HIGHLY PATHOGENIC NOTIFIABLE AVIAN INFLUENZA (HPNAI): “A REVIEW ON CONTROL OPTIONS”

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ABSTRACT
Avian Influenza, now coined with a new term “Highly Pathogenic Notifiable Avian influenza” (HPNAI) caused by viruses belongs to family Orthomyxoviridae, ruined the poultry industry in its outbreaks in various parts of the world. Apart from a serious, devastating menace to poultry industry “Avian Influenza” represents one of the major recent concerns for public health with the emergence of a dreaded virus’s strain i.e. H5N1, among other strains, to which human health shows vulnerability. Emergence of H5N1 from animal reservoir stirred up veterinarians, public health officials, and industrial circuit to cope with and eradicate it in its preliminary stages in target compartments by stamping out policy mainly of infected flocks, which was the first recommended control option and has been followed in most of the affected zones of the world. Along with stamping out policy to eradicate the disease completely from affected zones, strict biosecurity measures (encompassing bioexclusion and biocontainment) represents the first and most important means of prevention. If biosecurity measures of high standard are implemented and maintained, they create a firewall against infection penetration in the industrial circuit. However, breaches in biosecurity systems may occur. In such case, vaccination against AI can’t be underestimated. Vaccination has shown to increase resistance to field challenges, reduce virus shedding levels and transmission. All these measures along with effective vaccination contribute to controlling AI. However, experience has shown that, for successful controlling and eradication of the infection, vaccination programs must be part of a wider control strategy. Effective vaccination programme can be operated with quality Conventional vaccines (Inactivated homologous vaccines, inactivated heterologous vaccines) and Recombinant vaccines.

Emergency vaccination for AI has become an acceptable tool, in conjunction with other measures, for combating the spread of AI. Using emergency vaccination to reduce the transmission rate could provide an alternative to preemptive culling to reduce the susceptibility of healthy flocks at risk. Subsequently, a "Differentiation of Infected from Vaccinated Animals" (DIVA) strategy was used by Hong Kong to prevent the introduction of H5N1 into its territories. Although use of a DIVA system enabled international trade of poultry products to continue vaccination for AI is a new concept, which several countries are reluctant to even consider. Therefore vaccination can be a powerful tool to support eradication programs if combined with other control methods against “AI” to impede the flaring up of new pandemic virus to safeguard the human beings at stake.

KEYWORDS: Avian, influenza, infection, virus, chicken, pathogenic, flocks

INTRODUCTION
Notifiable avian influenza (NAI) is caused by infection with viruses of the family Orthomyxoviridae placed in the genus influenza virus A. Influenza A viruses are the only orthomyxoviruses known to affect birds.
Many species of birds have been shown to be susceptible to infection with influenza A viruses; aquatic birds form a major reservoir of these viruses, but the overwhelming majority of isolates have been of low pathogenicity for chickens and turkeys, the main birds of economic importance to be affected. Influenza A viruses have antigenically related nucleocapsid and antigenically related matrix proteins, but are classified into subtypes on the basis of their haemagglutinin (H) and neuraminidase (N) antigens (WHO 1980). At present, 16 H subtypes (H1–H16) and 9 N subtypes (N1–N9) are recognised. To date, the highly virulent influenza A viruses that produce acute clinical disease in chickens and turkeys have been associated only with the H5 and H7 subtypes (with the exception of two H10 subtypes that would also have fulfilled the above definition for HPNAI, although the reasons for this are not clear). Many viruses of H5 and H7 subtype isolated from birds have been of low virulence for poultry (Alexander 1993). Due to the risk of H5 or H7 virus of low virulence becoming virulent by mutation, all H5 and H7 viruses have been identified as notifiable avian influenza (NAI) viruses (OIE 2005).

Avian influenza (AI) represents one of the greatest recent concerns for public health. The reported number of outbreaks of AI in poultry for the last 40 years has increased sharply during the past 5 years. The number of birds involved in AI outbreaks has increased 100-fold, from 23 million from 1959 through 1998 to >200 million from 1999 through 2005. Since in late 1990s, AI infections have assumed a completely different profile in veterinary and medical communities. Some recent outbreaks have been minor, but other epidemics, such as the Italian 1999–2000, the Dutch 2003, the Canadian 2004, and the ongoing Eurasian, have been more serious. They have led to devastating consequences for the poultry industry, negative repercussions on public opinion, and in some instances, created major human health issues, including the risk of generating a new pandemic virus for human through an avian-human link.

Much of the current understanding of AI (and the recommendations of international organizations) is based on information from temperate climates, such as Europe and North America. Although there is much that is useful and applicable in this information, poultry production systems differ significantly in Asia, and these differences must be taken into account while designing and implementing surveillance and diagnostic systems. The severity of clinical signs depends on the pathotype of the influenza virus and in poultry, influenza A viruses are divided into two distinct groups on the basis of their ability to cause disease (Swayne and Halvorson 2003). The virulent serotypes cause highly pathogenic avian influenza which can result in flock mortality of 100% (Capua and Alexander 2004).

**Control Options**

**Adoption of the most appropriate control strategies:**

**Basic Principles**
The strategy adopted by governments concerning their countries, zones or compartments is determined by the perceived importance of the disease politically, socially and economically. Issues that must be considered include public health, economics, sustainability of farming enterprises and adverse publicity associated with repeated outbreaks of the disease. FAO recommends that the following items be addressed in all control programmes for HPAI:

- HPAI is notifiable; appropriate penalties for non-compliance are considered.
- If “stamping out” is used, farmers are compensated in some form (direct or indirect) for loss of stock.
- Probity and accountability in government decision-making and use of public funds.
- Effective surveillance and reporting to OIE according to member country obligations.

It is likely that the policies adopted to control HPAI will vary over time. FAO recommends that disease control strategies be developed iteratively, in light of experience, advances in scientific knowledge, changes in international standards and evolution of the disease situation.
For example, a country that embarks on eradication after the first incursion of virus may add vaccination as an additional control measure if repeated incursions occur or appear to be inevitable, thus providing additional protection for its commercial poultry. The response to detection of infection or disease should also vary with the local situation. In a country where infection is endemic and vaccination is practiced, FAO recommends that the detection of virus in domestic waterfowl not automatically lead to the destruction of the infected flock. This is particularly the case if the positive result is obtained as part of a planned surveillance programme that is designed to assess the prevalence of infection. The decision on disposition of the infected birds should be based on an assessment of the risk to human and public health and the economic costs, and benefits, of maintaining the flock. On the other hand, a country that is free of HPAI infection would normally destroy all poultry found to be infected.

**Disease Control**
Countries or compartments with high levels of infection may approach control in a progressive manner, first reducing the level of infection before moving to eradication. This may include the use of vaccine. Enhanced targeted surveillance must be part of an official vaccination programme and will provide a better understanding of the risk faced if/when vaccination is withdrawn. It is essential to have a good understanding of the nature and extent of reservoirs of infection before embarking on a programme of HPAI eradication.

**Disease Eradication**
Although it is possible to eradicate specific AI viruses (including H5N1 viruses) from compartments or countries and keep them free of disease for extended periods of time, it seems to be impossible to eradicate H5N1 HPAI virus from the entire Asian region in the near future. This means that countries or compartments that are free of infection and those that do eradicate the virus will continue to be at risk of re-infection and will be obliged to implement measures to prevent viral incursion. In the case of a new occurrence of infection in country or compartment that is historically free of HPAI, eradication is an appropriate immediate objective. Particularly for countries such as Japan and South Korea, which are historically HPAI-free and located at a distance from infected countries, this strategy is feasible. The investment of resources in active surveillance, enabling early detection of incursions and quick implementation of control measures greatly improves the prospect of eradication. FAO recommends that the system for management of disease incursions be based on systematic contingency planning, including the conduct of disease simulation exercises. In developing strategies for the control and eradication of HPAI, FAO recommends that governments conduct a risk assessment, taking into account the likelihood of re-infection and the economic costs and benefits of implementing the strategies needed to mitigate these risks.

**Developing a Vaccination Element in a Control Strategy**
The main objectives of vaccination are to reduce the production losses caused by the disease, to reduce the risk of spread of AI virus to animals and humans by reducing the shedding of viruses in the environment, to create (by way of vaccine induced immunity) barriers between infected and free areas/compartments and to help in the control and eradication of the disease. Several measures must be used in combination to control or prevent this disease. If vaccination is adopted, it must be used in conjunction with the other measures. It is difficult to prescribe a set of rules for vaccination of poultry against HPAI that cover all situations.

**Rationale behind vaccine**
Until recently, AI infections caused by viruses of the H5 and H7 subtype occurred rarely, and vaccination was not considered because stamping out was the recommended control option. Primarily for this reason, vaccinology for AI has not grown at the same rate as for other infectious diseases of animals. Data is being generated from experimental and field research in AI vaccinology, but the rather complex task of vaccinating poultry in different farming and ecologic environments still has areas of uncertainty. Vaccination can be a powerful tool to support eradication programs if used with other control methods. Vaccination has been shown to increase resistance to field challenges, reduce shedding and transmission levels in vaccinated birds (Capua I 2004), (Van Der 2005).
All these effects of vaccination contribute in controlling AI; however, experience has shown that, to be successful in controlling and ultimately in eradicating the infection, vaccination programs must be part of a wider control strategy that includes biosecurity and monitoring the evolution of infection. Vaccination against AI has proven to be a successful additional control measure implemented alongside controlled culling (Italy (H7N1 & H7N3), Mexico (H5N2), Pakistan (H7N3), Hong Kong (H5N1), Vietnam (H5N1) and Indonesia (H5N1)). In 2004 the FAO, OIE and WHO issued a joint statement that called for a targeted strategy, including poultry vaccination, to help curb AI in Asia.

The expected advantages of vaccination policy are two fold. Firstly, vaccination reduces susceptibility to infection, a higher dose of virus is necessary for establishing an infection in vaccinated birds. Secondly there is a significant reduction in the amount of virus shed by infected birds, thus less virus to contaminate the environment and thus reducing the risk of spread to other avian species and occupational risk faced by poultry workers. (Reducing the incidence of human infections reduces the chance of the AI strain mutating and the possible emergence of a new human influenza strain.) Reducing the amount of avian virus allowed to multiply in poultry also reduces the likelihood of mutations caused by random errors in transcription. Consistent with the Recommendations of FAO/OIE/WHO conferences held in Bangkok and Rome, in February 2004, vaccination can be used as a tool to support eradication or to control disease due to HPAI and to reduce the viral load in the environment. In situations where it may not be feasible or desirable to proceed with massive culling and in situations of high viral challenge, targeted vaccination may be the most appropriate means of 'dampening down' an HPAI outbreak.

Research is required to define more clearly the movement patterns of wild birds, including migratory pathways, to assess the risk of HPAI outbreaks in poultry arising from these birds. There is a need for studies to document and analyze the market flows of poultry and other avian species in Asia to help understand the movement of birds/products and their associated viruses. The need arises from reports that some village chickens apparently survived outbreaks, but it is not clear if they actually infected with or without clinical signs and then recovered, or whether the survivors were escaped infection.

**Emergency vaccination**

Recent outbreaks in developed countries, notwithstanding their efficient veterinary infrastructures and modern diagnostic systems, have resulted in the culling of millions of birds. Since the year 2000, AI epidemics in areas densely populated with poultry have resulted in 13 million dead birds in Italy in 1999–2000 (H7N1), 5 million dead birds in the United States in 2002 (H7N2), 30 million in the Netherlands in 2003, and 17 million in Canada in 2004. For each of these episodes, bio-security measures implemented at the farm level were found insufficient to prevent massive spread of AI. Emergency vaccination for AI has become an acceptable tool, in conjunction with other measures, for combating the spread of AI. Using emergency vaccination to reduce the transmission rate could provide an alternative to preemptive culling to reduce the susceptibility of healthy flocks at risk. The effectiveness of such a program depends on variables such as the density of poultry flocks in the area, level of bio-security and its integration into the industry, characteristics of the virus strain involved, and practical and logistical issues such as vaccine availability and adequate and speedy administration. For this reason, contingency plans that include decision-making patterns under different scenarios should be formulated. Pivotal work on emergency vaccination has been done in Italy. Application of the DIVA (Differentiation of Infected from Vaccinated Animals) strategy has resulted in the approval of the use of vaccination as an additional tool for the eradication of 2 epidemics of LPAI i.e. low pathogenic avian influenza (H7N1 and H7N3) without massive preemptive killing of animals. Vaccination complemented restriction measures already in place and was integrated into an intensive monitoring program that identified viral circulation in the area (Capua et al 2001) and culled infected birds. In 2000, heterologous vaccination against an H7 virus was used for the first time in the field as a natural marker vaccine. Subsequently, a DIVA strategy was used by Hong Kong to prevent the introduction of H5N1 into its territories. Although use of a DIVA system enabled international trade of poultry products to continue (Capua et al 2001), (OIE 2004) vaccination for AI is a new concept, which several countries are reluctant to even consider.
Government authorities ultimately decide whether vaccination should be used in a given country; their reluctance is probably driven by legislative and scientific uncertainties, coupled with doubts about how this practice will be used in the field. With reference to trade implications, a new chapter of the OIE Terrestrial Animal Health Code on AI enables the continuation of trade in presence of vaccination if the exporting country is able to produce surveillance and other data that confirm that notifiable avian influenza is not present in the compartment from which the exports come. Extensive work has been done by OIE experts and the OIE Central Bureau on the issue of reducing the effect of animal diseases through the use of vaccination which is contained in a recommendation document issued as a result of an international conference held in Buenos Aires (April 14–17, 2004) that strongly supports the use of vaccines for diseases on list A (OIE 2004).

Currently available vaccines

Conventional Vaccines

Inactivated Homologous Vaccines: These vaccines were originally prepared as ‘autogenous’ vaccines, i.e. vaccines that contain the same AI strain as the one causing problems in the field. They have been used extensively in Mexico and Pakistan during the AI epizootics (Bread et al 1991). The efficacy of these vaccines in preventing clinical disease and in reducing the amount of virus shed in the environment has been proven through field studies and experimental trials (Webster et al 1996). The disadvantage of this system is the impossibility of differentiating vaccinated from field-exposed birds unless unvaccinated sentinels are kept in the shed. However, the management (identification, bleeding and swabbing) of sentinel birds during a vaccination campaign is time-consuming and rather complicated, as they are difficult to identify and they may be substituted with seronegative birds in the attempt to escape the restrictions imposed by public health officials.

Inactivated Heterologous Vaccines: These vaccines are manufactured in a similar way to inactivated homologous ones. They differ in that the virus strain used in the vaccine is of the same H type as the field virus but has a heterologous neuraminidase. Following field exposure, clinical protection and reduction in viral shedding are ensured by the immune reaction induced by the homologous H group, while antibodies against the neuraminidase induced by the field virus can be used as a marker of field infection (Capua et al 2000). For both homologous and heterologous vaccines, the degree of clinical protection and the reduction in viral shedding are improved by a higher antigen mass in the vaccine (Swayne et al 1999). For heterologous vaccines the degree of protection is not strictly correlated to the degree of homology between the haemagglutinin genes of the vaccine and challenge strains (Swayne et al 2000). This is definitely a great advantage as it enables the establishment of vaccine banks because the master seed does not contain the virus that is present in the field and may contain an isolate (preferably of the same lineage) available before the epizootic.

Recombinant Vaccines

Several recombinant fowlpox viruses expressing the H5 antigen have been developed (Bread et al 1991, 1992, Swayne et al 1997, 2000, Webster et al 1996) and one has been licensed and is being used currently in Mexico (Swayne et al 2000). Experimental data have also been obtained for fowlpox virus recombinants expressing the H7 antigen (Boyle et al 2000). Other vectors have been used to successfully deliver the H5 or H7 antigens, such as constructs using infectious laryngotracheitis virus (ILTV). The only field experience with a recombinant virus to control AI has been obtained in Mexico, where it has been used in the vaccination campaign against a LPAI H5N2 virus. No such product has been licensed in the EU to date.

Discussion

The scientific veterinary community must control AI infections in poultry for several reasons: to manage the pandemic potential, to preserve profitability of the poultry industry, and to guarantee food security to developing countries. Although biosecurity is recognized as an excellent means of preventing infection, in certain situations the biosecurity standards necessary to prevent infection are difficult to sustain. Vaccination is a potentially powerful tool for supporting eradication programs by increasing the resistance of birds to field challenge and by reducing the amount and duration of virus shed in the environment.
Vaccination strategies that encompass monitoring of infection in the field are crucial to the success of such efforts. Timely information is needed about the efficacy of vaccination in a variety of different avian species, bearing in mind the diverse farming systems used in developed and developing countries. The outcome of such efforts should be made available to the international community because decision makers lack enough information to make educated choices. An enormous effort is required from national governments and funding bodies to make resources available to research programs to develop improved control measures that can be applied under different local conditions. In determining the strategy for control of H5N1 HPAI, all available control measures should be considered and those that are feasible and likely to be cost effective in the local situation should be adopted. The selection of measures should be based on risk assessment and a thorough understanding of the HPAI status in the country or compartment. Stamping out and vaccination are not mutually exclusive. Targeted vaccination has considerable value as part of a phased response strategy, allowing veterinary authorities to bring infection under control as a preliminary step on the road to eradication in specified compartments or the entire country, as appropriate to the circumstances.

Conclusion
In conclusion, recent events including devastating epizootics in densely populated poultry areas, public health concern on animal welfare issues and the introduction of novel technology to vaccinology have encouraged consideration of alternative control strategies for OIE List A diseases that were unthinkable only a few years ago. This has also been supported by the development of reliable, sensitive and specific diagnostic companion tests. Countries, areas and enterprises at risk of infection should imperatively implement surveillance programmes and have contingency plans in case of a disease outbreak, which may include vaccination. If the latter is considered as an option, the contingency plan must, among other issues, foresee the establishment of licensed vaccine banks that enable the ‘DIVA’ strategy to be enforced thus safeguarding animal health, animal welfare and international trade. The application of the different control options, which may include vaccination, should be used in different ways on the basis of the characteristics of the poultry producing sector in its entirety, the eco-epidemiological situation, the response capacity of the veterinary infrastructure and the availability of adequate resources. Previous experiences have indicated that in order to succeed in controlling and ultimately in eradicating the infection, vaccination programmes must be part of a wider territorial strategy. This strategy must include monitoring the evolution of infection (DIVA approach), early detection of any possible outbreaks, and enforcement of adequate biosecurity, restriction and eradication measures. Whenever such a strategy, as a whole cannot be implemented, the establishment of an endemic status due to sub-clinical virus circulation in the vaccinated poultry population cannot be ruled out.

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