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Making Avian Influenza Vaccines Available, an Industry Point of View (IFAH)

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Abstract: Vaccination against avian influenza (AI) has proved to be an efficient tool in the reduction of virus excretion and in increasing the threshold for infection. Vaccination in outbreaks, as part of a complete programme, has proved to be an essential component of control and eradication programmes.

Avian influenza is a serious threat to public health. In contingency plans for outbreaks of highly pathogenic AI (HPAI), the option of emergency vaccination, using inactivated or recombinant vaccines, should be considered. The availability of suitable vaccines has to be ensured in 'peace time' in a contract for a vaccine or antigen bank.

Unlike the human influenza vaccines, poultry AI vaccines have proved to provide protection against a wide range of strains within the same H-subtype. However, in case new H5 or H7 strains emerge in poultry, there is no regulatory guideline to support a swift reaction by the vaccine industry.

Production of HPAI virus should take place in facilities with a Biosafety Level 3 (BSL3) to safeguard containment of virus and to prevent infection of manufacturing staff. Vaccine strains for inactivated vaccines should preferably be low pathogenicity AI (LPAI).

In a new outbreak, it is essential to determine early which vaccine strain will provide protection against the field virus. Sequencing does not predict the protective capacity of vaccines. Challenge studies, providing essential information, take too much time and can be carried out only in BSL3 facilities. Serological matching of vaccine and field strains would provide a faster system. It is recommended that a matching system be developed and validated.

IFAH

IFAH is the International Federation for Animal Health representing manufacturers of veterinary medicines, vaccines and other animal health products in both developed and developing countries across five continents.

INTRODUCTION

The primary goal of the battle against avian influenza (AI) is to eradicate the disease. In countries where the disease is endemic, eradication might not be feasible in the short term and control of the disease might have to be the first step

towards eradication. Stamping out [1], vaccination [2] or a combination of these have proved to be essential tools in an eradication strategy. Once eradication has been achieved, it is of prime importance to prevent re-introduction.

VACCINES AND THEIR EFFICACY

Several vaccines are available in the market: inactivated vaccines; recombinant fowl pox H5 vector; combination vaccines of two AI strains [3]; and combination vaccines against AI and Newcastle disease. Vaccines, as part of an overall strategy against AI, have proved to be efficient in the control and eradication of AI.

Inactivated vaccines protect against clinical disease and mortality and, more importantly, reduce the ability of the AI virus to replicate in chickens, resulting in decreased excretion of virus after challenge [4]. Vaccination, in addition to quarantine, depopulation and biosecurity measures, was applied in the face of an outbreak in Hong Kong [5]. In two farms, the infection spread to vaccinated sheds with low rates of H5N1 mortality; the chickens were between nine and 18 days post-vaccination. After 18 days post-vaccination, no more H5N1 mortality occurred and intensive monitoring showed no evidence of asymptomatic virus shedding. It is concluded that this is an important aspect when dealing with a virus, which poses a significant risk to human health.

Inactivated vaccines can be used at all ages. Protection starts to develop at two weeks after vaccination and reaches a maximum from three weeks after vaccination. For a long duration of immunity, revaccination is recommended.

Recombinant fowlpox vaccine, containing an H5 influenza haemagglutinin gene insert, protected chickens against clinical signs and death following challenge with nine different field viruses [6]. The vaccine reduced detectable infection rates and shedding titres. There was a significant positive correlation in haemagglutinin sequence similarity between challenge viruses and vaccine, and the ability to reduce titres of challenge virus isolated from the oropharynx, but no similar correlation for reducing cloacal virus titres. The recombinant fowlpox vaccine is injected at day 1 and is typically indicated for vaccination of replacement birds.

MONITORING OF INFECTION IN VACCINATED FLOCKS

As long as AI virus circulates, the chance exists of a strain emerging that is infectious and pathogenic for people, carrying with it the risk of a new global influenza pandemic. Virus detection, in combination with measures to control virus circulation, is therefore essential. Although there is significantly less excretion of virus from vaccinated birds, circulation can still occur and it is important to monitor this.

Sentinel birds

A number of birds in the flock are left unvaccinated. The sentinel birds will show morbidity/mortality immediately when highly pathogenic AI (HPAI) is circulating in the vaccinated flocks. Sentinel birds will show antibodies if low pathogenicity AI (LPAI) virus is in circulation in a vaccinated flock.

DIVA approach

Differentiating infected from vaccinated animals (DIVA) is possible through the use of a vaccine that contains a neuraminidase (NA) that is different from that of the field strain [7]. Antibodies against the neuraminidase of the field virus indicate infection. This approach generally is combined with the use of sentinel birds.

Non-structural protein (NS) test

Conventional inactivated vaccines induce antibody titres against non-structural proteins that are considerably lower than the antibody titres after infection [8]. Field sera from poultry, vaccinated with commercial AI vaccines, were positive for antibodies in the Agar Gel Precipitin (AGP) test but negative on the NS1 Elisa. Sera from infected poultry were positive for both AGP and NS1 antibodies.

Serological methods for recombinant fowlpox vaccine

The vaccine only expresses the haemagglutinin of the AI virus and does not interfere with antibody tests against other antigens of the AI virus. As a result, a wide range of diagnostic methods can be used: classical AGP or nucleoprotein- or matrix-based ELISA, NA- and NS-based tests.

EVOLUTION OF AI STRAINS AND NECESSITY FOR VACCINE UPDATES

Avian influenza virus does not seem to undergo frequent antigenic drift. In a challenge study with inactivated vaccines, vaccinated birds were challenged with North American viruses isolated over a period of 27 years from separate geographical areas. In this study, there was no positive correlation between the genotype (haemagglutinin) of the vaccine and challenge strain and the ability of the vaccine to reduce the quantity of virus shedding from the cloaca and oropharynx [9].

The recombinant fowlpox vaccine also provided good protection against a wide range of challenge viruses [6]. There was a significant positive correlation in haemagglutinin sequence similarity between challenge viruses and vaccine, and the ability to reduce titres of challenge virus isolated from the oropharynx but no similar correlation for reducing cloacal virus titres.

The evolution of the Mexican field virus seems to show signs of antigenic drift [10]. Serologic analysis using the haemagglutination inhibition test and virus neutralisation tests showed major antigenic differences among isolates belonging to different sub-lineages. These results were confirmed in vaccine protection studies, which demonstrated that the vaccine used was not able to prevent virus shedding when chickens were challenged with antigenically different isolates.

Clearly the antigenic evolution of human influenza viruses is more rapid than that of the avian influenza viruses. Potential reasons might be: differences in the human and avian population; differences in the vaccine antigen and adjuvants between human and avian vaccines.

In spite of the low tendency for antigenic evolution of avian influenza virus, it is essential for vaccine efficacy to monitor the antigenic match between vaccine- and field-virus. At this moment, challenge studies are the model to test for antigenic variation, and the most important criterion is the ability of the vaccine to reduce virus shedding. Challenge has to be carried out in BSL3 facilities and requires time for the planning, preparation and virus isolation.

It is recommended that further research is done towards development of a model of serological matching that correlates with virus shedding after challenge. Such a system is used for Foot and Mouth Disease and is a fast and convenient method for matching field- and vaccine-virus.

CONTAINMENT OF AI VIRUS PRODUCTION

The OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (Appendix I.1.6.1.) describes the regulations for “International Transfer and Laboratory Containment of Animal Pathogens”. HPAI is a list A disease with potentially serious public health implications. Fully virulent HPAI virus should therefore only be handled in a BSL3 laboratory and vaccine production from HPAI strains must be in high containment facilities.

Because of the possible negative consequences, both for the poultry industry and public health, production of commercial inactivated vaccines should be based on LPAI production strains, which require normal containment standards for vaccine production.

EMERGENCY PREPAREDNESS

There is no proper regulatory framework for licensing emergency vaccines. For example, in Europe, emergency vaccines can be used under article 8 of the EU Directive for licensing [11]. In the event of a serious disease epidemic, a country may decide to use a non-licensed product. However, there is no regulation or guidance on the conditions for such a decision.

In countries free of a serious disease, there is generally a non-vaccination policy. In countries with a non-vaccination policy, which would only consider limited use of vaccines in case of an outbreak, there is no justification for a commercial company to invest in full-scale development and licensing of a vaccine. Emergency vaccination is included in most contingency plans and the availability of a licensed vaccine would greatly facilitate the political decision to use vaccination.

It is recommended that special and simplified legislation be developed for vaccines that are only used in case of emergency. Alternatively, governments should support the industry financially to fully license emergency vaccines.

There is no regulatory framework in the veterinary field for a speedy update of influenza vaccine strains. For every vaccine strain and for every update of the vaccine strain, a new registration is required. It is recommended that legislation is developed that allows, as is the case for human influenza vaccines, a speedy update of vaccine strains, should the need arise.

If vaccination is seen as an option in contingency plans, the availability of vaccines needs to be addressed. It is recommended that the availability of vaccines is arranged in a contract between the government and the industry in “peace time”.

REFERENCES

1 Stegeman A, Bouma A, Elbers AR, de Jong MC, Nodelijk G, de Klerk F, Koch G, van Boven M: Avian influenza A virus (H7N7) epidemic in The Netherlands in 2003: Course of the epidemic and effectiveness of control measures. *J Infect Dis* 2004; 190: 2088-2095.

- 2 Capua I, Marangon S: The use of vaccination as an option for the Control of Avian Influenza. 71st General Session of the International Committee of the World Organisation for Animal Health, Paris, 18-23 May 2003. http://www.oie.int/download/71SG_2003/A_71%20SG_12_CS3E.pdf.
- 3 EU Commission Decision of 29 September 2004 on introducing vaccination to supplement the measures to control infections with low pathogenic avian influenza in Italy and on specific movement control measures and repealing Decision 2002/975/EC. EU Commission Decision 2004/666/EC.
- 4 Swayne DE, Beck JR, Perdue ML, Beard CW: Efficacy of vaccines in chickens against highly pathogenic Hong Kong H5N1 Avian Influenza. *Avian Dis* 2001; 45: 355-365.
- 5 Ellis TM, Leung CYHC, Chow MKW, Bissett LA, Wong W, Guan Y, Peiris MJS: Vaccination of chickens against H5N1 avian influenza in the face of an outbreak interrupts virus transmission. *Avian Path* 2004; 33 (4): 405-412.
- 6 Swayne DE, Garcia M, Beck JR, Kinney N, Suarez DL: Protection against diverse highly pathogenic H5 avian influenza viruses in chickens immunized with a recombinant fowlpox vaccine containing an H5 avian influenza hemagglutinin gene insert. *Vaccine* 2000; 18: 1088-1095.
- 7 Capua I, Terregino C, Cattoli G, Mutinelli F, Rodriguez JF: Development of a DIVA (Differentiating Infected from Vaccinated Animals) strategy using a vaccine containing a heterologous neuraminidase for the control of avian influenza. *Avian Path* 2002; 32: 47-55.
- 8 Tumpey TM, Alvarez R, Swayne DE, Suarez DL: Diagnostic approach for differentiating infected from vaccinated poultry on the basis of antibodies to NS1, the non-structural protein of influenza A virus. *J of Clin Microbiol* 43 (2): 676-683.
- 9 Swayne DE, Beck JR, Garcia M, Stone HD: Influence of virus strain and antigenic mass on efficacy of H5 influenza inactivated vaccines. *Avian Path* 1999; 28: 245-255.
- 10 Lee CW, Senne D, Suarez DL: Effect of vaccine use in the evolution of Mexican lineage H5N2 avian influenza virus. *J Virol* 2004; 78 (15): 8372-8381.
- 11 Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products. EU Commission Directive 2001/82/EC.

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