EQUINE DISEASE QUARTERLY

FUNDED BY UNDERWRITERS AT LLOYD'S, LONDON

JULY 2016
Volume 25, Number 3

COMMENTARY

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"Nature doesn't break, it only bends." This quote was recently uttered on a television drama, which depicted an infectious disease clinician fighting a catastrophic epidemic that developed following a genetic mutation of a forgotten infectious disease agent. As a pathologist and former microbiologist, this reference to the constant evolution of microbes made me ponder, once again, how such relatively simple organisms rapidly and continually adapt to their environments to survive and replicate. It is unfortunate, at least for the host, when the intricate balance between host, environment, and microbe becomes offset and results in infectious disease.

This theme was exemplified in April 2016 when equine infectious disease experts from around the world gathered for the 10th International Equine Infectious Diseases Conference in Buenos Aires, Argentina. The conference, which is held every four years, provides excellent continuing education for equine clinicians and brings together equine infectious disease researchers who share recent developments and breakthroughs. The five-day event addressed infectious diseases of continued and historical concern, newly recognized and emerging diseases, and important reemerging infectious diseases of the horse. These motifs were addressed in 11 separate sessions on biosecurity, diagnostics, diseases of working equids, emerging and reemerging diseases, gastroenterology, international equine movement, neurology, parasitology, theriogenology (reproduction), respiratory diseases, and infectious diseases of other systems.

Although I enjoyed all of the presentations, I was particularly taken with the talks on emerging and reemerging diseases. Emerging viral agents that were discussed included: equine enteric coronavirus (a potential cause of necrotizing enteritis), Theiler's disease associated virus (the newly identified cause of equine serum sickness), and other viral causes of hepatitis (equine hepacivirus and equine pegivirus), Bunyamwera virus in Argentina (a cause of nervous disease and/or abortion), and Hendra virus (an acute fatal and zoonotic disease that frequently affects the respiratory and neurologic systems). Other interesting and noteworthy disease conditions comprised anthelmintic resistance (resistance of parasitic worms to treatment), the potential role of microbes in equine polyneuropathy, and strangles-like disease caused by *Streptococcus zooepidemicus.* The reemergence of West Nile virus (a cause of neurologic disease) in France and *Salmonella* Abortusequi (a cause of abortion and septicemia) in Argentina were also addressed. Although many of these diseases are emerging or reemerging in specific locations, one must be globally aware of them due to the increasing frequency with which equine athletes and breeding stock are transported around the world.

We may never break nature, but rest assured that clinicians and infectious disease researchers will continually attempt to challenge nature and develop new modalities to quickly detect, track, diagnose, treat, and hopefully learn to prevent and control infectious diseases as they occur.

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LLOYD'S

INTERNATIONAL

First Quarter 2016*

The International Collating Center, Newmarket, United Kingdom, and other sources reported the following disease outbreaks.

Three outbreaks of vesicular stomatitis in Colorado in February brought to a conclusion the 2015 occurrence of the disease in the USA. Of the eight affected states—Arizona, Colorado, Nebraska, New Mexico, South Dakota, Texas, Utah, and Wyoming—the greatest number of outbreaks was recorded in Colorado. The 823 reported outbreaks comprised 329 that were confirmed positive for the New Jersey serotype of the virus and 494 that were diagnosed based on clinical signs of the disease but not virologically verified.

Influenza was reported by the UK and the USA; in the latter country, the disease was considered to be endemic. Outbreaks were confirmed in California and Florida.

Equine herpesvirus 1 and 4 (EHV-1, -4) related diseases were recorded in Argentina, Australia, France, Germany, Ireland, Japan, South Africa, UK, and the USA. Respiratory disease caused by EHV-1 was recorded in France (two outbreaks), Germany (12 cases involving 11 premises), South Africa (two cases also with intercurrent equine piroplasmosis), and the UK (one case). Abortion due to EHV-1 was reported by Argentina (one vaccinated mare), Australia (one), France (four), Germany (three), Ireland (13 involving nine counties), Japan (51 vaccinated Thoroughbred mares on 19 premises), the UK (14), and the USA (three). Additionally, single cases of fulminant neonatal disease due to EHV-1 were diagnosed in the UK. Outbreaks of EHV-1 myeloencephalopathy were recorded in France (one 7-year-old mare with intercurrent signs of respiratory infection) and the USA (eight outbreaks at various premises). Affected states included Arizona (one), California (two), Florida (one), Georgia (one), Illinois (one), New Mexico (two), and Pennsylvania (one).

France, Germany, and the USA confirmed outbreaks of EHV-4 respiratory disease. Twelve outbreaks were recorded in France; the majority involved single cases of the disease. The latter was observed primarily in weanling foals in the USA. Limited evidence of EHV-2 and EHV-5 infection was recorded in the USA.

Strangles was reported by France, Germany, Ireland, Singapore, Switzerland, and the USA. Thirteen outbreaks, most involving single cases, were recorded in France, one in Germany, 11 in Ireland, one in Singapore, and one in Switzerland. The disease was stated to be endemic in the USA, with 42 outbreaks confirmed in 14 states, in eight of which multiple outbreaks were reported.

Infection with equine arteritis virus was confirmed in two stallions in Germany, each on a different premises.

Canada and the USA reported outbreaks of equine infectious anemia. Isolated cases on two farms in Saskatchewan were diagnosed in Canada. Infection was identified in five of 10 horses on a premises in New York, USA.

Equine piroplasmosis was reported as endemic by France; Switzerland recorded a single case of dual infection with *Babesia caballi* and *Theileria equi,* and the USA identified one case of *T. equi* infection in a Quarter Horse in New Mexico.

Germany confirmed the presence of *Taylorella equigenitalis* in four stallions and one mare. A single case of infection with equine herpesvirus-3 was diagnosed in Kentucky, USA.

The USA reported 11 cases of abortion due to *Leptospira pomona* var *kennewicki* and several cases of nocardioform placentitis associated with *Amycolatopsis* spp or *Crossiella* spp.

Outbreaks of salmonellosis were recorded by Germany (single case) and the USA (six cases associated with *Salmonella* Group B and six with untyped *Salmonella* spp). There was a single report of rotavirus infection in a foal from Germany. Three cases of infection with *Lawsonia intracellularis* were recorded in foals in Kentucky, USA. The USA also reported several outbreaks of clostridial enteritis in foals associated with *Clostridium perfringens* Toxin Type A.

Rabies was recorded in two horses in the USA, one each in Florida and South Carolina.

Rhodococcal related disease was reported as endemic in the USA, with numerous outbreaks diagnosed.

**2015 Fourth Quarter Report for Australia*

Equine Disease Quarterly

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Vector-borne Diseases and the Emergent Threat They Pose

Vector-borne diseases represent a singularly serious threat to the health of humans and domestic livestock species in countries or regions of the world in which they occur. Historically, many such diseases were frequently regarded as geographically restricted in their global distribution and not considered a risk to human and animal populations in far-distant countries in other continents or possibly other hemispheres. Major disease migrations in the last 20 years, however, have undermined that sense of security. No longer can the future distribution of specific infectious agents be predicted with confidence. This was most recently exemplified by the explosive and unexpected spread of Chikungunya and Zika viruses, both human pathogens, from where they were originally identified in Africa many years ago. Concerns are further highlighted by the risk of spreading yellow fever from Angola, Republic of Congo, and Uganda to European Union member states and even further afield to inter-tropical zones in the Americas and Asia.

The most significant group of emerging human and animal diseases is caused by arboviruses such as West Nile, Chikungunya, and Zika; they are single stranded RNA viruses which have spontaneous mutation rates as high as one base per 1,000 bases for each replication cycle. Arboviruses are transmitted in nature by arthropod vectors. With the exception of African swine fever virus, all arboviruses of medical or veterinary medical importance belong to one of the following four families: *Bunyaviridae, Flaviviridae, Reoviridae*, and *Togaviridae*. They are maintained in nature by cycling between a host (mammal, bird, reptile, amphibian) that is infected with a particular virus and a vector (mosquito, tick, sandfly, midge) that is a carrier and transmits the virus to other hosts.

Some of the most important viral diseases of humans are caused by arboviruses, many belonging to the *Flaviviridae* and *Togaviridae* families. These include the following notable examples: yellow fever, dengue fever, Japanese encephalitis (JE), West Nile encephalitis (WNE), Zika virus infection, Eastern and Western equine encephalomyelitis (EEE and WEE), Venezuelan equine encephalomyelitis (VEE), and Chikungunya virus infection. Arboviruses are also the cause of a number of highly significant equine diseases, the most important of which are African horse sickness (*Reoviridae*), VEE, EEE, and WEE (*Togaviridae*), JE, WNE, and Murray Valley encephalitis (*Flaviviridae*). It is evident from the foregoing that many of the listed equine diseases are caused by zoonotic pathogens.

Of major concern in assessing the health impact of arboviral diseases is the potential of the causal agents to evolve, giving rise to strains of enhanced pathogenicity for humans or animals. This is well exemplified by the emergence of variants of West Nile virus (lineage 2) in Europe that are highly pathogenic for horses. The same phenomenon has also been observed with respect to human infection with Chikungunya virus and most recently, also, with Zika virus. There is mounting evidence that strains of Zika virus have acquired marked neurotropic tendencies, being implicated as a cause of neurologic defects in unborn infants and an increased incidence of Guillain-Barre syndrome in people.

It is highly likely we will face future threats from the emergence of other arboviruses with epidemic potential. If we are to be successful in preventing such a threat becoming a reality, we need to identify those viruses with the potential for emergence and gain a greater understanding of their biology and epidemiology, complemented by development of more effective vector control strategies, active surveillance, and enhanced ability to diagnose such infections.

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NATIONAL

Mcr-1 and Other New Resistance Genes: What is the Threat to Horses?

Recent identification of the *mcr-1* resistance gene in bacteria from humans and animals has focused attention on the emerging epidemic of multidrug resistance. Multidrug resistant Gram-negative bacteria, particularly those of the *Enterobacteriaceae* family (e.g. *E. coli, Klebsiella,*

Enterobacter), are not new, as serial waves of resistance mediated by a wide range of genes have been encountered. Yet, emergence of *mcr-1* is of concern because it confers resistance to colistin, an antimicrobial that can be the only option for some highly drug-resistant infections. Concern has been expressed that *mcr-1* has ushered in the era of pan-resistant infections, infections where there are no antimicrobial options.

Equine medicine has not escaped the challenges posed by resistant bacteria, including multidrug resistant *Enterobacteriaceae*. In recent years, there have been various reports of extended spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* in horse. These are resistant to penicillins and most cephalosporins, and typically also have acquired resistance to various other antimicrobials, limiting treatment options. Susceptibility to only aminoglycosides (e.g. amikacin) and carbapenems (e.g. meropenem) is a common pattern. ESBL-producing bacteria have been identified in horses in multiple countries, both in healthy colonized horses and horses with clinical infections. While carbapenem use is very limited in horses, carbapenemase-producing *Enterobacteriaceae* (CPE) and *Acinetobacter*, which are resistant to penicillins, cephalosporins, and carbapenems, and usually a range of other antimicrobials, have been found in limited numbers in horses. With the common co-occurrence of resistance to other drug classes, infections by bacteria such as these approach the 'pan resistance,' from a practical standpoint, considering limitations in antimicrobials that can be used in horses. Of additional note is the fact that ESBLs found in horses are often the same types that are found in people (e.g. CTX-M-15), highlighting both the potential for zoonotic transmission and the likelihood that some equine infections are human in origin.

What does identification of *mcr-1* mean to the equine industry and equine veterinarians? The likelihood of encountering a horse infected with a bacterium possessing *mcr-1* is exceedingly low. However, if bacteria harboring genes such as these increase in humans, food animals, and the environment, equine infections are probably inevitable. Yet, while attracting less attention, the endemic level of resistance to cephalosporins, fluoroquinolones, and aminoglycosides is likely of greater relevance in horses because of their increasing incidence and the limited treatment options.

Regardless, awareness of emerging trends in humans is important. As new issues emerge in humans, it is possible that the same problems will emerge in horses given the close contact between humans and horses, the potential for interspecies transmission (in both directions), and the potential for common source infection (e.g. from food animals or the environment).

Veterinarians increasingly are encountering horses infected with multidrug resistant pathogens, and the pathogens of concern continue to change. Twenty years ago, MRSA and ESBLs in horses were of little interest. Now, they are far from rare. It is almost certain that the next 20 years (if not the next five years) will be accompanied with new antimicrobial resistant pathogens and challenges. There are no simple answers for battling the scourge of antimicrobial resistance. However, awareness of the issues, optimizing antimicrobial use, and focusing on infection control measures to reduce the need for antimicrobials are important basic and practical matters that every equine veterinarian and horse caretaker can undertake.

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Using Progesterone as a Diagnostic Tool during Equine Pregnancy

Progestogens are a class of steroid hormones largely responsible for sustaining the embryo and maintaining uterine quiescence. In horses, at least 10 known progestogens are present in maternal circulation during gestation. To date, only a few of them are known to be biologically active. Progesterone, the most renowned of this class of steroid hormones, is the only one with clinical diagnostic application. During early pregnancy, progesterone is produced in the equine ovary by the corpus luteum (CL), and its concentrations remain elevated and peak between 60 and 120 days of gestation. From that point on, progesterone slowly decreases until it becomes nearly undetectable around 180 to 200 days of gestation. During late gestation, other progestogens produced by the feto-placental unit are responsible for maintaining the pregnancy. These are first detectable by day 60 of gestation and are completely capable of maintaining pregnancy from around 120 to 140 days of gestation until term.

Circulating progesterone has been used diagnostically to evaluate luteal function during early pregnancy. When the circulating progesterone (P4) concentration is above 1 ng/mL, this is considered

consistent with the presence of luteal tissue, indicating that a follicle has ovulated, luteinized and is producing progesterone. When the circulating progesterone concentration is above 4 ng/mL, this is considered adequate for the maintenance of pregnancy. There are a number of reasons for monitoring and supplementing endogenous progesterone with progestins (synthetic progesterones) during pregnancy, such as uterine infections, history of pregnancy loss, and luteal insufficiency.

A few important issues regarding laboratory techniques and progestogens require clarification. To date, all clinical veterinary diagnostic laboratories use immunoassays to measure circulating progesterone. The specificity of these tests is limited by the antibodies used in these assays. Due to the structural similarities among different progestogens present in late gestation, after day 120 of gestation, antibodies are unable to differentiate between those different molecules and therefore can give false or inaccurate results. In addition, different progesterone antibodies will result in disparate amounts of cross reactivity; therefore, each progesterone assay will measure different amounts of progesterone, producing varying results between laboratories. It is important to emphasize that the best clinical interpretation for any progesterone result is the one provided by the clinical laboratory that measured the progesterone, as they have reference ranges for their specific equine progesterone assay. The specificity lacking in immunoassays and the inter-laboratory variations can be overcome with the use of liquid chromatography-mass spectrometry (LC-MS). LC-MS has allowed researchers to evaluate changes in different progestogens during late gestation and further elucidate links between placental compromise during late gestation and the changes associated with specific progestogens. It would be advantageous for clinical laboratories to switch to LC-MS to provide diagnostic panels of greater specificity and wider array of quantifiable progestogens.

In summary, current tests for progesterone in the mare are useful to evaluate the presence of luteal tissue (P4>1ng/mL) and to ensure that levels of circulating progesterone are adequate for maintenance of early pregnancy (P4>4ng/mL) until about 120 days of gestation. From that point until term, current clinical tests are somewhat unreliable due to the variety of progestogens present in maternal circulation. These limitations can be overcome with the use of LC-MS.

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KENTUCKY

Equine Congenital Cardiovascular Anomalies

Congenital cardiovascular malformations are rare in horses with an estimated prevalence of 0.1-0.5%. Male and female horses are similarly affected, and a clear-cut breed predilection is not evident. Cardiovascular malformations are broadly classified as either simple (a single anomaly) or complex (multiple coexisting anomalies). Each major category is further subdivided on the basis of the tissue affected: myocardium (heart muscle), blood vessels, or valves. Complex malformations typically involve multiple tissues and have the least favorable prognoses.

Clinical signs vary in severity and the age of onset. Typical clinical signs can include stunted growth, exercise intolerance, heart murmur, tachycardia, respiratory distress, and cyanosis. Affected horses are frequently found dead, however not all horses with cardiovascular malformations display clinical signs or die from the anomaly. In some cases, the cardiovascular defect is only identified at necropsy as an incidental finding and is not related to the cause of death.

Ventricular septal defect (VSD) is the most frequently reported congenital cardiac anomaly in the horse. This anomaly is represented by a patent channel in the interventricular septum that allows communication between the two ventricles, which play a critical role in pumping blood. The channel can result in altered pressures within the heart, the shunting of blood through the channel, compensatory hypertrophy (enlargement of the heart muscle), and systemic abnormalities (e.g. cyanosis) in severe cases. Horses with small defects may be asymptomatic or develop clinical signs at a later age. VSDs are also components of complex cardiac anomalies such as Tetralogy of Fallot and truncus arteriosus.

Equine Disease Quarterly Newsletter

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Other defects described in the horse include:

- Abnormal communications between the atria. Examples: atrial septal defect and patent foramen ovale.
- Abnormal communication between the great vessels. Example: patent ductus arteriosus.
- Malformed great vessels. Example: common truncus arteriosus (the division between the aorta and pulmonary artery does not develop and a single vessel leaves the heart).
- Abnormally positioned great vessels. Examples: complete transposition (the right ventricle pumps blood into the aorta and the left ventricle pumps blood into the pulmonary trunk) and double-outlet right ventricle (both the aorta and pulmonary trunk arise from the right ventricle).
- Heart valve abnormalities. Example: tricuspid valve atresia.
- Tetralogy of Fallot, which consists of a dextrapositon of the aorta, pulmonic stenosis, ventricular septal defect, and right ventricular hypertrophy.

Archives at the University of Kentucky Veterinary Diagnostic Laboratory were searched from 2010 to 2015 for cases of congenital cardiovascular malformations in the horse. Over that period, 18 cases were identified. Fourteen were in Thoroughbreds, two in American Saddlebreds, and one each in the Arabian and Standardbred breeds. Twelve of the animals were female and five were male; the sex of one animal was not identified. Ten cases of ventricular septal defect, which included nine simple and one complex anomalies, were diagnosed. The complex anomaly was associated with pulmonic stenosis. Two cases each of Tetralogy of Fallot and truncus arteriosus with VSD were identified, and single cases of atrial septal defect, over-riding aorta, right ventricular hypoplasia with pulmonary atresia and moderator band dysplasia were reported.

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