

Merck Animal Health Equine Respiratory Update

IN COLLABORATION WITH THE UNIVERSITY OF CALIFORNIA, DAVIS SCHOOL OF VETERINARY MEDICINE

How the Biosurveillance Program Delivered the Industry's Most Current Influenza Vaccine Protection

In February 2013, the annual Ocala Horse Shows in the Sun (HITS) event nearly came to a halt due to an outbreak of equine herpesvirus (EHV-1) and equine influenza virus (EIV) that impacted a large number of well-vaccinated horses. While the initial quarantine was established due to a positive EHV-1 case, it quickly became apparent through PCR testing of nasal swabs through the Merck Animal Health Respiratory Biosurveillance Program that many more horses were impacted by EIV.

Merck Animal Health selected one of the EIV-positive isolates to sequence. Specifically, a submission from a horse at HITS with a known vaccination history and significant clinical signs. The horse was vaccinated just four months earlier and had a fever of 103.8°F and mucopurulent nasal discharge. This isolate – named Florida '13 – represents a current, clinically significant strain responsible for a large influenza outbreak in well-vaccinated horses.

Florida '13 became the apex to an influenza trend we had already begun tracking through the biosurveillance program. Comparing published studies documenting trends in EIV incidence – one from 2008 to 2010¹ and the second from 2010 to 2013² – we learned that the incidence of positive EIV cases in vaccinated horses more than doubled from what it was during the 2008 to 2010

timeframe. It appeared that the circulating flu strains were changing since older horses were apparently susceptible and horses vaccinated with commercial flu vaccines were not necessarily protected.

“Influenza outbreaks in well-vaccinated horses are generally indicative of significant antigenic drift and inadequate protection,” says D. Craig Barnett, D.V.M., director of equine veterinary professional services for Merck Animal Health.

“Phylogenetic analysis of the Florida '13 strain confirmed that significant antigenic drift had indeed occurred and that this isolate was significantly different from viruses contained in current vaccines.”

Understanding the Significance of Florida '13

Flu strains are named based on the hemagglutinin (HA) and neuraminidase (NA) surface glycoproteins. Influenza virus is constantly undergoing random mutations in the amino acid composition of surface proteins. This process of minor evolutionary mutations and alterations, known as antigenic drift,

leads to new virus strains that a horse's immune system may not recognize.

Different strains of EIV can be compared to one another by sequencing the HA glycoprotein.

The HA glycoprotein is the most important of the two glycoproteins because it is the target for neutralizing antibodies generated by flu vaccines and it contains the receptor binding site that enables the flu virus to attach to host cells. As antigenic drift occurs, the HA glycoprotein changes so that pre-existing HA binding antibodies do not recognize the 'new' HA glycoprotein and do not bind. As antigenic drift continues, current circulating field isolates/strains may be quite different from older vaccine strains. Therefore, older vaccine strains may not stimulate production of appropriate HA antibodies.

Florida '13 differs from OH '03 (OIE recommended clade 1 isolate) by seven amino acid changes, and five of those mutations occur on the surface of the HA glycoprotein and are in or near regions associated with antibody binding or receptor binding sites³ – making them critically significant. This is likely why Florida '13 was able to “break through” and cause disease in these well-vaccinated horses competing at the HITS show.



Today's Equine Influenza

All current circulating strains of influenza in the horse are subtype A2 (H3N8). These strains originated from the American lineage and what's known as the Florida sublineage. The Florida sublineage is divided into two separate groups called clade 1 and clade 2.

Evidence confirms that the clade 1 strain primarily circulates in the United States while clade 2 predominantly circulates in Europe. (To date, no outbreaks of clade 2 have occurred in the United States.) The World Organisation for Animal Health (OIE) Expert Surveillance Panel on Equine Influenza currently recommends that vaccines contain both clade 1 and clade 2 viruses of the Florida sublineage.

NOTE: Equine influenza isolates (strains) are named according to the location and year of isolation.

SUBTYPE

Subtype A2 (H3N8) of influenza A virus was first identified in Florida in 1963 and is the only subtype circulating in horses today

LINEAGE

Mid-1980's diverged into American and European lineages, named according to geographic origin of isolates

SUBLINEAGE

Subsequently, strains within American lineage diverged into South American, Florida and Kentucky sublineages

CLADE

Today, the Florida sublineage is predominant and has evolved into two antigenically different clades: **CLADE 1 AND CLADE 2**

STRAIN



Prestige® vaccines include:

FLORIDA '13
RICHMOND '07
KENTUCKY '02

Meeting OIE and AAEP guidelines for Clade 1 and Clade 2 influenza protection

Reference: A Systematic Review of Recent Advances in Equine Influenza Vaccination. Vaccines 2014, 2, 797-831; doi: 10.3390/vaccines2040797

Merck Animal Health Introduces Updated Equine Influenza Strains

The Florida '13 isolate is the foundation of the next generation of Prestige® flu-containing killed virus vaccines from Merck Animal Health. The new flu-containing vaccines now include both clade 1 and clade 2 strains.

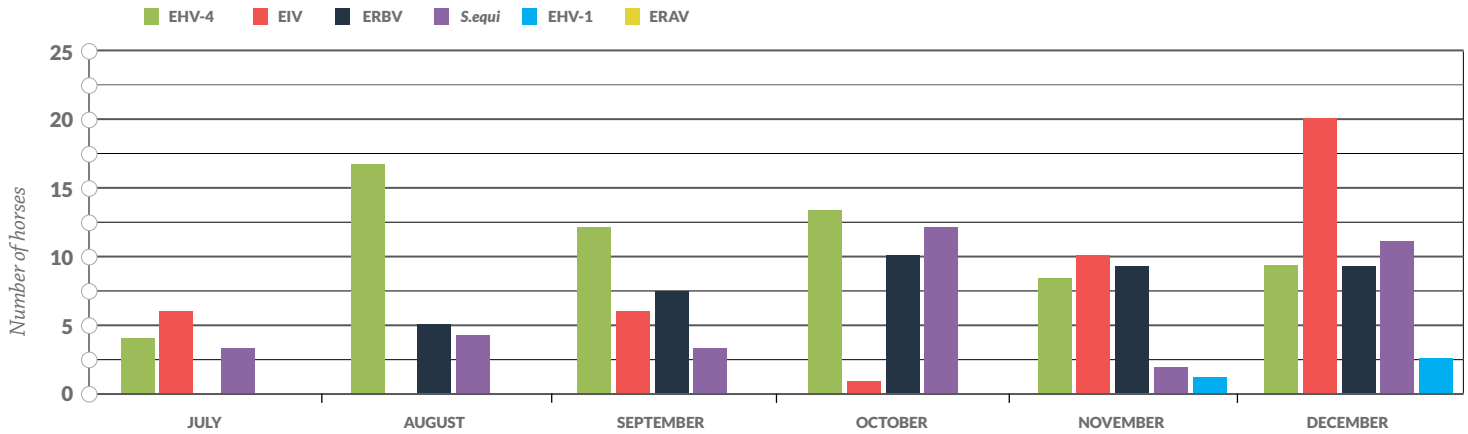
- **Florida '13 Clade 1:** Based on a highly pathogenic isolate from the 2013 Ocala, Fla., influenza outbreak that impacted a large number of well-vaccinated horses – exclusively identified and isolated through the Merck Animal Health Biosurveillance Program.
- **Richmond '07 Clade 2:** Meets World Organisation for Animal Health (OIE) and American Association of Equine Practitioners (AAEP) guidelines for clade 2 influenza protection.
- In addition, **Kentucky '02** will remain part of our flu-containing vaccine line.



Disease Trends from July to December 2017⁴

A total of 509 samples were submitted from July to December 2017, as compared to 422 samples submitted during the same timeframe in 2016. Overall, 36% of total samples submitted tested positive for one of the six primary pathogens (EHV-4, EIV, ERBV, *S. equi*, EHV-1, ERAV).

Disease Incidence July-December 2017

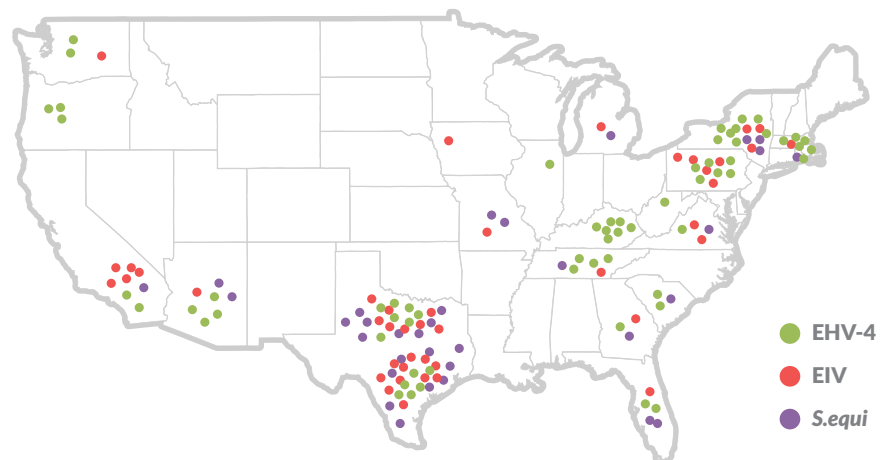


From July to December 2017, EHV-4 was the most prevalent infectious upper respiratory disease reported, followed by EIV.

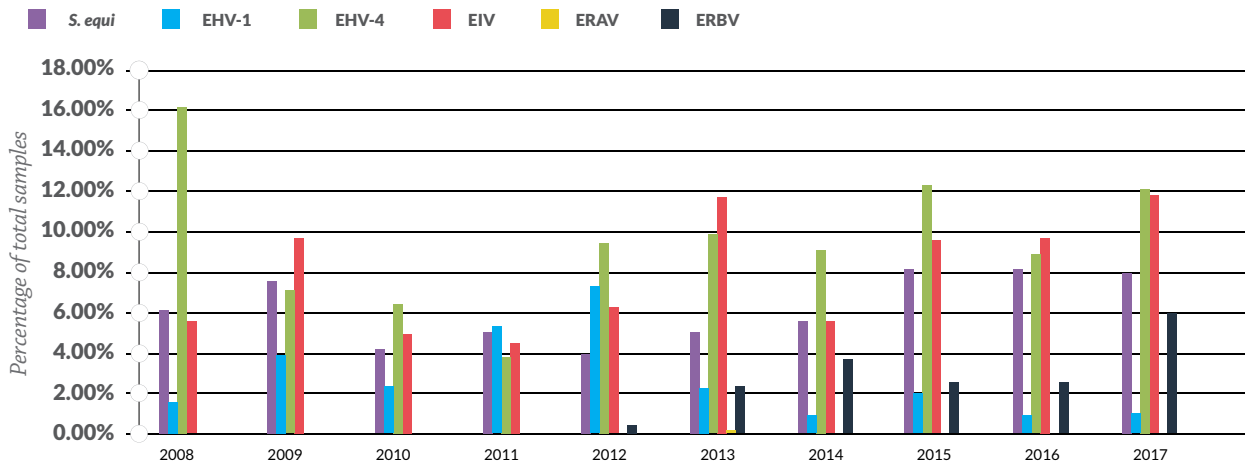
Demographic Summary	EHV-4 (63 Cases)	EIV (43 Cases)	<i>S. equi</i> (35 Cases)
Median Age	21 weeks Range: 2 months – 23 years	4 years Range: 4 months – 23 years	4 years Range: 10 months – 23 years
Predominant Breed(s)	Quarter Horse; Thoroughbred	Quarter Horse	Quarter Horse
Travel	Yes 44% No 38% Unknown 18%	Yes 35% No 51% Unknown 14%	Yes 31% No 46% Unknown 23%
Primary Discipline	Show	Show	Show

This table provides a summary of primary demographic parameters for the three major pathogens (July-December 2017).⁴

This map shows positive EHV-4, EIV, and *S. equi* cases from July to December 2017.⁴

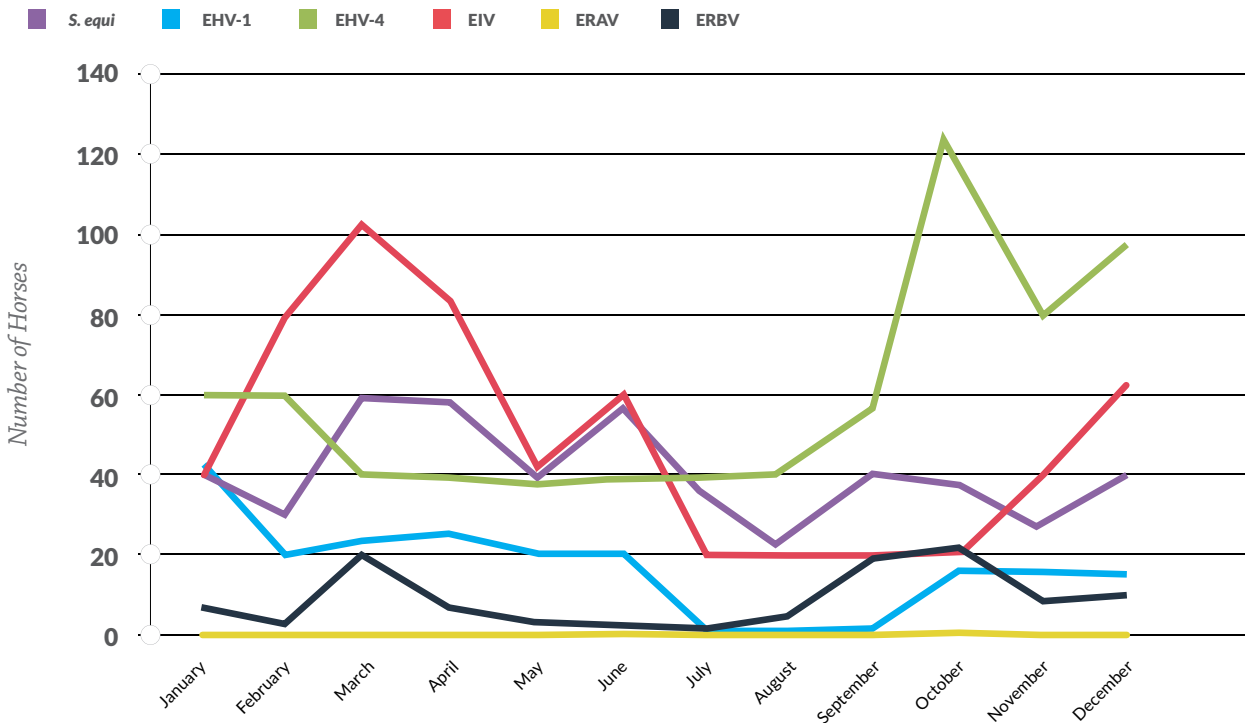


Biosurveillance Results 2008-2017⁴



Of the more than 7,300 samples submitted from 324 participating clinics across the United States, 29% have returned positive pathogen results. (The primary four pathogens have been tracked from the inception of the program. ERAV and ERBV were added in 2012.)

Biosurveillance Results Monthly Cumulative 2008-2017⁴



The monthly cumulative since program inception depicts the seasonal effect of respiratory pathogens. EHV-4 continues to be more prevalent in the fall months, in contrast to the other respiratory pathogens (especially EIV) that are more prevalent in the winter and spring months.

Practice Tips

Equine Disease Communication Center (EDCC) Sharing Biweekly Updates

The EDCC has begun sharing a confidential summary of positive disease cases detected through the Merck Animal Health Biosurveillance Program through its news page, a new section added this year to equinediseasecc.org.

The information is delivered in a very general manner to ensure the confidentiality of participating clinics and features a regional map and summary chart of positive disease cases. Positive cases are being reported for equine influenza virus (EIV), equine herpesvirus types 1 and 4 (EHV-1/-4) and *Streptococcus equi* subspecies *equi* (*S. equi*). The most recent posting can be found [here](#).

We are excited to partner with the EDCC to offer this important update to the industry. This partnership represents our ongoing commitment to infectious disease and biosecurity awareness. Your support is appreciated in this value-add program, and we welcome your input and questions.

Condensed Laboratory Submission Form and Questionnaire

The laboratory submission form and questionnaire have been consolidated into a one-page form. **Please use this streamlined version moving forward.** A copy of the form is available for [download here](#).

What Participating Veterinarians are Saying About the Program

"The Merck Animal Health Respiratory Surveillance program has solved the dilemma of treating from the hip without a diagnosis. We test every case we see that meets the criteria. Horses get the treatment they need rather than guessing. And clients are thrilled with the program.

A few months ago, we had two cases of strangles that presented with atypical histories. This is a reportable disease in Georgia and, as a result, 33 horses were quarantined along with two premises. We were able to identify an early case of purpura in an exposed horse that might not have been detected as early without the preliminary diagnosis. Multiple horses on one farm were scheduled for competitions in three states – those horses were kept at home.

"Recently, we had a case of influenza in a well-vaccinated horse. The Merck biosurveillance program helps all of us as health care providers to understand if our level of care is adequate in the equine athlete."

In every case where we have had a positive test, owners were open to suggestions for changes in their horse's health care to prevent a recurrence.

While the rich horse will always get the testing it needs, the poor horse likely will not. Merck will change the health care of many horses by meeting this need."

- Charlene B. Cook, D.V.M., Central Georgia Equine Services, Ft. Valley, Ga.

Quick Tips For Clients

NEW Equine Influenza Infographic

We're pleased to offer our biosurveillance program participants the first edition of the new [equine influenza infographic](#) to support client education. The infographic offers important facts on the disease, as well as the basics of why – like human flu vaccines – equine flu vaccines must be periodically updated to provide protection against currently circulating strains. Click to review and share with your clients on your website or through your social media properties:

[Equine Influenza Infographic](#)

About the Newsletter

This bi-annual newsletter is being sent as a value-added service to clinics enrolled in the biosurveillance program. Merck Animal Health is passionate about this program and is providing this newsletter to customer veterinarians to help them stay up-to-date on the latest trends and historical information the study has yielded to date. Technical veterinary advice, interpretation and case management support will be provided by Merck Equine Veterinary Professional Services (Drs. Barnett, Vaala, Gaughan, Craig, Bain and Chappell) and Nicola Pusterla, D.V.M., Department of Medicine and Epidemiology, UC Davis.

If you have questions about the program, please call our professional services team at (866) 349-3497, or email one of the professional services veterinarians at the addresses listed below.

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Relevant Supporting Research

For more information on the latest respiratory disease published research from Merck Animal Health, click on the links below.

- 1) ["Prevalence Factors Associated with EHV-2/5 Among Equines with Signs of Upper Respiratory Infection in the US."](#)
James, K., Vaala, W., Chappell, D., Barnett, D.C., Gaughan, E., Craig, B., Bain, F., Pusterla, N. ACVIM 2017 Abstract.
- 2) ["Prevalence factors associated with equine herpesvirus type 1 infection in equids with upper respiratory tract infection and/or acute onset of neurological signs from 2008 to 2014"](#)
Pusterla, N., Mapes, S., Akana, N., Barnett, D.C., Mackenzie, C., Gaughan, E., Craig, B., Chappell, D., Vaala, W. *Vet Rec*. 2015; doi: 10.1136/vr.103424.
- 3) ["Voluntary Surveillance Program for Equine influenza Virus in the United States from 2010 to 2013"](#)
Pusterla, N., Kass, P.H., Mapes, S., Wademan, C., Akana, N., Barnett, D.C., Mackenzie, C., Vaala, W. *J Vet Intern Med* 2015; 29:417-422
- 4) ["Surveillance programme for important equine infectious respiratory pathogens in the USA"](#)
Pusterla, N., Kass, P.H., Mapes, S., Johnson, C., Barnett, D.C., Vaala, W., et al. *Vet Rec*. 2011 July 2;169(1):12. doi: 0.1136/vr.d2157.
- 5) ["Voluntary surveillance program for important equine infectious respiratory pathogens in the United States"](#)
Pusterla, N., Kass, P.H., Mapes, S., Johnson, C., Barnett, D.C., Vaala, W., Gutierrez, C., et al. AAEP Proceedings 2010.

¹ Surveillance programme for important equine infectious respiratory pathogens in the USA. N. Pusterla, P.H. Kass, S. Mapes, C. Johnson, D.C. Barnett, W. Vaala, et al. *Vet Rec* 2011.

² Voluntary surveillance program for equine influenza virus in the United States from 2010 to 2013. Pusterla, N., Kass, P.H., Mapes, S., Wademan, C., Akana, N., Barnett, D.C., Mackenzie, C., Vaala, W., et al. *J Vet Intern Med* 2015; 29:417-422.

³ Data on file. Merck Animal Health.

⁴ Merck Animal Health and University of California, Davis School of Veterinary Medicine (Nicola Pusterla). Infectious Upper Respiratory Disease Surveillance Program. Ongoing research 2008-present.

About the Program

Since March of 2008, Merck Animal Health has been conducting an ongoing, voluntary equine biosurveillance program to study the prevalence and epidemiology of relevant viral and bacterial respiratory pathogens. More than 7,300 samples from U.S. equids of all ages, genders and breeds presenting with fever and signs of acute upper respiratory disease and/or acute neurological disease have been collected since the study began. Samples are submitted by participating Merck Animal Health customer clinics and tested via quantitative PCR at the University of California, Davis School of Veterinary Medicine (UC Davis). **To be eligible for testing, horses must have an unexplained fever (T ≥ 101.5°F) AND one or more of the following signs: Depression, nasal discharge, cough, and/or acute onset of neurologic disease.** The results are then returned to the Merck Animal Health customer within 24 hours and provide invaluable diagnostic and treatment information.

Four-Fold Purpose:

- 1) To provide a valuable diagnostic tool to participating Merck Animal Health customers to assist in obtaining an accurate and timely diagnosis during an acute respiratory disease outbreak so they can provide optimal treatment, quarantine and vaccination strategies to their clients and patients.
- 2) To provide the horse industry with a better understanding of the prevalence and epidemiology of these respiratory pathogens.
- 3) To identify and monitor the current circulating strains of major equine respiratory pathogens.
- 4) To evaluate the efficacy of current vaccination protocols.



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