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The Committee met on Tuesday, October 29, 2019 at the Rhode Island Convention Center in Providence, Rhode Island, from 8am to 12 pm. There were 8 members and 14 guests present. [Include other pertinent information regarding the beginning of your Committee session, such a review of previous resolutions, introductions, or other notices and announcements.]

CVB UPDATE

Byron Rippke, Director
Center for Veterinary Biologics At USDA, APHIS, VS

Budget- CVB's budget has remained relatively flat for the past ten years. 2019 has been no different. The President's budget indicated that FY2020 will be fairly similar. Congress has actually indicated an increase. Currently, we are under a continuing resolution, and we'll see what the House and the Senate agree to once an appropriation is approved for this fiscal year.

Staffing- The result of steady budgets is that with increases in salaries, benefits, etc., added to other costs of operation, the funding available to support positions is effectively less. That results in fewer on-board staff each year. Currently, CVB has about 30 positions that it does not have the funding to support. This means that we constantly are looking for more efficient ways to deliver our program, i.e. continuous process improvement.

Staff Transition- CVB was fortunate this fiscal year to have been able to replace everyone that we lost during that same period of time. Having said that, we are also in a time of generational turnover, and have lost staff with many years of experience to retirement. Fortunately, we have been able to hire some new, high quality individuals to help bridge those gaps. This retirement trend will be significant for the next several years.

NEPA- CVB published a new VS Memo 800.215 this year addressing the concept of categorical exclusions that was introduced as part of last year's NEPA final rule. This concept should allow subsequent live-recombinant veterinary biological products to make it to market in a shorter period of time.

Pharmacovigilance- Last year, CVB published a final rule on a mandatory pharmacovigilance program. This year, we are in the process of gathering input from the regulated industry, developing our guidance documents, piloting the reporting software, and standing up a more robust system for adverse event reporting for veterinary biologics.

Single-tier labeling- the project continues on to simplify veterinary biologics labeling to a single tier claim. This project is intended to standardize labeling and provide practitioners and animal owners with more information about how the veterinary biological products are evaluated at licensure. Product summaries are uploaded to our website and available for viewing there. The implementation for this rule will continue until Oct 31, 2021.

Cancer immunotherapies- CVB published a draft memo for public comment earlier this year. We are actively engaged with researchers and stakeholders to help determine the best approach to regulating these new products.

Autologous Products- This group of products needs to meet the standards for conditionally licensed products, which means full safety and purity need to be established prior to sale, and expectation of efficacy needs to be established. These products are intended for distribution to veterinarians only. They also need to satisfy the regulatory standards for experimental product.

NCAH Portal- The ability to send and receive electronic submissions continues to be a huge accomplishment for the CVB. This year we've expanded the functionality to include Research & Evaluation permits, transit permits, and permits for Sale & Distribution. This upgrade will allow us to retire the first two types of permits from the EPermits system which was used previously.

Salmonella sequencing- CVB has been working with FSIS and CDC to identify any Salmonellas showing up in slaughter and/or public health surveillance streams as being related to vaccine strains. This issue was raised in relation to a very low number of salmonellas that matched sequences of live Salmonellas found in vaccines. No changes to regulatory requirements have been made at this time, but the situation continues to be monitored closely.

Autogenous Product Policy- The regulations governing autogenous products have not been updated in years. There is interest in reevaluating the requirements for maintaining autogenous isolates, defining herd/flock of origin, approvals of non-adjacent use, and 3rd party distribution. This policy revision is early in the process, and we hope to have a draft document available for comment early next calendar year.

Ingredients of Animal Origin- With the concern about ASF, FMD, and other transboundary diseases, plus global movements of ingredients, CVB is taking a holistic look at how we regulate ingredients of animal origin. We have engaged with the regulated industry and other stakeholders to put together an updated VS Memo addressing this issue. It won't be publically available till sometime late this fiscal year.

Misc. topics- Included are a number of other pertinent CVB topics that will likely be covered by others, so I will not go into them at this point, unless questions arise later in the meeting.

Perspectives, Priorities, and Updates from the Veterinary Biologics Industry

Will McCauley, Director, Veterinary Biologics, Animal Health Institute

Dr. Will McCauley of the Animal Health Institute will deliver updates on current issues in the veterinary biologics industry. Topics discussed will include funding & staffing levels of the USDA's Center for Veterinary Biologics, development of an in vitro potency assay for rabies vaccines in the US, a new reference document for easily comparing various international regulatory frameworks, and potential new testing requirements for ingredients of animal origin, among others.

Swine influenza A viruses: A cornucopia of genetic diversity created by interspecies transmission episodes and the processes of antigenic shift and drift

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Influenza A virus (IAV) of the virus family *Orthomyxoviridae* is one of the most important respiratory pathogens of swine. Infection causes mortality and morbidity in many animals, resulting in significant financial losses through decreased production, vaccination, and treatment costs. The RNA genome allows for rapid genetic evolution through mutation or through exchange of the gene segments during coinfection, a process known as genetic reassortment. These two processes lead to immune evasion by antigenic drift and shift and can also allow for adaptation to new hosts.

Although only H1N1, H1N2, and H3N2 subtypes are endemic in swine around the world, much diversity can be found in the genes coding for major surface proteins, hemagglutinin (HA) and neuraminidase (NA), and in the other 6 internal gene segments. This diversity is the result of bidirectional transmission between swine and humans, the occasional transmission of an avian virus into swine, followed by periods of antigenic drift and shift.

Swine IAV emerged coincident with the 1918 Spanish flu, and genes derived from this lineage are classified as classical-swine H1N1 (1). In the late 1990s, triple-reassortant H3N2 viruses were identified containing gene segments derived from seasonal human H3N2 (HA, NA, and PB1), avian IAV (PB2 and PA), and the classical H1N1 swine IAV (NP, M, and NS) (2, 3). The HA persisted, evolving into phylogenetic clades that are detected to present day (Cluster-IV (C-IV) clades A-F) (4). The triple-reassortant H3N2 viruses also reassorted with classical-swine H1N1 viruses, driving diversification and new genetic clades of H1N1 and H1N2 viruses (5), but preserving the triple reassortant internal gene (TRIG) constellation.

Genetically distinct human seasonal H1 also spilled into and established in swine in the early 2000s (6, 7). In 2009, a virus with NA and M genes from Eurasian-avian H1N1 swine in addition to TRIG and classical-swine lineage genes emerged in swine, and infected humans as a pandemic (H1N1pdm09). Although sharing common ancestors, the human H1N1pdm09 genes were phylogenetically distinct from contemporary swine IAV. Via reverse zoonoses, the H1N1pdm09 continues to contribute to genetic diversity in swine, particularly the internal gene segments (8, 9). More recently, a human H3N2 virus was transmitted to swine, H3.2010.1, this virus is distinct from the H3N2 lineage C-IV viruses (10). In 2018, a live-attenuated influenza virus (LAIV) vaccine became commercially available in the U.S. (11). The LAIV uses HA (H1 and H3) and NA (N1 and N2) expressed on a TRIG internal gene backbone, with all components isolated from swine in the 1990s. These LAIV genes are distinct from contemporary IAV and reassorted viruses have been detected with vaccine-derived internal genes, and surface genes (12). Thus, interspecies transmission episodes and the processes of antigenic shift and drift have led to at least 16 distinct HA clades, 4 NA lineages, and 3 internal gene lineages circulating in the USA (13, 14).

Vaccine control efforts for IAV in swine have traditionally consisted of whole inactivated virus (WIV). In addition, individual production systems have implemented autogenous vaccines with the components derived from field sourced isolates. An RNA vaccine encoding the HA gene was recently made commercially available (15) as well as a live attenuated inactivated influenza vaccine (LAIV) based on mutations in the NS1 gene (11). While these licensed commercial vaccines are available, they are not updated as frequently as the virus evolves, or to reflect novel interspecies transmission episodes, resulting in antigenically mismatched formulations that can result in suboptimal protection. Custom or autogenous vaccines have the advantage of addressing updates more quickly, but may lack standardization or immunogenicity against all antigens in multivalent formulations.

Surveillance and monitoring of circulating IAV strains are the critical foundations for making vaccine decisions. Unfortunately, simple measures of genetic sequence similarity are not always predictive of vaccine cross-protection and efficacy. In swine H3 viruses, significant antigenic change has been associated with mutations occurring within six amino acids near the receptor-binding site of the HA (16, 17). Swine H1 viruses do not have quite as clear a picture, likely the result of more than 100 years of evolution in the swine population and repeated introductions of viruses from humans into pigs. Consequently, it is not clear whether single amino acid changes result in antigenic change, but observational data suggests that mutation in or near the receptor-binding site can have an important cumulative effect (18). Hence, antigenic characterization is a crucial step that should be used in combination with sequence analysis and epidemiological information to better inform on vaccine decision-making.

IAV in swine is highly diverse, with sustained transmission in the US of two major H1 lineages and multiple lineages of H3 from human seasonal IAV that have become established across several decades. Following the spread of the H1N1pdm09 pandemic in humans, annual introduction of this virus into pigs has driven reassortment and diversification of HA and NA in endemic swine lineages. This diversity has important implications for both swine health and control of IAV using vaccines. The USDA IAV surveillance system, implemented in 2009, has greatly increased our understanding of the diversity of IAV in swine and has enabled the detection of emerging lineages following interspecies transmission episodes. Ideally, vaccine formulation and updates of swine IAV vaccines should be objective, incorporating empirical data from the surveillance system, and the new formulations should match the genetic and antigenic diversity of circulating viruses including newly emerged antigenically distinct viral strains. Subsequent antigenic characterization is also required to understand the efficacy of vaccine antigens, and efficacy should be evaluated in the context of the multiple cocirculating genetic clades of viruses. Given how rapidly these dynamics occur, these efforts should occur within a regular assessment system that prioritizes and evaluates evolving swine IAV in the context of current control measures.

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AVMA Guidance and Advocacy: Antimicrobial Stewardship and Integrating Biologics, Including Autogenous Biologics, and the Therapeutic Use of Stem Cells and Regenerative Medicine

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Addressing concerns related to antimicrobial resistance is top-of-mind for veterinary practitioners. The AVMA has worked diligently over the past decade, but particularly aggressively during the past 5 years through the Committee on Antimicrobials, to define antimicrobial stewardship, develop core principles around it, and share resources that can help veterinarians effectively implement stewardship in their practices, including a veterinary “checklist” and guidance on judicious use. While judicious use of antimicrobials is key, the AVMA recognizes it is only a piece of the broader concept of Antimicrobial Stewardship in veterinary medicine, which encompasses a multi-pronged approach to reducing antimicrobial resistance and maintaining the effectiveness of antimicrobials. Part of stewardship involves attention to alternative strategies for disease prevention and control, including the use of vaccines, bacterins, and antisera, as well as appropriate attention to the development of more effective and efficient diagnostic tests that support the early identification of disease. Vaccines and bacterins have been suggested as the single most cost-effective medical countermeasure to address antimicrobial resistance. And, in the context of reducing antimicrobial use, a variety of viral and bacterial targets for vaccine improvements for poultry, swine, fish, and cattle have been identified. When no vaccine is available, or in the face of antigenic variation that is outside the spectrum of protection afforded by commercially available vaccines/bacterins, autogenous biologics are posited as an option, as long as careful attention is paid to meeting associated regulatory requirements. AVMA has developed guidelines for their use accordingly.

In addition to its attention to antimicrobial resistance, the AVMA has seen much more interest on the part of its members in the therapeutic use of stem cells (sometimes referred to as regenerative medicine) particularly—at this point in time—for treating musculoskeletal disorders in canine and equine patients. At the same time the association, and specifically its Council on Biologic and Therapeutic Agents, has recognized and advised its members that regenerative treatments should be formulated using evidence-based medicine and that veterinarians should refrain from recommending procedures when benefit has not been shown by way of clinical trials. Failure to do so poses unnecessary risk to the patient, compromises treatment success, impedes the collection of therapeutic data, and may expose the veterinarian to liability. The AVMA has created policy on the therapeutic use of stem cells and regenerative medicine that includes steps it believes veterinarians must take when using this modality. Among those steps is recognizing the FDA has often treated such cell-based products as ‘drugs’ and that associated regulatory requirements must be met.

ANTHRAX VACCINATION STUDY IN AMERICAN BISON

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In 2008, an anthrax outbreak killed 298 American Bison on a Montana ranch. The ranch had not experienced any prior exposure to anthrax and the use of anthrax vaccines in any bison had not been studied. The reported study mapped the effectiveness of anthrax vaccination by the only USDA-licensed Anthrax Vaccine. Serum IgG responses were measured by an ELISA developed in the aftermath of the 2001 anthrax bioterrorism attack in the US.

Sixty-six (66) male bison, weighing an average of 725 lbs., were allotted to 5 groups and vaccinated intramuscularly with the commercial vaccine. Groups were as follows:

A: 1 x 1 ml dose; B: 2 x 1 ml dose (different sites), 1 x 2ml dose, 2 x 2ml dose (different sites) and 1 x 2ml dose-airgun. Two non-vaccinated contact controls were included as sentinels. Blood samples were drawn prior to vaccination, at 1 month, 2 months, 4 months and 9 months post vaccination.

ELISA results indicated that all bison were serologically negative at time of vaccination and sentinel controls remained negative through 9 months. All vaccinated groups demonstrated 100% positive seroconversion by 1-month post-vaccination but differed at positive titers by 2 months (A- 88%; B- 93%; C- 80%; D-80%; and E- 100%). All titers waned by 4 months and were undetectable by 9 months. Throughout the study the airgun method of vaccination with a 2 ml dose provided the best responses.

Results of the study suggested using a 2 ml doses of anthrax vaccine with an airgun for all bison in future vaccination programs. Since this program has been implemented, no new cases on anthrax have been seen.

Committee Business:

Since we did not have a quorum (only 8 members) no resolutions were discussed.

The committee did discuss increasing membership through more biotechnology papers and representative. The Chair and Vice Chair will look into some of these matters, during the coming year. Since this committee deals with commercialization of products it is unique in the USAHA committees.