World Organisation for Animal Health

TECHNICAL ITEM II

High pathogenicity avian influenza and vaccination: application in Europe Region

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22/09/2022

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High pathogenicity avian influenza and vaccination: application in Europe Region

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Original: English

Summary: *Exceptional changes in risk profile for the Region from HPAI necessitates review of disease prevention and control options. Experiences of large-scale vaccination to control and prevent HPAI at population level are limited. The strategy and plans for vaccination programmes should be part of an overarching control strategy that includes strengthening biosecurity. These plans can accommodate new developments in vaccine design require detailed development if they are to deliver robust interventions with international acceptance. Furthermore, these plans need to provide levels of assurance necessary to permit movements of birds or their products, either locally or internationally. Several new generation vaccines offer improved outcomes whilst enabling the application of a DIVA programme. Careful selection of candidate vaccines is required by member countries informed by local factors and requirements. Vaccines used need to have assurance of efficacy against a diverse family of H5 HPAI with formal systems for regular review, appropriate regulatory control and licensing, together with flexibility to update as required. The vaccination programs need to be adapted to local risk factors and targeted if required to sectors known to be at high risk for disease incursion. Any vaccination program should meet international standards defined in WOAH Terrestrial Code and Terrestrial Manual. A key component of any programme will be to conduct surveillance in vaccinated populations to detect infection with wild type viruses and have further interventions to stamp out and control infected vaccinated flocks. Formal review of vaccine effectiveness will be required. Delivery of these programmes will require wide stakeholder collaboration and commitment under the supervision and control of the Veterinary Authority, to include industry (governance bodies, private vets, retailers and producers), veterinary services, national and/or private laboratories and reference laboratories and vaccine regulators. The potential use of vaccine banks may be considered as have proven beneficial in the control of other transboundary animal diseases.*

INTRODUCTION

Given the recent extensive upsurge and impact of HPAI outbreaks and uncontrolled spread through wild bird migration, a number of World Organisation for Animal Health (WOAH: founded as OIE) Members from different Regions are considering how vaccination could mitigate the impacts and contribute to safe prevention and control of HPAI. Some of these Members have never previously considered vaccination as a tool for threat mitigation, but due to ever increasing and ongoing threat are reviewing their prevention and control options. However, many aspects need to be collectively considered before engaging in such direction to inform decision makers and prepare stakeholders.

One of the core mandates of WOAH is to develop international standards for the prevention and control of animal diseases, including zoonoses, the facilitation of safe international trade, and the promotion of animal health and animal welfare. It is also to foster cooperation between its Members on these subjects.

Following recommendations from the Global steering committee of the GF-TADs, the management committee of the GF-TADs recently established a task force to review the FAO-WOAH Global Strategy for prevention and control of H5N1 HPAI, last revised in October 2008 for assessment and develop an updated strategy. A regional discussion on the vaccination against HPAI will contribute to inform the international organisations on the main areas to focus activities and at which level.

OBJECTIVES

The main objectives of the presentation of technical item II during the Regional Conference are (i) to set the proper framework of questions to make science-based decisions regarding the vaccination policy against *infection with highly pathogenicity avian influenza viruses* (HPAI) in Europe, and (ii) to organise the mechanism which would support WOAH and Members in addressing these questions. It is not to set specific vaccine choices or recommendations on types of vaccines to apply.

This paper presents the state of the art and draws together the key factors that need to be considered as relevant for the Region when defining vaccination policy.

Problem statement

With devastating consequences for the poultry industry, farmer's livelihoods, international trade, health of wild birds, and potential threat to human health, avian influenza has captured the attention of the international community over the years. The primary strategy for avian influenza control used in many countries has been immediate eradication through education and awareness, biosecurity, early disease identification and surveillance, and culling of infected and suspected poultry, sometimes associated with preventive measures. Where outbreaks have occurred, most of the affected Members have often applied the stamping out policy to eradicate HPAI. Mass culling of poultry, whether infected or healthy, to contain the spread of avian influenza represents heavy economic losses for farmers and a long-lasting impact on their livelihoods, food loss and societal as well as environmental concerns.

Avian influenza is also a concern for public health due to the capacity of some high and low pathogenic virus strains to acquire zoonotic potential.

In 2021-2022, in the Europe Region, the outbreaks of HPAI have had a major socioeconomic impact on the poultry sector. WOAH Members wish to define science-based policy in response to the recurring episodes of the outbreaks that are often introduced and transmitted by wild birds.

Chapter 10.4 of the *Terrestrial Animal Health Code (herein after referred to as Terrestrial Code)* provides a set of provisions for mitigating animal and public health risks posed by avian influenza viruses. It provides possibilities to prevent and control outbreaks through biosecurity measures, culling, and stamping out procedures. The *Terrestrial Code* also recognises that vaccination can be used as an effective complementary control tool when a stamping out policy alone is not sufficient and could be part of a disease control programme (21). The standards on the requirements for vaccines are available in the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (herein after referred to as Terrestrial Manual)*, and on the surveillance methods for detecting infection in vaccinated flocks and vaccinated birds are available (22).

Different regions and countries will have different approaches to vaccination:

- vaccines may either be used routinely to protect poultry flocks, with a choice on the type of production to target

- *they may be used as* an adjunct control measure during an outbreak,

- *they may be used* to protect valuable species such as zoo birds from highly virulent viruses such as H5N1.

Depending on the country and the situation, vaccination will sometimes be restricted and require different levels of approval before being implemented. The *Terrestrial Code* provides for the possibility to demonstrate freedom from HPAI when vaccinating, provided surveillance is conducted correctly and demonstrates absence of virus circulation, among other requirements.

WHY IS THE USE OF VACCINATION BEING CONSIDERED AS A SUPPLEMENTARY CONTROL OPTION?

Following the emergence of H5 HPAI viruses in a wide area of Southeast Asia since the early 2000s, there has been an unprecedented global spread. These viruses first reached the Europe Region in 2005 and initially caused epidemic waves primarily through the winter months with variable impacts. Infections cycled over successive years with epidemic waves linked to primary introduction via migratory birds. Initially these epidemic waves were separated by a few years and resulted from a change in the virus strain, however since 2016 these events have become almost annual across the region including endemic infection in some WOAH Members. At the time of writing many Members in the Region are experiencing the worst ever outbreak of HPAI which has led to the death and culling of millions of birds with huge cost to government and industry and major impacts on society. Increased risk for zoonotic infection has been recognised although to date the Region has had a very small number of human cases.

Underlying these fundamental changes in the epidemiology of the disease is antigenic shifts in the virus itself which has led to a dynamic and constant evolutionary change. The viruses can be readily maintained in wild bird populations with a high degree of 'fitness' contributing to efficient maintenance and dissemination into the environment creating multiple risk pathways for introduction to domestic birds, which in turn can be a source of infection for wild birds. Threat has become an annual cycle and indeed in many areas at present the infection is being maintained through the summer months, a new feature that creates further and continuous risk to poultry production. Epidemiological patterns, such as the north/south transmission pattern in Africa, contribute to this increased threat. The scale and size of such disease burden has presented significant pressures, challenges, and costs to stakeholder communities, despite biosecurity efforts from some producers. Conventional control methods whilst achieving success in eliminating infection and return to country freedom may not now be sustainable and additional tools and options to prevent and mitigate infection are required. A further challenge has been the breadth of domestic and kept birds that are affected by such epidemic waves, ranging from large commercial production to small backyard populations to captive birds kept in zoos or collections. This effect has been underpinned by successful spread amongst a greater range of wild bird species which in turn creates additional environmental contamination and risk to poultry populations.

Vaccination against HPAI is not a new concept and in fact has been applied by several Members for over 20 years. Most of the Members practising vaccination are in Asia undertaking such programs because veterinary services and infrastructure became overwhelmed with fast spreading disease outbreaks. The levels of success have been variable ranging from elimination of infection in a country's population to persistence of virus in some poultry production systems. This has been influenced by multiple factors which will be examined later in the paper. Recognising the important role that vaccination may play in the future for reducing infection burden and mitigating against HPAI, WOAH revised the *Terrestrial Code* in 2021. The code made clear provision that where a vaccination program was applied in an appropriate manner with the necessary safeguards and controls it should not be an obstacle to safe trade. Furthermore, based on innovations and improvements in vaccine design greater possibilities exist for effective vaccination strategies.

Vaccines to HPAI can reduce disease, increase resistance to infection, limit virus shedding and reduce transmission (4). There is however variability in vaccine efficacy which will be dependent on a number of factors. Generically these vaccines are rarely able to induce extended sterilising immunity and so it is possible that vaccinated birds can still be infected with wild-type viruses but infection outcomes in these circumstances will be attenuated with infection often being subclinical. Therefore, this requires that in any vaccination program a complementary surveillance program or monitoring program is deployed in order to detect early incursion of wild type virus, and possible cryptic spread within a vaccinated population. Vaccination should be considered as one component of an overall prevention and control program and not seen as a substitute for an overall environment with weak biosecurity in the face of high risks. However, when used as part of a multifaceted control and prevention program positive outcomes can be achieved. If used alone vaccination will not deliver

desired outcomes. In a worst-case scenario where vaccination is not deployed in a robust manner, it can lead to significant spread of infection and endemicity in a population. Vaccination should not lead to unintended consequences such as negative effects on production, welfare, expense without cost benefit and not lead to trading bans, hence careful stipulation of requirements within WOAH *Terrestrial Code*.

Most vaccine "failures" have resulted from problems in the vaccination process itself i.e., failure to adequately administer the vaccine to at-risk poultry resulting in lack of population immunity, while fewer failures have resulted from antigenic drift of field viruses away from the vaccine viruses. It is currently not feasible to vaccinate wild birds against H5N1 HPAI. Ultimately the best method to protect wild birds is to control and reduce the infection burden in domesticated populations. On a global scale vaccination will be an important tool to achieve this aim that will lead to reduced environmental contamination and eventual eradication of the virus in domestic poultry particularly in countries with extensive outdoor systems enabling close contact with wild birds.

AVIAN INFLUENZA VACCINES

Swayne and Sims (19) proposed eight criteria for vaccine suitability: inexpensive; usable in multiple avian species; provide protection after a single dose; can be applied by low-cost mass application methods; allow easy identification of infected birds within the vaccinated population; produce a protective humoral response in the presence of maternal antibodies; be applied at one day of age in hatchery or *in ovo*; and be antigenically close to field virus. However no current vaccine or vaccine technology meets all eight criteria so the user must select the licensed vaccine that best meets their needs.

Over 420 billion doses of avian influenza H5 vaccine have been used in poultry since 2002 as oil-emulsified, inactivated whole AIV vaccines (>90%) and live vectored vaccines (<10%). Over 99% of the vaccine has been used in the four H5N1 HPAI enzootic Members: China (People's Rep. of) including Hong Kong (>90%), Egypt, Indonesia, and Vietnam where vaccination programs have been nationwide and routine to all poultry (19). Other Members more recently using H5 vaccination have included Bangladesh and Iran. Some Members have used vaccine in poultry in a focused, risk-based manner but this accounted for less than 1% of the vaccine used.

Several Members in the Region are currently undertaking vaccine discovery and efficacy studies with a view to meeting regulatory requirements and application to urgent use in approved programs; and also to explore the question of efficacy in different susceptible species such as ducks and geese. The studies cover a range of vaccine types including vectored vaccines (with/without mosaic antigen) and subunit recombinant proteins, whilst in the future considering the use of mRNA technology.

Inactivated vaccines

Avian influenza vaccines for poultry are based on the haemagglutinin (HA) gene and protection is specific to individual serotypes. Universal vaccines are currently not available although development work especially for application in a human setting is subject of much research effort. The majority of vaccines used to date have been based on inactivation of whole virus and often delivered with an oil adjuvanted system and injected subcutaneously or intramuscularly. Inactivated viral vaccines are often low in immunogenicity and require booster doses and formulation with adjuvants for longer lasting immunity. Immune responses induced by inactivated vaccines typically consist of humoral immunity with a slow onset period and are generally unsuitable for a DIVA (Differentiating Infected from Vaccinated Animals) strategy based on differential immune responses (20). In addition, protection is compromised by pre-existing maternally derived antibody in young birds. Importantly, administering inactivated vaccine through intramuscular injections is a laborious process and ill-suited for high-density farming and often leads to inefficiencies in vaccine delivery. Nevertheless, these vaccines are relatively cheap to produce, can be applied to multiple host species and it is possible to adapt to field virus whilst there is extensive experience in licensure. DIVA options based on immune responses are not available for field application since these vaccines are made from whole virus.

Vectored vaccines

Vector vaccines are being increasingly used and offer several advantages over conventional inactivated vaccines. These use live virus vectors (typically herpes virus of turkeys or fowl poxvirus) containing an HA gene insert (i.e. H5) and are relatively cheap to produce, easy to standardise and can be rapidly adapted to a changing field virus (by changing the insert) such has been seen with H5 HPAI (14). These vaccines are phenotypically stable, do not revert to virulence and are rarely transmitted horizontally (9). Furthermore, they can be applied in-ovo at the hatchery or by subcutaneous injection at

one day of age (1) and provide options for DIVA by serology since only one component of the virus is included in the vaccine. New approaches have computationally optimized broadly reactive antigen to design an H5 HA insert against genetically diverse H5 HPAI viruses with promising results (3). The so called resulting 'mosaic' antigen has already been used in licensed products. Drawbacks with these vaccines can be the host population needs to be defined as vectors by definition have host specificity and will not replicate in all species. If the vector is naturally present in a population to be vaccinated natural immunity in the population to the vector virus can compromise uptake together with interference from maternally derived antibody. Systems or regions containing multiple population types may be problematical if using a single vectored vaccine given host specificity unless targeting is being applied. Finally due to more limited use there is less experience in a field setting and in countries where these vaccines have been used it has rarely been in conjunction with a formal DIVA programme.

Subunit or nucleic acid vaccines

The whole pathogen is not essential to confer complete protection against the disease and using selected virus proteins can induce protective immunity. AI recombinant vaccines based on baculovirus expressing recombinant protein or defective replicating alpha virus RNA particles expressing HA protein (16) or DNA vaccines with an HA gene insert have been used but field application knowledge very limited. Although recombinant subunit protein vaccines are DIVA compatible (20) they have major disadvantages including relatively low yield and complex purification process that can result in high manufacturing costs. As a recombinant protein, a subunit vaccine possesses low immunogenicity and requires high dosage, frequent boosters, and adjuvants to enhance the protective response (18). Virus like particles (VLPs) are structural proteins with morphological features that resemble virus structures. Due to the similarity in structure, VLPs have successfully been utilized as novel vaccines against several viral pathogens. Experimental studies have shown VLPs to confer high levels of protection against avian influenza in chickens (17). Nonetheless, the high cost of expression and purification, cold chain requirement and stability in field conditions currently limit their use for commercial application. Production of VLPs in plant-based expression systems offers potential advantages in increased safety and scalability at a low cost.

Additionally, mRNA vaccines as applied for COVID-19 are attracting interest and have high potential for low-cost rapid production with adaptability to a changing virus and applicable to a DIVA strategy. These vaccines introduce a short-lived synthetically created fragment of the RNA sequence of an AI virus into the bird being vaccinated. These mRNA fragments are taken up by dendritic cells through phagocytosis. The dendritic cells use their internal machinery to read the mRNA and produce the viral antigens that the mRNA encodes. Current limitations with some of these innovations in vaccine delivery is they are not proven in a complex environment with multiple types of poultry so delivery and induction of protective immune responses may be challenging in some systems.

Live attenuated vaccines

Live attenuated AI vaccines developed from wild type strains are not recommended for poultry by WOAH/FAO/EU due to the potential risk of reversal of the attenuated strain into an HPAI by reassortment or mutation.

BEST PRACTICES ON VACCINATION AGAINST HPAI

Any long-term strategy for preventive vaccination would benefit from formal process of review of outcomes in vaccinated populations, results from monitoring systems and assessment of potential changes in the virus that necessitates vaccine update. The most comprehensive experience to date is the system that has been used in China (People's Rep. of) for around 20 years, whereby there is frequent review of flock and population immunity in the context of contemporaneously circulating viruses (7). Additionally, the emergence of new strains or re-emergence of previous strains is closely monitored through passive surveillance systems (vaccinated and non-vaccinated populations). This program has led to 14 updates in the vaccine used mandatorily in commercial poultry in China (People's Rep. of) (8). Furthermore, due to the diversity of viruses co-circulating more than one strain has been included in recent vaccines in order to achieve broader protective effect.

The system in China (People's Rep. of) and almost all other currently vaccinating Members is not to apply DIVA principles even if vaccine design lends to such a system. These requirements need to closely align with the vaccination strategy and the ability to freely move birds or products especially across international boundaries. To date most vaccines have been of the inactivated type but because of drawbacks in the use of DIVA strategies and the inability to easily update such vaccines without large costs there is increasing moves towards the use of live vectored vaccines (or mRNA) and indeed current research activities in Europe are closely evaluating such vaccines for utility in the region.

STRATEGIC GOALS AND OBJECTIVES FOR USE OF VACCINATION

The *Terrestrial Code* (21) specifically sets out a strategic approach for safe and effective use of vaccination as part of an HPAI threat mitigation and control programme. Vaccination should be used as part of an integrated strategy with other containment and outbreak management and disease mitigation tools recommended in the *Terrestrial Code* and Terrestrial *Manual (Codes)*

Importantly the *Terrestrial Code* states 'The use of vaccination against avian influenza may be recommended under specific conditions. Any vaccine used should comply with the standards described in the *Terrestrial Manual*. Vaccination will not affect the high pathogenicity avian influenza status of a free *country* or *zone* if surveillance supports the absence of infection. Vaccination can be used as an effective complementary control tool when a stamping-out policy alone is not sufficient. Whether to vaccinate or not should be decided by the *Veterinary Authority* based on the avian influenza situation as well as the ability of the Veterinary Services to implement the vaccination strategy including the post vaccination surveillance and monitoring practices. The *Terrestrial Code* goes on to set out requirements for surveillance in vaccinated populations and to provide evidence to show the effectiveness of the vaccination programme.

Potential application in the Region

Any vaccination program needs to consider benefits, cost, risks, and challenges. In the context of the Region, a framework can be developed that enables safe vaccination without risk for disease transmission and includes relevant surveillance approaches to provide assurance to stakeholders including trading partners or neighbouring countries.

Across the Region there are opportunities to develop harmonised approaches, share best practices and utilise high quality scientific evidence. These principles can be applied to issues such as: defining performance characteristics for high quality vaccines; tools and systems for effective DIVA; developing robust approaches for assessing cost benefit; a formal framework for assessing updates to vaccine to meet changing viruses; possible benefits of establishing a vaccine bank, and options for rapid supply of vaccine adapted to circulating strains. Wider issues would include developing the necessary assurances for safe trade following the principles laid down in the *Codes*. Ideally a system should enable the rapid detection, identification and characterisation of viruses detected in vaccinated populations with data informing both veterinary and public health. Some Members across the Region already have established frameworks whilst others are developing a legal basis to enable use of vaccination. These approaches could include both preventive and emergency vaccination applied on the basis of a local risk assessment. They can be underpinned by a regulatory framework that allows the use of vaccine solutions for prevention or control purposes and could include licensure that for example will use new science approaches, assessing vaccine suitability to protect against a changing group of threat viruses.

Targeted vaccination or all sectors (framework for application) and approach

Epidemics across the Region in the last 10 years have involved multiple sectors and populations furthermore husbandry practices in some populations contributes to increased risk for onward transmission of virus where such production systems have close connectivity and sub-optimal biosecurity. The risk of incursion into higher risk production systems is increased further in more northerly latitudes where in autumn and winter there are substantive populations of migratory waterfowl, which introduce the virus to a member country or population. Secondary spread is high risk in densely populated poultry areas (DPPA) especially with species of high susceptibility such as ducks and turkeys. Therefore, the risk profile and the demographics of any member countries' poultry population should shape and influence the scale and application of any vaccination program if it is to be targeted. Indeed, the *Terrestrial Code* on vaccination states "The target population may include the entire susceptible population or an epidemiological relevant subpopulation depending on the likelihood of exposure, the consequences of the disease, the role of the different subpopulations in the epidemiology of the infection and the resources available" (21).

An overarching framework should ideally be developed that can be adapted and applied to individual country needs. To control an infection such as HPAI can be more difficult to achieve through emergency vaccination, unless used to mitigate a fast-spreading event by vaccinating birds in buffer zones (presumably DPPA) or to preserve rare species or collections. This strategy has not been applied so experience of utility to HPAI control is limited with preventive vaccination being the preferred method; while the disease can remain endemic in countries where vaccination has been used. The development of such an overarching framework could be facilitated by modelling, and by calculating the resources necessary to implement control through vaccination versus the resources for outbreak control through classic control measures, obtained by having proper understanding of the different value chain components of the poultry sectors.

Improved outcomes are achieved when vaccination programs are applied in conjunction with other disease outbreak management and threat mitigation tools. This especially includes applying good levels of biosecurity, taking effective and fast action to stamp out vaccinated infected flocks, imposition of quarantine zones, rapid tracing to establish source and spread risk, rigorous control of the movement of birds through licensure, pre- movement testing and continuing to assess the utility of the vaccination program.

POST VACCINATION SURVEILLANCE AND MONITORING

The *Terrestrial Code* provides guidance on expectations to conduct surveillance in vaccinated birds, to demonstrate freedom from HPAI and gathering evidence for the effectiveness of the vaccination program. If vaccines are antigenically well matched to the field strain they will prevent disease, substantially reduce virus shedding (level and duration) and limit transmission to naive birds. If vaccines are poorly matched to field strains, whilst they will reduce disease signs and may partially reduce shedding, they will not stop transmission between birds in a flock so therefore it is imperative in those circumstances to have proper vaccine matching, and hence the application of active monitoring programs in vaccinated flocks using DIVA principles (15).

Failure to detect persistence of wild type virus in a vaccinated population immunised with poorly matched vaccines is that it may induce the selection of vaccine escape variants which if of high replicative fitness could spread and emerge in vaccinated populations thereby influencing virus change and diversity. It is therefore desirable to ensure that any vaccine registered meets prescribed standards for immune induction and cross protective responses to target viruses. In addition, viruses detected in vaccinated populations should be carefully and rapidly assessed to determine a) any virus correlates consistent with escape (rather than due to inadequate vaccinal immunity) and b) in the context of zoonotic risk to ensure there is no change in risk profile due to genetic mutations in any escape variants.

Enhanced passive surveillance should be implemented in vaccinated flocks including clinical examination, check of records to determine clinical history and monitoring baseline mortality. Recent investigations support early warning for presence of infection with H5 HPAI through a system of routine examination of ‘normal’ mortality rates (13).

Approaches to Differentiation of Infected from Vaccinated Animals (DIVA)- HPAI

A strategy that allows DIVA, has been put forward as a possible solution to the eventual eradication of HPAI and H5/H7 LPAI without involving mass culling of birds and the resulting economic damage, especially in developing countries (11). This strategy has the benefits of vaccination (less virus in the environment), but the ability to identify infected flocks, would still enable the implementation of additional control measures, including stamping out of infected flocks. DIVA strategies use one of two broad detection schemes within the vaccinated population: 1) detection of influenza A virus (‘virus DIVA’), or 2) detection of antibodies against influenza A field virus infection (‘serological DIVA’). At the flock level, a simple method consists of regularly monitoring sentinel birds left unvaccinated in each vaccinated flock, but this approach does have some management problems, particularly with regards to identifying the sentinels in large flocks and has largely been abandoned. As an alternative system, testing for field exposure may be performed on the vaccinated birds either by detection of field virus or antibodies against the virus. To detect the field virus in vaccinated flocks, oropharyngeal or cloacal swabs from a) baseline daily mortality or sick birds b) statistical random sample of a flock to prescribed limits (i.e., 95% confidence of detecting 5% prevalence) can be tested, individually or as pools, by molecular methods, such as real-time RT-PCR or antigen capture ELISA (22). Such testing should have a defined frequency.

To use serological DIVA schemes, vaccination systems that enable the detection of field exposure in vaccinated populations should be used. Several systems have been used. First, use of a vaccine containing a virus of the same haemagglutinin subtype but a different neuraminidase (N) from the field virus. Antibodies to the N of the field virus act as natural markers of infection (5). Problems with this system arise for H5 HPAI since field viruses in recent years have carried multiple different N types. An improved second serological DIVA option is the use of vaccines that contain only HA, e.g., replicating (vector based) or non-replicating recombinant vaccines, which allows validated, laboratory assays (i.e., ELISAs) that detect antibodies to conserved core proteins amongst AI viruses, indicative of infection in vaccinated birds. Finally, for inactivated vaccines, a test that detects antibodies to viral components only produced during active infection (2), but these systems are yet to be validated in the field.

If virus DIVA systems are used (at time of writing more easily available to deploy with quality assurance proven) they have the limitation they only provide information on status on the day of sampling whilst serological DIVA provides information on historical exposure but would likely lead in the case of positive results, to further investigation to exclude presence of

active infection via tests for viral antigen or genetic material. Schemes in the EU are proposing testing (with some caveats) at least every 30 days for preventive vaccination and 14 days for emergency vaccination regardless of system used (10).

SETTING REQUIREMENTS AND A FRAMEWORK FOR THE HARMONISED USE OF VACCINATION AGAINST HPAI IN THE EUROPE REGION

The key elements for decision-makers in considering the need for a vaccination program should have clearly defined objectives and the purpose for which vaccination will be used as part of a wider control program. This will include the following elements:

- Programme scope (targeted/non targeted; preventive or emergency option with associated exit strategy for the latter; species to be vaccinated; localised or all) and integration in overarching disease control and threat mitigation strategy
- Programme duration should ideally be defined even if open ended or linked to continual evaluation of risk to the 'region'
- Vaccine type
- Surveillance requirements including DIVA approach
- Safeguards for movements of birds and products
- Trade impacts (as applicable)
- System for continuous review of programme implementation and effectiveness including cost benefit analysis
- System for continuous assessment of vaccine effectiveness and need for updates
- Programme financing and legal framework (from vaccine market authorization to proper training in vaccination)
- Management of possible impacts for public health and social perception.
- Vaccination should be part of contingency planning even if not adopted

GLOBAL INTELLIGENCE AND VACCINE STRAIN MATCHING

The H5 HPAI viruses have been circulating across the world for over 25 years and as a result have diversified in discrete niches and populations across many regions. This has led to extensive genetic evolution resulting in multiple sub-families of the virus. Cross protective immunity between the sub families of H5 viruses is less well defined but may be difficult to achieve with some vaccines, so careful consideration needs to be taken with regards the risk viruses for incursion and selection of vaccines that might afford broader protective responses. It is not clear whether the emergence of antigenic variants is related to use of vaccines or improper use of vaccines, but the emergence of resistance has necessitated the change in vaccine seed strains to antigenically match the circulating field strains (6). All of the outbreaks since 2016 in the Region have been due to a single genetic group or subfamily but other groups are circulating around the world and their ability to spread to birds in the Region and beyond is highly possible. It is imperative therefore that international laboratory networks continue to scan for emerging threats, track changes in viruses and formally develop systems to recommend updates to vaccine strains to ensure good efficacy. Viruses obtained from outbreaks, should be assessed for genetic and antigenic variation as part of an ongoing program for assessing vaccine effectiveness in the field. These systems are already in place for human health and global animal influenza networks such as OFFLU (WOAH and FAO network on animal influenza) track changes in the virus and relevance to currently deployed vaccines in order to predict protective effect at population level. Vaccines that are not protective should be discontinued and replaced with vaccines containing either updated inactivated vaccine seed strains or HA inserts within other vaccine platforms. Furthermore, multiple and newly validated in-vitro tools are available to predict strain matching (12) therefore reducing the need for costly and time limiting studies to assess efficacy in-vivo for each update but would still need to take into account species specific factors.

In some situations, more than one seed strain or a mosaic antigen may be necessary to cover all the threat viruses to a country. Only high quality and potent vaccines should be approved for use in control programmes (22). Proper administration of high quality, potent vaccines is critical in inducing protective immunity in poultry populations

STAKEHOLDER ENVIRONMENT FOR VACCINATION

Potential moves to HPAI vaccination across the region are a major change in threat mitigation and disease control and will require effective stakeholder collaboration and engagement. Whilst programs will come under the jurisdiction of the *Veterinary Authority*, they can only succeed in strong partnership with others especially including industry (governance bodies, private veterinary surgeons, and companies/producers) to ensure commitment and compliance, along with communication with marketers / retailers of poultry products and the wider public, to avoid rejection by consumers. It will require regulators of vaccine products and manufacturers to adapt to a new landscape (with market opportunity!) for market authorisation with a framework for product review accommodating the need for different or updated vaccines. Veterinary infrastructure (official or private) will need to deliver the administration and implementation of surveillance programs. Veterinary laboratories both official and private will be required to provide underpinning services and support including the necessary testing capacity. WOAH Reference Laboratories will need to oversee harmonised testing and conduct quality science to deliver evidence to decision makers,

KEY CONCLUSIONS

- Substantive increased risk to the region from annual waves of HPAI leading to large epidemics.
- Spread being initially introduced and mediated via migratory birds. The viruses are continuing to evolve in these populations and present challenges to identify protective vaccines
- Multiple new vaccines using different approaches are in development with some undergoing efficacy testing with a view to urgent use in newly developed vaccination programmes
- Vaccines strain selection and delivery systems need careful selection to ensure efficacy against a diverse family of H5 HPAI threat viruses to region
- DIVA is a key element in any vaccination programme
- Surveillance for detection of infected vaccinated flocks is an important component of any programme and dependent on vaccine and methods selected there is a choice of options
- Monitoring of viruses from vaccinated flocks and their characteristics with respect to possible reduced vaccine efficacy and further evolution (including public health risk) is required
- Review of vaccination effectiveness, cost benefits, processes for vaccine licensure as an ongoing process
- Multiple stakeholder support under the control of the *Veterinary Authority* is required. Any vaccination program should meet international standards defined in the *Terrestrial Code* and *Terrestrial Manual.*

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