Vaccines of today and products needed for the short-, intermediate- and long-term

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Influenza A reservoir & transmission

H3N8, (H5N1)
pH1N1

H3N8

H1-16N1-9
H5N1

H7N7

H9N2, H5N1, H7
pH1N1

H1N1, H3N2, H1N2
pH1N1, (H5N1), H9N2

H1N1, H3N2, pH1N1
(H5N1, H7N7, H9N2, H7N9)
Product Availability

Avian Influenza vaccines are available from a large range of companies

Most of AIV vaccines are classical inactivated (whole virus / produced on embryonated eggs): wild type isolates or re-assortants

● Key parameters for killed AI vaccines

- Isolate
- Antigen load
- Antigen quality (inactivation process and downstream process)
- Nature and quality of adjuvant

2 commercial vaccines based on the same isolate can be quite different in quality
### Different types of licensed influenza vaccines

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Human H1N1, H3N2, B + pand.</th>
<th>Avian H5N1, H5N2, H9N2, H7N3</th>
<th>Equine H3N8</th>
<th>Swine H1N1, H3N2, H1N2</th>
<th>Canine H3N8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Rev. Gen. inactivated</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Attenuated</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Subunit</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Vector</td>
<td>-</td>
<td><strong>Fowlpox</strong> Av. Paramyxov. Herpesvirus</td>
<td>Canarypox</td>
<td>Alphavirus Replicon</td>
<td>-</td>
</tr>
</tbody>
</table>
Types of Vaccines

Current commercially registered recombinant AI vaccines:

- Trovac-AI H5 (fowlpox vector) Merial
- Volvac (fowlpox vector) Boehringer Ingelheim
- Fowlpox vector-AI H5 not used Harbin Institute China
- NDV-AI H5 Avimex
- NDV-AI H5 Harbin Institute China
- Vectormune HVT-AI CEVA
Issues for vaccine supply & distribution

- ≥4 month lead time for delivering a first vaccine batch: necessity to secure in advance a stock/bank of adequate size
- Insufficient manufacturing capacity (even if egg supply is ensured) if vaccination generalized
- Movement restrictions on eggs caused by AI outbreaks may block all manufacturing and create *de facto* a vaccine shortage
- Cold chain for storage and transport to be respected

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Requirements for efficacy in the field

- All birds in a flock have to be vaccinated (except sentinels)
- Vaccines should induce high antibody titers in a few days after one shot
  - Greater amount of virus needed to establish infection in vaccinated birds
  - Vaccinated & challenged birds have greatly reduced virus excretion
  - Both the above points greatly reduce the spread from vaccinated, infected chickens to vaccinated contact chickens
- In an infected flock, vaccination stopped spread of virus after 18 days (Hong Kong, Ellis et al 2004)
Consequences of Vaccination for poultry industry

● Italian model (H7N3) and Chinese model (H5N1) demonstrated that vaccination is a workable solution for efficiently controlling outbreaks

● Monitoring using a DIVA strategy and sentinel birds will require preparation & appropriate resources (lab training, diagnostic tests/reagents bank stocks)

● Good planning is possible, and an outbreak can be handled if the field response is well organised (people training, emergency plans updated on a regular basis…)

● Export issues must be considered if vaccination is implemented preventatively
Regulatory Issues and needs

- Current Regulatory framework is an obstacle for a Fast Track registration of AI vaccines
  - Member States take different positions in relation to authorisation of emergency vaccines - full versus emergency registration
  - Full dossier requirements are practically impossible to achieve, especially for emergency needs (e.g. field trials in EU)

- There is today no approved concept for an easy strain updating for AIV vaccines – but this is essential, due to the nature of AI virus…

- Only exception : H5N1 inactivated vaccine (rapid switch to new isolates)
Emergency Preparedness

- Vaccine production has finite timelines, which cannot be modified for the following reasons:
  - Scheduling in IO facilities
  - Raw materials & egg supply (slow and linear increase, not exponential increase…)
  - Antigen production & testing
  - Finished vaccine QC testing for batch release

- Typical timeline is 4 to 8 months for the whole process
Prime-boost principle for increasing and broadening the antibody responses against avian influenza

Different antigen presentation
- **Fowlpox**: Cell-Mediated Immunity
- **Inactivated**: Humoral Immunity

Boost directed to protective antigen (HA)

Boost with a different HA

\[ B + B \Rightarrow B \text{ mainly} \]
\[ A + B \Rightarrow AB + ABC \]

(2 shots of inact.)
(prime-boost)
Exemple of Heterologous prime-boost

Prime at the hatchery with **fowlpox vector** vaccine

(H5N8)

Boost at the farm with **inactivated** vaccine

(H5N9)
Conclusion on prime-boost strategy

- Optimal immune responses
- Broader antibody response against various Ags
- Overcomes AI MDA interference on inactivated vaccine
- Multi-species (chicken, ducks)

- To be evaluated in H5N1 field conditions
- Breeder vaccination program should be organized
- Test potential of a double heterologous prime-boost
Short term needs for Vaccines and the Animal Health Industry

- Fast Track process for registration new AIV vaccines (context of outbreaks with new serotypes)

- Eased regulatory requirements allowing for rapid switch/updating of AIV isolates in existing commercial vaccines

- Vaccines for hatchery use (*in ovo*, SC injection…)

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Mid-term needs for Vaccines and the Animal Health Industry

● New manufacturing technologies for reducing the lead time in delivering « first batch »

● *In vitro* assays for rapid QC batch release

● Double heterologous prime-boost vaccine schedule
  - Prime at hatchery with Vaccine Technology X + HA A
  - Boost in the farms with Vaccine Technology Y + HA B
Long term needs for Vaccines and the Animal Health Industry

- Mass vaccination
  - *in ovo* route, drinking water
  - spray vaccination

- « Universal Flu vaccine »

- Combination with other routine vaccines
Conclusion 1/2

- Animal Health Industry is fully willing to cooperate with authorities / stakeholders

- Need well-structured, and permanent dialogue for changing the current regulatory concept

- Need clear visibility on vaccine demand / contractual commitments on sales and vaccine use, for planning manufacturing capacity and safety stock size (industry doesn’t want to repeat the H5N1 / H5N9 story in EU)
Conclusion 2/2

- Need to have authorities leading clear communication to the public on the benefits of using avian influenza vaccination in poultry

- CVOs, Regulators, EU Commission, Industry need to work in collaboration for a successful outcome

- Closer coordination with institutions and networks responsible for surveillance and monitoring / planning on zoonoses: ETPGAH, OIE, FAO, WHO, ECDC, USDA, CSIRO, STAR-IDAZ, China ACDC, Asia (AVA Singapore), etc.
Thank You