AVIAN FLU: A GROWING CHALLENGE

New approaches needed for fighting the spread of this devastating disease.

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VACCINATION AGAINST AVIAN INFLUENZA: WHAT HAS CHANGED, AND WHAT NEEDS TO BE CHANGED?
Avian Flu: A Growing Challenge

Avian Influenza (AI), also called Avian Flu, has severely hit the U.S. poultry industry in recent months. As of early June, 2015, about 15 states had reported outbreaks in domestic birds, chickens or turkeys. Considering this very limited time span and this wide geographical spread, this had never been seen before except in Asia in the early 2000s. This is a very severe epizootic.

Considering the suddenness as well as the gravity of this epizootic, many questions have been raised regarding actions to be implemented to control the disease including the potential of using vaccination as a complementary tool to control measures already in place.

However, it is still believed that biosecurity and sanitary police can be sufficient to control the situation and that vaccination is not necessary. It is even said that vaccination would make things worse by helping the disease become endemic, as happened in some countries in Asia and the Middle East, and particularly in China, Indonesia, Vietnam and Egypt.

To some extent, the fact that vaccination against AI is just a no-go has become a dogma.

The situation has changed. The biology of the AI viruses affecting the United States is different from previous outbreaks, the structure of the poultry industry is different, the available technical and financial means are different, and we have learned lessons from the past. So today we have a better understanding of why AI vaccination in Asia and Middle East did not lead to eradication.

In addition, a vector vaccine which has recently been developed in the U.S. and introduced on the market has shown properties and potential making it very different from the old vaccines that are still in use in many vaccinating countries. This vaccine has shown better efficacy and allows monitoring the disease situation in the presence of vaccination.

Times have changed. The decision to vaccinate is a tough one. Important information and facts have to be considered before casually discarding the vaccination option, or blindly applying it.

The objective of this article is to present in brief what has changed regarding the disease, the vaccines and vaccination against AI. More data has been published regarding what is presented in this document and is available upon request or via the internet at: www.avian-influenza-vaccines.com
The H5N8 virus affecting poultry in Northern Europe and the U.S. has shown no tendency to infect humans.

**Table 1:** Comparison between the 2014 H5N8 and the 2003 H7N7 outbreaks in the Netherlands:

<table>
<thead>
<tr>
<th></th>
<th>HPAIV</th>
<th>H5N8</th>
<th>H7N7</th>
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<tbody>
<tr>
<td><strong>Period</strong></td>
<td>End of 2014</td>
<td>2003</td>
<td></td>
</tr>
<tr>
<td><strong>Number of outbreaks</strong></td>
<td>5</td>
<td>255</td>
<td></td>
</tr>
<tr>
<td><strong>Number of birds culled</strong></td>
<td>345 thousand</td>
<td>30 million</td>
<td></td>
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<tr>
<td><strong>Number of Human cases</strong></td>
<td>0</td>
<td>86 (1 fatal)</td>
<td></td>
</tr>
<tr>
<td><strong>Total cost (approx.)</strong></td>
<td>50 million Euros</td>
<td>500 million Euros</td>
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THE RISE OF THE MOST DEVASTATING DISEASE.

In just over a decade, AIV has become one of the major viral poultry pathogens. This is the consequence of a dramatic increase in the frequency of outbreaks, its persistence in certain territories as endemic disease, as well as the extension of its geographical presence. It is now directly (as a disease) or indirectly (as a threat) plaguing the poultry industry world-wide and no country can be considered as entirely free or out of risk.

The factors responsible for these recent major changes are not fully understood.

Some of them are likely associated with the changes in poultry production including a strong and sustained growth necessitating bigger volumes, more farming units, larger units, heavier densities, higher geographic concentrations without being always accompanied by the necessary corresponding biosecurity measures. Also human factors are involved with very heavy movements of people from countryside to towns without changing their habits of buying living chickens at wet market places. These markets have become consequently larger and larger, resulting in more commercial exchanges and transportation of poultry.

There are probably also factors associated with the evolution of the wild bird populations, their migratory flyways and related ecosystems.

But the major source of changes appears to be related to the virus itself.

“IN JUST A LITTLE OVER A DECADE, AI VIRUS HAS BECOME ONE OF THE MAJOR VIRAL POULTRY PATHOGENS. NO COUNTRY CAN BE CONSIDERED ENTIRELY FREE OF RISK.”
WHAT HAS REALLY CHANGED RECENTLY?

At the end of the 1990s, AI was reported in China and soon after in various countries of South East Asia, Middle East, Africa and Europe. The Highly Pathogenic Avian Influenza Viruses (HPAIV) responsible for this epizootic, were all of the same H5N1 subtype. They were hosted by migratory wild birds and transmitted by them to domestic poultry. This was the first big wave of AI breaks, almost all of them caused by the H5N1 HPAIV. This wave peaked in 2006 with 35 countries (from all continents except South America) sending reports to the World Organization for Animal Health/Office International des Epizooties (OIE), the international structure in charge of collecting this information (table 2). This particular virus had the ability to spread from birds to humans during close contacts.

Table 2: Evolution of OIE reports related to Highly Pathogenic Avian Influenza (1) as of June 2015

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<td>119</td>
<td>259</td>
<td>202</td>
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<td>65</td>
<td>69</td>
<td>116</td>
<td>127</td>
<td>63</td>
<td>126</td>
<td>209</td>
</tr>
<tr>
<td>Number of Countries</td>
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<td>17</td>
<td>56</td>
<td>35</td>
<td>28</td>
<td>18</td>
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<td>2</td>
<td>4</td>
<td>5</td>
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</tr>
<tr>
<td>H5N1</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>H5N2</td>
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<td>x</td>
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<tr>
<td>H5N6</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>x</td>
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<tr>
<td>H5N8</td>
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<td>x</td>
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<tr>
<td>H7N2</td>
<td>x</td>
<td>x</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>H7N3</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>H7N7</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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</table>

AI outbreaks among poultry peaked in 2006, according to reports gathered by the World Organization for Animal Health (OIE). They are once again on the rise.

Because of various interventions including stamping out of infected flocks, improvement of biosecurity and implementation of comprehensive contingency plans, some affected countries eradicated the disease. But in others, farm-to-farm spreading of AI virus soon became the major route of transmission and the disease rapidly turned endemic. It was everywhere, affecting all types of productions including broilers, breeders, layers and ducks. This occurred in China, Vietnam, Indonesia, Bangladesh, Egypt and some other neighboring countries.

“MORE THAN 48 MILLION BIRDS HAVE BEEN KILLED OR DEPOPULATED SINCE DECEMBER 2014.”

But then, starting in 2011-2012, new HPAIVs came into the picture – coming not only from mutations of the H5N1 but also from exchanges of genes between very different viruses, including HPAIV as well as Low Pathogenic Avian Influenza Viruses (LPAIV). Other viruses were recognized as being of the H5 (H5N2, H5N6, H5N8) or the H7 subtype (H7N2, H7N3, H7N7). Some of the new viruses were non-pathogenic for wild ducks and consequently acquired the capacity to be carried for much longer distances and affect much wider territories.

This explains why the first cases of the recent epizootics observed in the U.S. (with H5N8 and, more importantly with H5N2, which originates from an exchange of genes, i.e. a re-assortment, between the H5N8 and a HxN2 AI virus (10) as well as in The Netherlands (with H5N8) were so geographically distant one from each others, confirming the transmission from wild bird to domestic poultry. This made it extremely difficult for the authorities and poultry industry to contain AI. The expected pattern of “invasion” was not happening: it was not one farm (the epicenter) contaminated by the wild birds and then contaminating the neighboring farms in a limited territory; it was many farms hit simultaneously by the virus within a short period of time, each of them becoming an epicenter (figure 1).

“AI IN A HIGH-PRODUCTION AREA LIKE DELMARVA COULD BE CATASTROPHIC.”

The virus mutating very frequently, endless and constantly updated lists of H5N1 mutant HPAIVs scientifically grouped into “clades” or “sub-clades”, with very different antigenic properties, have been regularly published.
In less than 6 months (December 19, 2014 – June 17, 2015), more than 220 outbreaks of HPAI have been confirmed by USDA’s National Veterinary Services Laboratories, affecting turkey, layers, chickens and pheasants from commercial as well as backyard operations spread over 15 states. More than 48 million birds have been killed or depopulated (2).

Many findings have also been reported in wild birds from 5 different states.

While H5N8 was exclusively detected in territories of the migratory birds’ Pacific flyway, H5N2 was detected in the migratory birds’ flyway of the central Mississippi. However, on May 10, an outbreak of H5N8 HPAI in a backyard poultry farm was also detected in Indiana, showing a large jump of the virus from Pacific to Mississippi flyways. Indeed, this jump was confirmed with about 75 detections in Iowa up to June 17, being most of them in commercial chickens.

In the U.S. as well as The Netherlands, the most densely poultry-populated areas have not been hit. The same scenario occurring in a high-production area like Delmarva could be catastrophic. This is the possibility the industry needs to be prepared for. As the saying goes, “the postman always rings twice!”

Figure 1: Spreading of H5N2, H5N8 and H5N1 outbreaks in Poultry and Wild Captive birds in North America – From UK-DEFRA Animal & Plant Health Agency-International Disease Monitoring (3) update May 12, 2015.

Report of H5N1, H5N2 and H5N8 HPAI outbreaks in poultry and wild or captive birds in North American, 2014/2015
WHAT ARE THE VACCINES AVAILABLE FOR CONTROL OF AI AND WHAT ARE THEIR ADVANTAGES, DRAWBACKS AND LIMITATIONS?

As of today, only two categories of AI vaccines are commercially available for poultry, depending on the countries:

**The “classical” killed (inactivated) adjuvanted AI vaccines.** They are made from an AIV that is inactivated (by a chemical agent like formalin) and mixed with a combination of mineral oils used as adjuvant in order to boost the immune response. For real efficacy, the selected virus must be “homologous” i.e. carrying the same type of hemagglutinin HA as the field virus it is expected to protect the birds from. This AIV used for production can be a HPAIV or a LPAIV or a laboratory strain created by the Reverse Genetic (RG) technique.

**Using HPAIV** is very dangerous because it is still fully pathogenic, which poses problems regarding the potential contamination of workers, as well as the possible spreading outside production facilities. They are also rapidly killing the embryonated eggs used for propagation, and consequently limiting the production yield. Most of the countries have prohibited their use.

**LPAIV** can be used with good efficacy. Unfortunately, because of the need to have them “homologous” to the field virus, they cannot always be found which makes this approach not always possible.

**Reverse genetic (RG) AI virus utilized for vaccine production uses a human influenza virus as the backbone, which grows well (to ensure a good yield) in production substrate and whose HA gene has been replaced by the HA of the field virus, after conversion of the HP cleavage sequence by a LP one, using the RG technique. This is the technique most commonly used for production of inactivated vaccines, for animals as well as for humans.

**The recombinant vector AI vaccines.** These vaccines are made from a live attenuated virus or bacteria (the “vector”) inside the genome of which, a gene (the “insert”) encoding for the major immunogenic part of AIV (the HA), has been inserted. When it replicates in the birds, the vector expresses the HA, which creates immunity (protection).

As of today, only 3 types of attenuated viruses have been used as vector for recombinant AI vaccines: the Influenza vector vaccines are abbreviated as rFP-HA, rNDV-HA and rHVT-HA. A number can be used to indicate the subtype of the donor AIV. rHVT-HA5 indicates that the insert comes from an AIV of the H5 subtype.

All these vaccines, killed or live recombinant vectors show significant differences when it comes to production, route of administration, safety, quality of induced immunity as well as capacity to overcome the Maternally Derived Antibodies (MDA) against AIV present in day-old chicks, or day-old pouls, when the breeders have been vaccinated (25). For recombinant vectors, interference from MDA directed against the vector also needs to be considered.

"TWO CATEGORIES OF AI VACCINES ARE COMMERCIALLY AVAILABLE FOR POULTRY: CLASSICAL INACTIVATED VACCINES AND RECOMBINANT VECTOR VACCINES:"

<table>
<thead>
<tr>
<th>TYPE OF VACCINE</th>
<th>Cost of Production</th>
<th>Safety</th>
<th>Spectrum of Protection (H5)</th>
<th>Interference with MDA</th>
<th>Possible routes of administration at day-old</th>
<th>Possible use at later age (emergency)</th>
<th>Need for booster in long-living birds</th>
<th>Possible use in Turkeys</th>
</tr>
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<tbody>
<tr>
<td>KILLED</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>RG</td>
<td>High</td>
<td>Narrow</td>
<td>Only SQ - Difficult because on volume of injection</td>
<td>Only SQ - Difficult because on volume of injection</td>
<td>Possible - SQ or IM</td>
<td>Yes</td>
<td>Possible</td>
<td></td>
</tr>
<tr>
<td>VECTORS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rFPV</td>
<td>Moderate</td>
<td>Unknown</td>
<td>SQ (or In-ovo*)</td>
<td>SQ (or In-ovo*)</td>
<td>Possible - SQ or WW*</td>
<td>Yes</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>rNDV</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Spray</td>
<td>Spray</td>
<td>Possible - Spray</td>
<td>Yes</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>rHVT</td>
<td>Moderate</td>
<td>Unknown</td>
<td>SQ (or In-ovo*)</td>
<td>SQ (or In-ovo*)</td>
<td>Unknown</td>
<td>No (long lasting immunity)</td>
<td>Possible*</td>
<td></td>
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</table>

* if accepted by registration authorities
Another important point, and probably the most critical one to consider in the case of vaccine prevention against AI, is the capacity of the vaccine to cover the continuous antigenic variations of the virus.

The table 3 presents a summary of the advantages, drawbacks and limitations of the various AI vaccine types.

As of today, when considering these factors, the most attractive vaccine solution is the rHVT-HA5:

- Compared to killed vaccines, it can be used in the hatchery on the first day of age, even in the presence of specific MDA and shows a long duration of immunity. Its efficacy seems to be unaffected by the antigenic variations of the field virus, which is the major weakness of the killed vaccines. rHVT-HA5 has a proven record of efficacy against significant variations of HPAIVs of the H5 serotype, and does not require booster vaccinations.

“AS OF TODAY, WHEN CONSIDERING THESE FACTORS, THE MOST ATTRACTIVE VACCINE SOLUTION IS THE rHVT-HA5.”

- Compared to other vectors, it circumvents MDA (when the rFP-HA is neutralized by MDA against AIV and the rNDV-HA by MDA against the vector NDV).

INFORMATION AND PERFORMANCE REGARDING A NEW rHVT-HA5 VACCINE

The development of a rHVT-HA5 vaccine started in 2005 and it was officially licensed by USDA in 2012, and from there in other countries. It is now commercially available under the trade name of Vectormune® AI (or Vectormune® HVT AIV).

In order to complement information included in the original registration file, many more scientific investigations, controlled trials and field studies have been conducted to increase the knowledge regarding the characteristics and performances of Vectormune® AI, so the prescription and decision for usage can rely on broader information. Field experience from large commercial use has also enriched this experience and knowledge.

The construction: This rHVT-HA5 vectored vaccine is a recombinant vaccine constructed from the FC126 strain of HVT inside the genome of which, a gene (the “insert”) encoding for the HA of an H5N1 HPAIV has been inserted. The sequence at the cleavage site has been modified so to ensure safety of the vaccine.
Avian Flu: A Growing Challenge

"THE LACK OF ANTIBODY RESPONSE TO THE NUCLEOPROTEIN OF THE VIRUS ALLOWS FOR A POSSIBLE DIVA MONITORING STRATEGY NECESSARY FOR DETECTION OF FIELD INFECTION AND ERADICATION."

**Antibody response to vaccination:**
(figure 2) After vaccination of SPF chickens, this rHVT-HA5 vaccine induces antibodies easily detectable by the Hemagglutination Inhibition (HI) test (using homologous antigen), as soon as 3 weeks post vaccination in the majority of the tested animals. At 4 weeks of age, all vaccinated SPF chickens seroconvert with HI titer values reaching 5 to 6 log2. This antibody response keeps on increasing until at around 9 weeks of age, and reaches a plateau with high titer values of 9 to 11 log2. In commercial chickens carrying MDA against HVT and AIV, under similar conditions of testing, HI antibody response keeps on increasing despite it is slower to rise and reaches lower values than on SPF chickens at the same time points (figure 2).

Challenge experiments have shown that a high level of protection is reached before homologous HI test antibodies are detected in all chickens, as well as despite low level of antibodies detectable by HI test using antigen homologous to the challenge virus.

The lack of antibody response to the nucleoprotein of the virus allows for a possible DIVA monitoring strategy necessary for detection of field infection and eradication.

**Figure 2:** monitoring of antibody response to vaccination with a rHVT-HA5 vaccine (Vectormune AI) in commercial broilers provided or not with MDA against HVT and AIV (Ceva Scientific Investigation Study ref. SCI 193-2011)
"PROTECTION AGAINST MORTALITY WAS GENERALLY GOOD TO VERY GOOD, VARYING FROM 70 PERCENT TO 100 PERCENT."

Protection against challenge (table 4): To assess protection against virulent HPAIV challenge, 2 criteria are considered as important:

- Protection against mortality
- Reduction of shedding of the challenge virus after inoculation

In the experiments, the rHVT-HAS vaccine was always injected subcutaneously on the first day of age and challenge given between 2 to 8 weeks of age with a dose of 10^5 or 10^6 EID50 of challenging HPAIV.

Protection against mortality was generally good to very good, varying from 70% to 100% depending on the experiments. These results included challenges with strains of different clades of H5N1 (1, 2.2, 2.2.1, 2.2.1.1, 2.1.3, 2.3.2.1), or different subtypes (Mexico 1994 H5N2, Germany 2014 H5N8 clade 2.3.4.4) showing very significant antigenic differences from the strain used to construct the vaccine. This suggested the conclusion of “cross clades protection against HPAIV of the H5 type” (12). It is believed that immunity induced by this vaccine is of humoral (antibody) as well as of cellular types, and of general as well as of mucosal types (12, 20). Obviously, the criteria generally used to indirectly assess protection induced by classical killed vaccines, and in particular antibody response to the challenging virus, are not applicable to this vaccine.

A significant reduction of shedding considering the percentage of shedders as well as amount of virus shed was always observed but with different intensities. It is believed that the different experimental conditions and procedures (RT-PCRs of different types, virus isolation) partly explain these variations.

A recent experiment conducted in SPF chickens vaccinated on the first day of life with rHVT-HAS vaccine and challenged 4 weeks later with a H5N8 HPAIV isolated in Germany end of 2014 demonstrated 100% protection with significant reduction of shedding

"ALL EXPERIMENTS OBSERVED A SIGNIFICANT REDUCTION OF VIRAL SHEDDING."

(24). This HPAIV used for challenge showed close to 98% amino acid similarity with H5N8 and H5N2 HPAIV isolated in 2015 in the USA, so that it is believed that this vaccine would induce very high degree of protection against the H5N2 circulating these days in the Midwest and would consequently significantly protect chickens and turkeys and contribute to the control of the disease.
“rHVT-HA5 WORKS IN THE PRESENCE OF MATERNALLY DERIVED ANTIBODIES.”

Onset of Immunity: In chickens free of MDA against AIV, early protection comes exclusively from the active immunity induced by the vaccine replication. According to controlled studies, 2 weeks are necessary to reach protection (8, 9), although earlier resistance to challenge has not been tested yet.

In chickens with MDA against AIV, protection comes also from MDA which are actually protective (9), and it has been observed that active immunity induced by vaccination cumulates with MDA protection so that overall early protection is increased. For this reason, in endemic countries, vaccination of breeders against AI complements and does not contradict day-old vaccination of broilers and pullets.

“rHVT-HA5 VACCINE IS A HATCHERY VACCINE.”

Duration of Immunity (DOI) Data regarding efficacy of rHVT-HA5 to protect long-living chickens against very late challenge are not available yet. However, the following elements are suggesting of a long-lasting protection:

» HVT is known to persist permanently in vaccinated animals, so that expression of the HA insert inside the rHVT-HA5 vaccine and the protection it offers is also likely to persist

» Monitoring the HI test AB response (homologous antigen) to rHVT-HA5 vaccination up to 12 weeks of age in commercial layer pullets with or without MDA against H5N1 revealed titers increasing and then keeping steady (figure 2).

» Layer pullets of 2 different breeds, vaccinated at the hatchery and reared under the heavy diseases challenge conditions of Egypt, were transferred at 19 weeks of age to BSL3 facilities for virulent challenge.

» Protection levels of 73% and 60% were recorded, which were partly due to non AI related disease problems. (15).

Target species: Experiments have demonstrated replication of rHVT-HA5 and induction of protection in chickens of the SPF, broiler and layer types, as well as in turkeys (11), waterfowl such as the Goose, Muscovy ducks and Mallard ducks but not Peking type (17).

WHAT ARE THE OBJECTIVES AND CONDITIONS OF AN EFFECTIVE AI VACCINATION? WHAT TO EXPECT FROM AN EFFECTIVE AI VACCINE?

As far as vaccination against AI is concerned, 2 points need to be defined:

1) Objectives
2) Specifications for the vaccine

1) What are the objectives of AI vaccination?

In a country or a territory hit by AI, vaccination is primarily a tool to prevent clinical and economical losses due infection with AIV. It is also a complement to sanitary and biosecurity practices to reach eradication and recover the AI free status. If it is used as the sole mean to combat the disease, vaccination cannot lead to eradication. This is why vaccination against AI needs to be organized, coordinated and accompanied with disease monitoring and eradication plans.

In a country free of AI, vaccination can also be used to lower the risk of being hit and slow down the spreading of the virus once a farm is affected.

2) What are the specifications for a good AI vaccine?

When it comes to efficacy, an AI vaccine must meet five requirements:

1. The capacity to remain efficacious despite the frequently occurring antigenic variations of the challenging virus

2. The capacity to overcome MDA that are present in the young chicken as soon as the breeders are vaccinated (or exposed)

3. The possibility to be used at the hatchery where the conditions to achieve a maximal vaccine coverage are present.

4. The need for a long lasting immunity so revaccinations are not necessary.

5. The possibility to keep on monitoring spreading of the challenge virus in the presence of vaccination, so that vaccination does not present an obstacle to eradication plans.

a) Antigenic variability of the challenging virus deeply affects the efficacy of classical inactivated vaccines (including the reverse-genetics ones) and possibly the recombinant vector vaccines of the rFP-HA or rNDV-HA types.

Classical inactivated vaccines induce an immunity that is mostly, if not exclusively, composed of antibodies. For this reason, antibody response must be strong and specific, which can only be achieved if the vaccine is well manufactured with a high antigenic mass and regularly updated according to the evolutions of the field virus. In theory, this is possible when the Reverse Genetic technique is used.

“VACCINATION NEEDS TO BE COORDINATED WITH SANITARY AND BIOSECURITY MEASURES, DISEASE MONITORING AND ERADICATION PLANS.”
"THE \textit{rHVT-HA5} vaccine remains effective even if very significant changes occur in the field virus."

But in real life, it is just impossible to know when the field virus will mutate, and at the end, which virus will challenge the farms i.e. which vaccine strain should be used. The vaccine update can only be made after vaccination failures are observed and the necessary reverse genetic antigen made. Even so, this does not answer the question of territories where field strains of various antigenic profiles are present. The use of multivalent killed vaccines, or multiple vaccinations using different killed vaccines is just not realistic.

\textit{The \textit{rHVT-HA5} vaccine has demonstrated its capacity to remain efficacious even if very significant changes in the field virus occur, as long as the virus is of the H5 subtype (which is the case in the U.S.).}

\textbf{b) Interference with MDA occurs very soon after implementation of vaccination.} Breeders are the most valuable animals of the poultry chain, and are generally first to be vaccinated. Then, soon after, they are carrying antibodies that are transmitted to their progeny, the MDA. Interference between classical killed AI vaccines and MDA has been well documented. The only way to overcome MDA is to delay the age at vaccination and wait until MDA have waned. Thus an optimal time for vaccination is difficult to determine for a given flock, and implies the risk of an early field infection. Besides, MDA prohibits the administration at the hatchery, which is necessary to achieve optimal coverage.

Interference between MDA and vaccine has also been shown for \textit{rFP-HA} and \textit{rNDV-HA} type of recombinant vector AI vaccines. For the \textit{rFP-HA} vaccine, the dominant interference is related to expression of the HA insert; the Fowl Pox virus being capable to replicate even in the presence of anti-Pox MDA. For the \textit{rNDV-HA} vaccine, the interference is more related to the NDV vector itself, which is well known for vaccination against the Newcastle disease (5). Early vaccination against ND with a live ND vaccine reduces and shortens the immunity.

\textit{Interference of MDA when using the \textit{rHVT-HAS} vaccine is not a major issue. Many years of use of HVT vaccine to prevent the Marek’s disease have established its capacity to replicate in the presence of MDA against the vector. Besides, many experiments have also demonstrated the absence of significant interference of MDA directed against AIV on the take of this vaccine (8, 14, 15, 22, 23).}

\textbf{a) Possible use at the hatchery is critical and cannot be avoided.} It is the only way to ensure good vaccine coverage, so that, in case of challenge, a minimal percentage of birds are left susceptible. Because of interference with MDA, and also because of the difficult
administration of a large (0.5 ml) dose by the subcutaneous route, killed vaccines (if not concentrated, which is generally the case) are obviously not suitable for hatchery vaccination. This is even truer if in-ovo vaccination is the only available route of administration.

Similarly, because of interference with MDA, the recombinant vector AI vaccines of the rFP-HA or rNDV-HA types can hardly be reliably used in the hatchery.

Because of its nature and its capacity to escape from interference with MDA, the rHVT-HAS vaccine is by definition a hatchery vaccine, and is presented in a way the users in the U.S. are familiar with.

b) The capacity to induce a long lasting immunity is critical. In endemic countries where vaccination with killed AI vaccine is used, long living birds like layers or breeders are vaccinated up to 6 times (China) to ensure an acceptable level of protection! This is costly, not practical and shows the limitation of killed vaccines. As of today, no other alternative is available when classical killed vaccines are used.

As described above, some experience with rHVT-HAS vaccine has shown that much longer lasting immunity can be expected, but this needs to be further investigated, either using the rHVT-HAS vaccine alone or in combination with killed vaccine in the same vaccination program.

c) The possibility to monitor the spreading of the field HPAIV in vaccinated flocks is usually named the DIVA strategy i.e. the possibility to Differentiate Infected from Vaccinated Animals. Killed vaccines are made from whole inactivated AIV so that antibody response to infection can hardly be differentiated from antibody response to vaccination, especially when a vaccine homologous to the field virus is used. This is why “vaccination against AI” is often accused of masking the infection.

The rHVT-HAS vaccine does not contain the whole AIV, and for this reason, induces antibodies only against the HA insert, and not against the nucleoprotein or the neuraminidase that are other components of the virus. Antibody response to vaccination can then be detected using the HI test. In case vaccinated birds are infected, the field virus will replicate (although to a much lower degree), and some antibody response to the nucleoprotein or the M2 protein will be detected (6, 16, 24). This will need further investigation but on a short term, infection could also easily be detected by PCR so that a real DIVA strategy can be applied with this vaccine. Vaccination with rHVT-HAS vaccine does not prevent the monitoring of the spreading of the field virus and can help ensuring the AI free status of flocks or territories. This is a strong argument to maintain exports in the presence of vaccination.

“rHVT-HAS VACCINE DOES NOT INTERFERE WITH MONITORING A FIELD VIRUS’ SPREAD.”
WHAT ARE THE RISKS OF AI VACCINATION?

Even when an efficacious vaccine is used, the risks identified with AI vaccination are still the same as the ones already identified for other vaccinations, against the Newcastle disease, Infectious bronchitis, Marek’s disease or any other diseases.

“All critical steps of the vaccination process need regular checks.”

An excess of confidence in vaccination. Vaccination is a powerful aid in the control of infectious diseases but can never be a standalone solution. Vaccines often protect against the disease i.e. the consequences of infection, not against the infection itself, so that the field virus can still infect, replicate and be re-excreted. There are only very few veterinary vaccines that have the capacity to totally block the pathogenic agent, which is scientifically called “sterile immunity”. Even if limited, or reduced, the shedding of the challenging infectious agent is always possible. Thanks to vaccination, the risk is lower, but not totally eliminated. Strong biosecurity programs always need to be in place, having in mind that the best protection against any kind of challenge is simply to avoid the challenge.

“If the immune system is compromised, then protection is also compromised.”

A poor quality of vaccine application. At the level of a flock there are always birds that are missed during the vaccination process. It is generally acceptable for an epizootic disease like Avian Influenza (or Newcastle Disease) if the percentage of missed birds remains low (less than 3-4%) and if the challenge pressure is not constantly applied to every chicken (as it is for the Infectious Bursal Disease of Marek’s disease).

Vaccination at the hatchery is much easier to control making it far more reliable than any other type of vaccination, particularly from vaccination at farm (18). But vaccination at hatchery does not mean big mistakes cannot be made. There are flocks where as many as 50% of improperly vaccinated chickens can be detected, so monitoring and assessment of vaccination is always necessary.

“The factors of a good immune response. Vaccination stimulates the immune system to produce an immune (protective) response. If immune system is compromised, at the time of vaccination or later, then protection is also compromised. This is why vaccination works so well in some farms, and not so well in others. Quality of day-old chickens or day-old poults, housing, feed, environment, farming, ventilation, as well as control of intercurrent infections are also critical factors for the success of vaccination.

“Thanks to vaccination, the risk is lower, but not totally eliminated. Strong biosecurity programs always need to be in place.”

When it comes to using a vaccine like Vectormune AI, it is also particularly important to keep in mind that this vaccine does not spread, so that if not vaccinated, the chicken will never be protected by the vaccine received by its hatch mates. For this reason, all the critical steps of the vaccination process need regular checks including storage, distribution, reconstitution and injection.

One of the important advantages of vaccination in the hatchery, is also to eliminate the risk of transmission of AI by the vaccination crews going from farm to farm.
WHY VACCINATION HAS NOT WORKED PROPERLY IN COUNTRIES THAT HAVE APPLIED IT?

The fact that Avian Influenza is still endemic in countries where AI vaccination has been applied is often presented as an argument to refuse vaccination. In fact this situation is the consequence of many factors:

» In all countries, most, if not all, AI vaccines used were of the classical inactivated types, so they were unable to:
  • Ensure a good vaccine coverage of the flocks after injection at the hatchery,
  • Where hatchery vaccination was in place, interference with maternally derived antibodies neutralized the vaccines' action (4)
  • They could not answer the key problem of evolution of the field virus and maintain a steady level of efficacy whatever the challenging virus.

» The rFP-HA vaccine was tried in Vietnam, as well as the rNDV-HA in China, but soon revealed inefficacious when administered to chickens carrying MDA against AIV or NDV.

» The rHVT-HA5 vaccine has been recently introduced in Mexico, Egypt and Bangladesh but, as of today, at a limited scale so that the benefit cannot yet be seen. However, a survey conducted in Egypt under the supervision of FAO and CIRAD (a French agricultural research organization) has shown that vaccination at the hatchery with this vaccine was clearly beneficial (18)

As of today, no real field experience of using the rHVT-HA5 vaccine can be presented to support the statement that implementing vaccination with it is not useful.
CONCLUSION: WHAT ABOUT THE FUTURE OF AI VACCINATION?

Avian Influenza has dramatically and deeply changed during the past few years, and is now induced by more types of viruses than before, also present in more countries than before. These more recent viruses are also better “adapted” to wild waterfowl populations. They are not behaving as HPAIV in wild waterfowl so that they can be carried on much longer distances. This is unfortunately helping the spread of the disease and has changed the vision we had of it and of its control. The risk is much higher than before and now is time to discard old dogmas and adapt to this new situation.

In the meantime, fortunately, a new vaccine has been developed that can answer most of the old objections against vaccination. Many experiments have already been conducted with it, and it has shown strong capacities to protect against a wide variety of different H5 type HPAIV as well as to overcome the presence of MDA and be used reliably at the hatchery. These features did not exist for classical vaccines used until now. It is believed that, as of today, with the availability of this new rHVT-HAS vaccine, vaccination can no longer be neglected but needs to be considered as a real tool to protect the poultry industry against clinical and economical losses without impairing the implementation of a truly efficacious disease monitoring system aiming at eradication. Recent experiments have demonstrated the efficacy of this vaccine against circulating HPAIVs of the H5 serotype.

More funds should be dedicated to research on AI vaccines. It is not enough to understand the rain and the ways to control it. It is now time to work more intensively on umbrellas.
References


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It's time to think again about the way we approach the world's health. Animals and humans have never been so dependent and yet so far apart. Whether it’s serving the needs of a pet owner in the world’s growing cities, or a large group working to feed a population of 9 billion by 2050 - the animal health industry has a vital role to play. At Ceva we are committed to meeting these challenges and together, with you, we will help build a healthy New World.

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