New technology vaccines and their application in poultry production

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The quality and performances of vaccines have improved a lot since the pioneer work of Edward Jenner and Louis Pasteur in the 18th and 19th century respectively. Industrial production of classical vaccines based on modified-live or inactivated pathogen agents was initiated in the second half of the 20th century. In 1973, the cloning of a foreign DNA fragment into a bacteria plasmid using restriction enzyme was the start of the rapidly evolving genetic engineering area which led to the modern biotechnology. Thirteen years later (1986), the first 'biotech vaccine' was licensed against human hepatitis B; it was a subunit vaccine produced in yeast and it replaced the first generation vaccine made from plasma of infected patients. In the veterinary field, a vaccinia-vectored vaccine was first licensed in 1994, enclosed into a bait to vaccinate wildlife against rabies. Since then, many new biotech vaccines have been developed, especially for veterinary applications, the most numerous ones being in the poultry sector.

The classical avian vaccines

The classical vaccines are based on the production of the target agent. There are two main types of classical vaccines: modified-live (MLV) and inactivated or 'killed' (KV) vaccines. There are diseases, such as Marek's (MD) and fowlpox (FP), for which MLV vaccines are the only vaccines that can induce sufficient protection, and others, such as avian influenza (AI) and egg drop syndrome (EDS), for which no MLV is available. Both MLV and KV are available for other diseases such as Newcastle (ND), infectious bursal (IBD), and infectious bronchitis (IB) diseases.

These vaccines have been very successful to control diseases in poultry production, but some may have potential limits such as residual pathogenicity or reversion to virulence, short duration of immunity, and extraneous agents contamination for MLV, and local reactions, slow onset of immunity, incomplete inactivation, and parenteral individual administration for KV. Both MLV and KV performances may be decreased due to maternally-derived antibodies (MDA) interference in the young chick, and these classical vaccines may not be compatible with the DIVA (differentiating infected from vaccinated animals) strategy. Biotechnologies have been applied to generate new vaccines that can solve some of the issues related to the classical vaccines.

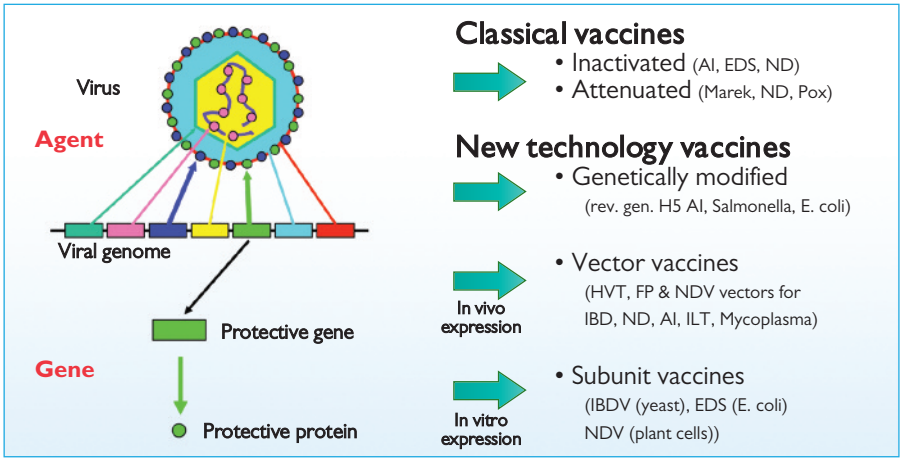

Fig. 1. Schematic representation and examples of the different types of classical and new technology vaccines for poultry.

New types of vaccines

Vaccines based on genetically modified target agents

The different new technology vaccines are shown in Fig. 1. Biotechnologies allow modification of the genome of the pathogenic agents to produce a genetically modified target agent. As an example, the reverse genetics technology is used to genetically attenuate H5N1 highly pathogenic avian influenza viruses that are safer to produce as an inactivated vaccine than the wild type highly pathogenic virus. This technology has also been applied to live bacteria vaccines (for example Salmonella spp. and E. coli) in the genome of which a gene coding for a virulence factor or a factor important for bacteria metabolism has been deleted.

Subunit vaccines

An alternative way to produce new technology vaccines is to focus on the 'protective gene(s)' of the pathogenic agent. Protective genes are genes coding for protein(s) ('protective protein'), which are able to induce a protective immune response. The protective genes of most viruses are known but those of most bacteria or parasites still need to be discovered. Protective genes can be expressed into protective proteins in vitro (in the manufacturing facility) using an expression system. The most widely used expression systems are based on bacteria (mainly E. coli), yeast, insect cells (baculovirus), mammalian cells or plants (plant cells or whole plants). The produced protein is then purified and mixed with an adjuvant to produce a subunit vaccine. Several subunit vaccines have been developed for poultry diseases such as for IBD, EDS and ND, but they are not widely used so far. The properties of these vaccines are similar to those of KV but with no risk of incomplete inactivation. Subunit vaccines induced an immune response focused on the protective antigens only, and not on other irrelevant antigens that are also present in KV.

Vector vaccines

The protective gene(s) may also be inserted into the genome of a vector which will be produced as a vector vaccine. After vaccination, the vector will express in vivo (in the vaccinated animals) the protective gene into the protective protein that will

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induce a protective immune response. The most widely used vectors are viral vectors. Vector vaccines may be bivalent if the vector is itself a live vaccine. They may be replicative (for instance, HVT or fowlpox vectors in chickens) or non-replicative (for instance, canarypox vector in mammals).

Three replicative viral vectors, herpesvirus of turkey (HVT), fowlpox (FP) and NDV vectors, have been developed for poultry and have been licensed against IBD, ND, ILT, AI, and Mycoplasma gallisepticum diseases in at least one country. The performances of these vector vaccines depend on many factors including the target disease, the vector itself, the inserted protective gene, the locus of insertion into the vector genome, and the promoter inserted upstream from the protective gene. The HVT vector has the advantages over FP to be suitable and safe for both in ovo and subcutaneous hatchery administration and to provide a life-long immunity. The market penetration of vector vaccines has been highly variable, the most successful being the HVT-IBD VAXXITEK HVT+IBD, which was launched in 2006 and is being used today in more than 60 countries. Indeed, it allows the three major issues related to classical MLV IBD vaccines to be solved:

- Drinking water vaccination, which is not easy to apply correctly in the field.
- Induction of bursal lesions and consequent immunodepression.
- Presence of an 'immunity gap', a time window in which vaccinated birds are not protected due to MDA-dependent delayed onset of immunity.

This vaccine fully replaces and outperforms all IBD classical vaccines, including the immune complex vaccines that has been developed in the early 1990s for hatchery vaccination and that solved only the first issue of MLV IBD vaccines. The situation is different for HVT-ND vaccines since live ND vaccines are needed to palliate the slow onset of immunity and the absence of local immunity induced by these HVT-based vector vaccines. Similarly, ILT vector vaccines were shown to be safer but less efficacious than classical live CEO vaccines. The multiplicity of licensed vector vaccines poses the problem of compatibility: most licensed HVT-vectored vaccines are not compatible.

The correct handling, preparation, and administration of these vaccines are key factors of success. Some vector vaccines can also be used to prime the immune response before the administration of a classical vaccine. As an example, the immunity induced by a fowlpox-vectored H5 AI vaccine administered at the hatchery followed by a boost with a killed H5 vaccine at the farm was shown to be broader than single or double vaccination with KV.

- **DNA vaccines**

DNA vaccines are another type of vector vaccine: the protective gene is inserted into a plasmid (a small piece of circular DNA) vector, which is produced in E. coli bacteria. After administration, the plasmid DNA penetrates into the nucleus of host cells where the protective gene is expressed. This type of vaccine, which has been licensed for companion animals, may be too expensive to produce for poultry and the efficacy may be lower than the requested level.

- **Chimera vaccines**

Chimera vaccines may also be considered as a type of vector vaccine. So far, only viral chimera vaccines have been described. In chimera vaccines, the vector is a virus which is very similar to the target virus. The protective gene of the target pathogenic agent is replacing the homologous gene of the vector in order to create a chimeric virus. For instance, the yellow fever virus (YFV) has been used as a vector for West Nile virus in horses and is being developed in humans against Dengue. In chickens, chimeric NDV vaccines, in which the protective F gene of a NDV vaccine strain (for instance, the La Sota strain) has been replaced by the modified F gene from a local field isolate (genotype V or genotype VIId), have been recently licensed in Mexico and in Korea, respectively.

Conclusion

Classical MLV and KV have been successful to control most poultry diseases but they have their limits that may be solved by developing new technology vaccines. The most successful type of new technology vaccine in poultry production is the viral vector vaccine. HVT-IBD vector vaccine can fully replace the MLV IBD vaccines and solve their issues of administration, safety and efficacy. HVT-ND and HVT-ILT have improved safety but their efficacy is not at the level of classical vaccines. A combination of new and classical vaccine technologies may provide optimal immunity.

Future research on biotech vaccines should be focused on solving the current problems observed with the use of theses vaccines and, in particular, their compatibility, the lack of induction of local immunity, and the slow onset of immunity.

The challenge of poultry veterinarians will be to understand how these new vaccines are working and performing in the field and to find the optimal vaccination program including both new technology and classical vaccines adapted to the epidemiologic situation of the poultry farms. ■

References are available from the author on request