USDA United States Department of Agriculture

Highly Pathogenic Avian Influenza H5(EA) – Status of Vaccines for Avian Species' Immunization in the United States

Executive Summary

The use of vaccination for control and eradication requires highly effective vaccines to reduce viral shedding, reduce clinical signs and mortality, and ideally allow the differentiation of infected from vaccinated animals (DIVA). Currently, no vaccines licensed or permitted in the United States are demonstrated to have those qualities against the current highly pathogenic avian influenza (HPAI) H5 Eurasian (EA) outbreak strain. Development of potential products for conditional licensure for one or more poultry species is in progress; however, each has technical, regulatory, legal, or financial obstacles. USDA issued a request for proposals in August 2015 to encourage the development of an efficacious product to be available for the fall 2015 migration season.

Background

On June 3, the USDA published "Additional Criteria Must Be Met Before Emergency Use of Vaccine for Highly Pathogenic Avian Influenza Can Be Approved." It stated: ". . . the Department evaluated the efficacy of current vaccine options for HPAI in addition to economic impacts of vaccination and has determined that, as it currently stands, additional criteria must be met before a vaccine can be approved for emergency use. . . . USDA will continue to encourage development of vaccines for HPAI and will approve vaccines as they are developed and evaluated. Currently, there is lack of a well matched, effective vaccine for HPAI . . ."

Efficacy in Poultry

Current poultry vaccines involve eliciting a protective immune response specific for the hemagglutinin (HA) protein of the influenza virus in question; "universal vaccines" do not exist for avian influenza (AI). Both H5N2 and H5N8 have been implicated in recent poultry outbreaks, but all viruses detected to date have an HA gene derived from the same EA H5. Ongoing monitoring of field viruses is required to detect antigenic drift that may impact vaccine efficacy. New seed strains will be needed if new distinct strains of H5(EA) emerge.

It should also be noted that at least **two doses** of H5 AI killed virus vaccines are recommended to induce effective immunity in chickens, and probably turkeys, for a production cycle and the immunity takes 7-10 days to develop. For inactivated vaccines, the first dose typically is not administered prior to 3 weeks of age per label indications. Other products may be given at one day of age and boosted with an inactivated product or other alternative vaccine.

Licensed Vaccines

There are currently six H5 AI vaccines that are commercially available in the *List of Licensed Veterinary Biological Products*; four are fully licensed (two inactivated products, a live herpevirus product, and a fowlpox vectored product) and two conditionally licensed (inactivated products). All of the H5 AI vaccines have label claims for chickens, but none for turkeys. Recent trials at the USDA Agriculture Research Service (ARS) Southeast Poultry Research Laboratory (SEPRL) of representative inactivated and vectored vaccines generated from H5(NA) found that none adequately protected chickens.

Although the inactivated Zoetis (FluFend) product and the live HVT-vectored CEVA vaccine (Vectormune AI) contain older H5(EA) inserts, neither is antigenically well matched with the current outbreak H5(EA).

Potential Vaccines

Conventional (whole virus) inactivated AI vaccines produced directly from an outbreak HPAI isolate or a low pathogenicity isolate with a well-matched HA have been shown to be very effective at preventing clinical disease and decreasing virus shed. Animal and Plant Health Inspection Service (APHIS) guidance prohibits the use of HPAI vaccine seeds for production of conventional inactivated products. There are no natural low pathogenic isolates antigenically matched to the outbreak strain.

SEPRL has generated a low pathogenic seed virus using reverse genetics that contains an HA gene modified from the current outbreak H5(EA) virus. Experimental inactivated vaccines produced from the seed have demonstrated good protection in chickens and turkeys, and further trials are ongoing. A Select Agent exemption has been granted for this construct, which will allow vaccine production in conventional manufacturing facilities. SEPRL has transferred the seed virus to a commercial partner for development and production.

RNA particle vaccines (Harrisvaccines) are another promising technology. The company has a CVB-licensed multivalent swine influenza RNA particle vaccine. Published experimental data with this technology using an avian influenza RNA particle has shown protection in chickens against other avian influenza viruses, and further trials are ongoing.

DNA vaccines, and other live-virus vectored vaccines expressing a well matched HA(EA) protein are additional possibilities under investigation.

Other Vaccine Issues

Updating the insert of a live vectored vaccine to match the circulating strain would entail a lengthy environmental clearance process unless alternative methods to satisfy the need are found. Field trials of vaccine candidates will likely be needed to provide data for licensure.

A solicitation to purchase and stockpile H5(EA) AI vaccines which meet licensing or permitting and use requirements was published August 17, 2015. This does not mean a decision to vaccinate has been made. Rather it is a means to having another tool available. If a vaccination program for HPAI is implemented, it will be important to have an exit strategy for stopping vaccination and a surveillance plan to prove freedom from disease and infection.

Surveillance using a DIVA strategy is expected to help mitigate concerns with the trade of poultry and poultry products should vaccines be used to control future disease outbreaks. Where only vectored or subunit vaccines are used, current influenza A serologic assays would allow DIVA discrimination. Agent detection assays (e.g., current RT-PCR) could be used in conjunction with vectored, subunit, or whole-virus inactivated vaccines. Antibody detection of a different neuraminidase protein compared to an inactivated vaccine is an option, but would be much harder to implement and would require development of new diagnostic assays. Ongoing vaccination-challenge trials include investigation/confirmation of DIVA compatibility.

Current Activities

USDA is actively involved in facilitating the development, evaluation, licensure, and acquisition of efficacious vaccines for the fall 2015 migration season. ARS and APHIS are conducting vaccination-challenge trials in biosecure animal facilities using a current outbreak virus. APHIS is processing vaccine license applications and investigating environmental release requirements. Other USDA staffs have been involved in permitting, exemptions, agreements, acquisition, use policies, and communication with trading partners relative to vaccination and specific vaccines.