

Barriers to Vaccination

Some of the “reasons” given for rejecting use of preventive vaccination – not all are valid and all can be overcome



- Detail will be covered in the series of presentations
- Many countries have been reluctant to use vaccination even to improve food security which includes some countries where H5 HPAI is endemic
- In some endemic countries where vaccination is not allowed there is illegal vaccines of unknown quality being used
- Several issues have inhibited the use of vaccination in places with a zero tolerance for infection including trade restrictions, silent infection, antigenic drift, complications to existing surveillance systems & fears that use of vaccination will result in endemic infection, etc.

How will this meeting be structured?

- A series of presentations covering the issues described above
- Two sessions in which panels have been tasked to develop vaccination programs for specific scenarios/mock countries
- The first panel will consider solving 3 common barriers in a poultry vaccination programs
- The second panel will consider "emergency" vaccination in a North American country based on scenarios similar to late 2014 and 2021 when Eurasian H5 HPAI viruses arrived via wild birds

How will this meeting be structured?

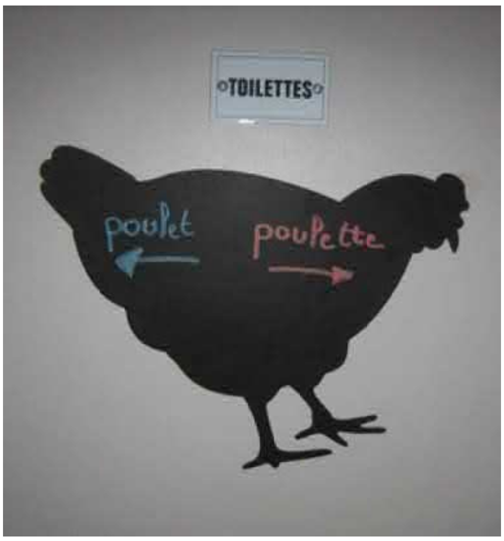
- After each panel there will be break out sessions involving all participants in which you have the chance to consider the program presented by the panel and suggest alternative approaches
- The findings from the break-out groups will then be provided back to the panels for a final round of discussion
- The meeting will also hear from several countries with endemic infection where vaccine has been used and their lessons learned
- We will summarise the findings from the meeting in a wrap up session at the end of day 2
- The findings from this meeting and several companion papers on surveillance, barriers to vaccination, and vaccines will be published

GOAL

Our goal is to find ways to overcome barriers to vaccination and we are expecting you to help us in this task

David E Swayne USDA

Merci Beaucoup!



David E Swayne USDA

附件3

Factors that inhibit usage of preventive vaccination and ways to overcome them

Leslie (Les) Sims
Asia Pacific Veterinary Information Services
apvis@bigpond.net.au

SCIENCEINSIDER | HEALTH

Wrestling with bird flu, Europe considers once-taboo vaccines

Overwhelmed by the toll of culling, some countries launch vaccine trials in poultry despite trade implications and public health risks

11 MAY 2022 · 12:30 PM · BY ERIK STOKSTAD

Lancaster Farming | Farming News | Country Life | Classifieds | Auctions | Mailbox Markets

October 17, 2022 ANDERSON TRACTOR SUPPLY 52°

Trade Bans Limit Appeal of Avian Influenza Vaccines

Philip Gruber, pgruber@lancasterfarming.com Oct 9, 2022 Updated Oct 14, 2022

Some background

This presentation is based on 20 years experience with vaccination against HPAI, starting in Hong Kong in 2002

Based on observations and evidence that vaccination can add an additional layer of protection, and not result in endemic infection if the program is well managed

No vested interest/affiliation to any vaccine company

Experiences also from countries where viruses were entrenched/endemic before vaccination.

Results from these countries should not be applied directly to high income countries/regions considering vaccination (that have the capacity to monitor vaccinated flocks)

Barriers to Vaccination

Some of the “reasons” given for rejecting use of preventive vaccination – not all are valid and all can be overcome

- Causes endemic infection
- Must have exit strategy
- Vaccine being misused
- Drives antigenic change
- Silent shedding
- Prevents trade
- Farmers won’t report disease
- Reduces incentives for biosecurity
- Has not resulted in eradication
- All vaccinated flocks must be monitored
- Leads to more reassortment
- Danger to human health
- Inhibits move to eradicate
- Stamping out preferred
- No suitable vaccines available

“Vaccination will lead to silent infection and shedding”

Based largely on concerns that vaccines do not, in many cases, produce sterilising immunity – shedding can occur in some challenged, vaccinated birds.

Several models predicted silent infection (e.g. Savill et al 2006)

But not field-validated or consistent with findings from the field (e.g. Ellis et al 2004)

Avian Pathology ›
Volume 33, 2004 - Issue 4

Original Articles

Vaccination of chickens against H5N1 avian influenza in the face of an outbreak interrupts virus transmission

Trevor M. Ellis, Connie Y. H. C. Leung, Mary K. W. Chow, Lucy A. Bissett, William Wong, Yi Guan & ...show all

Pages 405-412 | Received 28 Feb 2004, Accepted 05 Apr 2004, Published online: 12 May 2010

Vaccine challenge studies using transmission to in-contact birds provide a different perspective on the significance of shedding and the likelihood of silent infection at a flock level

Research article

Role of vaccination-induced immunity and antigenic distance in the transmission dynamics of highly pathogenic avian influenza H5N1

Ioannis Sitaras, Xanthoula Rousou, Donata Kalthoff, Martin Beer, Ben Peeters and Mart C. M. de Jong

Published: 01 January 2016 https://doi.org/10.1098/rsif.2015.0976

Vaccine transmission experiments, including low dose vaccination

(Sitaras et al 2016)

Va

Vaccine Strain	HI Titre		Challenge Strain	HI Titre	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
H5N1 t/T	16	16	H5N1 t/T		NT	-/-	-/-	-/-	-/-	-/-	-/-
H5N1 t/T	64	64	H5N1 t/T		NT	-/-	-/-	-/-	-/-	-/-	-/-
H5N1 t/T	128	128	H5N1 t/T		NT	-/-	-/-	-/-	-/-	-/-	-/-
H5N1 t/T	128	128	H5N1 t/T		NT	-/-	-/-	-/-	-/-	-/-	-/-
H5N1 t/T	-	-	H5N1 t/T		NT	-/-	-/-	-/-	-/-	-/-	-/-
H5N1 t/T	16	16	H5N1 t/T	Same as Vaccine Strain	+/-	+/-	+/-	+/-	+/-	-/-	-/-
H5N1 t/T	256	128	H5N1 t/T		+/-	+/-	-/-	-/-	+/-	-/-	-/-
H5N1 t/T	8	8	H5N1 t/T		+/-	+/-	+/-	+/+	+/+	-/+	-/+
H5N1 t/T	32	32	H5N1 t/T		+/-	+/-	+/-	+/-	+/-	-/-	-/-
H5N1 t/T	32	32	H5N1 t/T		+/+	+/-	+/-	+/-	-/-	-/-	-/-

Vaccinated contacts

Challenged birds

10	S	H5N1 t/T	16	16	H5N1 t/T		NT	-/-	-/-	-/-	-/-	-/-	-/-
10	S	H5N1 t/T	64	64	H5N1 t/T		NT	-/-	-/-	-/-	-/-	-/-	-/-
10	S	H5N1 t/T	128	128	H5N1 t/T		NT	-/-	-/-	-/-	-/-	-/-	-/-
10	S	H5N1 t/T	128	128	H5N1 t/T		NT	-/-	-/-	-/-	-/-	-/-	-/-
10	S	H5N1 t/T	-	-	H5N1 t/T		NT	-/-	-/-	-/-	-/-	-/-	-/-
10	I	H5N1 t/T	16	16	H5N1 t/T	Same as Vaccine Strain	+/-	+/-	+/-	+/-	+/-	-/-	-/-
10	I	H5N1 t/T	256	128	H5N1 t/T		+/-	+/-	-/-	-/-	+/-	-/-	-/-
10	I	H5N1 t/T	8	8	H5N1 t/T		+/-	+/-	+/-	+/+	+/+	-/+	-/+
10	I	H5N1 t/T	32	32	H5N1 t/T		+/-	+/-	+/-	+/-	+/-	-/-	-/-
10	I	H5N1 t/T	32	32	H5N1 t/T		+/+	+/-	+/-	+/-	-/-	-/-	-/-

Table S10: Overview of Transmission Experiment 2, Group 10.

"Vaccination will lead to silent infection"

Other transmission studies have shown similar results (e.g. van der Goot et al 2005)

A well vaccinated flock (good immune response to field virus) has a very low probability of sustained infection

Should exploit this and change the way we think about the risk posed by well vaccinated flocks

Surveillance for virus should be coupled with serological monitoring for response to vaccination.

Can focus more attention on less well vaccinated flocks (targeted surveillance)

True silent infection probably occurs rarely

- True silent infection probably occurs rarely on a flock basis
- If transmission in a flock is sustained, signs of infection likely to be seen in galliformes
- Routine dead bird testing should allow early detection of infection in vaccinated flocks even before mortality rates increase
- May see changes in serological profile as used with other diseases (increased titres not linked to recent vaccination, changes to coefficient of variation)
- Need to use experiences from COVID-19 to explore and develop alternative testing systems that include environmental sampling (e.g. waste water, drinking water, dust sample swabs), egg surface washes, etc, as alternatives to testing of live birds

scientific reports

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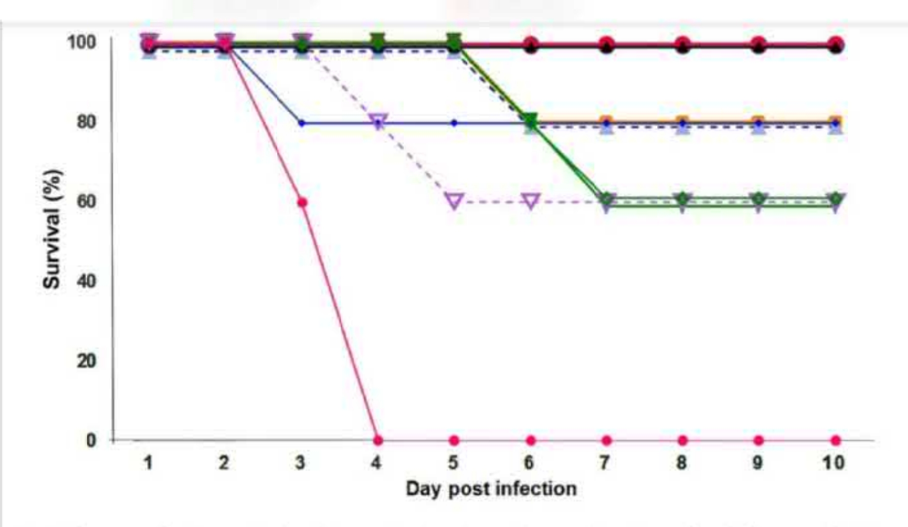
nature > scientific reports > articles > article

Article | Open Access | Published: 26 June 2018

Efficacy of commercial vaccines against newly emerging avian influenza H5N8 virus in Egypt

Ahmed Kandeil, Jamal S. M. Sabir, Ahmed Abdelaal, Ehab H. Mattar, Ahmed N. El-Taweel, Mumdooh J. Sabir, Ahmed Aly Khalil, Richard Webby, Ghazi Kayali & Mohamed A. Ali

Scientific Reports 8, Article number: 9697 (2018) | Cite this article



Survival curves of unimmunized and immunized poultry with tested vaccines after challenge with 0.5

"Vaccination will result in selection of antigenic variants"

Antigenic variants have arisen in places where vaccines are used (but also in places where vaccines are not used (H6 in China)

Depends on the extent of infection in vaccinated birds and levels of immunity encountered

Multiple cases where antigenic "variant" was "imported", not developed locally (e.g. Indonesia - 2.3.2.1c, Viet Nam - various)

In some places same vaccine antigen has been used successfully without updating antigens for 5+ years (e.g. southern Vietnam with clade 1 derivatives)

"Vaccination will drive antigenic change"

- Recognised when vaccination was introduced that antigenic changes would occur
- Need measures in place to detect and respond to antigenic variants
- OFFLU antigenic characterisation project for avian influenza viruses expected to help
- Need ways to update vaccines based on strains encountered or likely to be encountered

"Vaccination prevents trade"

- Still regarded by many as the biggest barrier to usage of preventive vaccination
- "Legal" aspects covered in other presentations later (should not be a barrier)
- Some countries may still be opposed to allowing poultry/poultry products from countries where vaccine is used, regardless of the international rules or surveillance system in place
- Trade should only be inhibited if an appropriate surveillance systems for detection of infection in vaccinated birds is not in place

“All vaccinated flocks need to be tested if vaccination is used”

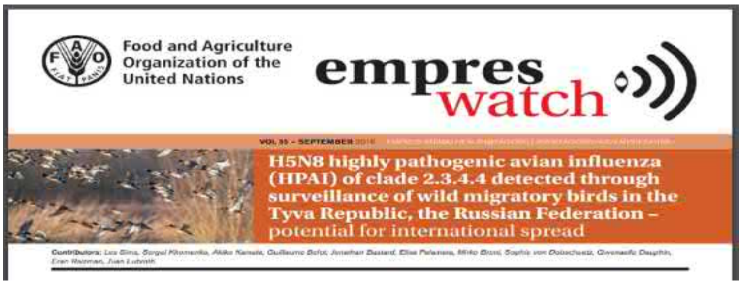
- Will likely be a requirement from trading partners but potential to use more targeted testing and explore options to keep cost down
- Best to have a multi-layered system adapted from the system applied in Hong Kong (serology for response to vaccination, testing on farm, testing in live bird markets)
- Must be both affordable and sufficiently comprehensive to demonstrate sustained infection is not occurring. If not affordable it will likely inhibit uptake of vaccination, as seen in 2006 in Europe
- Explore ways that do not require official veterinarians to take samples on farms, use sensible pooling of samples, and allow certified private labs to conduct testing
- Vaccinated flocks should not be disadvantaged given apparent silent infection can also occur in unvaccinated flocks (see for example Hulse-Post et al and Gobbo et al 2022)
- More in a subsequent presentation on surveillance by Timm Harder.

“Suitable vaccines are not available”

- Well-matched killed antigen non-DIVA-compatible vaccines have been used successfully (e.g. Hong Kong SAR) . Other vaccines are also available (e.g. HVT vector, sub-unit vaccines)
- Majority of vaccine against HPAI is produced in China with many European and North American companies no longer producing vaccine against HPAI viruses
- Commercial reality that vaccines will only be produced if there is a market for the product (explore alternative funding methods?)
- Need to recognise experiences of vaccine companies from 2005 onwards (produced products for which there was no or a limited market)
- Need to look at options for rapid updating of vaccine antigens that do not require full re-registration (“cassette method”)
- May need to consider systems that do not rely on fertilized eggs such as production in plants or mRNA provided they afford similar protection from disease and virus shedding/transmission

“Suitable vaccines are not available”

- Concerns that novel strains will arrive for which a suitable vaccine is not available (but many vaccines do afford reasonable cross protection)
- Usually some warning of strains on the move
- OFFLU antigenic matching programme (AIM) will assess new strains but need good global intelligence and virus/sequence sharing
- See earlier re “cassette system” for updating vaccines



Other “barriers” – endemic infection, better to use stamping out, need an exit strategy

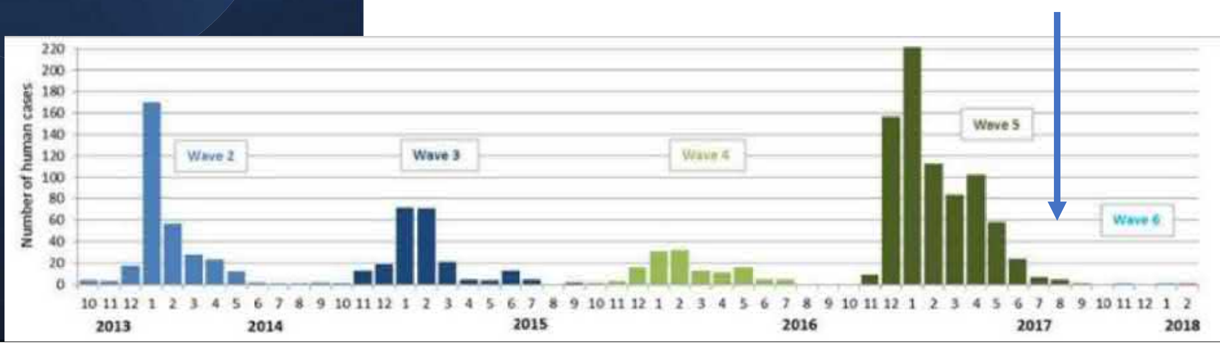
- Most places using vaccination did so because the virus was already endemic
- Hong Kong SAR (zero tolerance for infection) does not have endemic infection despite using vaccines for 20 years
- Vaccination will reduce the need for stamping out
- Stamping out will still be used on farms if virus is detected Unlikely to need to cull millions of birds if appropriate vaccines are used
- Exit strategy is a misnomer – need to regularly review the need for vaccination and if situation changes consider alternative approaches

Other “barriers” - vaccination will inhibit use of other biosecurity measures, farmers won’t report disease

- Both can be managed
- Biosecurity is not just about avian influenza
- In some places farms need to meet certain standards
- Farmers who don’t report will be found out quickly given surveillance systems in place for vaccinated flocks

Other “barriers” - vaccination will increase risks to public health

- Vaccination will reduce the quantities of virus produced if a flock does get infected compared to situations where no vaccine is used
- If a vaccinated flock requires stamping out there will be lower levels of virus in the affected flocks
- Mandatory monitoring programme will allow detection of infection allowing action to be taken
- No reason why vaccination will increase reassortment as has been suggested
- See later presentation by Richard Webby on public health aspects



Other “barriers” – inhibits moves to eradicate the virus; places where vaccine is being used have not eliminated virus

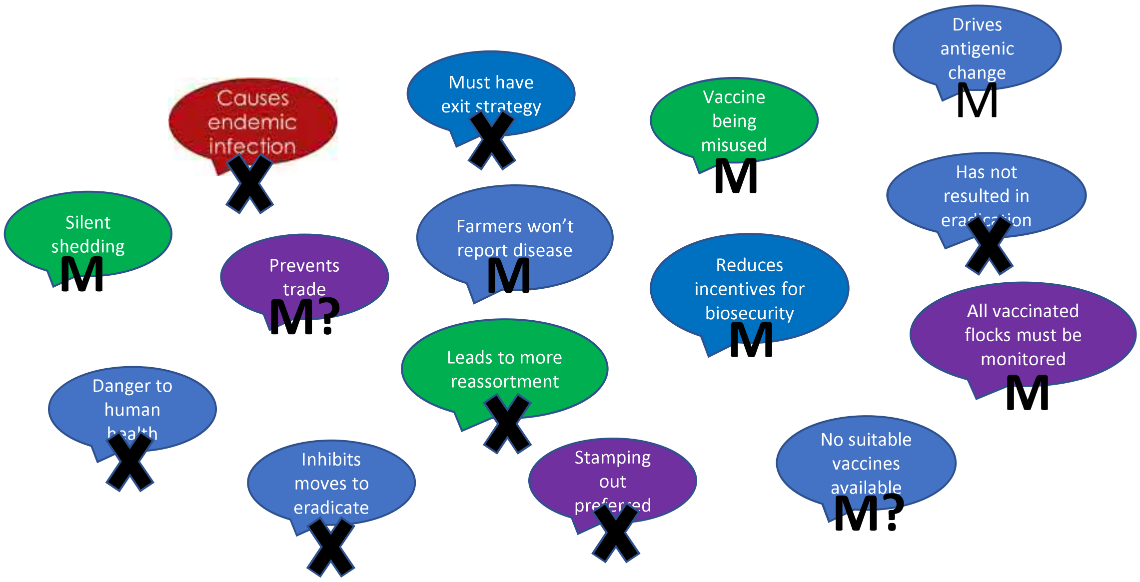
- Not if there is a well designed monitoring programme and zero tolerance for infection
- Virus was eliminated from Hong Kong using vaccination in conjunction with other measures but it was only after vaccination was compulsory for all birds going to live bird markets (late 2003) that virus was no longer detected in markets (one exception involving an antigenic variant in 2008 managed by stamping out)

Some conclusions

- A number of the supposed barriers are based on false equivalence with countries where virus elimination was not possible and vaccination is being used to limit, but not eliminate infection
- Need to regard well vaccinated flocks as low risk for sustained infection rather than high risk, but still conduct appropriate monitoring
- Need to recognise that HPAI has changed and approaches to this disease need to change as well
- All of the barriers can be addressed but several will likely take more time than others to be overcome
- Need to consider multi-faceted and targeted monitoring and surveillance to provide trading partners with confidence that the virus is not circulating in vaccinated poultry
- Vaccination is a very powerful tool to assist in prevention of HPAI – if we don’t use it we are not using all of the tools in the toolbox
- Time to rebalance the pros and cons of vaccination

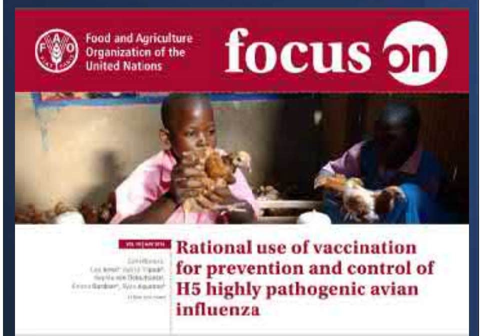
Barriers to Vaccination

Some of the "reasons" given for rejecting use of preventive vaccination – not all are valid (X) and all can be overcome (M or have the potential to be overcome(M?)



Thank you!

- Thanks to IABS for organising this meeting and to all participants for working to find ways around barriers to vaccination
- Vaccination should be considered to help overcome problems such as the headlines below



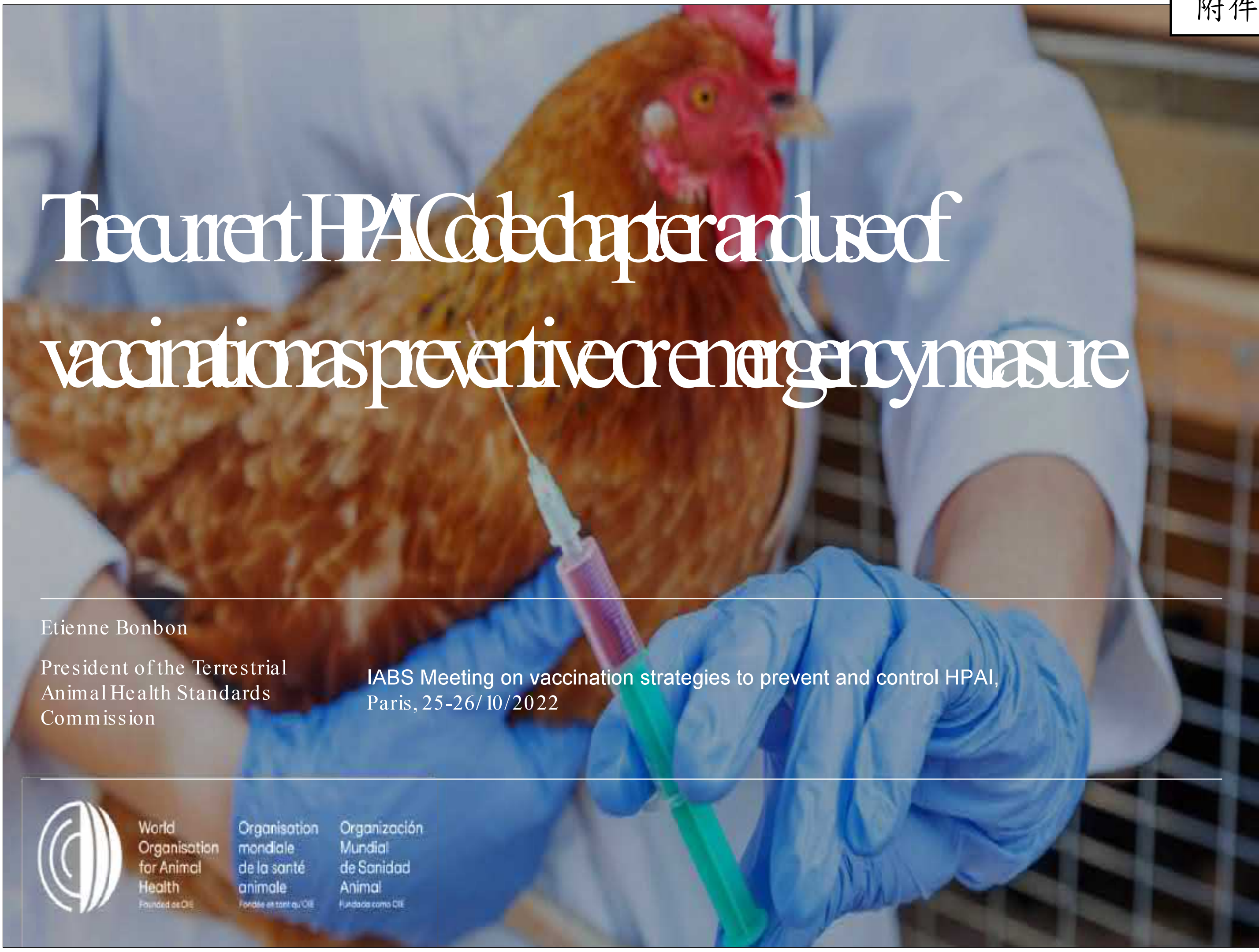
The end of free-range eggs? Year-round bird flu outbreaks may keep hens inside

4 minute read · October 18, 2022 9:30 PM GMT+11 · Last Updated 2 days ago

Bird flu kills close to a record number of poultry in the U.S.

By Tom Polansek

附件4



The current HPAI Code chapter and use of vaccination as preventive or emergency measure

Etienne Bonbon

President of the Terrestrial Animal Health Standards Commission

IABS Meeting on vaccination strategies to prevent and control HPAI,
Paris, 25-26/10/2022

World Organisation for Animal Health | Organisation mondiale de la santé animale | Organización Mundial de Sanidad Animal

Index

1. Generalities
2. Key aspects of the HPAI Chapter of the Terrestrial Code
   - Title, scope
   - Case definition
   - Status
   - Trade
   - Surveillance
3. Key points on HPAI vaccination in the chapter
   - Why / What for?
   - How?
   - Consequences?
   - Others

Generalities

- Recent update (2021, but took four years!), to adapt: epidemiology, trade, trends …
- Since then, situation has evolved…mostly in Europe
- And the Code is still relevant as it had taken all situations into account, and gives practical options to the Veterinary Authorities for the prevention and control of HPAI
- Need for more? Up to the Members to say, when applied!

Key aspects of the chapter

- On HPAI only, but H5 and H7 LPAI should be monitored and managed
- Case definition = test; no link with clinical severity
- Free status = self-declaration of freedom; thorough surveillance + proven management
- Trade from HPAI free zones; no current certificates for animals or fresh meat from infected zones
- Surveillance = 'passive' + 'active', including if free

Key points on vaccination

1. vaccination against HPAI is an effective complementary control tool when a stamping out policy alone is not sufficient
2. vaccination does not affect the HPAI status of a free country or zone if surveillance supports the absence of infection
3. vaccination is decided by the Veterinary Authority on the basis of the HPAI situation as well as the ability of the Veterinary Services to implement vaccination and the appropriate surveillance strategy
4. tests should be performed to ensure the absence of virus circulation, at a frequency proportionate to the risk; use of sentinel poultry may provide further confidence
5. evidence to show the effectiveness of the vaccination programme should also be provided

Others

- Complementarity between vertical and horizontal WOAH Standards
- Important chapters (I): Chapters 1.4. on Surveillance & 4.18. on Vaccination
  - No vaccination possible without planning and surveillance
- Important chapters (II): Chapters 4.4. on Zoning and Compartmentalisation…and 4.5. on Application of Compartmentalisation!
  - No vaccination possible without biosecurity, traceability and movement controls
- Important chapters (III): Chapter 4.19. on Official control programmes

Thank you

12, rue de Prony, 75017 Paris, France
T. +33 (0)1 44 15 19 49
F. +33 (0)1 42 67 09 87

woah@woah.int
www.woah.org

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附件5

European Commission

VACCINATION RULES IN THE EU

IABS MEETING ON

HIGH PATHOGENICITY AVIAN INFLUENZA VACCINATION STRATEGIES TO PREVENT AND CONTROL HPAI : REMOVING UNNECESSARY BARRIERS FOR USAGE

Paris, 25-26 October 2022

European Commission,
DG Health and Food Safety
Unit G2 – Animal Health

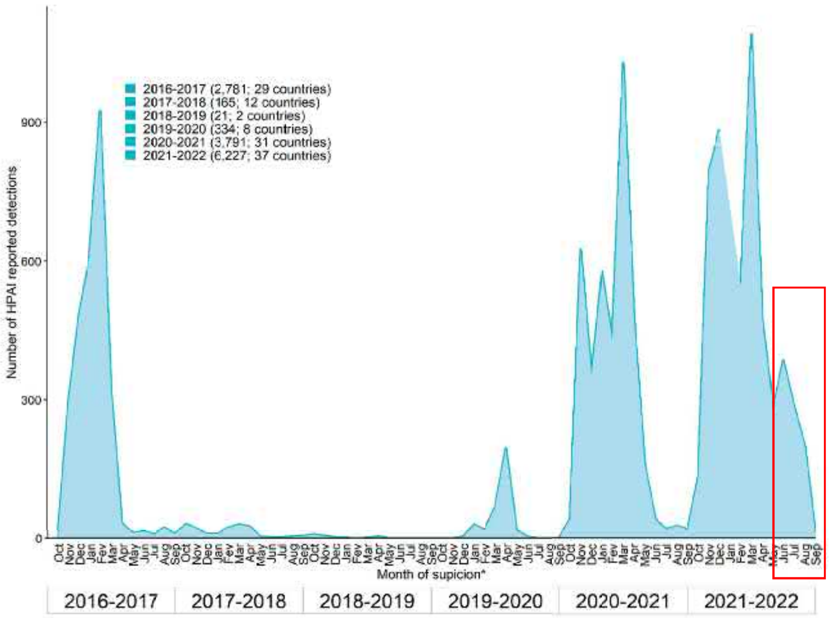
Health and Food Safety

Outline of the presentation

- ❑ HPAI situation in the EU
- ❑ Animal Health Law – new legislative framework for animal health
- ❑ Future rules on vaccination
- ❑ Conclusions

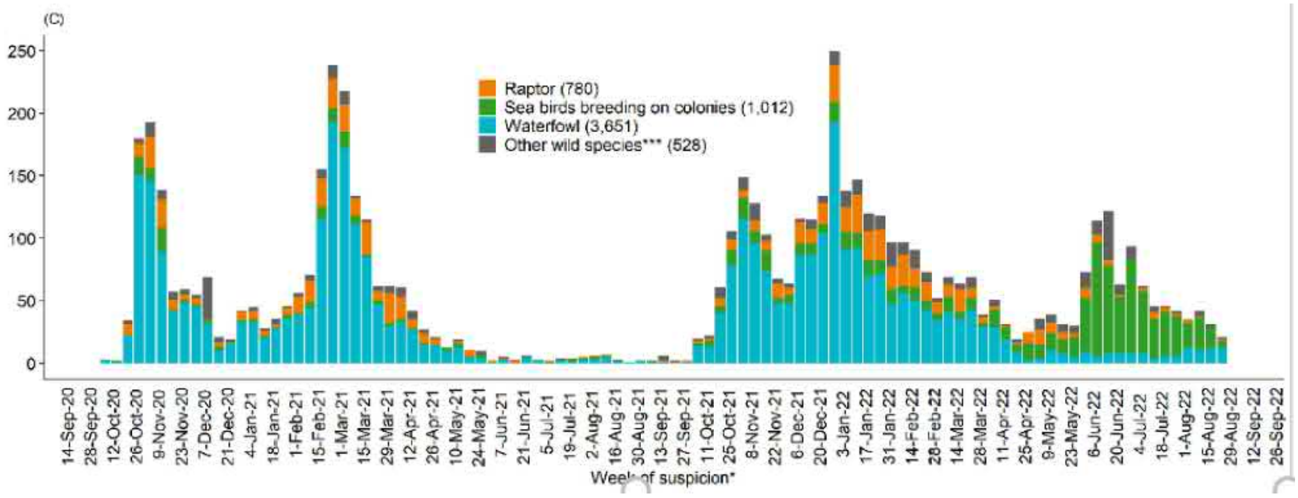
HPAI situation in the EU

Number of HPAIV detections in Europe since 2016



Source: EFSA / ECDC / EURL "AI overview June-Sept. 2022",
https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2022.7597

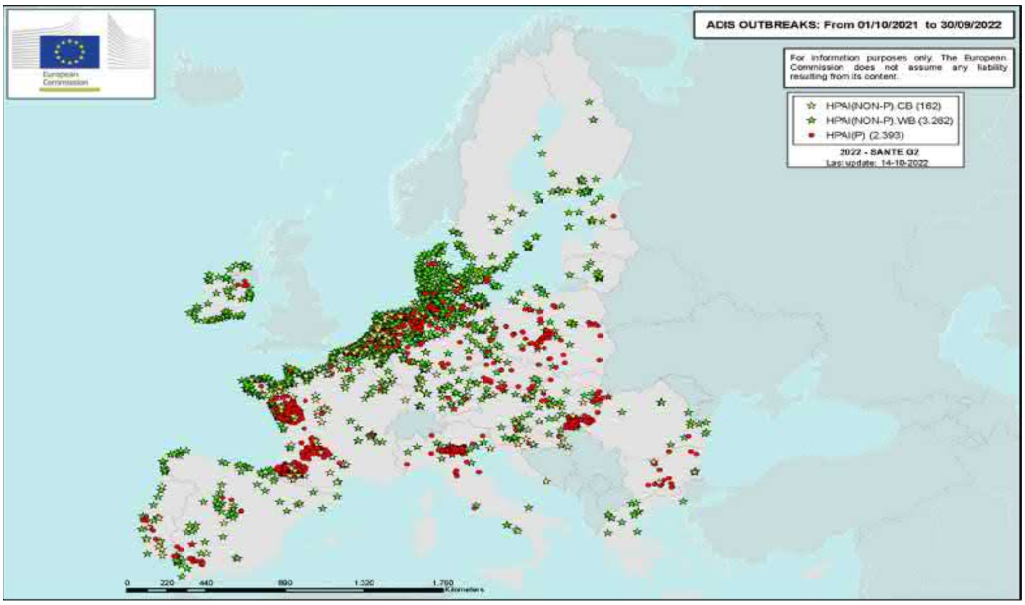
Number of HPAIV detections in different wild bird categories



Source: EFSA / ECDC / EURL "AI overview June-Sept. 2022",
https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2022.7597

European Commission

Geographical distribution of HPAI in the EU, *2021-2022 epidemic season*



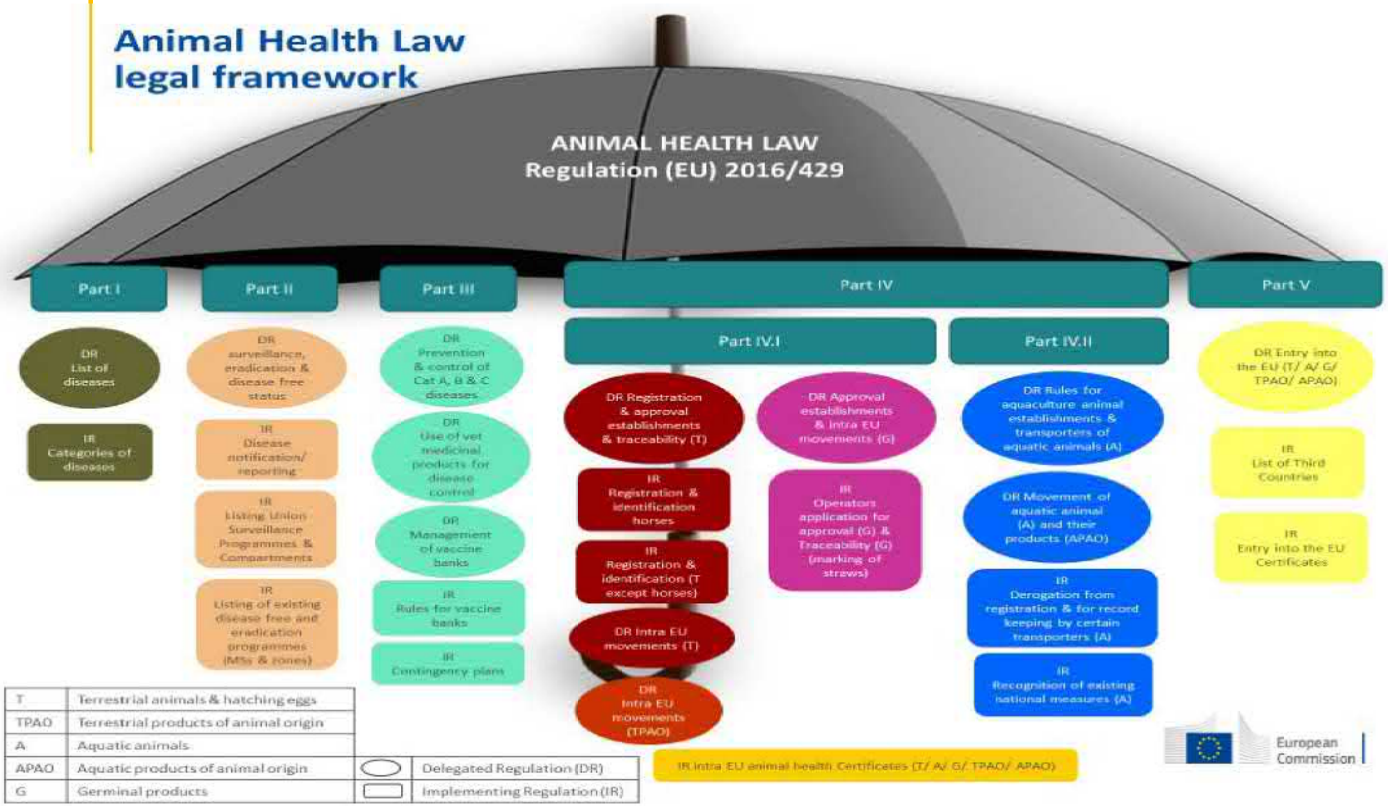
European Commission

Animal Health Law

– new legislative framework

for animal health

European Commission



European Commission

Part 3 – disease awareness, preparedness and control

- Contingency plans and simulation exercises
- **Use of veterinary medicinal products for disease prevention and control**
- Antigen, vaccine and diagnostic reagent banks
- Disease control measures for Category A diseases
- Disease control measures for Category B and C diseases

AHL: Rules for the use of VMPs for disease prevention and control

Article 46(1)

Provides for the possibility for the Member States to take measures concerning **the use of (ALL) veterinary medicinal products** to ensure the most efficient **prevention or control** of (ALL) listed diseases. These measures may cover prohibitions, restrictions and compulsory use of veterinary medicinal products and must be previously assessed as appropriate and necessary.

Article 47(1) (empowerment)

Empowers the Commission to adopt delegated acts concerning:

- ✓ prohibitions and restrictions on the use of veterinary medicinal products;
- ✓ specific conditions for the use of veterinary medicinal products for a specific listed disease;
- ✓ risk-mitigation measures to prevent the spread of listed diseases through animals treated with the veterinary medicinal products or products from such animals;
- ✓ surveillance for specific listed diseases following the use of vaccines and other veterinary medicinal products.

Article 69 - Emergency vaccination:

To take into account Art. 46(1) and delegated acts adopted pursuant to Art. 47

Draft Delegated act

on the use of veterinary medicinal products for disease prevention and control

European Commission

Proposed approach

Rules on the use of certain VMPs for prevention and control of certain listed diseases - Terrestrial and Aquatic animals

- Circumstances under which **vaccines for category A** diseases can be used
- Which **VMPs cannot be used for category A and B** diseases *(including some vaccines, i.e. Rinderpest and Mycobacterium tuberculosis complex)*

Rules on the use of vaccines for prevention and control of category A diseases – Terrestrial animals (partially Aquatic)

- Preconditions
- Strategies
- General rules
- Risk-mitigation measures (movement restrictions)

Disease-specific conditions

- Implementation + post vaccination surveillance
- Measures (movement prohibitions for animals and products) in the vaccination zone
- Recovery of the previous animal health status

This (draft) Act does not interfere with the scope of **Regulation (EU) 2019/6**

European Commission

Use of vaccines in animals for Category A diseases

Member States allow

The competent authority decides and controls

Vaccination is part of official measures put in place by the CA for prevention and control of category A diseases

In accordance with the general rules/measures in the Regulation

In accordance with the disease-specific conditions in Annexes (Terrestrial)

Exceptions for Newcastle disease

Vaccination strategies for prevention and control of category A diseases of poultry

- Vaccination
  - Emergency
    - Suppressive
    - Protective
  - Preventive

Link to disease control measures

SPECIAL CASES

Preventive vaccination

✓General rules

✓Disease-specific conditions **available only for HPAI** [for the moment]

Vaccination against Newcastle Disease

✓ **Special status** for *"routine precautionary vaccination"*

European Commission

Decision Making - Implementation process

for the use of vaccines in animals for Category A diseases

Member state

- **Assessment of the situation** based on specific criteria *(Annexes)*
- **DECISION TO VACCINATE *(strategy selection etc.)***
- (*Preparation of official vaccination plan*)

Member State

- Preliminary information sent *to the other MS and the COM*
- **INITIATION OF VACCINATION**
- Official vaccination plan sent *to the other MS and the COM*

COM

Review of the national measures in the official vaccination plan in accordance with Article 71 of Regulation (EU) 2016/429

Member State

- **Regular reports** sent *to the other MS and the COM* *(content / intervals according to the vaccination strategy – Annexes)*
- **Disease-specific Surveillance – Risk mitigation measures – Recovery periods**

European Commission

State of play

- Rules discussed in 8 Expert group meetings (incl. a questionnaire to MS experts) (Doc SANTE 7144/2020) from March 2020 until May 2022
- Finalisation of internal consultation and final modifications: July 2022
- Public feedback: 5 August – 2 September 2022 https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12173-Veterinary-medicines-vaccines-conditions-for-use_en
- Translation: August – October 2022
- Adoption by the COMM: November 2022
- EP and Council objection period: November – December 2022
- OJ Publication: December 2022 / January 2023

Mandate to EFSA

COM **request** to EFSA **for a new scientific opinion on vaccination against HPAI**

- ✓ formally sent to EFSA in July 2022
- ✓ accepted by EFSA

Questions regarding:

1. Vaccines
2. Vaccination strategies
3. Surveillance
4. Risk mitigation measures

Delivery of opinion:

- ✓ by 31 July 2023 for questions 1 and 2
- ✓ by 31 March 2024 for questions 3 and 4

Conclusions

European Commission

Conclusions

- 2021 - 2022 the **worst ever** HPAI epidemic in poultry in EU
- **Risk** for poultry **still present** during summer in large parts of EU
- **Biosecurity** remains the cornerstone for preventing infection of poultry
- **Paradigm shift** with EU Animal Health Law **on vaccination**
- EU legal framework to **enable vaccination** as an **additional tool** to prevent and control HPAI under development, in line with WOAH standards
- Poultry sector in EU not uniform, thus **no "fit for all" vaccination strategy** and EU rules leave **flexibility for Member States** to decide on vaccination as preventive or control measure for HPAI

European Commission

Thank you

VACCINES AVAILABLE AND SYSTEMS FOR USAGE IN THE FIELD

Erica Spackman, MS, PhD
US National Poultry Research Center
US Dept. of Agriculture
Agricultural Research Service
Athens, GA, USA

USDA Agricultural Research Service U.S. National Poultry Research Center Southeast Poultry Research Laboratory

Disclaimer

- No vaccine type or manufacturer is being endorsed
- References are <u>not exhaustive</u> and are mostly provided where data are new or otherwise limited
- Acknowledgements

“Protection” or ”Efficacious”

- Maintain animal health and minimize production losses
  - No mortality or morbidity
- Reduce virus spread/onward transmission
  - Reduce shed titers 100X or more
- Reduce public health risk
  - e.g., vaccination of ducks for H5N1

TECHNICAL CONSIDERATIONS

Good quality vaccine

- Has an adequate antigenic load to induce immunity
- Contains an antigen which is:
  - Antigenically closely related to the field strain (and the field strain is monitored for antigenic drift)
  - Sufficiently immunogenic

  → Autogenous vaccines work well if adequately immunogenic
- Contains a sufficient antigenic load
- Effective adjuvant
- Administered effectively to birds

Antigen selection/optimization

- Matching:
  - Antigenic cartography
  - Protective epitopes
  - OFFLU program to monitor antigenic variants
- Breadth of response:
  - Mixing antigens: Prime/boost with different vaccines
  - Computationally optimized broadly reactive antigen (COBRA) induces a broader response (Bertran, Vaccine 2021)
- Immunogenicity:
  - Adjuvants

Adjuvants

- Inactivated vaccines must be adjuvanted
- Most evaluation work has been done in chickens
- Many mineral oil-based adjuvants are commercially available
- Novel/experimental adjuvants for poultry:
  - Interleukins, Rig-I ligands, poly I:C, chitosan, *B. subtilis* spores, novel mineral oil formulations

Inactivation method

- Cost
- Safety
- Preservation of epitopes
  - Cross-linking of proteins
  - pH changes

Chemical

- Formalin
- Beta-propiolactone (BPL)
- Binary ethylenimine (BEI)

Irradiation

- Experimental (Bortolami, Frontiers in Vet Sci 2022)

Vaccine availability

- No technical barriers to producing vaccines
  - Supply of sufficient quantities of suitable vaccine
    - Stockpiles/vaccine banks
      - Which antigen?
  - Production considerations
  - Regulatory considerations

VACCINE TYPES

Live vaccines

- Will be covered by Dr. Brown

Experimental vaccine platforms

- Influenza is a proof-of-concept agent for vaccines
  - Most are developed for human use
- Examples:
  - Non-type 1 avian paramyxoviruses
  - Infectious Laryngotracheitis virus
  - Bat influenza vectors
  - Adenovirus
  - *Salmonella*
  - *E. coli*
  - Yeast
  - Plant based

Inactivated vaccines

- Chemically inactivated whole virus, adjuvanted oil emulsion
  - 95.5% of all AIV vaccine use by dose (Swayne, Rev Sci Tech 2011).
- Effective in numerous species
  - Most efficacy data have been produced with chickens and turkeys
  - Limited data with other species: Pekin Ducks, Domestic geese, indicate broad efficacy. (Rudolf, Rev Sci Tech 2009; Kilany, PLOS ONE 2016; Pantin-Jackwood, Av Dis 2019)
  - Efficacious for many species, could potentially protect zoo birds, endangered species in addition to poultry
    - Data lacking on non-poultry species

Inactivated vaccines

- Primarily induces humoral immunity
- Requires:
  - Strain that replicates to high titers in eggs
  - Low pathogenic cleavage site
- Inactivated vaccines relatively expensive to administer
- Regulatory withdrawal time for meat birds in some countries
- Inactivated vectored APMV-1
  - Bi-valent AIV – NDV with HA insert

Vectored Vaccines

- Induce cellular immunity
- Licensing varies by country
- May be affected by prior exposure or maternally derived antibody (MDA) to the vector or AIV insert
- Some vectors species specific
- Proteins not altered by chemical inactivation
- Egg-free production
  - Logistics and mutations
- Subunit vaccines
  - Allow for antigen updates (can be affected by regulations)
  - Applicable to some DIVA strategies

Common vectors and sub-unit vaccines

- Replicating Vectors
  - Herpes virus of turkeys (HVT)
  - Fowlpox virus (FPV)
  - Avian paramyxovirus type-1 (APMV-1) Newcastle disease vaccines
- Non-replicating vectors
  - Alphavirus virus-like particles (VLP)
  - Baculovirus VLP
  - Inactivated APMV-1
- Nucleic acid
  - Self amplifying-RNA (sa-RNA)
  - DNA & mRNA

Herpes virus of turkeys (HVT)

- Stable well characterized vector
- Induces cellular immunity
  - Can tolerate antigenic variation better than inactivated vaccines
  - Immunity not fully inhibited by AIV MDA (Bertran, Vaccine 2018)
- Can be mass applied to chickens (*in ovo*)
- Immunity can be enhanced when used as a priming vaccination
- Efficacious for chickens and turkeys

Herpes virus of turkeys (HVT)

- Pekin ducks (*Anas platyrhinchos domesticus*)
  - Vector does not replicate sufficiently, and protection is poor (Pantin-Jackwood, Av Dis 2016; Palya, Av Dis 2016)
- Muscovy ducks (*Cairina moschata*) and Mule ducks
  - Vector replicates better and confers some protection (Kilany, PLOS ONE 2016; Palya, Av Dis 2016)
- Domestic geese (*Anser anser*)
  - Vector replicated better than other waterfowl, but less than chickens (Palya, Av Dis 2016)

Duck enteritis virus

- Herpesvirus which causes an important disease in domestic ducks that is controlled by vaccination
- Disease from H5 HPAIV in ducks varies by strain, duck age and duck species.
  - Can reduce shed titers and virus spread
- Has been shown to be efficacious in domestic ducks and chickens (reduced mortality and virus shed) (Liu, J. Virol 2011; Liu, Antiviral Res. 2013; Chen, Vaccine 2019)

Fowlpox virus (FPV)

- One of the oldest vaccine vectors for poultry (Taylor, Vaccine 1988)
- Administration primarily by wing-web stab
- Not fully inhibited by FPV MDA
- Limited host range: Most efficacious in Chickens
  - Has been shown to work in Pekin and Muscovy ducks with inactivated vaccines booster (Steensels, Vaccine, 2009; Niqueux, Vaccine 2013;)
- Best as a live prime in chicks

Avian paramyxovirus type-1 (APMV-1) Newcastle disease vectored vaccines

- Used in Mexico and China
- Can be mass applied – spray, water
- Induces mucosal and cellular immunity
- Most data from chickens and turkeys, but may be able to protect other avian species
- Interference from APMV-1 MDA (Bertran, Vaccine 2018) or exposure to widely used live ND vaccines limit application
  - Live prime vaccine after MDA wane or naïve chicks

Alphavirus virus-like particle

- Non-replicating vector, virus-like particles without packaging machinery
- Multiple doses can be used (does not interfere with itself)
- Data are much more limited than older vaccines, but appears to be efficacious in numerous species:
  - Chickens (Bertran, Vaccine 2017; Ladman, Av Path, 2019)
  - Turkeys (Santos, Vaccine 2017; Kapczynski, Vet Imm 2017)
  - Pekin ducks (Pantin-Jackwood, Av Dis 2019)
- Licensed in US

Baculovirus based vaccines

- Native antigen presentation
- Immunostimulatory
- Multiple doses can be used
- Virus-like particles
- Purified protein
  - Quadrivalent vaccines for seasonal influenza (Arunachalam, NPJ Vaccines 2021)
- Bivalent LPAIV vaccine immunogenic in chickens (Sun, Front Imm 2022)
- Bivalent HPAIV vaccine protective in chickens (Hu, Front Vet Sci 2021)
- Intranasal and oral administration has been protective in mice (Kumar, PLOS ONE, 2013; Basak, PLOS ONE 2020)

Self amplifying-RNA (sa-RNA)

- Viral (non-segmented, positive sense ssRNA, e.g., alphavirus) replicase drives amplification of RNA and subsequent translation of the antigen

- More efficient than DNA or mRNA
  - Lower dose vs mRNA vaccine (1/64) was protective for mice challenged with influenza (Vogel, Gene & Cell Ther. 2017)

- May be encapsulated for better stability

Vaccines being tested in the EU

- HVT-AI old and new inserts
- NDV-AI inactivated
- sa-mRNA
- DNA
- Baculovirus based, H5 subunit vaccine

List courtesy of Francesco Bonfante

THANK YOU FOR YOUR ATTENTION

附件7

Meeting on HPAI Vaccination Strategies
Removing unnecessary barriers for usage

The view of vaccine producers

Paris WOAH, October 2022

Carel du Marchie Sarvaas
Executive Director
carel@healthforanimals.org
www.healthforanimals.org

HealthforAnimals

29 Regional & National Associations
Working in 40 countries

Vaccines, parasiticides, diagnostics
digital services, antibiotics, etc.

Ten Largest Animal Health Companies
Working in 100+ countries

What needs to be done?

Scientific

- Increase understanding/assessment of current and predicted AI spread
- Who?: Public Health agencies, IGOs, academics, etc.

Policy/trade

- Political decisions whether to continue culling alone or combine with vaccination, WOAH standards compliance
- Who?: governments, WOAH

Societal

- Continued societal acceptance of mass culling is questionable, biodiversity issues, zoonotic potential, retail and consumer views
- Who?: all

Technical

- Getting new vaccines and types of vaccines to market allowing easier preventive or emergency vaccination
- Who?: vaccine producers, government assessors

What are vaccine producers doing?

- Significant investment in new AI vaccine solutions
- Multiple companies active
- DIVA vaccines will be required
- Not all technical answers are available yet
- Ongoing technical discussions with assessors
- Engaging in international fora to send the message that technical solutions are in development, but that movement is needed in other areas

Sending market signals

HealthforAnimals
global animal health association

- Within vaccination companies - there is always competition between potential investment areas
- Decisions to invest in an AI vaccine (or in something else) depend on projected potential ROI
- A fundamental part of the ROI decision is size/predictability of the potential market

Clear policy guidance accompanied by market demand is essential for the animal health industry in order to make the timely investment decisions needed.

Observations

HealthforAnimals
global animal health association

Things take time

- Takes time it takes time to move to authorization, and to get authorizations
- Takes time to get to the volume of vaccine supply needed
- Takes time to vaccinate at mass level (large distribution network needed)
- Surveillance tools needed for DIVA vaccination require involvement of diagnostics manufacturers
- Are surveillance systems ready?

Thank you

Health for Animals
global animal health association

HealthforAnimals.org
Resources.Healthforanimals.org

Twitter.com/Health4Animals

Facebook.com/HealthfrAnimals

Linkedin.com/company/HealthforAnimals

附件8

Developing appropriate surveillance systems that provide confidence that HPAI virus is not circulating in poultry

https://www.autostraddle.com/magic-button-make-everything-ok-106898/

Timm Harder*, Sjaak de Wit, Jose L. Gonzales, Jeremy H.P. Ho, Paolo Mulatti, Teguh Y. Prajitno, Arjan Stegeman

*National, WOAH and FAO Reference Laboratory for Avian and Animal Influenza,
Friedrich-Loeffler-Institute, Isle of Riems, Germany

25-6 October, 2022
Paris, IABS

FRIEDRICH-LOEFFLER-INSTITUT
FLI
Bundesforschungsinstitut für Tiergesundheit
Federal Research Institute for Animal Health

Trust is good.

FRIEDRICH-LOEFFLER-INSTITUT
FLI
Bundesforschungsinstitut für Tiergesundheit
Federal Research Institute for Animal Health

Where is trust required with AI vaccination?

- A matching, safe and immunogenic vaccine is being selected and used (research and licensing)
- Vaccine application ensures sufficient coverage in flocks
- Adequate population immunity is induced and maintained
- Trading partners and consumers reward the added efforts of vaccinating poultry producers (marketing)
- **HPAIV circulation is excluded from vaccinated flocks = safety of vaccinated poultry and products thereof**

● Surveillance-related item

Control is better!

Ascribed to V.I. Ulyanov

FRIEDRICH-LOEFFLER-INSTITUT FLI Bundesforschungsinstitut für Tiergesundheit Federal Research Institute for Animal Health

Surveillance enforces vaccination control

Surveillance strategies and diagnostic methods require careful adaptation to

- The epidemiological situation: endemic, epidemic or sporadic occurence of HPAI
- The capacities of public veterinary services
- Socio-cultural environments
- The scope (local, regional, sectorial, integrative, etc.) and aims (emergency, waling prevention, etc.) of vaccination

Surveillance achieving zero tolerance of HPAIV circulation in vaccinated flocks can be financially demanding.

Surveillance approaches

Passive surveillance

- relies on farmers/veterinarians/traders etc. reporting suspicions
- more or less continuously in place, variable quality between farms
- less effective in vaccinated populations

***Active surveillance*,**

- inspection, sampling and testing prescribed by protocol of the surveillance programme
- transparent and structured sampling frame (farms, type and number of samples, sampling frequency, tests) defines precision of surveillance
- not continuous
- pre-testing signal enhancement (e.g., bucket sampling) required, if no clear clinical or production-related signs expected

1. Monitor vaccine coverage and population immunity

- Vaccination governance (registration of holdings)
- Vaccination distribution and uptake
- Assessment of vaccine-induced protection
    - Antigenic match with circulating viruses
    - Definition of surrogate of protection (i.e., HI titer)
      and of threshold of protection
    - May depend on vaccione type and poultry species
    - Vaccination-challenge trials may be required to fix definitions (central institutions)

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2. Prove absence of HPAIV circulation in vaccinated flocks

- Detection of new outbreaks in vaccinated flocks
    - avoid significant spread within and between flocks (Ro between farms below 1)
    - passive surveillance difficult, threshholds for vaccinated undefined
    - unvaccinated sentinel strategies increasingly discouraged
    - active surveillance using RT-PCR
    - targeted rather than random sampling recommended (bucket sampling)
    - environmental sampling can be highly informative

- Precision of surveillance depends on aims of vaccination and on the epidemiologic situation

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Control is an illusion!

Ellen Langer et al. (1975); doi:10.1037/0022-3514.32.6.951

Sober interpretation of reliable facts is required

"When rolling dice in a craps game people tend to throw harder when they need high numbers and softer for low numbers.":

More frequent boostering helps to push protective levels of immunity.

No, there are many factors that influence induction of protective immunity.

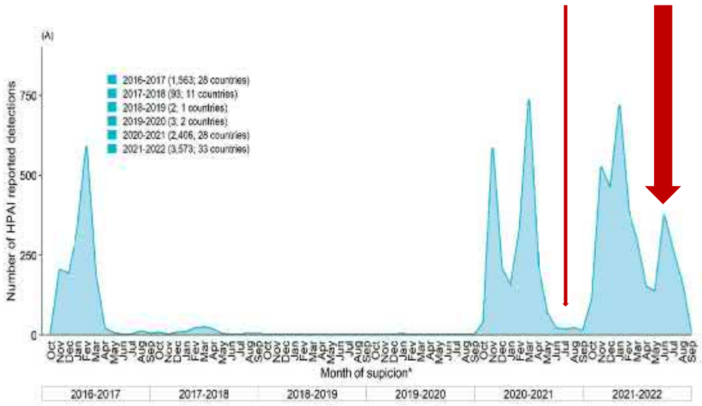
"The *irrational primacy effect* is involved when people give greater weight to information that occurs earlier in a series.":

Previous examples have shown that vaccination always fosters silent virus spread.

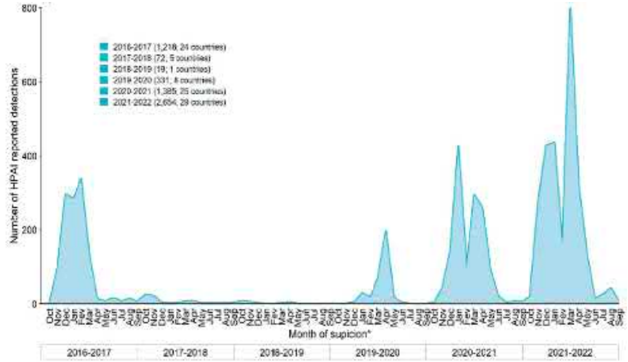
No, but the beneficial effects of vaccination can be corrupted by various factors; careful planning and surveillance are required to stay in control.

HPAI in wild birds and poultry is tightly linked

Wild birds



Poultry



Data: European Food Safety A, Avian influenza overviews,
e.g. EFSA J. 2021-22;19:e06497.

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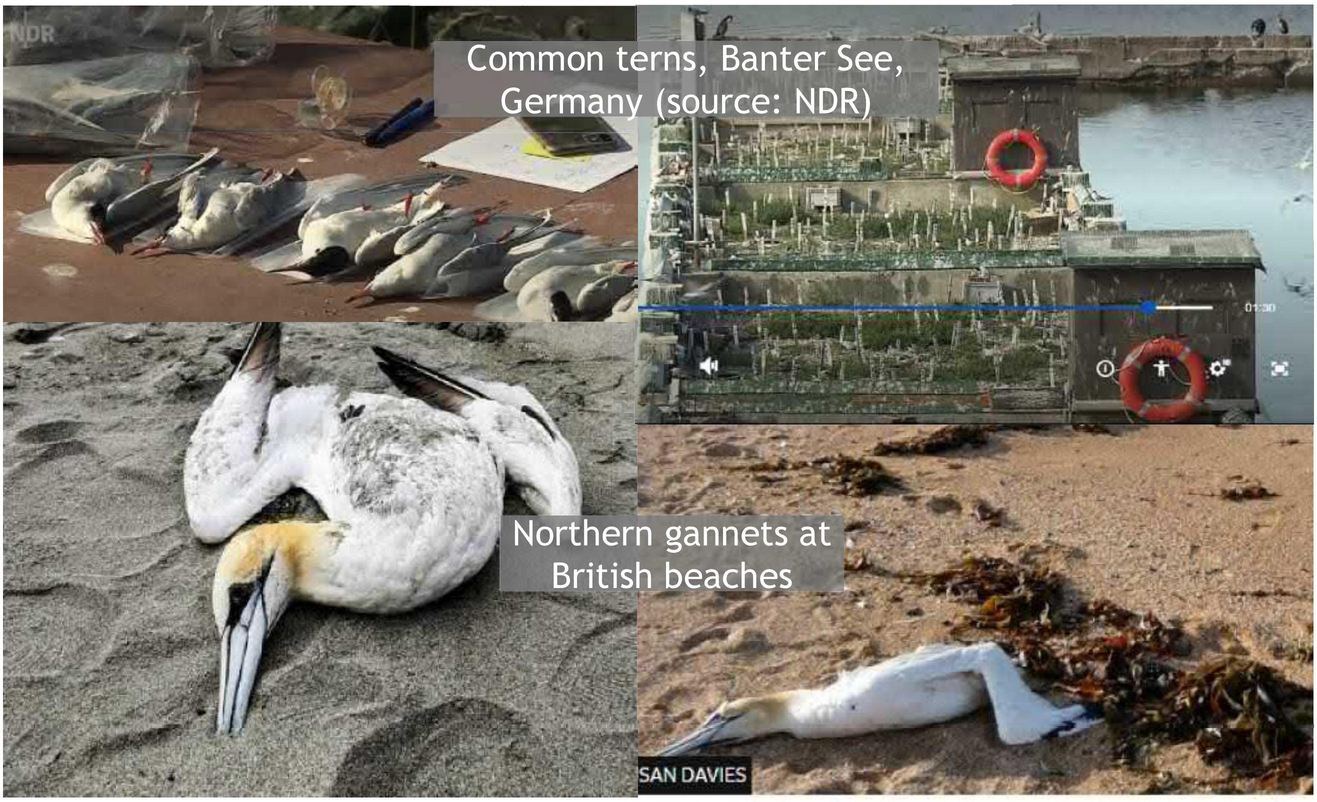
FLI
Bundesforschungsinstitut für Tiergesundheit
Federal Research Institute for Animal Health

Enzootic gs/GD HPAI in Europe?



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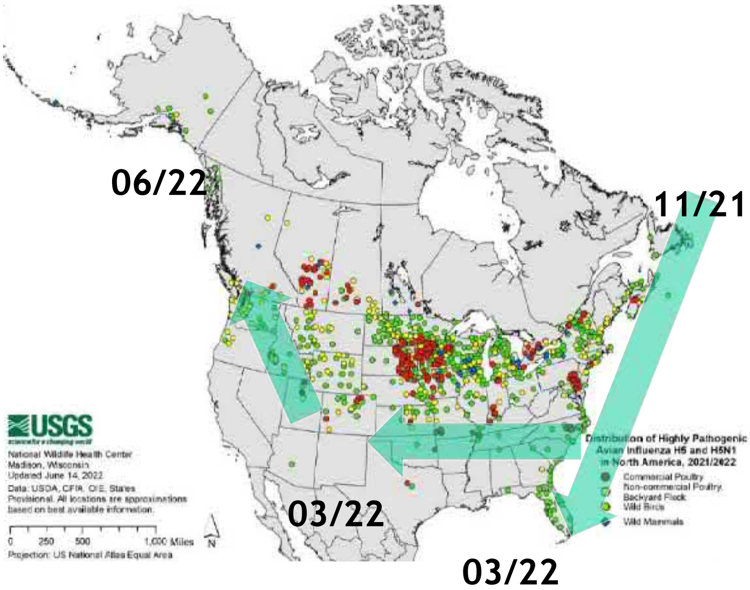
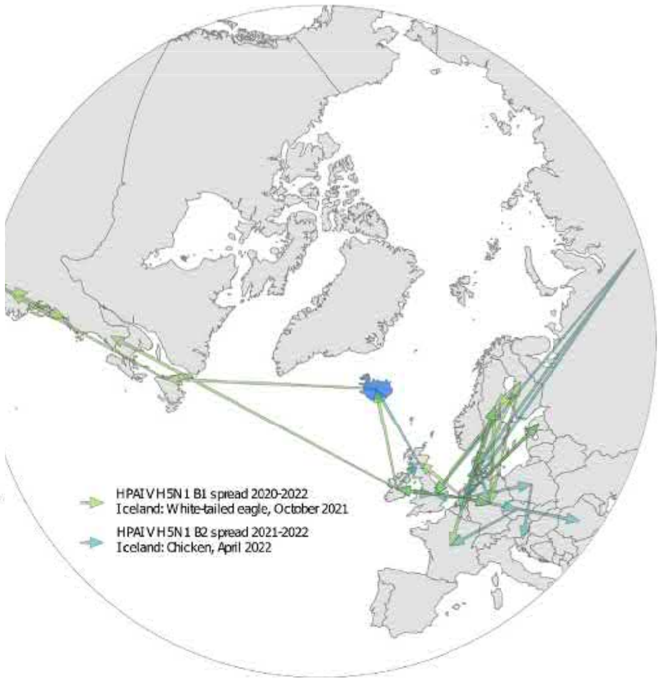
Bundesforschungsinstitut für Tiergesundheit
Federal Research Institute for Animal Health

Transatlantic spread to North America





https://www.usgs.gov/centers/nwhc/science/distribution-highly-pathogenic-avian-influenza-north-america-20212022

Figure modified from Günther et al., 2022

Continuing risks of new virus releases into the wild

https://vietnamnews.vn/life-style/451746/ducks-raised-in-the-field-a-specialty-of-viet-nam.html

https://www.wvi.org/stories/kenya/chicken-droppings-boost-fish-farming-communities

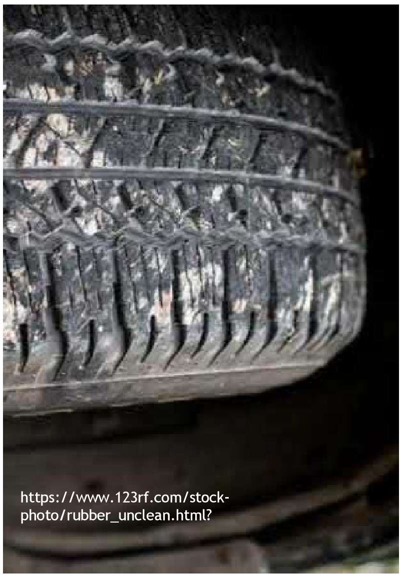
Chicken Droppings Boost Fish Farming for Communities

https://www.nrdc.org/onearth/lure-landfills-how-garbage-changes-animal-behavior

Illegal food imports at airports („wurst case scenario")

https://thewurstcasescenario.tumblr.com/

Continuing risks of new virus incursions



- Virus excretion with faeces: All faeces-contaminated objects are potential virus carriers.
- Viral tenacity is often underestimated

3. Assess HPAIV circulation in unvaccinated sectors

- Follow the trends of infection in such regions or in parts of the population that may be at increased risk of incursions
- Combine passive and (low scale) active surveillance
- Serosurveys in a region can best be done according to a two-stage sampling design: select farms first, then samples of birds
- Seropositive results: Virological follow-up.
- Efficacy depends on type of vaccine (DIVA) and (absence of) interfering LPAIV infections

- Assess incursion pressure from wild bird populations

Thinking outside the box: AI vaccination of wild birds

https://coastalreview.org/2021/06/drones-allow-for-birds-eye-view-of-seabird-colonies/

- Protection against disease
- Reduced virus load in the environment
- Conservation-compliable accessibility of wild birds
- Mass-applicable, baited, drone-delivered (GMO) vaccines tolerable?
- Successful examples of red fox (rabies) and wild boar (classical swine fever) bait vaccination in Europe

Full control is an illusion!

Other obstacles have been overcome

A certain level of risk, i.e. no full control, is accepted even in air transportation!

Photo: Lilienthal Museum, Anklam, Germany

附件9

Utrecht University

IABS

GD

What do we have in the commercially available toolbox now and what are the advantages and disadvantages of excisting systems?

J.J. (Sjaak) de Wit

DVM, PhD, EBVS® European Specialist in Poultry Veterinary Science

Royal GD (Deventer) and Faculty of Veterinary Medicine, Utrecht University, the Netherlands

Vice President World Veterinary Poultry Association (WVPA)

IABS Meeting on High Pathogenicity Avian Influenza Vaccination Strategies to prevent and control HPAI : Removing unnecessary barriers for usage

October 25-26, 2022 – Paris, France

Diagnostic tools: for which situation, which question?

B. DIAGNOSTIC TECHNIQUES

Table 1. *Test methods available for the diagnosis of avian influenza and their purpose*

Method	Purpose					
	Population freedom from infection	Individual animal freedom from infection prior to movement	Contribute to eradication policies	Confirmation of clinical cases	Prevalence of infection – surveillance	Immune status in individual animals or populations post-vaccination
Detection of the agent[1]						
Virus isolation	+	+++	+	+++	+	–
Antigen detection	+	+	+	+	+	–
Real-time RT-PCR	++	+++	++	+++	++	–
Detection of immune response						
AGID	+ (Influenza A)	+ (Influenza A)	++ (Influenza A)	+ (convalescent)	++ (Influenza A)	++ (Influenza A)
HI	+++ (H5 or H7)	++ (H5 or H7)	+++ (H5 or H7)	++ (convalescent)	+++ (H5 or H7)	+++ (H5 or H7)
ELISA	+	+	++	+ (convalescent)	++	++

Key: +++ = recommended for this purpose; ++ recommended but has limitations;
+ = suitable in very limited circumstances; – = not appropriate for this purpose.
RT-PCR = reverse-transcription polymerase chain reaction; AGID = agar gel immunodiffusion;
HI = haemagglutination inhibition test; ELISA = enzyme-linked immunosorbent assay.

1 A combination of agent identification methods applied on the same clinical sample is recommended.

Potential goals for use of AIV diagnostics?

- Showing freedom of infection
- Diagnostic need: acute infection?
- Check take of vaccine
- Estimation of level of protection induced by vaccination against a certain challenge virus
- Epidemiology, source of infection

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Factors to consider

- Host species?
- Vaccinated vs non-vaccinated flocks
  - Whole virus or DIVA vaccines?
- Epidemic vs endemic
- Multiple HA-subtypes involved?

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  - Whole virus or DIVA vaccines?
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Validated as fit for purpose

Virus detection

- Antigen capture immune assays (point-of-care)
  - Mostly developed/validated for human strains, for influenza A viruses in general
  - Varying sensitivity, often 3 to 4 $\log_{10}$ less sensitive compared to VI
  - Recommended for strongly positive samples only (like HP, clinically affected or dead birds, flock level)
- RT-PCR
  - Conserved gene (usually M), HA subtype specific (e.g., H5), N-subtypes
  - Should be properly validated using clinical material to demonstrate tests as ‘fit for purpose’
  - Highly sensitive (high CT might not mean an active infection anymore)
  - Importance of continuously monitoring primers and probes (combination of M and Np might be best)
  - All species

Antibody detection

- Agar gel immune diffusion test
  - Influenza A specific (antibodies against nucleoprotein and matrix antigens)
  - Precipitating antibodies, suitable for chicken and turkeys, less reliable in other species
  - Best in detecting acute infections, flock diagnosis
- Hemagglutination inhibition test
- ELISA

Antibody detection

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  - Influenza A specific (antibodies against nucleoprotein and matrix antigens)
  - Precipitating antibodies, suitable for chicken and turkeys, less reliable in other species
  - Best in detecting acute infections, flock diagnosis
- Hemagglutination inhibition test
  - Subtype specific
  - All species
  - Non-chicken sera might need absorption with chicken red blood cells before testing to prevent nonspecific agglutination.
  - Potential nonspecific inhibition of agglutination caused by steric inhibition when the tested serum contains antibodies against the same N subtype as the H antigen used in the HI test.
    - Use of two antigens for each haemagglutinin subtype with heterologous neuraminidase (i.e. H5N1 and H5N6)
      - No H5N2 antigen in H9N2 endemic areas
    - Alternatively, the H antigen used can be recombinant or purified H protein that lacks N protein
  - Strong correlation between HI titres and level of protection when homologous antigen is used
- ELISA

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      - No H5N2 antigen in H9N2 endemic areas
    - Alternatively, the H antigen used can be recombinant or purified H protein that lacks N protein
  - Strong correlation between HI titres and level of protection when homologous antigen is used

- ELISA
  - Antigen: whole virus, nucleoprotein or HA H5 (some other proteins less immunogenic)
  - Indirect (chicken/turkey conjugate), blocking (all species)
  - ELISA titres have poor correlation with protection (all kind of antibodies, not only 'protective' antibodies)

Current H5 vaccines and DIVA options

- Vaccines
  - Inactivated complete virus
  - Subunit vaccine,
  - Live vectored vaccines (HVT, Pox, others)
  - mRNA, DNA, ……

Only antibody response against insert (e.g.) H5
Not against other proteins (M, Np, …..)

Find a suitable DIVA combination

- Tests
  - RT-PCR, virus isolation, staining, on-site, ELISA (general), ELISA (specific proteins), genotype specific ELISA, HI-test, AGPT

- Field situation, non-H5 strains/vaccinations?

Check for freedom of subtype H5 virus (infection), success of vaccination (commercially available tests/antigens)

Field situation	AGID	HI H5	ELISA			Antigen	RT-PCR	
			Whole virus	Np	H5		M	H5
No AIV vac, no other subtype chall	+	++	++	++	++	+	++	++
No H5 vac, other subtype vac/chall	-	++ (N!)	-	-	++	+	++	++
H5 vac using whole virus	-	-	-	-	-	+	++	++
H5 DIVA vac, no other subtype vac/chall	+?	-	-	++	-	+	++	++
H5 DIVA vac + other subtype vac/chall	-	-	-	-	-	+	++	++
Level of take of H5 vaccine	±	++ (hom vaccine)	++		++	-	-	-
Estimation H5 protection level	-	++ (hom field)	-	-	±	-	-	-

Check for freedom of subtype H5 virus (infection), success of vaccination (commercially available tests/antigens)

Field situation	AGID	HI H5	ELISA			Antigen	RT-PCR	
			Whole virus	Np	H5		M	H5
No AIV vac, no other subtype chall	+	++	++	++	++	+	++	++
No H5 vac, other subtype vac/chall	-	++ (N!)	-	-	++	+	++	++
H5 vac using whole virus	-	-	-	-	-	+	++	++
H5 DIVA vac, no other subtype vac/chall	+?	-	-	++	-	+	++	++
H5 DIVA vac + other subtype vac/chall	-	-	-	-	-	+	++	++
Level of take of H5 vaccine	±	++ (hom vaccine)	++		++	-	-	-
Estimation H5 protection level	-	++ (hom field)	-	-	±	-	-	-

Check for freedom of subtype H5 virus (infection), success of vaccination (commercially available tests/antigens)

Field situation	AGID	HI H5	ELISA			Antigen	RT-PCR	
			Whole virus	Np	H5		M	H5
No AIV vac, no other subtype chall	+	++	++	++	++	+	++	++
No H5 vac, other subtype vac/chall	-	++ (N!)	-	-	++	+	++	++
H5 vac using whole virus	-	-	-	-	-	+	++	++
H5 DIVA vac, no other subtype vac/chall	+?	-	-	++	-	+	++	++
H5 DIVA vac + other subtype vac/chall	-	-	-	-	-	+	++	++
Level of take of H5 vaccine	±	++ (hom vaccine)	++		++	-	-	-
Estimation H5 protection level	-	++ (hom field)	-	-	±	-	-	-

Check for freedom of subtype H5 virus (infection), success of vaccination (commercially available tests/antigens)

Field situation	AGID	HI H5	ELISA			Antigen	RT-PCR	
			Whole virus	Np	H5		M	H5
No AIV vac, no other subtype chall	+	++	++	++	++	+	++	++
No H5 vac, other subtype vac/chall	-	++ (N!)	-	-	++	+	++	++
H5 vac using whole virus	-	-	-	-	-	+	++	++
H5 DIVA vac, no other subtype vac/chall	+?	-	-	++	-	+	++	++
H5 DIVA vac + other subtype vac/chall	-	-	-	-	-	+	++	++
Level of take of H5 vaccine	±	++ (hom vaccine)	++		++	-	-	-
Estimation H5 protection level	-	++ (hom field)	-	-	±	-	-	-

Check for freedom of subtype H5 virus (infection), success of vaccination (commercially available tests/antigens)

Field situation	AGID	HI H5	ELISA			Antigen	RT-PCR	
			Whole virus	Np	H5		M	H5
No AIV vac, no other subtype chall	+	++	++	++	++	+	++	++
No H5 vac, other subtype vac/chall	-	++ (N!)	-	-	++	+	++	++
H5 vac using whole virus	-	-	-	-	-	+	++	++
H5 DIVA vac, no other subtype vac/chall	+?	-	-	++	-	+	++	++
H5 DIVA vac + other subtype vac/chall	-	-	-	-	-	+	++	++
Level of take of H5 vaccine	±	++ (hom vaccine)	++		++	-	-	-
Estimation H5 protection level	-	++ (hom field)	-	-	±	-	-	-

Check for freedom of subtype H5 virus (infection), success of vaccination (commercially available tests/antigens)

Take home message

Field situation	AGID	HI H5	ELISA			Antigen	RT-PCR	
			Whole virus	Np	H5		M	H5
No AIV vac, no other subtype chall	+	++	++	++	++	+	++	++
No H5 vac, other subtype vac/chall	-	++ (NI)	-	-	++	+	++	++
H5 vac using whole virus	-	-	-	-	-	+	++	++
H5 DIVA vac, no other subtype vac/chall	+?	-	-	++	-	+	++	++
H5 DIVA vac + other subtype vac/chall	-	-	-	-	-	+	++	++
Level of take of H5 vaccine	±	++ (hom vaccine)	++		++	-	-	-
Estimation H5 protection level	-	++ (hom field)	-		±	-	-	-

- For any situation, DIVA testing using commercially available tests is possible
- However, the number of options varies depending on the field situation

Thank you for your attention