Avian Influenza Vaccines: global possibilities and pitfalls

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Introduction

- This presentation is based on over 20 years' experience with vaccination against high pathogenicity avian influenza (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 or company
- No vaccine type or manufacturer is being endorsed
- Frustration that there has not been greater acceptance of vaccination against HPAI (hundreds of millions of birds destroyed that could have been protected if vaccines were deployed)

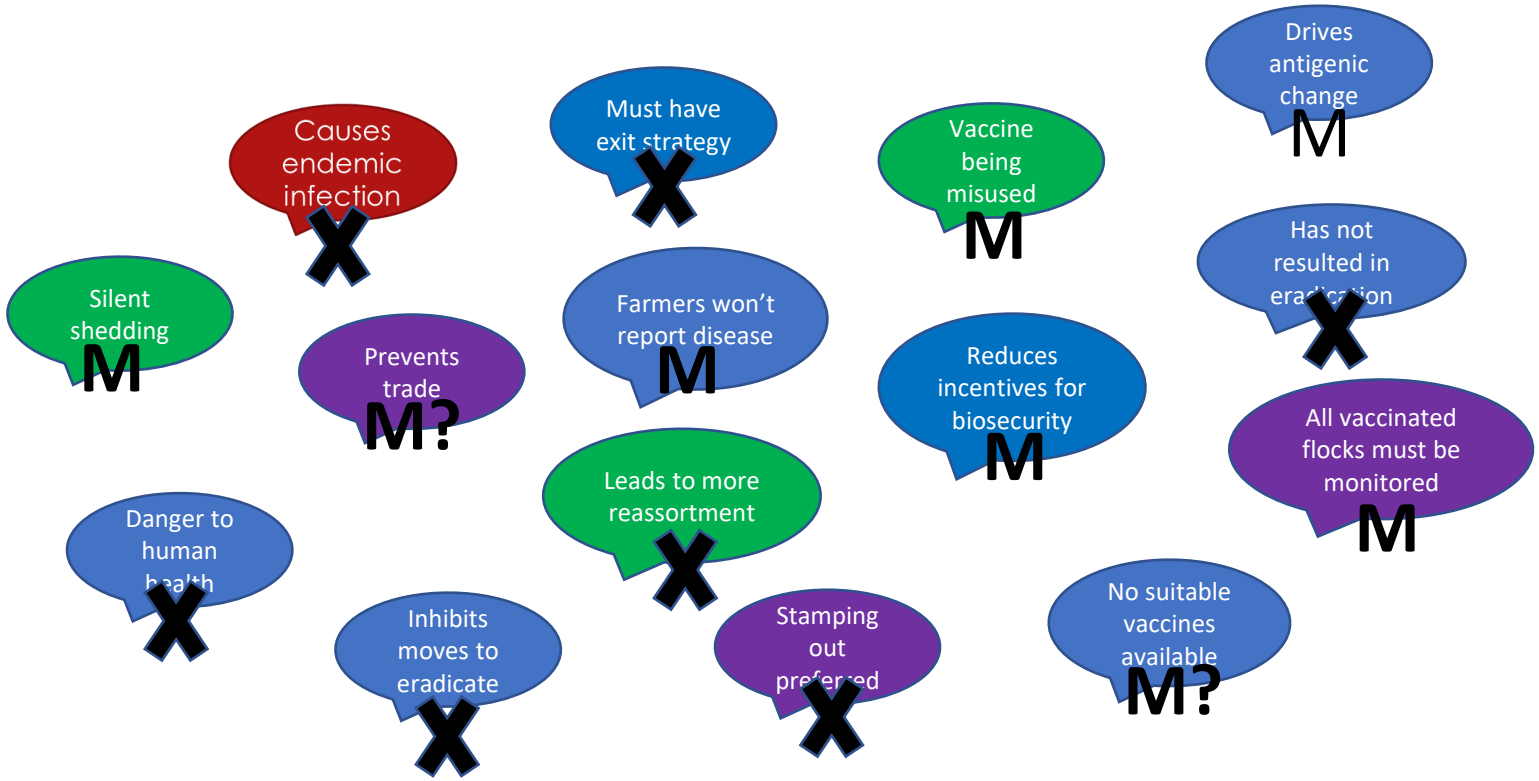
Avian Influenza Vaccines: Global possibilities and pitfalls

Introduction

- HPAI has changed (almost continual threat from wild birds)
- Biosecurity measures, as implemented, have not been sufficient to prevent infections for certain industry sectors, especially longer-lived poultry (turkeys, layers, breeders, foie gras ducks)
- Greater global acceptance of the role that vaccination can play in preventing HPAI (WOAH General Assembly)
- Finally seeing a shift in the balance between “negative” and “positive” aspects of vaccination against HPAI (IABS meeting October 2022 on barriers to vaccination)
- Still many misconceptions and unwarranted opposition

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?)



Avian Influenza Vaccines: Global possibilities and pitfalls

Current situation

- Vaccines are already being used against high pathogenicity avian influenza (HPAI) in multiple countries, especially in Asia
- Seeing an increase in uptake globally (EU, Central and South America, Philippines)
- Some countries still totally opposed to usage of vaccines despite the benefits it can bring
- In the past, vaccination was mainly used in places where the virus was already endemic and there was little or no likelihood of elimination of virus from poultry (not directly relevant to Canadian situation)
- But also used in places at high risk of exposure (Hong Kong SAR, France) free from infection in poultry (more relevant to Canada)

Main ways that vaccination can be used

- Vaccination can be used (in partnership with other measures):
  - as a **preventive measure**, in high-risk places before infection occurs in poultry. It might be in response to an increase in the threat level (one form of WOAH Code emergency vaccination) or as an on-going programme (one form of WOAH Code systematic vaccination)
  - as an **aid to control new outbreaks** when they occur (another form of WOAH Code emergency vaccination)
  - to **reduce the likelihood of infection and prevent disease** in poultry and humans in “endemic” countries (another form of WOAH Code systematic vaccination)
  - to **support virus elimination** from poultry, where this is possible

Types of vaccines deployed

- Mainly killed antigen whole virus vaccines (usually reverse genetics) with adjuvant
- Vector vaccines based on herpesvirus of turkeys (HVT) with an H5 insert
- Both require individual injection of birds but HVT vector vaccine can be delivered in hatchery and provides broader protection against a range of H5Nx strains
- Subunit vaccine has also been deployed (e.g. baculovirus-generated vaccine being used in France)
- Other vaccines have been tested including self amplifying RNA vaccine
- Preference for “DIVA-compatible” vaccines in some countries but not essential
- Should not be the main reason for selecting vaccines given other methods are available to detect infection other than DIVA serology

Types of vaccines deployed or being developed

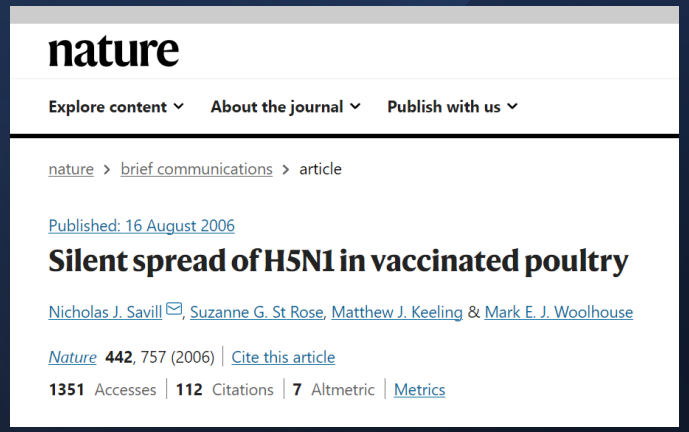
- Still lacking a suitable vaccine for mass application that does not suffer from interference from maternal antibody or exposure to field virus (e.g. APV-1 vector)
- Several vaccines under development including Salmonella, duck virus enteritis, Tembusu virus, other APV's as vectors
- Live attenuated avian influenza vaccines won't be deployed due to concerns about reversion to virulence or reassortment with other field viruses

Other issues related to vaccines and vaccination programs

- High cost of administering vaccines that require individual bird injection
- May not have sufficient labour
- Vaccine companies will only produce vaccines if there is a definite market for the product
- Need time to plan and arrange vaccination
- Need system for rapid registration of updated vaccines

"Vaccination will lead to silent infection and shedding"

- Based largely on concerns that vaccines do not, in many cases, produce sterilising immunity in experimental trials – shedding can occur in some challenged, vaccinated birds (high dose challenge)
- Several widely cited models predicted silent spread (e.g. Savill et al 2006)
- But not field-validated or consistent with findings from the field (e.g. Ellis et al 2004)
- Some papers do report silent infection and transmission under experimental or field conditions (e.g. Poetri et al 2014, Ma et al 2014) but interpret carefully


nature

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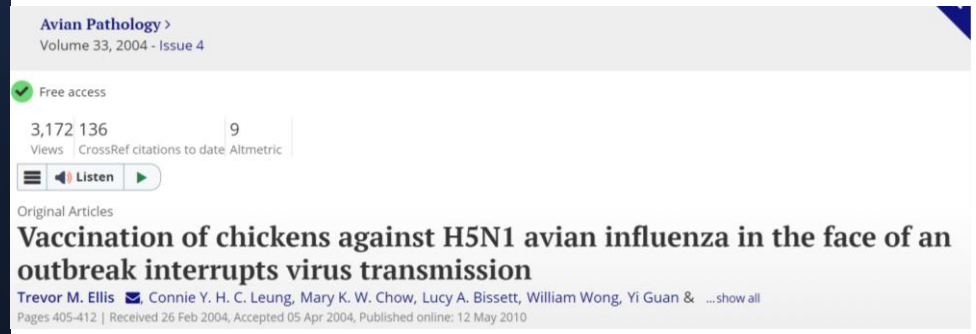
Published: 16 August 2006

Silent spread of H5N1 in vaccinated poultry

Nicholas J. Savill, Suzanne G. St Rose, Matthew J. Keeling & Mark E. J. Woolhouse

Nature **442**, 757 (2006) | Cite this article

1351 Accesses | **112** Citations | **7** Altmetric | Metrics


Avian Pathology ›
Volume 33, 2004 - Issue 4

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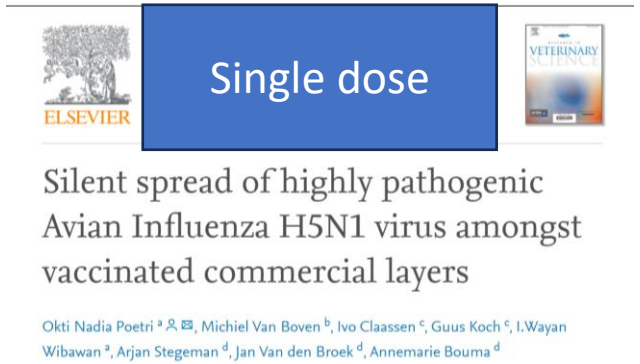
Original Articles

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 26 Feb 2004, Accepted 05 Apr 2004, Published online: 12 May 2010


ELSEVIER

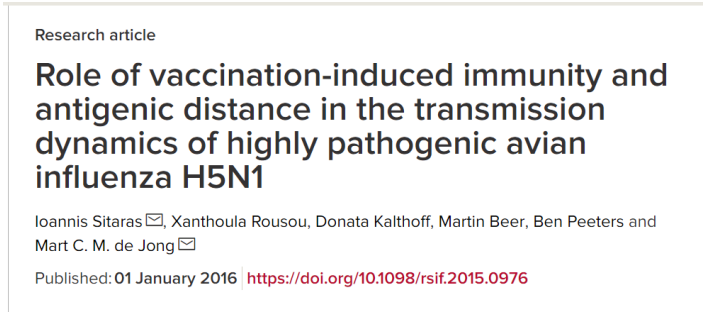
Single dose

Silent spread of highly pathogenic Avian Influenza H5N1 virus amongst vaccinated commercial layers

Okti Nadia Poetri [a], Michiel Van Boven [b], Ivo Claassen [c], Guus Koch [c], I.Wayan Wibawan [a], Arjan Stegeman [d], Jan Van den Broek [d], Annemarie Bouma [d]

“Vaccination will lead to silent infection and shedding”

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

PNAS ARTICLES FRONT MATTER AUTHORS TOPICS

RESEARCH ARTICLE | BIOLOGICAL SCIENCES

Quantification of the effect of vaccination on transmission of avian influenza (H7N7) in chickens

I. A. van der Goot, G. Koch, M. C. M. de Jong, and M. van Boven Authors Info & Affiliations

December 5, 2005 | 102 (50) 18141-18146 | https://doi.org/10.1073/pnas.0505098102

Experimental vaccination of mule ducks under field conditions against highly pathogenic avian influenza A (H5N1) virus of clade 2.3.4.4b

Interim report 2 :

« Experimental evaluation of transmission among vaccinated ducks after challenge at 7 weeks of age »

B. Grasland, A. Schmitz, E. Niqueux, M. Andraud, R. Busson, N. Morin, C. Guillemoto, A. Orosco, F. Souchaud, FX. Briand, C. Martenot, M. Cherbonnel, P. Massin, K. Louboutin, I. Pierre, M. Delpont, L. Pouvelle, S. Soubies, N. Rose, M. Amelot, A. Keita, J-L. Guérin, N. Eterradossi

Publications

Transmissiestudie met vier vaccins tegen H5N1 hoogpathogeen vogelgriepvirus (clade 2.3.4.4b)

Germeraad, E.A.; Velkers, F.C.; de Jong, M.C.M.; Gonzales, J.L.; de Wit, J.J.; Stegeman, J.A.; Beerens, N.

Publication information

Source Lelystad: Wageningen Bioveterinary Research (Rapport / Wageningen Bioveterinary Research 2300528)

Department(s) WIAS

Virology & Molecular Biology

Epidemiology, Bio-informatics & Animal models

Quantitative Veterinary Epidemiology

Type of publication Research report

Year of publication 2023

Vaccine transmission experiments, including low dose vaccination

(Sitaras et al 2016)

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

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Vaccinated contacts

Challenged birds (vaccinated)

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			+/+	+/-	+/-	+/-	-/-	-/-	-/-

No transmission

Vaccinated contacts

Challenged birds (vaccinated)

Vaccine Strain	HI Titre		Challenge Strain	HI Titre		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
H5N2	128	128	H5N1 R65	4	4	NT	+/-	-/+	+/-	+/-	+/-	+/+
H5N2	16	16	H5N1 R65	-	-	NT	-/+					
H5N2	32	32	H5N1 R65	4	4	NT	+/+					
H5N2	16	16	H5N1 R65	-	-	NT	+/-					+
H5N2	32	32	H5N1 R65	-	-	NT	+/+	+/-	+/+	+/+	+/+	+/+
H5N2	-	-	H5N1 R65	-	-	+/+	+					
H5N2	16	16	H5N1 R65	-	-	+/+	+					
H5N2	-	-	H5N1 R65	-	-	+/+	+					
H5N2	8	8	H5N1 R65	-	-	+/+	+					
H5N2	8	8	H5N1 R65	-	-	+/+	+/+	+				

Transmission and deaths

“Vaccination will lead to silent infection and shedding”

- 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
- Silent infection also occurs in unvaccinated older ducks
- And to some extent in unvaccinated chickens with current clade 2.3.4.4b A(H5N1) viruses in which transmission is limited

Open Access Article

Silent Infection of Highly Pathogenic Avian Influenza Virus (H5N1) Clade 2.3.4.4b in a Commercial Chicken Broiler Flock in Italy

by Federica Gobbo [1,*], Claudia Zanardello [2], Marco Bottinelli [3], Jane Budai [1], Francesca Bruno [1], Roberta De Nardi [4], Tommaso Patregnani [4], Salvatore Catania [3] and Calogero Terregino [1]

Experimental vaccination of mule ducks under field conditions against highly pathogenic avian influenza A (H5N1) virus of clade 2.3.4.4b

Interim report 2 :

« Experimental evaluation of transmission among vaccinated ducks after challenge at 7 weeks of age »

B. Grasland, A. Schmitz, E. Niqueux, M. Andraud, R. Busson, N. Morin, C. Guillemoto, A. Orosco, F. Souchaud, FX. Briand, C. Martenot, M. Cherbonnel, P. Massin, K. Louboutin, I. Pierre, M. Delpont, L. Pouvelle, S. Soubies, N. Rose, M. Amelot, A. Keita, J-L. Guérin, N. Eterradossi

JOURNAL OF GENERAL VIROLOGY

Volume 104, Issue 5

Research Article | Open Access

Clade 2.3.4.4b H5N1 high pathogenicity avian influenza virus (HPAIV) from the 2021/22 epizootic is highly duck adapted and poorly adapted to chickens

Joe James[1,2], Elizabeth Billington[1], Caroline J. Warren[1], Dilhani De Sliva[1], Cecilia Di Genova[1], Maisie Airey[1], Stephanie M. Meyer[1,2], Thomas Lewis[1,2], Jacob Peers-Dent[1], Saumya S. Thomas[1], Abigail Lofts[1,2], Natalia Furman[3], Alejandro Nunez[3], Marek J. Slomka[1], Ian H. Brown[1,2], Ashley C. Banyard[1,2]

View Affiliations

Trade issues and vaccination

Canada puts temporary ban on France's poultry, eggs

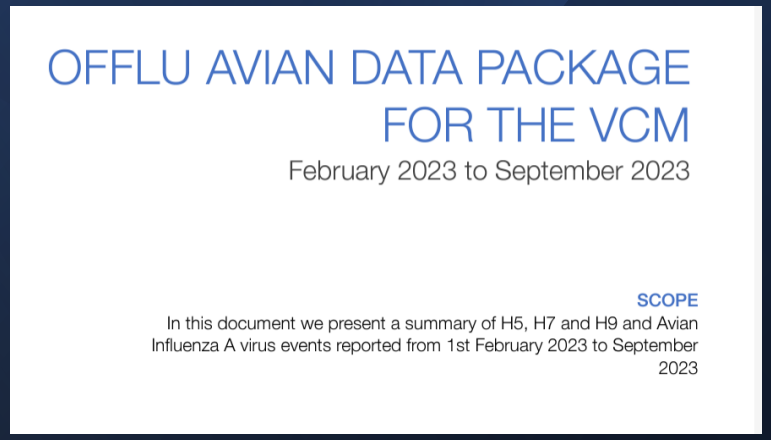
CFIA move to 'manage the risk' from bird flu vaccination plan

- Trade issues remain the biggest barrier to uptake of vaccination
- Some large exporting countries have expressed little to no interest in using vaccination driven by concerns about lost markets
- Seem to be forgetting the toll of this disease on health and welfare of birds
- Some trading partners will implement total bans on imports or on meat from one sector (e.g. unvaccinated broilers) even if vaccination is only used in an unrelated sector (e.g. vaccinated turkeys)
- No valid scientific or "legal" reason why use of vaccine should affect trade provided there is an appropriate surveillance system in place for detecting infection in vaccinated (and unvaccinated) flocks (WOAH code explicit on this point)

Trade issues and vaccination

- Need to consider the threat posed by undetected infection in unvaccinated birds
- Should vaccinated flocks be required to do more surveillance than unvaccinated flocks?
- Is the risk of importing from unvaccinated flocks higher than vaccinated flocks?
- Relative risk needs to be considered, comparing aerial assault from wild birds carrying virus in the importing country versus the very low risk associated with trade in well vaccinated and monitored birds
- All countries would benefit if countries using vaccination with an appropriate and verifiable monitoring/surveillance system were allowed to trade vaccinated birds and products

Vaccination and emergence of antigenic variants


OFFLU AVIAN DATA PACKAGE FOR THE VCM

February 2023 to September 2023

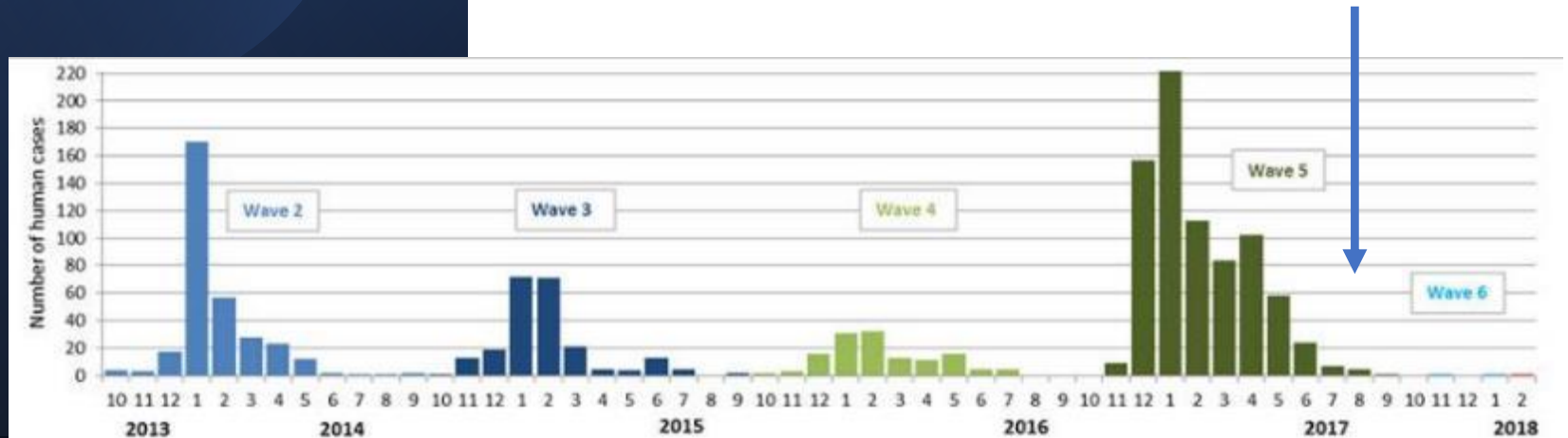
SCOPE

In this document we present a summary of H5, H7 and H9 and Avian Influenza A virus events reported from 1st February 2023 to September 2023

- Expected to occur over time if vaccinated birds are exposed to virus
- Occurs more rapidly if vaccinated birds are exposed repeatedly to virus
- Can develop if birds have low level immunity (allowing breakthrough infections)
- Also occurs when vaccination is not being used (e.g. H6 viruses in China)
- May not be due to local use of vaccines (imported variants – e.g. 2.3.4.4b to Indonesia)
- Need monitoring system in place and, when appropriate, update of vaccines
- OFFLU-AIM will provide information on antigenic changes relevant to poultry vaccines
- WHO VCM, via OFFLU, provides information on antigenic variants for selection of pre-pandemic human vaccine antigens

Vaccination and reductions in risk to public health

- Evidence of benefits of vaccination from China with A(H7N9) zoonotic infections
- 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 flock so lower zoonotic threat
- Mandatory monitoring programme will allow detection of infection allowing action to be taken on affected flocks
- No reason why vaccination will increase reassortment as has been suggested by some



Vaccination and surveillance

- Surveillance system must match the situation, capacity and objective of vaccination as well as local/regional regulations
- Can devise systems that give high degree of confidence that HPAI virus is not transmitting in vaccinated flocks
- Well targeted surveillance is generally more effective and cheaper than random sampling, even for demonstrating “freedom from infection” in vaccinated flocks
- Serological DIVA only one method for detecting evidence of infection in vaccinated flocks and not generally applicable if other AI virus also circulating.
- Does not provide information on recent infection (c.2 weeks before testing)
- Preference for tests for virus that give an indication of current infection status

Vaccination and surveillance

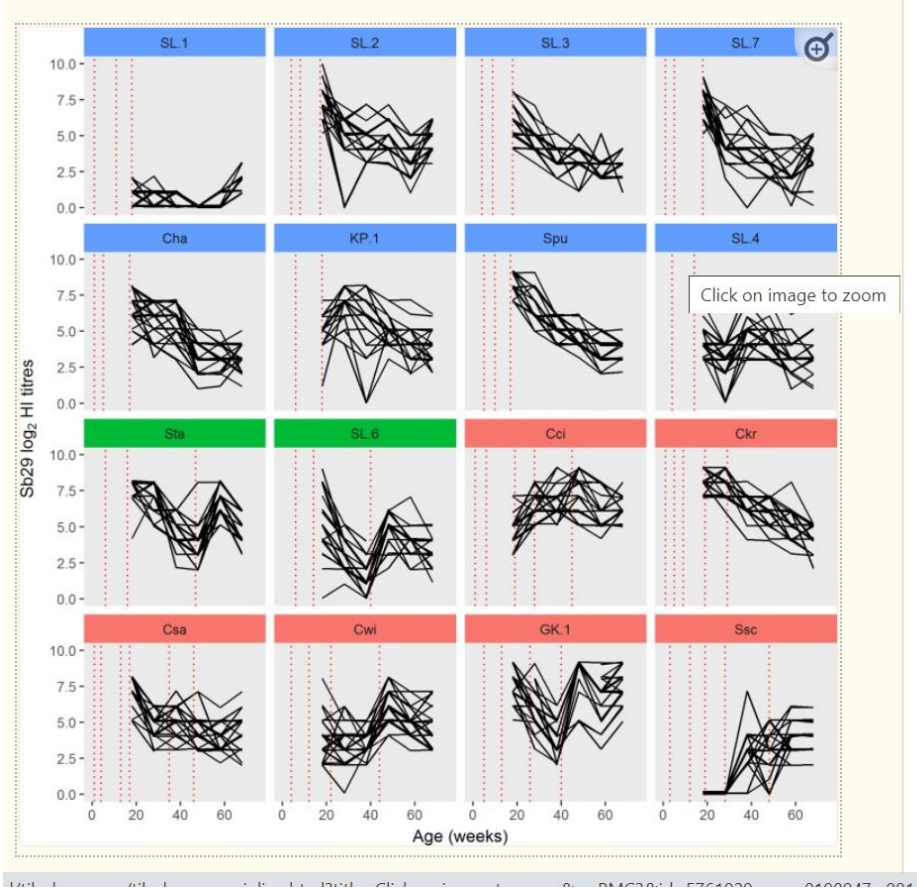
Surveillance in vaccinated French ducks complying with Delegated Regulation (EU) 2023/361

HPAI post-vaccination enhanced surveillance		
Parameters	Enhanced passive surveillance	Active surveillance
Where?	The epidemiological unit	
Who?	Farmer or technical worker	Official veterinary
Frequency?	Weekly	Every 30 days: virological testing On batch completion: serological testing
How?	Swabs (tracheal/oropharyngeal) from 5 dead birds	Every 30 days : Swabs (tracheal/oropharyngeal) from 60 birds; At batch completion: blood samples from 20 birds
Testing?	Virological using M gene RT-PCR. If the result is positive, screening for H5/H7	Virological using M gene RT-PCR (If the result is positive, screening for H5/H7) and NP ELISA serology
Type of laboratory?	A recognised laboratory	An approved laboratory

Vaccination and surveillance

- Preferred methods for targeted surveillance include dead bird monitoring, environmental samples (e.g. wastewater from farms and slaughterplants, water from drinkers, swabs of cutting boards, egg washes, dust samples, etc)
- Need more studies to confirm the utility of these alternative methods. This is happening and have experiences from COVID-19 wastewater testing.
- What is the appropriate frequency of surveillance?
- Sentinel birds not required and difficult to manage
- Multilayered system is preferred, starting with evidence of response to vaccine and testing at multiple points along the value chain (e.g. testing wastewater at slaughterplants)

Example: Serology in vaccinated layers



PLoS One. 2018; 13(1): e0190947.
Published online 2018 Jan 10. doi: 10.1371/journal.pone.0190947
PMCID: PMC5761929
PMID: 29320563

Field effectiveness of highly pathogenic avian influenza H5N1 vaccination in commercial layers in Indonesia

Simson Tarigan, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing,[1,*] Michael Haryadi Wibowo, Conceptualization, Data curation, Project administration, Resources, Supervision, Validation, Writing – original draft,[2] Risa Indriani, Investigation, Resources,[1] Sumarningsih Sumarningsih, Investigation, Resources,[1] Sidna Artanto, Investigation, Resources,[2] Syafrison Idris, Supervision,[3] Peter A. Durr, Conceptualization, Methodology, Writing – original draft, Writing – review & editing,[4] Widya Asmara, Conceptualization, Investigation, Project administration, Resources,[2] Esmaeil Ebrahimie, Formal analysis,[5] Mark A. Stevenson, Formal analysis, Resources, Visualization, Writing – original draft,[6] and Jagoda Ignjatovic, Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing[6]

Different approaches to vaccination across Asia

- Neighbouring countries with similar disease status have different approaches to vaccination
- Unregistered vaccine is used in some countries, especially in large farms
- Better to regulate vaccination rather than have vaccines of unknown quality being used
- Guidance available on introduction of vaccination for countries considering vaccination

Farm density high in certain areas facilitates virus transmission

What and where to vaccinate?

- Areas that have experienced outbreaks in the past (e.g. Fraser Valley?)
- Known sites frequented by migratory birds and other birds that can carry HPAI virus
- All farm types or only some?
- Depends on farm density and types of farm/bird
- Many breeders have argued they would not want their birds vaccinated especially if exporting

Vaccination and white-feathered broilers

Can be difficult to vaccinate effectively because of short life span

Some places use biosecurity measures to limit infections rather than vaccination

If killed antigen vaccine is used usually need two doses for effective protection

Vaccination and endemic infection

- Vaccination commenced in countries such as China, Viet Nam, Indonesia and Egypt **because the virus was already endemic** and standard control measures could not eliminate the virus from poultry
- In these places **virus elimination from poultry was a distant goal** (and one that might never be achieved)
- Importance of "**AI vaccine stewardship**" and adherence to the "**AI vaccine cycle**" to ensure progress in disease prevention and control

“AI Vaccine Stewardship”

Some similarities to “Antimicrobial Stewardship”

1. Vaccines should not be used as a replacement/substitute for other methods of disease prevention but to add an additional layer of biosecurity/protection *
2. The decision to use vaccine is just the beginning of the process, not the end
3. Need to choose appropriate vaccines that provide protection against circulating strains
4. Use vaccines in accordance with manufacturer’s recommendation (dose and timing)
5. Monitor selected vaccinated flocks to ensure vaccine is producing the desired immune response, to plan timing of boosters (if required) and (if used) to monitor for infection **

*one exception is free-ranging ducks for which few biosecurity measures are feasible at the production level

**may be all flocks if elimination/demonstration of freedom in vaccinated flocks is the target

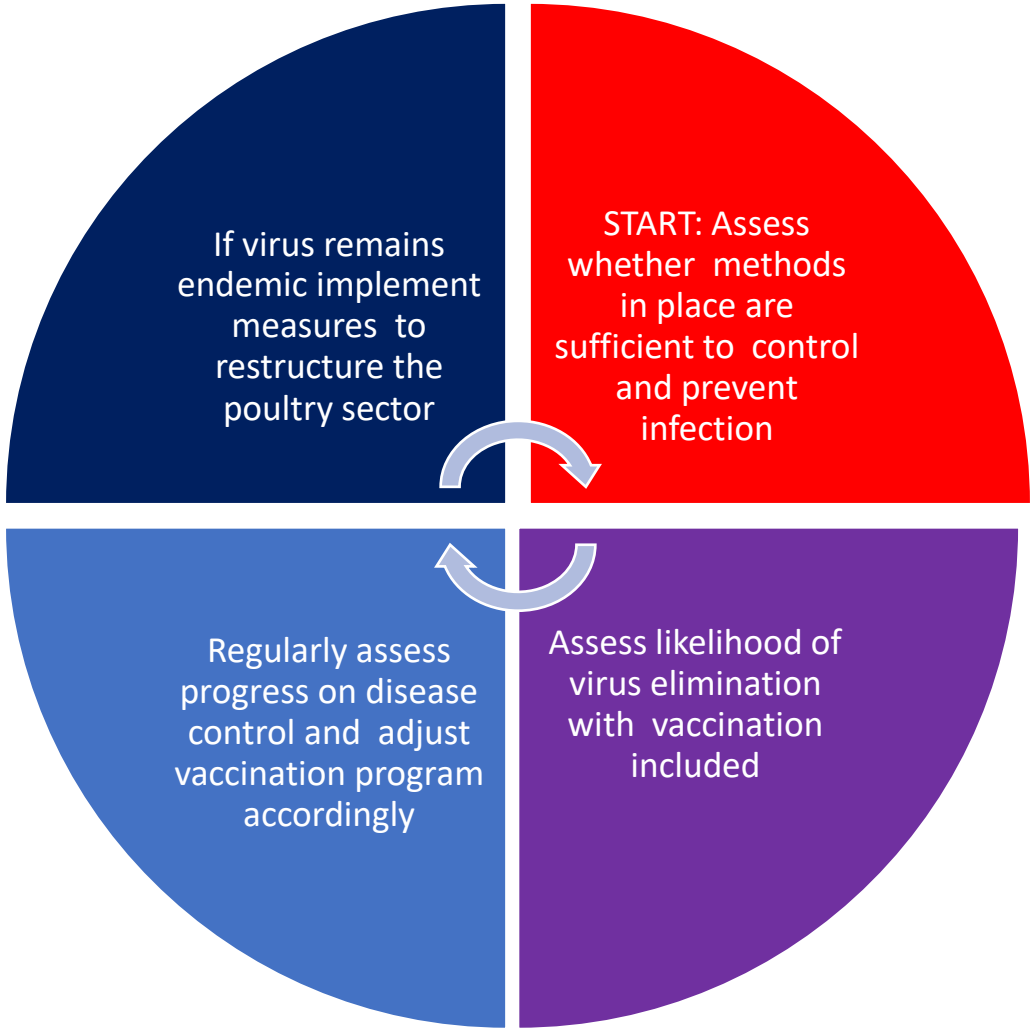
“AI Vaccine Stewardship”

6. Need to monitor viruses regularly for evidence of antigenic changes and update vaccines when required
7. Beware of import of novel antigenic variants (trade or wild birds)
8. Replace (deregister) vaccines that no longer afford protection from disease and virus shedding/transmission
9. Ensure vaccination is done in a manner that does not transmit the virus

“AI Vaccine Stewardship”

10. Regularly re-assess the need for and nature of vaccine programmes and modify programmes accordingly (see AI vaccination cycle)
11. Special attention should be paid to farms or markets where infection occurs or persists, despite appropriate usage of vaccines
12. Examine ways to modify production and selling practices that facilitate transmission and replication of the virus

The “AI Vaccination Cycle” in places where HPAI is occurring in poultry



H9N2

- Killed antigen vaccines can help prevent disease due to H9N2 but may not eliminate all transmission
- Need better vaccines for H9N2 if the goal is to stop transmission rather than just preventing disease

J Virus Erad. 2021 Sep 22;7(3):100055. doi: 10.1016/j.jve.2021.100055. eCollection 2021 Sep.

Vaccination with inactivated virus against low pathogenic avian influenza subtype H9N2 does not prevent virus transmission in chickens

Hongrui Cui [1 2], Mart Cm de Jong [2], Nancy Beerens [3], Monique M van Oers [4], Qiaoyang Teng [1], Luzhao Li [1], Xuesong Li [1], Qinfang Liu [1], Zejun Li [1]

Conclusions

- Need to recognise that HPAI has changed and approaches to prevention of this disease also need to change
- Vaccination is a very powerful tool to assist in prevention of HPAI – if we don't use it, we are not using all the tools in the toolbox
- Need to regard well vaccinated flocks as low risk for sustained infection rather than high risk, but still conduct appropriate monitoring/surveillance
- Experiences from countries where the virus is entrenched and surveillance on all vaccinated flocks is not performed should not be equated to those from high income countries with capacity to undertake appropriate vaccination and monitoring
- All the barriers to vaccination can be addressed but several (trade and vaccine availability) will likely take longer than others to 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
- Increased uptake of vaccination in high-risk areas/production sectors, where it is needed, will only occur if there is greater acceptance of products from vaccinated flocks by importing countries, applying WOAH standards