Policy and Approach to HPAI Vaccination

The current Animal and Plant Health Inspection Service (APHIS) policy for avian influenza (AI) vaccination, as described in VS Memorandum 565.12, allows "H5 and H7 vaccines to be used as a tool for combating any potential outbreak of highly pathogenic avian influenza (HPAI) in the United States." AI vaccines may be prepared from any serotype, including H5 and H7, and may be recommended for use in chickens or turkeys subject to the requirements and restrictions specified in VS Memorandum 800.85v2. The memorandum allows H5 and H7 vaccines to only be used under the supervision or control of USDA-APHIS-Veterinary Services (VS) as part of an official USDA animal disease control program. The VS Center for Veterinary Biologics (CVB) implements the provisions of the Virus-Serum-Toxin Act to ensure that veterinary biologics available for the diagnosis, prevention, and treatment of animal disease are pure, safe, potent, and effective.

APHIS supports that vaccination should be available as part of a science-based influenza control strategy that includes: (1) enhanced biosecurity; (2) an eradication plan; (3) controlled vaccination for flocks deemed to be at risk; (4) suitable monitoring of all flocks at risk and of all vaccinated flocks; and (5) a repopulation plan. The management of AI must continue to be based on sound scientific principles. However, innovative strategies will be required to eliminate these persistent and adaptive viruses.

Assumptions to be Used Throughout this Policy/Approach:

The use of vaccine will be through USDA supervision and will only be distributed under the approval of each State Veterinarian. USDA will cover the cost of purchasing vaccine. USDA will not incur the costs associated with administering the vaccine. Vaccine will be used as part of disease suppression (i.e., preventing further spread) and eradication. In certain unique economically significant circumstances, it may be used as a protective effort to maintain production. The use of a vaccine strategy in an outbreak situation does not mitigate the need for increased biosecurity efforts. All HPAI testing will be done at a National Animal Health Laboratory Network (NAHLN) Laboratory and National Veterinary Services Laboratories (NVSL). VS will provide recommendations for use of specific vaccines in line with testing and surveillance methods. Vaccinated birds will be identified, and vaccinated flocks will be monitored. Vaccinated birds will not move outside of the vaccination area (those States or regions where vaccine is used under this strategy). Products from vaccinated birds may be moved outside of the vaccination area, but must not be exported. Poultry from outside States will be allowed to transit the vaccination area in accordance with all other procedures for transiting a control area.

Factors and Triggers Preceding Vaccination:

Vaccination may be considered as part of a suppression or eradication strategy in an outbreak. Certain unique circumstances may call for protective vaccination. The factors or triggers to consider for any decision to vaccinate include the following:

- Probability that the disease cannot be rapidly contained

- Proximity of high-value genetic birds to the rapidly spreading disease focal point
- Poultry density in the area
- Increased risk of introduction due to the presence of HPAI in neighboring areas
- The extent to which disease is found in waterfowl, other wild birds, backyard flocks, or in live bird markets
- Availability of physical and economic resources

An outbreak situation in a poultry-dense area that is rapidly spreading and does not appear to be contained by active response efforts (including surveillance, strict biosecurity, quarantine, and rapid depopulation of affected flocks) would be a target for the suppressive/eradication vaccination strategy. In this strategy, all commercial poultry in a defined geographic area would be vaccinated. However, there may be justification for not vaccinating certain commercial subpopulations within and area, such as short-lived birds (broilers, ducks) or primary breeders that are under high biosecurity or compartmentalization. Each vaccination area will need to be evaluated for these circumstances and vaccination decisions made in consultation with States and producers.

If suppression/eradication emergency vaccination is used as a strategy in a geographic area, there may be unique situations in surrounding areas where a protective vaccination strategy could be employed at the same time. This would only be for long-lived birds where infection could be economically significant nationwide – for example, a geographic area densely populated with layer flocks. There are technical and logistical constraints around this type of protective vaccination strategy. Protective vaccination of layer flocks would be applied only to replacement pullets, as the resource challenges and limited effectiveness of vaccinating production layers would preclude success.

Zoological collections in a geographic area where emergency vaccine is used would also be considered for a protective vaccination strategy. This off-label use of vaccine would require approval by the State Veterinarian for each individual collection, with signed agreement by the facility attending veterinarian for appropriate monitoring and control of any vaccinated birds.

Prioritizing Vaccines:

When vaccine or vaccination resources are limited, prioritizing will be necessary. Criteria for prioritization include demonstrated vaccine efficacy in the target species/age, commodity impacted, geographic proximity to outbreak or infected birds, population density, outbreak pattern, and type of flock (e.g., grandparent flock vs. commercial meat turkeys or table egg layers).

APHIS has developed models to allow estimation of total economic impact of choices using the criteria and will utilize these models as part of the vaccination strategy during an outbreak. Animal disease spread simulations can be modeled within 24 hours of the first detection of HPAI. Initial work using the models offers the following information on vaccination options:

1. Generalized epidemiological modeling results suggested that disease spread is more predictable in geographic areas with consistently high commercial poultry population density (uniformly dense populations). In these areas, vaccination tended to be triggered

frequently, and offered a clear benefit in reducing the number of depopulated flocks when compared to scenarios not incorporating vaccination into control strategies. Additionally, earlier start times for vaccination relative to first detection of HPAI resulted in shorter outbreaks with fewer infected flocks. Economic modeling estimates indicated the benefits of reduced spread due to vaccination in the uniformly dense populations of commercial poultry simulated in the epidemiological model may offset the costs of heightened trade restrictions under vaccination.

2. Conversely, simulating disease spread in regions characterized by pockets of, or lower commercial poultry population density, generated less predictable results. The number of infected flocks was typically lower, unless disease spread into a cluster of farms within the densely populated area. Consequently, disease spread in these less densely populated production areas may be staggered with a difficult to predict rise in the number of infected flocks, complicating the triggering of vaccination and reducing the effectiveness of reactive vaccination as a control and prevention strategy.

Approval of Vaccine Use:

The APHIS Administrator or his designee will approve the potential use of vaccines based on several criteria, including the status of HPAI detections, vaccine efficacy, and the availability of doses. A suppression/eradication vaccination strategy would be applied only under the supervision of the active incident command in that area. The incident command (including State, Industry, and Federal involvement) team would be responsible for developing and forwarding the plan for vaccination use, reporting vaccine use, permitting movements, and monitoring activities as part of their regular reporting. If vaccinated birds remained alive after the active incident was resolved (for example, a breeder flock in the vaccination zone), the State Veterinarian will be responsible for monitoring and routine reporting on the flock.

In those unique situations where protective vaccination is used, the State Veterinarian would be required to develop a plan for vaccine use within their State (including poults/pullets shipped to their State) to include regular reports on vaccine use, monitoring activities, and movement permits. The State will submit this plan to USDA (Assistant Director in conjunction with National Poultry Improvement Plan (NPIP) office) for review.

Oversight of Vaccination:

USDA would require a memorandum of understanding (MOU) with the States using vaccines and their poultry producers. The MOU would include adherence to an approved State eradication plan using vaccination as a tool to eventually ensure that HPAI virus has been eliminated from each individual poultry premises. The MOU would include the following requirements:

- Maintain accurate records of all commercial vaccine purchased and used;
- Monitor and confirm to USDA that vaccine use is strictly limited to the defined vaccination zone as outlined in the national strategy;
- Monitor and confirm that the accepted vaccination protocol is being followed;
- Ensure that there is active monitoring of vaccinated poultry through diagnostic testing of vaccinates or sentinel birds and dead bird surveillance;
- Allow USDA to review and have access to all production and mortality records;

- Develop a flock eradication plan that includes details for regarding the use of vaccine for each premises vaccinating birds to be signed by each producer or company and co-signed by the State Veterinarian and VS Assistant Director for the State;
- Have a record of GIS coordinates for each vaccinated premises; and
- Ensure that vaccine records show only vaccinated birds are being housed under an all- in/all-out system in test-negative houses on the premises.

As part of the MOU, APHIS would do the following:

- Provide oversight and monitoring on the use of AI vaccine and testing of vaccinates or sentinel birds as needed and agreed;
- Provide laboratory support through the NAHLN (screening tests) and NVSL; and
- Provide logistical support, testing media, and assistance to the vaccinating States to ensure compliance with the suppression/eradication vaccination program.

APHIS would re-evaluate and potentially halt the vaccination program at a national level if either of the following occurred:

- There is genetic evidence that HPAI isolates have mutated toward an antigenically new highly pathogenic form;
- There is an indication that vaccine effectiveness is inadequate for the purpose (considering host factors, vaccine type and delivery) of controlling disease spread.

A State MOU will be considered null and void, authorization for use of the vaccine will be withdrawn, and the vaccination program will be cancelled if the State fails to meet the requirements of the MOU or if the vaccine fails to prevent the spread of virus beyond the vaccination area.

Exit Strategy:

Vaccination brings with it constraints and risks, including additional costs, export consequences, routes of administration, the time required to achieve immunity, the need for boosters, potential for viral spread by vaccination teams, and the cost and need for surveillance.

For an exit strategy, vaccination should cease once the last infected premises in a control area is cleaned and disinfected and no virus is isolated in the last infected premises for at least 42 days (two times OIE incubation period for AI). That means there should be no new case of HPAI for at least 42 days in the control area and the last infected premises is cleaned and disinfected, with negative results on environmental samples.

Surveillance must continue after vaccination is stopped. This is done to demonstrate that there is no residual HPAI H5 circulating after vaccination ceases, and to provide early detection so that other measures (such as stamping out) can be used early.

The HPAI status of each vaccinated premises can be monitored either through a validated strategy to differentiate vaccinated from infected animals (DIVA), by influenza A serologic

assays, rRT-PCR monitoring of non-vaccinated sentinel birds maintained in the same environment, or by dead bird surveillance of other birds in the same environment.

Surveillance Requirements in Vaccinated Flocks:

Specific surveillance protocols would be developed and modified in accordance with the vaccine that is in use. The guidelines included in this document are general suggestions, based on what we know of vaccine possibilities, and would be targeted to the specific vaccine chosen for any vaccination effort. This document will be updated as needed.

For the current rHVT vaccine, the DIVA strategy will not only discriminate between infected and vaccinated birds, but also will help identify vaccinated birds that become infected with avian influenza. A strategy would be to use agar gel immunodiffusion (AGID) or hemaglutination inhibition (HI) assay for examination of an immune response to field strain virus exposure and/or a reverse transcriptase polymerase chain reaction (rRT-PCR) based approach utilizing the standard matrix AI assay for the direct detection of active AI virus in tissues or swabs. Both of these tests will be negative in rHVT vaccinated, unexposed chickens. However, this approach is muddied by the use of conventional inactivated swine lineage H1 and H3 vaccination in turkeys, as these vaccinates will have positive AGID or HI results. Accordingly, all vaccinated turkey poults will be required to have periodic oropharyngeal samples obtained and tested via rRT-PCR per the MOU with the controlled States. Birds presumptive positive via the matrix rRT-PCR test and found to be presumptive positive for H5 must have samples forwarded to NVSL for confirmation of H-type and determination of pathogenicity status. Any birds found to be positive for HPAI must be immediately quarantined depopulated and indemnified and the premises must undergo the full cleaning and disinfection process outlined in the Red Book.

Surveillance Protocol for Turkeys:

Vaccinated turkeys will be sampled routinely. The house will be sampled once a week, with rRT-PCR tests, until the birds are 6 weeks of age. Subsequently, rRT-PCR testing by house will be done every 3 weeks for the life of the flock when over 6 weeks of age. Immediate testing will be conducted whenever triggering events of mortality or reduced egg production occur as described in the draft Secure Turkey Supply Plan for monitoring within the control zone. This could be incorporated into regular serological monitoring generally conducted every 3-4 weeks on breeding stock post-vaccination. Use of sentinels is discouraged. Unvaccinated birds would represent a multiplication risk that could overwhelm induced immunity in vaccinated stock thereby defeating the purpose of vaccination. Turkey breeders in production are handled individually at least weekly for artificial insemination and any HPAI present should manifest quickly, especially if breeder toms supplying semen to those flocks are affected. Weekly testing of breeder toms in production should be considered.

Surveillance Protocol for Table Egg Layers:

Surveillance would be through serological testing of vaccinates and dead bird surveillance using rRT-PCR followed by confirmatory testing at NVSL.

- Pullet house (vaccinates and dead bird tested)
    - 80-100 birds/house

    - Pullets tested by AGID, rRT-PCR, VI prior to placing
    - After 2 weeks –30 vaccinated birds are tested by serology, rRT-PCR and VI (to see if there is an infection circulating in the house)

- Layer house (vaccinates and dead bird tested)
    - One day/week – Tracheal swabs from all daily mortality (min 10 birds) tested by rRT-PCR and VI
    - 30 of 100 laying birds monitored every 2 weeks by serology, rRT-PCR, VI and HI (to help demonstrate titers post immunization and to provide evidence that virus spread is not occurring through vaccinated flock)

- Spent hens (3 weeks prior to depopulation)
    - One day/week – test all daily mortality (up to 30 birds) by rRT-PCR and VI

Detecting Infected Flocks:

We can detect infected flocks through the use of live birds and dead bird surveillance. For flocks that are vaccinated with the vectored AI, a seroconversion for AI in vaccinated flock will denote infection.

RRT-PCR testing will be used to test flocks suspected to be infected with HPAI. Dead birds should be submitted to the local NAHLN lab for necropsy and testing and recorded and results reported to the State Veterinarian, APHIS and the producer.

Response if Vaccinated Flock is Infected:

If a vaccinated flock is determined to be infected with HPAI, then we will depopulate the flock and provide indemnity to minimize a source of virus that can infect other susceptible flocks. If the vaccinated flock that is infected is of very high value (i.e., pure lines necessary for breeding), then it will be the discretion of APHIS to depopulate or not depending on the economic impact of such depopulation to the poultry industry as a whole.

Identification of Vaccinates:

We will track vaccinates by approval of vaccine use and permitted movements of vaccinated poultry. Each State will have to maintain a record of all vaccinated flocks and the results of the required monitoring test results. This record will be shared with the USDA.

Impact on NPIP Status and Requirements:

If vaccination is adopted as a suppressive or protective strategy for HPAI in the United States, NPIP surveillance requirements may need to be amended by each State that is implementing a vaccination strategy via their existing approved Initial State Response and Containment Plan. Currently, all NPIP commercial broilers, commercial meat turkeys, and commercial table egg layers must test negative to H5/H7 AI to maintain their official certification as a **H5/H7 Avian Influenza Monitored** flock. Breeding turkeys must test negative to H5/H7 AI to maintain their official certification as a **H5/H7 Avian Influenza Clean** flock. Further, primary and multiplier

egg-type and meat type chicken breeders must test negative to all subtypes of AI to maintain their official certification as an **Avian Influenza Clean** flock. Therefore, if birds are vaccinated for and test negative on an NPIP-approved test cleared for use with vaccinates, their certifications will be maintained. However, if a flock is infected and tests positive for AI, certification will be lost. In order for any NPIP participating hatchery to maintain their NPIP certifications, they must only accept hatching eggs that are derived from NPIP flocks that have tested negative to AI. NPIP hatcheries that accept hatching eggs from NPIP participant flocks that have been vaccinated and test negative will maintain their certification; NPIP hatcheries that accept hatching eggs from flocks that are infected and have tested positive will lose their certification.

NPIP regulations permit the use of vaccination in poultry if the following principles are fully met:

- If vaccine is used, methods must be used to distinguish vaccinated birds from birds that are both vaccinated and infected.
- If vaccination is considered as an option, a written plan for use must be in place with proper controls and provisions for APHIS approval of any use of vaccine. The plan will define procedures to prevent the spread of HPAI by vaccination teams. Surveillance must continue to assess vaccination effectiveness and detect any antigenic change. The vaccinated premises will be subject to risk assessments, surveillance requirements, and biosecurity procedures. Considerations must be given to any national or OIE standards or conditions for movement as well. The requirement for a written plan is addressed through the MOU which is required for use of vaccination, as detailed earlier in this document.

Interstate Movement Requirements and Impacts:

Interstate movement of birds that are not vaccinated should not be affected. NPIP status of non-vaccinated flocks should not be affected by the use of vaccine, and therefore should not impact interstate movements. Movement of vaccinated birds will not be allowed outside of the vaccination area, unless done in a controlled and permitted manner to slaughter. The movement of hatching eggs/day-old chicks derived from vaccinated breeder flocks should not be restricted, nor should these be considered vaccinates. However, these shipments should be permitted and tracked so that any subsequent positive test results could be appropriately interpreted.