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Animal influenza
Prevention and control

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Overview EU-funded projects

Project	Species covered by the project				Area covered by the project
	Human	Pig	Poultry	Other species	Prevention and control
AIV VACC DIAGNOSIS	No	No	Yes	No	High
AVIFLU	No	No	Yes	No	High
ConFluTech	No	Yes	Yes	Yes	Medium
DISCONTOOLS	No	Yes	Yes	Yes	Low
EPIZONE	Yes	Yes	Yes	Yes	Low
FLUAID	No	Yes	Yes	No	High
FLUPIG	No	Yes	No	No	Medium
FLURESIST	No	No	Yes	No	Low
NOVADUCK	No	No	No	Yes	High

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AIV VAC DIAGNOSIS (Dec 2006 – Nov 2010)

The primary aim has been to develop better AI vaccines that can be mass applicable through spray, drinking water or eye drop. Constructs of optimized Newcastle Disease Virus (NDV) vectors and conventional vaccine virus strains have been made and tested for safety and efficacy.

AVIFLU (Oct 2002 – Sept 2006)

Marker vaccines expressing several influenza virus proteins have been generated for ducks and better understanding of the immunity afforded by VLPs gathered and means to differentiate vaccinated chickens has been obtained.

FLUAID (Jan 2006 – Oct 2010)

Prototype vaccines were developed for H5N1, H5N3 and H7N3.

NOVADUCK (Jan 2007 – Mar 2010)

The project delivered proof-of-concept of the use of a NDV-based vector vaccine in day-old ducklings. This vector allows the mass application of vaccine at the hatchery and is compatible with the DIVA strategy. The project highly increased the knowledge on the immune response of ducks, on H5N1 challenge models for the different types of ducks and on the AI vaccine evaluation and performances to be expected in ducks.

Major issues in inducing protective immunity

- Immunization with **one strain of a subtype does not necessarily protect against other strains** within the subtypes (drifts) or other subtypes (shifts) or other types of Influenza
- **HA appears to be one of the most important antigens** for inducing protective immunity through neutralizing antibodies,
- **Mucosal vaccination** can confer better protection than systemic vaccination as mucosal vaccination induces a mucosal as well as a systemic response, enabling the animal to fight the pathogen at the entry site and consequently reduces more virus spread.
- **Live vaccines** should confer better protection than dead vaccines as they have a broader immune response, i.e. CD4 as well as CD8 (CTL) responses.
- Live vaccines can be administered mucosally so having the benefit of inducing mucosal protective responses as well as inducing CD8+ responses.
- **Several influenza antigens** seem to confer more or less protection, including HA, NA, NP, M2.
- Some of these antigens appear very susceptible to antigenic drift and consequently appear to change their antigen specific epitopes for B (and T?) cells.
- The important neutralizable B cell epitopes of an antigen are **structural (tridimensional) epitopes** which are dependent for their tridimension on their own sequence as well as the sequence of the rest of the antigen.
- The use of live vaccines can generate new subtypes of strains through recombination events between or within ‘–‘ssRNA segments.

Poultry vaccines

January 2015, G. Koch

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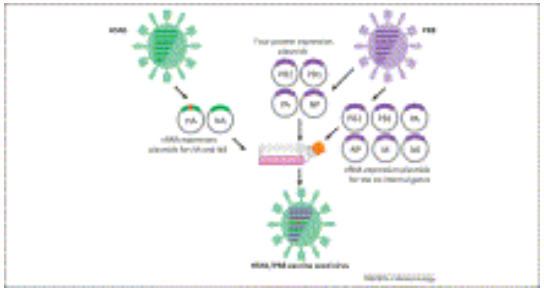
Vaccination programmes

- Routine vaccination
  - Avian influenza is enzootic
  - In most countries to lower human exposure
  - To sustain poultry production
  - Can be incorporate in routine vaccination programmes
- Preventative or prophylactic vaccination
  - In case of high risk of incursion
  - Early detection/rapid response might be insufficient
- Emergency vaccination
  - In face of an epidemic

Routine vaccination

- When disease is enzootic
- Other control measures cannot be enforced
- To decrease virus loads to lower zoonotic risk
- Mostly inactivated vaccines: whole killed virus emulsified with water in oil
- Fit for purpose to the region
    - No ‘universal’ seed virus
    - Local HPAI viruses as seed virus
    - LP virus produced by reverse genetic virus
- Vaccines used in enzootic regions account for 99% of usage worldwide



Vaccination

- Disadvantaged
  - Vaccinations interferes with serological monitoring
  - Vaccination masks infection because infected birds do not develop disease or die
  - Silent spread
  - Antigenic (escape) variants
  - Can have negative effect on trade
- Countermeasures
  - Monitoring effectiveness of vaccination
  - Surveillance to detect infection of vaccinated flocks

DIVA = Differentiating Infected from Vaccinated Animals

Vaccine types

- Inactivated vaccines: whole killed virus emulsified with water in oil
- Live vector vaccines:
  - recombinant vaccines HA and or NA gene inserted in genome of other virus (vector)
  - H5 in NDV, HVT and FP used in the field
  - Allows for DIVA
  - H5-NDV allows mass application by spray
  - Interference by existing immunity against vector
  - ‘only’ 11 billion doses used between 2006-2012

Emergency vaccination:

- In case of an outbreak to prevent spreading in highly dense poultry area
  - Many birds to be vaccinated in short time
  - Onset of immunity
  - Existing immunity
    - against vector

Emergency vaccination

- High number of birds
  - Mass applications systems required
  - Knowledge of factors that impact the vaccination response
- Vaccines
  - Require single dose
  - Early onset and long lasting immunity
  - In face of passive or prior immunity
  - Inducing broad resistance
  - Allowing detection of infected animals (e.g. DIVA)

Thank you for your attention

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Vaccination against influenza in swine

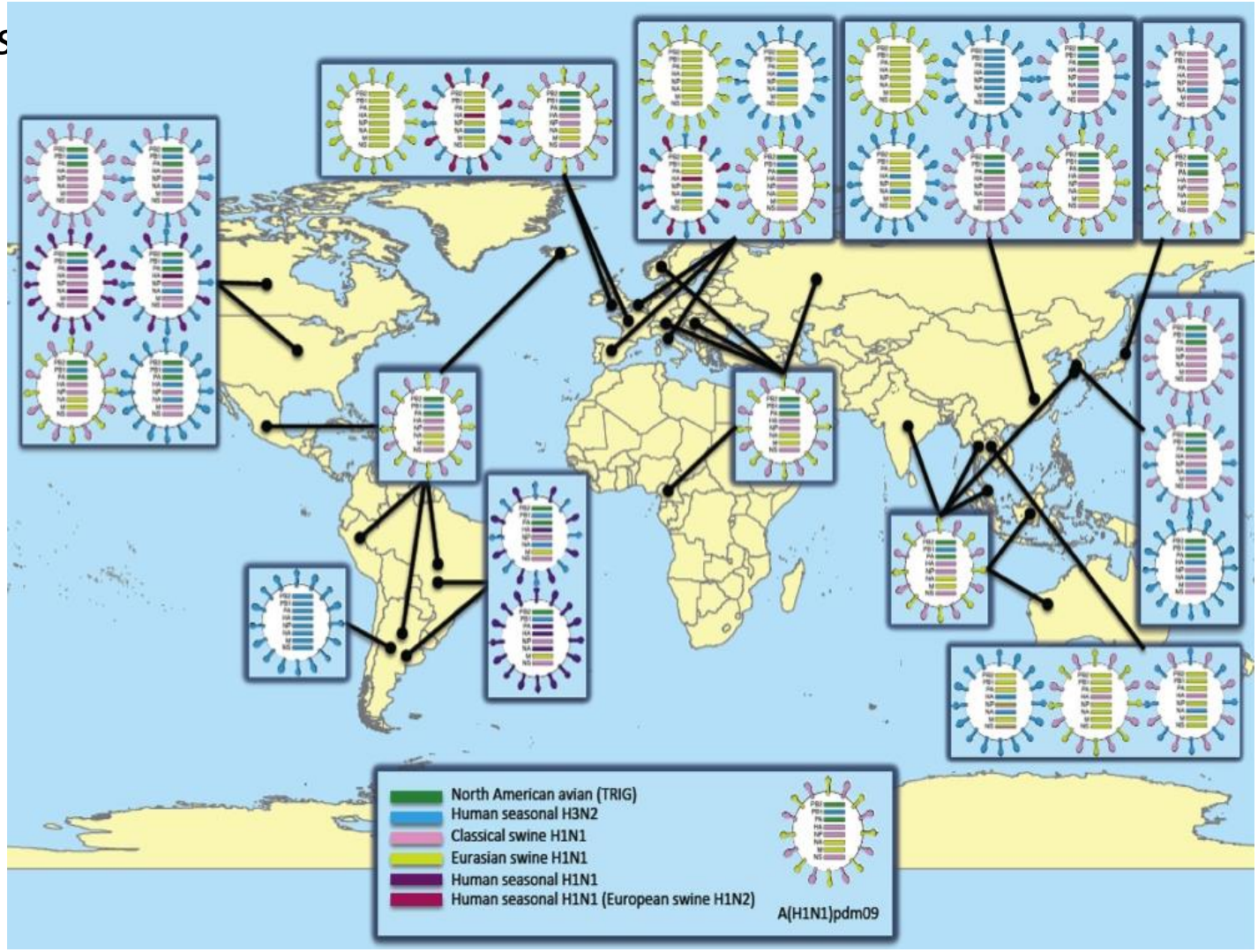
Swine Influenza Virus Vaccines: To Change or Not to Change—That's the Question

Kristien Van Reeth and Wenjun Ma

Current Topics in Microbiology and Immunology 2012

Prof. Kristien Van Reeth, Ghent University, Belgium

Review of influenza A virus in swine worldwide ... *Zoonoses and Public Health 2013, Amy Vincent and members*



Review of influenza A virus in swine wo

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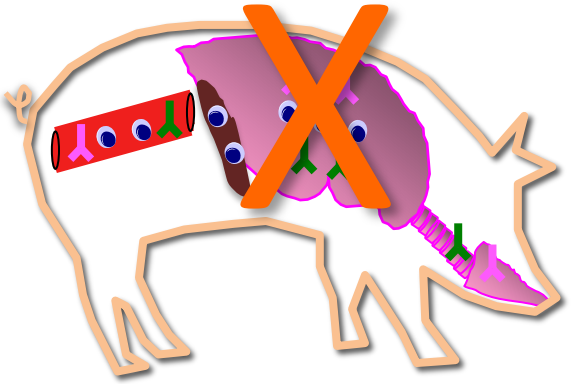
- Concurrent circulation of H1N1, H3N2, H1N2, multiple lineages
- Distinct SIV lineages in North America, Europe, Asia, regional differences
- Human and avian viruses repeatedly transmit to pigs, adaptation to pigs by reassortment/mutations
- Pigs as reservoirs for older human (and avian) virus genes

SIV vaccines are killed vaccines + adjuvant (oil)

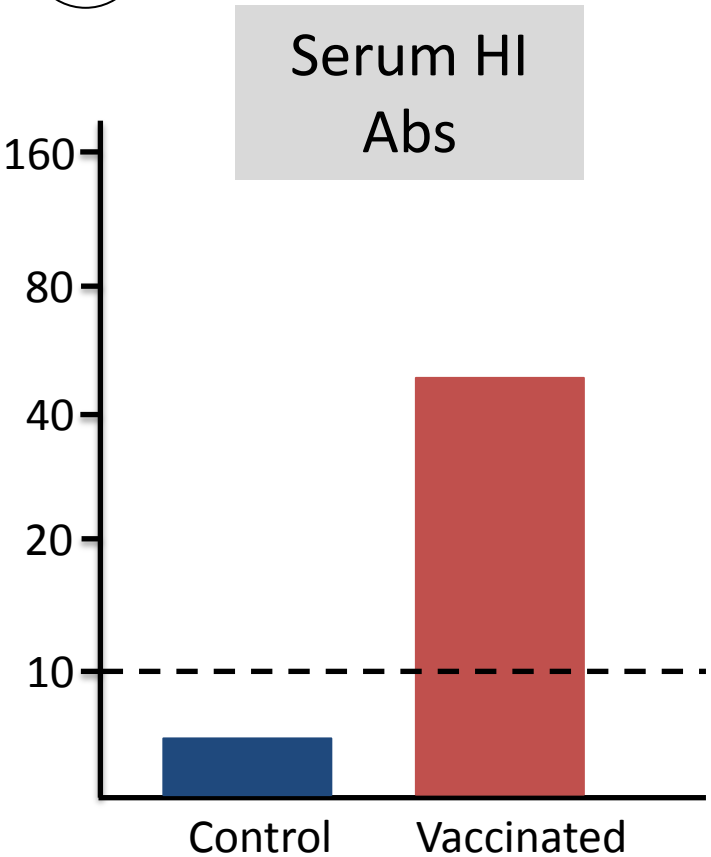


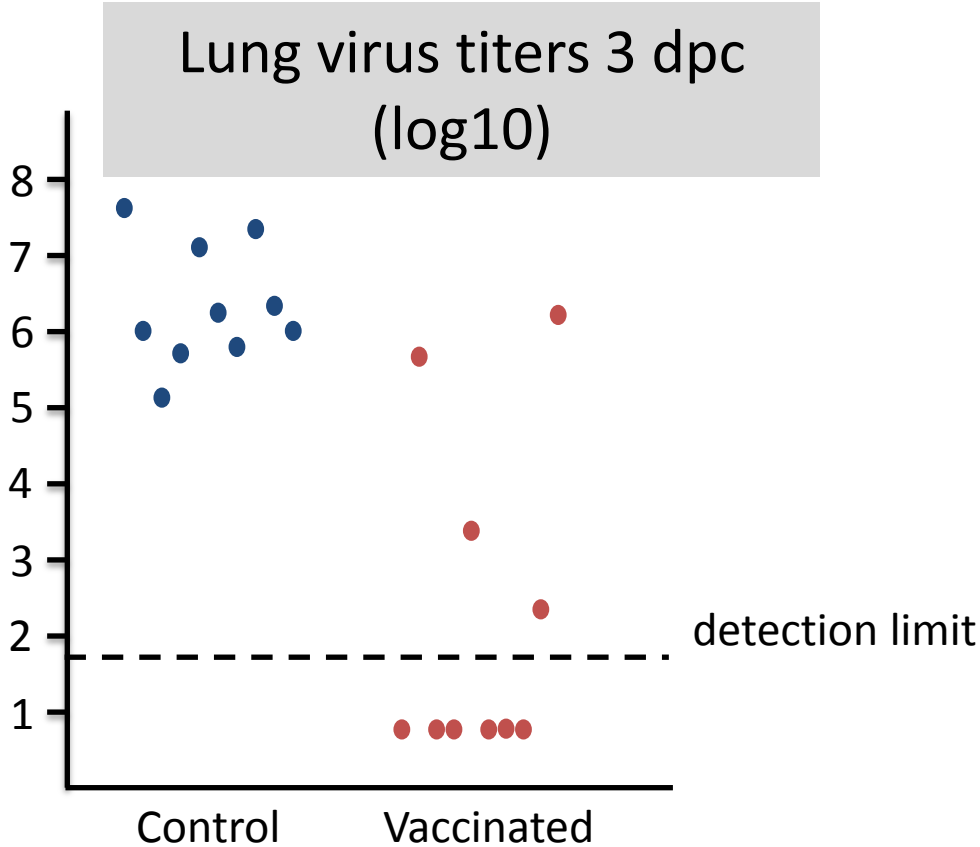
- Serum HI Ab titers 80-160 (to challenge virus) may fully protect against virus replication in lungs
- Multivalent, H1N1(N2) + H3N2: 2-3 (Eu) or 2-5 strains (US)
- No standardisation of vaccine strains, antigen dose and adjuvant
- No/rare updates of vaccine strains

SIV vaccines and cross-protection

: commercial European vaccine, 2x sw/Netherlands/80 (H1N1) + Port Chalmers/73 (H3N2)

: challenge with sw/Gent/172/08 (H3N2), 84% aa homology with vaccine H3N2 strain





SIV vaccines - summary

- Drift (within H1 or H3 virus lineage) is slower in swine than in humans and does not necessarily make vaccine strains obsolete
- (Oil) adjuvants broaden immune response!
- A variety of H1 and H3 SIV lineages in swine worldwide, usually no cross-protection between lineages: e.g. Eu H1N1 vs Eu H1N2, Eu H3N2 vs US H3N2
- Novel generation vaccines (proteins, vector, DNA, live attenuated) have not yet reached the market
- “Universal” SIV vaccine is an illusion

Knowledge and data gaps based on previous initiatives

Lack of availability, delivery mechanisms and efficacious cross-protective vaccines:

- Vaccines have limited cross-protection against antigenic variants within a subtype, even less protection between subtypes (eg multivalent vaccines).
- Veterinary and human health coordination in vaccine seed strain selection to minimize generation of drift mutants and to maximize vaccine efficacy.
- A strategy based on DIVA-vaccines is missing.
- Lack of vaccine delivery mechanisms that could be used in large scale (e.g. via drinking water).
- Evaluation of antigenic consequences of genetic diversity, including epitope mapping
- Public/private partnership to develop emergency vaccines
- Perform vaccine efficacy studies in conditions similar to field situation
- Duck vaccination is important in endemic countries

DAY 2

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Ideas on the production of a cross-protective vaccine by

- engineering **chimeric HA proteins** containing neutralizing epitopes of the different subtypes or strains within a subtype through bicistronic or polycistronic mRNA
- engineering **chimeric influenza viruses** containing different HA subtypes (Finch et al. 2015)
- engineering **computationally optimized broadly reactive antigen** (COBRA) of HA subtypes targeting immune reponses towards conserved epitopes on HA which can interfere with neutralizing epitopes (Kirchenbaum and Ross 2014)
- production and analysis of **subunit vaccines** with the monomorphic M2 protein in isolation of more immunodominant antigens to direct immunological memory towards M2 protective epitopes which can favour booster responses upon challenge towards M2 on exposure to wild virus strains (Kim et al. 2014)

Ideas on more mucosally directed immune responses

- Constructing live attenuated vaccines which cannot make recombinants with circulating influenza viruses to avoid safety problems of recombinations (Pena et al. 2013; Finch et al. 2015)
- Producing/adding adjuvants for/to (inactivated) vaccines modulating systemic inoculations/responses towards mucosal responses by e.g. the use of Pam3 (TLR2 agonist) (St. Paul 2014a, 2014b; Oh et al. 2014)
- Producing chimeric HA genes between type A and type B influenza viruses to avoid recombination with wild type (Finch et al. 2015)

Possible research topics based on previous initiatives

Priority basic research:

- Improve resistance of poultry to avian influenza infection by selecting for genetic resistance or develop interventions that can block virus replication.
- Identify correlates of protection (measurable signs of protection) which result from vaccination.

Short-term applied research priorities:

- Validate and compare (in terms of effectiveness, cost, and social acceptability) specific interventions to decrease environmental influenza virus burden at sites where there is potential for high viral load and exposure to other species (e.g. markets, farms, mass gatherings (animal, human or both), transport).

Possible research topics based on previous initiatives

Longer-term applied research priorities:

- Develop vaccines which induce immunological protection to a broader range of virus strains and subtypes, to reduce disease burden and risk of infection.
- Develop vaccines which can elicit immunity with a single dose.
- Develop vaccines for younger animals that overcome interference from maternal antibodies, and which can be applied by mass application to produce earlier onset and longer lasting immunity.
- Develop vaccines that interrupt transmission of infection in addition to preventing disease and death.
- Develop vaccines with protection across a broader range of virus strains and subtypes, independent of HA variability, in the face of passive or prior immunity.
- Develop an immunological toolkit to measure correlates of protection (measurable signs of protection) for next generation vaccines and matching diagnostics to identify vaccinated animals or to differentiate vaccinated animals from infected animals.