The role of vaccines and vaccination in high pathogenicity avian influenza control and eradication

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"The eradication of H5N1 high pathogenicity avian influenza has been more complex than the other 29 high pathogenicity avian influenza epizootics because it has involved multiple countries, affected more diverse types of poultry production systems, infected wild birds and had a major public health element."

Thirty epizootics of high pathogenicity avian influenza (HPAI) or fowl plague have occurred in poultry and other birds in the world since influenza virus was discovered to be the etiological agent of the disease in 1955 [1]. The largest epizootic of the past 50 years was the H5N1 panzootic, which began in the Guangdong province of southern China in 1996 and has since spread to affect 63 countries, resulting in the death or culling of over 250 million poultry and wild birds. Twenty four epizootics were eradicated using a four-component stamping-out strategy that included education, biosecurity, rapid diagnostics and surveillance, and elimination of infected birds. However, the inability of the stamping-out strategy to eradicate H5N2 HPAI in Mexico and H7N3 HPAI in Pakistan during 1994–1995 challenged the dogma of immediate eradication being achievable under all national political structures, poultry production systems, economic conditions and HPAI outbreak situations using traditional eradication methods [2]. Therefore, Mexico and Pakistan initiated the use of a fifth control component, increasing resistance of poultry to HPAI viruses by vaccination, which had been used previously to control low pathogenicity avian influenza (AI) in the USA and Italy [3–6]. More recently, vaccines for HPAI control have been utilized in the Democratic People's Republic of Korea against H7N7 HPAI (2005) and in 13 of the 63 countries affected with H5N1 HPAI (1996 to present) [2]. Although the H5N1 HPAI panzootic continues, the H5N2 Mexican, H7N3 Pakistani and H7N7 Korean HPAI epizootics have ended. The recent Chinese Taipei (H5N2; 2012) and South African (H5N2; 2011) epizootics are nearing eradication using stamping-out programs only.

The ability to eradicate HPAI is influenced by the competency of the governmental veterinary medical authority, the density of poultry within the country and the level of governmental participation [7,8]. The eradication of H5N1 HPAI has been more complex than the other 29 HPAI epizootics because it has involved multiple countries, affected more diverse types of poultry production systems, infected wild birds and had a major public health element. The latter aspect has involved 607 hospitalized cases with 358 deaths, and the H5N1 HPAI virus has the potential to become a future pandemic virus [101]. This public health aspect resulted in mobilization of a global effort to eradicate H5N1 HPAI from poultry, but the veterinary infrastructure and finances have not been adequate to conduct an effective stamping-out campaign in all countries [8]. Therefore, vaccination was administered in order to decrease bird susceptibility to infection,

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reduce the number of birds infected and their subsequent deaths, and decrease the amount of HPAI virus shed into the environment, thereby reducing transmission to both birds and humans. This new strategy has prevented disease and death in poultry and allowed maintenance of rural livelihoods and food security within affected countries [9,10]. Such a strategy has bought time to restructure poultry production systems and veterinary services to work towards a long-term goal of H5N1 HPAI eradication. Vaccines have been primarily used in some developing and transition countries, but with less usage in developed countries.

Between 2002 and 2010, 113.98 billion doses of AI vaccine were used to protect an at-risk national poultry population of 131 billion (41.9% coverage rate) in 15 countries from HPAI and were comprised of 95.5% inactivated vaccines administered by injecting individual birds and 4.5% live recombinant vectored vaccines administered by mass application – that is, spray [2]. The majority were used in four countries affected by enzootic H5N1 HPAI and were applied in nationwide campaigns to protect poultry in commercial, semicommercial and village production systems. China, the world's largest poultry producer and consumer, has used the most H5 vaccine (103.72 billion doses; 90.99%), followed by Egypt (5 billion doses; 4.65%), Indonesia (2.6 billion doses; 2.32%) and Vietnam (1.6 billion doses; 1.43%). Vaccine usage began after H5N1 HPAI became enzootic in poultry populations. The remaining ten countries or regions had minor usage of vaccine, accounting for less than 0.7% of the total, and the vaccine was used in targeted vaccination programs to high-risk poultry either as a preventative measure, or as a management tool during eradication. The percentage of vaccine usage in least developed, developing/transition and developed countries is as follows: Russia (0.37%), Pakistan (0.12%), Hong Kong Special Administrative Region (0.08%), Kazakhstan (0.03%), Côte d'Ivoire (<0.01%), Democratic People's Republic of Korea (<0.01%; H7N7 HPAI only), France (<0.01%), Israel (<0.01%), Mongolia (<0.01%), The Netherlands (<0.01%) and Sudan (<0.01%).

> "…since 2006, some field viruses in H5N1 enzootic countries have not been protected by one or more H5 vaccines."

Vaccine for the H5N1 panzootic was initially administered in Hong Kong (2002), followed by Indonesia (2003) and Mainland China (2004). Initially, poor vaccine quality and inadequate manufacturing capacity were major limitations to implementing effective field vaccination programs, but vaccines have improved in quality and efficacy over past decade, with manufacturing capacity exceeding demand by the end of 2006. Currently, reserve vaccine manufacturing capacity is available, primarily in China. The available vaccines have utilized seed strains shown in multiple experimental studies to be efficacious against H5N1 field viruses [11,12]. However, since 2006, some field viruses in H5N1 enzootic countries have not been protected by one or more H5 vaccines [12–14]. This need for changes in vaccine seed strains has been met by development, licensing, manufacturing and field application of vaccines based on reverse genetic (rg) seed strains containing the hemagglutinin gene of relevant field viruses that have been altered to be low virulence. China has lead this effort with commercialization of vaccines with four different rg vaccine seed strains, and all vaccine manufactured in China since late 2006 have utilized rg seed strains [15]. In the majority of situations, the vaccine seed strains have matched the circulating field viruses and provided good protection. However, vaccination has not been a panacea for eradication of H5N1 HPAI, not because of vaccine seed strain failures, but because of inability to obtain population immunity in susceptible poultry species [16,17]. The principle issue has been logistical – that is, inability to organize and vaccinate all at-risk poultry populations, especially in the numerous small farm and village poultry, which predominate in developing countries. For example, in two mass campaigns to vaccinate village and small farm poultry in Egypt and Indonesia, only 20–40% were vaccinated. However, even in a developed country, The Netherlands, vaccination was difficult with only 0.07–0.27% of hobby poultry being vaccinated [2,18,19].

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Vaccine usage rates have varied in individual countries with the highest being almost 100% in Hong Kong after full implementation of vaccination in 2004 [2]. Hong Kong achieved poultry population immunity to H5N1 HPAI, which is emphasized by having only one outbreak of H5N1 (one farm) since 2004, an antigenic variant clade 2.3.4 H5N1 HPAI virus that overcame vaccinal immunity [102]. Unfortunately, China, Egypt, Vietnam and Indonesia have not consistently attained the 60–80% vaccine coverage rate necessary to achieve national population immunity. For each year, the individual country vaccination coverage rates ranged from 11.1 to 83.3%, depending on population estimates of village and small farm poultry. These production sectors are logistically the most difficult to implement vaccination programs. For example for 2006–2010, the average vaccine coverage rate in Egypt was 69.9% based on World Organization for Animal Health production numbers, but only 27.8–48.6% when based on higher small farm and village poultry estimates of the Egyptian Ministry of Agriculture [2]. By contrast, the ten nonenzootic countries/regions used targeted vaccination strategies, which translated into lower national vaccine coverage rates (<15%), but these programs have been more effective and have resulted in elimination of vaccine usage or greatly reduced usage. Although these coverage rates fall short of the 60–80% vaccine coverage rate to have national population immunity, their targeted approach to one or more subsets of poultry populations, based on risk assessment and reliable surveillance data, achieved immunity in the at-risk population:

- Eradication in France, The Netherlands, Cote d'Ivoire, Israel and Sudan followed by elimination of vaccination;
- Eradication in Hong Kong (2009) with vaccination continuing as an extra preventative measure;

- Continued preventative vaccination in Kazakhstan and Mongolia but without HPAI in poultry;
- No HPAI cases in Russia and Pakistan since 2008 with proposed cessation of vaccination.

Over the next 5 years, the highest priority needs for improving vaccines and vaccination in H5N1 HPAI enzootic control programs include:

- Restructuring and modernization of veterinary services in order to develop, implement, monitor and revise poultry vaccination programs, as well as restructuring poultry production systems to improve movement control, enhance biosecurity and better educate farmers on HPAI control and eradication;
- Improving national HPAI surveillance programs to determine geographic locations, poultry species and production sectors where the virus resides and use such data to develop targeted vaccination programs to achieve 60–80% coverage in at-risk poultry populations and provide continual feedback to modify the program as local conditions change;
- Restructuring funding for H5N1 HPAI control so that sufficient funds are available to veterinary medicine and agricultural production systems to develop effective control and eradication programs that will prevent human infection and eliminate the virus, since domestic poultry are the reservoir of this zoonotic virus, and effective control must be initiated at the virus source to eliminate the public health threat;
- Improving vaccination rates among domestic ducks, which are a large asymptomatic reservoir of H5N1 HPAI virus in Asia, by linking control of an economically significant disease such as duck virus enteritis (DVE) with H5N1 HPAI through the potential use of recombinant live DVE vaccine with H5 gene insert, thus providing protection from both DVE and H5 HPAI in a single vaccine;
- Developing new vaccine vector platforms for cost-effective vaccination of short-lived meat chickens that do not require catching and handling of individual birds (e.g., through using spray or *in ovo* application), and provide protection after a single vaccination. Recombinant Newcastle disease viruses (NDV) with H5 hemagglutinin gene insert (rNDV-AIV-H5) can be applied by spray application, but rNDV-AIV-H5 has had limited field use as a vaccine because of inhibition of a protective primary immune response by maternal or field-derived antibodies to the NDV vector, but rNDV-AIV-H5 is effective in a prime-boost two-dose vaccination program. The newly developed recombinant herpesvirus of turkeys can be applied *in ovo* or at 1 day of age in the hatchery and provide protection in meat chickens throughout their short production life using only one vaccination, but this vaccine needs extensive testing in the field to determine its utility. Development of other spray-administered viruses could provide additional vectors for delivering H5 genes if maternal antibodies and/or field-induced antibodies are lacking against the vectors within the poultry population;
- Continuing development of antigenically relevant, rg AI seed strains for use in inactivated vaccines as field viruses drift antigenically away from current AI vaccine seed strains, and these seed strains may need to be region specific as the H5N1 viruses became geographically isolated and evolve into different genetic subclades or antigenic subgroups;
- Developing a more time-responsive vaccine licensing and registration process by the national veterinary biological authorities for replaceable ‘vaccine cassettes’, which would allow vaccine seed strains to be updated more quickly.

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