Food and Agriculture Organization of the United Nations

focus on

VOL 10 | MAY 2016

Rational use of vaccination for prevention and control of H5 highly pathogenic avian influenza

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Abstract/overview

Vaccination can play a valuable role in control, prevention and elimination of highly pathogenic avian influenza (HPAI) viruses. In places where HPAI remains endemic, vaccine has been used to reduce the quantities of virus shed into the environment, which, in turn, reduces human exposure and the likelihood of zoonotic and pandemic influenza, as well as the risk of severe disease in poultry. In other countries (China, Hong Kong SAR and Mexico), vaccination has been used successfully to assist in the elimination of virus. Despite these positive experiences, considerable resistance to use of vaccine exists because of perceived and actual adverse consequences associated with vaccination as well as concerns about availability of sufficient resources to conduct vaccination programmes. The adverse effects can be overcome or managed, and benefits of vaccination maximized if vaccine is used rationally. Rational use involves five core principles and requires: i) clear objectives and regular reviews of progress towards these objectives; ii) design of the programme so as to achieve high-level immunity in vaccinated populations through use of appropriate, locally-registered vaccines and implementation of post-vaccination monitoring; iii) passive surveillance systems able to identify flocks in which virus might be circulating so that these can be reported and investigated; iv) application of other appropriate management practices and biosecurity measures at farms and markets aimed at reducing the risk of infection with HPAI: and v) an appropriate cost-sharing mechanism with the private sector. ●

Why opt for vaccination?

Since it emerged in 1996, HPAI caused by Goose/Guangdong-lineage H5 viruses (H5 HPAI) has become a major risk and constraint to poultry production on four continents and a cause of sporadic severe zoonotic disease in humans. It also remains as a potential human pandemic influenza threat. In most places, control of avian influenza can be achieved primarily by stamping out. However, the effectiveness of this strategy depends on early detection of all infected poultry and swift ac-

Table 1

Different scenarios for the use of vaccination as a tool in HPAI control

	Scenarios		
	Recent outbreak in a country previously free of the virus	When stamping out alone is not achieving virus elimination in an infected country	With no prospect of virus elimination in the next 2+ years in an endemic country
Objective	Virus elimination	Virus elimination	Outbreak containment and reduction in virus circulation
Use of vaccination and other measures	Emergency vaccination with stamping out	Targeted vaccination added as a control measure to facilitate stamping out	Targeted vaccination; Less emphasis on stamping out; Introduce changes to farm and market practices to reduce risk
Vaccines	Need to have a stockpile of suitable vaccine	Locate and use suitable vaccine	Locate and use suitable vaccine
Other requirements	Rapidly detect all infected flocks and take swift action	Detect infected flocks and take swift action; Regularly review scope, effectiveness and the need for vaccination	Regularly review scope, effectiveness and the need for vaccination. If/when feasible revert to virus elimination
Duration	Short (if successful)	Short to medium	Usually long

Note: Distinct from Nepal isolates; detected in poultry and wild birds (crows).

An aviary technician vaccinates a chicken at a training session for poultry farmers in Chad.

Vaccination is performed on newly hatched chicks.

tion to prevent these birds from spreading the virus. The costs of stamping out are high, not only in terms of the intervention itself but because of the compensation provided to affected owners, which is necessary to encourage reporting and to help defray losses to people's livelihoods.

Evidence suggests that virus elimination in poultry is unlikely in a number of countries where the virus remains endemic (FAO, 2012). In these places, all available tools for prevention and control of the disease should be considered, including vaccination using appropriate and quality biologicals. Table 1 provides possible scenarios for the use of vaccination.

Control and elimination of H5N1 is achieved by reducing the number of infected and susceptible poultry, thereby also reducing the amount of circulating virus able to establish onward transmission.

Vaccination can help achieve these objectives by increasing resistance to infection, decreasing the likelihood of disease and reducing shedding of the virus in those birds that do become infected. Unvaccinated infected chickens shed much higher concentrations of virus than their vaccinated, infected counterparts (Swayne, 2006). Once vaccinated, marked reduction of onward transmission of virus can occur within seven days post-vaccination (van der Goot *et al.*, 2005). In one example in China, Hong Kong SAR, in which vaccination was used in the face of an outbreak, transmission ceased within 18 days (Ellis *et al.*, 2006).

Despite the potential benefits of vaccination, many countries continue to restrict their control options to stamping out even after it is evident that this method is not working as intended. This creates a major burden for poultry producers and does not halt the spread of disease as farmers will often sell flocks of poultry when they first notice increases in mortality, which, in turn, exacerbates the outbreak and increases the public health risk in the case of zoonotic influenza viruses.

Minimizing unwanted consequences: When implementing a vaccination programme, several challenges need to be faced, all of which can be overcome or minimized. Concerns include:

- viral shedding in clinically healthy, vaccinated birds, or the so-called "silent infection" (see, for example, Poetri *et al.*, 2014);
- the use of vaccination as a substitute for other important measures, such as improvements to biosecurity;
- a false sense of security leading to the underestimation of clinical signs consistent with HPAI or of milder clinical signs, jeopardizing the immediate detection of HPAI in vaccinated flocks (Vergne *et al.*, 2012);
- the potential impact on trade in poultry products (Pongcharoensuk *et al.*, 2012;
- the emergence of antigenically variant strains (Cattoli *et al.*, 2011).

Though each of these concerns is legitimate, the rational use of vaccination can help ensure that the overall effect remains

Box 1

Real-life examples: Success of vaccination against avian influenza – China, Hong Kong SAR, Italy, Mexico, United States of America, Viet Nam

Vaccines were first used successfully against low pathogenic avian influenza (LPAI) viruses and these experiences demonstrated the potential for use against highly pathogenic avian influenza (HPAI) viruses. Poultry in turkey farms in the United States of America were among the first to be vaccinated successfully against a range of LPAI viruses (Halvorson, 2009). Vaccination since has been used effectively in a number of places including northern Italy (LPAI), Mexico (H5 and H7 HPAI) and China, Hong Kong SAR (H5 HPAI) to prevent infection and to control and eliminate virus. In these places, vaccination was coupled with other measures such as raised biosecurity standards, active surveillance and stamping out. Other countries where avian influenza virus was endemic and where stamping out had not achieved the desired goal have used vaccination to reduce viral loads. The experiences with HPAI in Viet Nam during 2003–2004 warrant consideration given that some 45 million head of poultry had been lost, most through culling. This loss represented 17 percent of the total standing poultry population. It is likely that depopulation did reduce viral loads, but by 2005, Viet Nam was experiencing more human cases of Influenza A(H5N1) disease than any other country, demonstrating that any positive effects from the stamping out were short-lived. Poultry vaccination, along with a number of other measures, was implemented to reduce human health risk resulting in a marked reduction in human cases. Viet Nam continues to use vaccination and conducts regular review of the need for vaccination, the scope of the programme and the vaccines to be used.

Box 2

Real-life example: Selling of sick birds – a report from the 2006–2008 Nigerian outbreak

In an assessment of market chains in Nigeria conducted in 2008, it was found that when birds get sick, 41 percent of respondents organize salvage slaughter, 31 percent isolate the sick birds for treatment and 27 percent sell the sick birds at low prices (FAO, 2008). This demonstrated that disease reporting was not occurring, which can reduce the effectiveness of stamping out. This assessment was done shortly after payment of compensation had been discontinued.

positive. To overcome these concerns, vaccination programmes should be designed to maximize benefits and minimize unwanted consequences.

Appropriate timing: The option to vaccinate should be assessed early in the face of disease and should not be considered as a last resort. Regular review points that consider the possibility of vaccination should be included in HPAI contingency plans. Apart from the benefit of controlling disease, the use of vaccination can help to:

- reduce the cost of control when effective vaccine delivery can be ensured;
- decrease disruptions to the poultry sector;
- secure public health;
- protect high value stock – Note: in those endemic countries where vaccination is prohibited, smuggling and use of vaccine of unknown origin and potency by the private sector is to be expected and has occurred (Sims, 2013);
- control the virus when it has become endemic despite implementation of other measures;
- maintain consumer confidence and mitigate potential market shocks.

What vaccines are available?

Two main types of poultry vaccine are available for avian influenza at present: killed antigen in an oil-based adjuvant and vaccines that rely on a viral vector to deliver the antigen.

Killed antigen vaccines have been used for decades in the prevention and control of avian influenza and work effectively. They require individual injection of birds and usually multiple doses are needed starting at about two weeks of age. In some countries, a withdrawal period applies before birds can be sent to slaughter for consumption, as specified by the manufacturer and/or veterinary authorities. This can limit the value of vaccination in short-lived meat birds. (However, no known public health risk is associated with consumption of a vaccinated chicken; the withdrawal period is related to the additives mixed in the vaccine to improve its stimulatory properties or preservatives). Maternal antibodies (conferred via egg yolk in the embryo) can interfere with the immune response generated by these vaccines (Maas *et al.*, 2011) and generally vanish by two to three weeks of age after hatching. When these are expected to be present (if parent stock has been well vaccinated or exposed to the virus), delivery of killed antigen vaccine in the progeny should be delayed for approximately one week (to three weeks of age). The efficacy of killed antigen vaccines is determined by the antigenic relationship between the vaccine and field strain, the immunogenicity of the antigen and the quantity of antigen in each dose. Effectiveness in the field is influenced by: the manner of vaccine storage prior to administration (the vaccines require maintenance at 4–8°C as they are not heat-stable); concurrent immunosuppressive diseases in vaccinated birds; and species of bird and the vaccination schedule, including age of first administration.

As these vaccines contain whole (inactivated) virus, antibody is generated to the haemagglutinin (HA) and neuraminidase (NA) proteins of the antigen. The antibody to the HA is most important for protection from disease and for reducing viral shedding.

A number of different viral vectors have been used for delivering HA antigens including fowl pox virus, Newcastle disease virus, alphavirus replicons and herpes virus of turkeys. Several experimental vectors are also being assessed including duck enteritis virus. Some of these vaccines appear to be effective in the presence of maternal antibodies and can be administered in ovo or at hatching (Rauw *et al.*, 2012). Vectored vaccines may afford broader protection against viruses of different strains and clades, perhaps, in part, because they also stimulate cell-mediated immune responses. Nevertheless, it is preferable for the HA insert in the vector to be a reasonable match to the circulating strains of virus. Most vectored vaccines are used to prime the immune system and are followed several weeks later by a dose of killed vaccine. Vaccine research development is ongoing and constantly evolving (see, for example, Kapczynski *et al.*, 2016, Rahn *et al.*, 2015).

Apart from efficacy in the target population, the choice of vaccine will depend on other factors, including price and availability. These factors can change over time, providing additional reasons for regular review of vaccination strategies and management of the programme. ●

Principles of rational vaccine use

Five core principles of rational vaccine use

1. Set clear objectives and regularly review strategies for vaccination, consistent with the overall prevention and control plan.
2. Use high-quality vaccines, registered by national authorities, shown to be a good antigenic match to the circulating field strain(s).
3. Strengthen the passive surveillance system and farmer compensation scheme especially if virus elimination remains the immediate goal.
4. Strengthen concurrent biosecurity measures and good farm management practices.
5. Agree on a cost-sharing scheme between public and private sectors, based on vaccination objectives.

1 The vaccination programme must have **clear objectives**, established by government in consultation with the private sector, that relate to the overall prevention and control plan (such as mitigating production losses and reducing human exposure to virus). It must be assessed regularly (at least annually) in order to review progress towards the objectives and update or modify the objectives as necessary. The objectives must justify the activities carried out. For example, large-scale vaccination of smallholder and household poultry flocks, with birds of different ages and rapid turnover, can usually only be justified on public health grounds and then only if resources are available to ensure that appropriate levels of flock immunity are maintained in these birds (especially during periods of high risk of transmission). Past experience suggests that this is difficult to maintain over large areas but can be successful at the local level.

The programme should include **clear goals and criteria for ending vaccination**.[1] Vaccination should be used for as long as is necessary to control and prevent infection and may be required for an extended period in places where the virus is entrenched and prospects of virus elimination are poor. Vaccination can be stopped when the disease is controlled or eliminated, when the risk of re-incursion is low, and when new outbreaks can be detected and managed rapidly. It is possible to use emergency vaccination even after routine use of vaccination ceases. Unrealistic time lines on the expected duration of vaccination programmes should be avoided especially in places where infection is already widespread.

2 Only **high quality vaccines** that are a good antigenic match to circulating strains and at an appropriate dose should be used. They should be produced in accordance with good management practices using international standards.[2] They should also be good immunogens, i.e. able to induce a good immune response in vaccinated birds.

Before implementing a large-scale vaccination programme the effectiveness of the vaccine(s) chosen should be assessed under laboratory and field conditions against circulating viruses. The levels of antibody in vaccinated chickens to field virus generally correlate with levels of protection; (high antibody titres against the field strain provide better protection than low titres and can prevent virus shedding and disease) (Swayne, *et al.*, 2015). Regulation of licensed vaccines is necessary to avoid the use of inefficient/ineffective vaccines. A properly managed government vaccine registration/licensing process is, therefore, needed. It may be necessary to de-register vaccines if significant antigenic drift[3] occurs or new strains of virus are detected through monitoring programmes against which existing vaccines provide little or no protection. Governments can enter into contracts with private/academic institutions to carry out this function. A coding system for the different vaccines to be tested should be used to rule out subjectivity (such as manufacturer preference). Facilities producing vaccines should be separate from agencies that verify the vaccine's quality and efficiency.

3 Agreements should be in place to ensure that farmers **immediately alert veterinary authorities** in case of mortality of vaccinated poultry above agreed baseline levels. This will facilitate early detection of vaccine failures or antigenic variant viruses that may arise during the course of a vaccination programme. If increased mortality due to avian influenza occurs in a vaccinated flock, the government should provide appropriate and timely compensation[4] for the flock owner if the flock is destroyed.

4 Wherever possible, vaccination should be accompanied by other measures to reduce the likelihood of exposure to and transmission of the virus. These should include **enhanced farm and market biosecurity** measures such as all-in-all-out flock management, banning overnight stay of birds in markets, etc. (FAO, 2015a; FAO, 2015b; FAO, 2015c). For some production systems, such as free-grazing ducks, the only biosecurity measures available are reducing direct and indirect contact between domestic ducks and other types of poultry, and tight movement management. The potential for spread of virus by vaccinators moving between premises must be recognized and appropriate hygiene measures put in place, including cleaning and

[1] This is often termed 'exit strategy'.

[2] For procedures see the OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals, at http://www.oie.int/fileadmin/Home/eng/Health_standards/tahm/2.03.04_AI.pdf.

[3] Antigenic drift: small changes in the genome of influenza viruses that happen continually over time during virus replication, eventually changing the antigenic properties of the virus.

[4] For more information on compensation please see http://www.fao.org/avianflu/en/compensation.html

Poultry vaccination against H5 avian influenza, along with a number of other measures, was implemented in Viet Nam in 2003–2004 to reduce human health risk.

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disinfection of boots or change of boot covers and coveralls between farms, and disinfection or change of vaccination equipment.

5 **Cost-sharing of vaccination** (and post-vaccination monitoring) should be applied between the government and the private sector. If industry will derive significant production and marketing advantages from vaccination, they should pay most of the costs. A case for subsidized vaccination can be made if the main purpose is to protect public health. ●

Key questions in designing a vaccination strategy for disease prevention and control

In deciding whether or not to use vaccination, the key question to ask is:

Can vaccination assist in prevention and control of avian influenza and reduce the risk of human cases and, if so, how?

In answering this question, the effectiveness of existing control and preventive measures must be assessed, as well as their costs (economic and social) compared to those of vaccination. Synergy between methods may mean that some costs associated with stamping out can be reduced if vaccination is used.

Another important issue that needs to be considered is the **efficiency of case detection**. If a high proportion of cases are undetected and action is not taken early enough to prevent virus transmission, the likelihood of disease elimination using stamping out is often poor in areas with a high density of poultry farms. This is the situation in the places where H5N1 HPAI viruses remain endemic (FAO, 2011).

Guidance for the decision-making process has been developed (Castellan *et al.*, 2014, OFFLU, 2014). Key questions for decision-making on vaccination are:

Is a suitable vaccine available? Could one be made available? And how is it to be administered?

Decision-making requires assessment of the antigenic characteristics of existing viruses in the field and comparison with available vaccines and vaccine antigens. It also requires ongoing monitoring for changes from antigenic drift in existing viruses or the introduction of a new strain (e.g. in Indonesia where introduction of a well-matched vaccine was followed by improved control of clade 2.1 viruses and the introduction of clade 2.3.2.1 H5N1 virus in 2012 was followed by introduction of vaccination against this strain).

It is preferable to assess vaccines against a number of local viruses as there can be subtle differences. This assessment is important in places where the virus has been present for some time and has evolved into different sublineages (Spackman *et al.*, 2014). It is also necessary to perform *in vitro* testing (i.e. cross HI tests using sera from vaccinated poultry versus the vaccine antigen and field antigens), which can also be used for antigen mapping, an aid in antigen selection for inclusion in the vaccine (Swayne *et al.*, 2015). Multivalent vaccines containing different antigens can be used provided appropriate quantities of each antigen are incorporated (that is, at levels equivalent to monovalent vaccines for each antigen).

Ultimately, the best test for a killed antigen vaccine is a laboratory challenge study under a high biosafety and biosecurity environment using birds vaccinated at three weeks of age and challenged three weeks later. Challenge studies with the circulating field strain(s) should be conducted in places where appropriate facilities are available. It may be possible to obtain relevant information from other countries that have tested vaccines against similar viruses. If a suitable vaccine is not available it may be necessary to have one manufactured from a local strain of virus (or closely related strain) in facilities using good management practices. In most cases, it is better to have this done by companies that specialize in this area; (if several vaccines are to be tested, a system of 'coding' is urged). Use of an unmodified HPAI virus as a seed strain is not generally recommended due to the potential risks from insufficient antigen production or, if zoonotic, to possible occupational hazards. Most vaccine antigens are natural LPAI strains or are HPAI strains genetically modified to become LPAI viruses. The OIE/FAO Network of Expertise on Animal Influenzas (OFFLU) can advise on this process.[5]

Is a vaccine antigen which is a good antigenic match also a good immunogen?

Not necessarily. Not all virus strains are equal as immunogens as some appear to stimulate a stronger level of immunity than others. This may be due, in part, to the glycosylation patterns of the HA protein. Immunogenic performance of vaccine antigens is best evaluated in challenge experiments (Zhang *et al.*, 2015).

What types of poultry should be prioritized for vaccination?

This is a crucial question.

If the main target population is chicken layers or parent flocks then it is possible to develop high-level immunity in these birds prior to the point of lay (usually using a three-dose course of vaccine).

[5] Please contact secretariat@offlu.net


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A hatchery employee examines recently hatched ducklings.


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Rwanda - A poultry farmer feeding the chickens on his farm.

Meat birds that live for less than 50 days are not good candidates for use of killed antigen vaccines, as it is not usually possible to obtain high-level immunity with only a single dose of the currently available commercial killed vaccines. However, it may be possible to use hatchery vaccination (i.e. vaccination of day-old chicks) with an appropriate vector vaccine followed by one or more booster doses of killed antigen vaccine, with the first booster usually given two to three weeks later. If a vectored vaccine is used on day–old chicks, it must be able to work in the presence of maternally derived antibodies to the vector and the avian influenza virus.

When meat chickens are kept for more than 50 days it is possible to obtain protection by vaccination at around two weeks of age and boost after four weeks. Examples include Chinese-style yellow-feathered birds that are usually reared for at least 70 days before entering the consumer market.

Vaccination of birds reared by small-scale producers is not normally recommended since maintaining adequate levels of immunity and instituting significant changes in hygiene practices proves very difficult in settings with a high turnover of poultry given the associated costs of the programme. The exception is in areas where large numbers of human cases are occurring. However, the logistical difficulties of implementing large-scale vaccination across thousands of household flocks must be recognized.

In some countries, there are large populations of ducks. Effective vaccines and vaccination schemes for ducks have been more difficult to achieve than for chickens. Vaccination of ducks can reduce viral shedding if there is a very good antigenic match between the vaccine strain and the field strain, and sufficient doses of vaccine are administered. Single dose vaccination does not usually provide appropriate protection from viral shedding. Limited information is available on the effects of vaccines in other poultry species, although some studies have been performed on zoological collections (Koch *et al.*, 2009).

How can existing vaccination programmes be leveraged for vaccination against AI?

Most industrially-reared poultry are being vaccinated against other diseases such as Newcastle disease, infectious bursal disease or duck viral enteritis. In these situations, if appropriate systems are in place to ensure these products are delivered to birds and the vaccines are correctly stored along the entire chain, then similar systems can be implemented for AI vaccines. Another issue to consider for large poultry flocks is that killed antigen vaccines require injection of individual birds.

Can high-level immunity be generated in the target population?

One objective of all vaccination programmes is to achieve high-level immunity in vaccinated flocks. It is usually possible to do so in relatively long-lived poultry, especially when birds are reared on an "all-in/all-out" basis. Layers may not generate sufficient levels of immunity during the end stages of their life, which can be further complicated by the hesitance of farmers to vaccinate birds in lay due to perceived egg production losses. Poor nutrition or the presence of other infectious agents on a farm may influence the immune response generated by vaccines (e.g. concurrent infection with infectious bursal disease virus can compromise the immune response to avian influenza vaccination). Post-vaccination monitoring (PVM) of antibody levels[6] in selected vaccinated flocks should be used to assess the response to vaccination and to make changes to the vaccination programme based on field investigations if levels of immunity are lower than expected or required. The number and type of flocks and the number of birds per flock to test will vary from place to place and need to be designed for each programme by an experienced epidemiologist. The monitoring programme represents only a small part of the overall cost of a vaccination campaign.

As a rule, **a single dose of a killed antigen vaccine is not sufficient** to produce a strong and long-lasting immunity and should only be used for emergency vaccination.

[6] Cut-off titres need to be established. As a general rule a titre of 1:32 in chickens against the field strain will prevent mortality and a titre of 1:128 will normally prevent shedding of virus if the birds are subsequently exposed to the virus (Swayne *et al.*, 2015).

Issues arise with household-level flocks where there is a high turnover of poultry, which results in a rapid reduction of flock immunity. This challenge can be overcome with strong local coordination and responsive veterinary services so that new poultry are vaccinated as they reach the appropriate age, as specified in the manufacturer's guidance, and as previously discussed.

What percentage of poultry needs to be vaccinated or immune?

Much of the research in this area is theoretical and has assumed that the objective of vaccination is virus elimination. In practice, percentage of poultry to be vaccinated depends on a number of factors including the current objectives of the control programme, the stage of the vaccination programme and the types of housing and poultry.

Vaccine use should induce a sufficiently high level of immunity in the majority of the vaccinated poultry. In general, vaccination should aim to have 70 to 80 percent of birds with acceptable, protective antibody titres. In most cases this will require a minimum of two doses of vaccine (and additional doses in long-lived poultry). ●

Potential drawbacks of vaccine use

Concerns about silent infection

When a vaccinated bird is exposed to a HPAI virus there are three potential results: i) no clinical disease and little to zero quantities of virus are shed; ii) sufficient antibodies to prevent clinical disease but some viral shedding; and iii) full clinical disease (Kumar *et al.*, 2007). When a flock is vaccinated, a range of antibody titres will be developed. If a HPAI virus enters a vaccinated chicken flock, those birds with low or no antibody titres will die if infected, indicating infection in the entire flock. With only a few deaths in this case, infection is more subtle to detect than in non-immune flocks where mortality will be much higher. Many of the so-called silent infections actually occur as unreported mortalities in these situations.

The virus can be detected in infected flocks through dead bird testing on vaccinated farms or, alternatively, through discriminatory serological tests that distinguish antibodies generated via infection in vaccinated birds (DIVA strategy; i.e. detecting infection in vaccinated animals). The former provides more immediate information on the infection status of a flock when managed appropriately. Suitable criteria need to be set for alerting veterinary services (e.g. doubling of daily mortality or a >30 percent fall in egg production). These trigger-points are only of use in places where farmers keep flock records – a good practice which is highly recommended.

If widespread silent infection is occurring, the vaccine antigen should be examined to assess whether it is still working against circulating strains of virus and, if not, a new antigen should be developed and used.

Concerns regarding vaccination leading to a false sense of security

A reduction in farmer notification of outbreaks to veterinary services following introduction of vaccination, as was occurring in Egypt (Vergne *et al.*, 2012), indicates the importance of avoiding a false sense of security amongst vaccinated farms. It is important for all involved to recognize that vaccination is not a 'magical solution' and will not solve all problems. Expectations need to be tempered.

Appropriate risk communication strategies which highlight that vaccination alone will not prevent all signs of avian influenza infection can help ensure biosecurity measures are continued. At the same time, these communication strategies should promote passive surveillance. In parallel with vaccination, biosecurity improvement programmes such as FAO models in Viet Nam and Indonesia (FAO, 2015a; FAO 2015b) can and should be implemented. Farmer notification of infected vaccinated flocks can be encouraged by ensuring appropriate compensation is available if a report of disease results in the destruction of a flock, and by setting lower trigger-points that generate an investigation. This requires good cooperation between industry and government veterinary services.

It is highly encouraged to have the veterinary public sector meet with industry and other poultry producers on a regular basis. Similarly, the veterinary public sector should engage the private professionals to share information and provide guidance.

Concerns about impact on trade

The effect of vaccination on trade is a genuine concern that needs to be addressed between trading partners, preferably during periods when the disease is not occurring. It has been one of the main factors inhibiting uptake of vaccination, even in emergency situations, (e.g. Thailand and the United States of America), but one that can be overcome with appropriate surveillance and monitoring systems in place. In countries with minimal export trade (e.g. Indonesia, Viet Nam) the concern remains limited.

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A backyard chicken flock belonging to a household in the Ukraine.

Concerns about the development of antigenic variant strains of virus

The possibility that antigenic variants could emerge in places where vaccine is being used has been recognized since vaccination was first introduced for Goose/Guangdong-lineage (Gs/GD-lineage) H5N1 HPAI. Circulation of antigenically variant strains may result in insufficient protection of vaccinated flocks and can lead to outbreaks in vaccinated populations. Monitoring of circulating field viruses and vaccine matching is therefore critical.

With the exception of China and Indonesia, which have systems in place for regular updating of vaccine antigens, most developing countries that vaccinate are still building systems for vaccine updates. Progress has been made in identifying antigenic variant viruses in most countries, but the next step of updating vaccine antigens is less well advanced. Both China and Indonesia often have a 12 to 24-month period between emergence of a new strain and production/uptake of a vaccine incorporating the new antigen (as was the case with clade 2.3.4.4 viruses that emerged as an important cause of losses to poultry producers in China from 2013).

Genetic changes can potentially enhance human infectivity or virulence and novel antigenic variant strains need to be identified for pandemic preparedness. Therefore, information on genetic and antigenic characteristics needs to be shared by national governments with the World Health Organization (WHO) in a timely and regular manner (i.e. at least twice a year) so that they can prepare human vaccine antigens for pandemic preparedness (WHO, 2015). This valuable information can only be obtained if there are appropriate monitoring systems in place to detect virus in poultry in places where vaccine is used. ●

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A young chick in a chicken coop - the Gambia.

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A chicken and chicks perching on a rock in Nicaragua.

Does use of vaccination lead to endemic infection?

Perhaps the main concern raised by countries and their agriculture or public health authorities is that use of vaccination may allow viruses to remain endemic or facilitate development of endemic infection because immunity is not sterilizing.[7] Despite being a legitimate concern, it is also important to recognize that in certain places where vaccination is being applied, the virus would remain endemic even if vaccination was not being used (as was or is the case in China, Egypt, Indonesia and Viet Nam). Vaccination in these places was introduced as a response to endemic or widespread infection.

Vaccination can contribute to an endemic situation if the following occur:

- Vaccination is not markedly reducing the levels of shedding of virus in vaccinated birds that are exposed to virus (owing to, for example, insufficient vaccine coverage in the target population or area, poor antigenic match, poor quality vaccine or insufficient doses of vaccine).
- Vaccinated flocks are not sufficiently monitored.
- Farmers do not see any need to report increased mortality in vaccinated flocks.
- Farmers vaccinate poultry at inappropriate ages.
- Farmers mix vaccinated with unvaccinated poultry.
- Farmers see vaccination as the answer to all their problems.
- Vaccination assists in driving antigenic change, thereby reducing the value of existing vaccines (unless vaccine antigens are regularly updated as needed).
- These issues need to be considered and addressed in the design stage of a vaccination strategy. ●

Conclusion

If used rationally, vaccination can help to control and even eliminate HPAI. Vaccination is not a 'magic solution' that will solve all problems and should be used in conjunction with other control and preventive measures. Unless managed appropriately, it can cause some unintended consequences. Vaccination should be considered by all countries struggling to control HPAI using stamping out alone because it can help to contain the disease and reduce risk of human infection. This document provides an outline of the main issues that need to be considered when contemplating use of vaccination. Additional advice can be obtained directly from FAO or OFFLU. ●

[7] This means that some vaccinated birds that are subsequently exposed to the virus will still become infected and shed virus.

References

Bouma, A., Claassen, I., Natih, K., Klinkenberg, D., Donnelly, C.A., Koch, G. & Van Boven, M. 2009. Estimation of transmission parameters of H5N1 avian Influenza virus in chickens. *PLoSPathog*, 5(1): e1000281.

Castellan, D.M., Hinrichs, J., Fusheng, G., Sawitri, E., Dung, D.H., Martin, V., McGrane, J., Bandyopadhayay, S., Inui, K., Yamage, M., Ahmed, G.M., Macfarlane, L., Williams, T., Dissanayake, R., Akram, M., Kalpravidh, W., Gopinath, C.Y. & Morzaria, S. 2014. Development and application of a vaccination planning tool for avian influenza. *Avian Dis*, 58(3): 437–452.

Cattoli, G., Fusaro, A., Monne, I., Coven, F., Joannis, T., El-Hamid, H.S., Hussein, A.A., Cornelius, C., Amarin, N.M., Mancin, M., Holmes, E.C. & Capua, I. 2011. Evidence for differing evolutionary dynamics of A/H5N1 viruses among countries applying or not applying avian influenza vaccination in poultry. *Vaccine*, 29(50): 9368–9375.

Ellis, T.M., Sims, L.D., Wong, H.K., Wong, C.W., Dyrting, K.C., Chow, K.W., Leung, C. & Peiris, J.S. 2006. Use of avian influenza vaccination in Hong Kong. *Dev Biol (Basel)*, 124: 133–143.

FAO. 2008. *Assessment of the Nigerian poultry market chain to improve biosecurity.* Rome (available at http://www.fao.org/3/a-ak778e.pdf).

FAO. 2011. *Approaches to controlling, preventing and eliminating H5N1 highly pathogenic avian influenza in endemic countries.* Rome.

FAO. 2015a. *Improvement of biosecurity and production practices in hatcheries and parent flocks.* Rome (available at http://www.fao.org/3/a-bb033e.pdf).

FAO. 2015b. *How simple biosecurity measures can change a farmer's life.* Rome (available at http://www.fao.org/3/a-bb014e.pdf).

FAO. 2015c. *Biosecurity guide for live poultry markets.* Rome (available at http://www.fao.org/publications/card/en/c/5a3c4d30-efd1-47f2-a805-589676cacfef/).

Halvorson, D.A. 2009. Prevention and management of avian influenza outbreaks: experiences from the United States of America. *Rev Sci Tech*, 28(1): 359–369.

Kapczynski, D.R., Tumpey, T.M., Hidajat, R., Zsak, A., Chrzastek, K., Tretyakova, I. & Pushko, P. 2016. Vaccination with virus-like particles containing H5 antigens from three H5N1 clades protects chickens from H5N1 and H5N8 influenza viruses. *Vaccine*, 34(13): 1575–81.

Koch, G., Steensels, M. & van den Berg, T. 2009. Vaccination of birds other than chickens and turkeys against avian influenza. *Rev Sci Tech*, 28(1): 307–318.

Kumar, M., Chu, H.C., Rodenberg, J., Krauss, S. & Webster, R. G. 2007. Association of serologic and protective responses of avian influenza vaccines in chickens. *Avian Dis*, 51(s1): 481–483.

Le, T.H. & Nguyen, N.T.B. 2014. Evolutionary dynamics of highly pathogenic avian influenza A/H5N1 HA clades and vaccine implementation in Vietnam. *ClinExp Vaccine Res*, 3(2): 117–127.

Ma, Q.X., Jiang, W.M., Liu, S., Wang, S.C., Zhuang, Q.Y., Hou, G.Y., Liu, X.M., Sui, Z.H. & Chen, J.M. 2014. Subclinical highly pathogenic avian influenza virus infection among vaccinated chickens, China. *Emerg Infect Dis*, 20(12): 2152–2154.

Maas, R., Rosema, S., VanZoelen, D. & Venema, S. 2011. Maternal immunity against avian influenza H5N1 in chickens: limited protection and interference with vaccine efficacy. *Avian Pathol*, 40(1): 87–92.

Middleton, D., Bingham, J., Selleck, P., Lowther, S., Gleeson, L., Lehrbach, P., Robinson, S., Rodenberg, J., Kumar, M. & Andrew, M. 2007. Efficacy of inactivated vaccines against H5N1 avian influenza infection in ducks. *Virology*, 359(1): 66–71.

OFFLU. 2014. OFFLU technical meeting: Developing guidance on vaccines and vaccination against HPAI from lessons learned. (available at http://www.offlu.net/fileadmin/home/en/meeting-reports/pdf/OFFLU_Beijing_2013/OFFLU_Recommendations_Beijing_Dec_2013_final.pdf).

Poetri, O.N., VanBoven, M., Claassen, I., Koch, G., Wibawan, I.W., Stegeman, A., Van den Broek, J., & Bouma, A. 2014. Silent spread of highly pathogenic Avian Influenza H5N1 virus amongst vaccinated commercial layers. *Res Vet Sci*, 97: 637–641.

Pongcharoensuk, P., Adisasmito, W., Sat, L.M., Silkavute, P., Muchlisoh, L., Hoat, P.C.. & Coker, R. 2012. Avian and pandemic human influenza policy in South-East Asia: the interface between economic and public health imperatives. *Health Policy Plan*, 27(5): 374–383.

Pu, J., Wang, S., Yin, Y., Zhang, G., Carter, R.A., Wang, J., Xu, G., Sun, H., Wang, M., Wei, Y. Wang, D. Zhu, B., Lemmon, G., Jiao, Y., Duan, S., Wang, Q., Du, Q., Sun, M., Bao, J., Sun, Y., Zhao, J., Zhang, H., Wu, G., Liu, J., Webster, R.G. 2014. Evolution of the H9N2 influenza genotype that facilitated the genesis of the novel H7N9 virus. *Proc Natl AcadSci USA*, 112(2): 548–53.

Rahn, J., Hoffmann, D., Harder, T.C., & Beer, M. 2015. Vaccines against influenza A viruses in poultry and swine: Status and future developments. *Vaccine*, 33(21): 2414–2424.

Rauw, F., Palya,V., Gardin, Y., Tatar-Kis, T., Dorsey, K.M., Lambrecht, B. & van den Berg, T. 2012. Efficacy of rHVT-AI vector vaccine in broilers with passive immunity against challenge with two antigenically divergent Egyptian clade 2.2.1 HPAI H5N1 strains. *Avian Dis*, 56(4 Suppl): 913–922.

Sims, L.D. 2007. *Risks associated with poultry production systems.* Rome, FAO (available at http://www.fao.org/ag/againfo/home/events/bangkok2007/docs/part2/2_1.pdf).

Sims, L.D. 2013. Intervention strategies to reduce the risk of zoonotic infection with avian influenza viruses: scientific basis, challenges and knowledge gaps. *Influenza Other Respir Viruses*, 7 Suppl 2: 15–25.

Spackman, E., Swayne, D.E., Pantin-Jackwood, M.J., Wan, X.F., Torchetti, M.K., Hassan, M., Suarez, D.L. & Sá e Silva, M. 2014. Variation in protection of four divergent avian influenza virus vaccine seed strains against eight clade 2.2.1 and 2.2.1.1. Egyptian H5N1 high pathogenicity variants in poultry. *Influenza Other Respir Viruses*, 8(6): 654–662.

Swayne, D.E. 2006. Principles for vaccine protection in chickens and domestic waterfowl against avian influenza: emphasis on Asian H5N1 high pathogenicity avian influenza. *Ann N Y AcadSci*, 1081: 174–181.

Swayne, D.E., Suarez, D.L. & Sims, L.D. 2013. Influenza. *In* D.E. Swayne, J.R. Glisson, L.R. McDougald, V. Nair, L.K. Nolan & D.L. Suarez, eds. *Diseases of Poultry.* Ames, Iowa, Wiley-Blackwell. 181–218.

Swayne, D.E., Suarez, D.L., Spackman, E., Jahao, S., Gwenaelle, D., Kim-Tochetta, M., McGrane, J., Weaver, J., Daniels, P., Wong, F., Selleck, P., Wiyono, A., Indriani, R., Yupiana, Y., Siregar, E.S., Prajitno, T., Smith, D. & Fouchier, R. 2015. Emergence of antigenic variant indonesian H5N1 high pathogenicity avian influenza viruses resistant to multiple poultry vaccine. *J Virol*, 89(7): 3746–3762.

van der Goot, J.A., Koch, G., de Jong, M.C.M. & van Boven, M. 2005. Quantification of the effect of vaccination on transmission of avian influenza (H7N7) in chickens. *Proc Natl AcadSci USA,* 102(50): 18141–18146.

Vergne, T., Grosbois, V., Jobre, Y., Saad, A., El Nabi, A.A., Galal, S., Kalifa, M., El Kader, S.A., Dauphin, G., Roger, F., Lubroth, J. & Peyre, M. 2012. Avian influenza vaccination of poultry and passive case reporting, Egypt. *Emerg Infect Dis,* 18(12): 2076–2078.

WHO. 2015. Antigenic and genetic characteristics of zoonotic influenza viruses and development of candidate vaccine viruses for pandemic preparedness. *Wkly Epidemiol Rec,* 90(12): 109–120.

Zhang, X., Chen, S., Jiang, Y., Huang, K., Huang, J., Yang, D., Zhu, J., Zhu, Y., Shi, S., Peng, D. & Liu, X. 2015. Hemagglutinin glycosylation modulates the pathogenicity and antigenicity of the H5N1 avian influenza virus. *Vet Microbiol,* 175(2–4): 244–256.

Notes

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Recommended citation
Sims, L., Tripodi, A., von Doschuetz, S., Garnder, E. and Aguanno, R. 2016. Rational use of vaccination for prevention and control of H5 highly pathogenic avian influenza. *FOCUS ON*, No. 10, May 2016. Rome

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I5625E/1/05.16

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