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EQUINE DISEASE QUARTERLY

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RESEARCH SPOTLIGHT

Unveiling the Battle Against *Rhodococcus equi*: Innovative Approaches to Combat Antibiotic-Resistant Infections

Rhodococcus equi (*R. equi*) is a leading cause of pneumonia and death in foals less than 6 months old worldwide. Initial exposure to *R. equi* occurs through contact with the soil and contaminated farm environment. In farms where the bacteria are endemic, morbidity rates can reach up to 40%. Importantly, the threat of infection can also be extended to immunocompromised people. The economic losses caused by *R. equi* are attributed to the lengthy, potentially expensive treatment of infected foals, and guarded prognosis for those severely affected, making *R. equi* a significant problem for the equine industry worldwide. The lack of vaccines to prevent *R. equi* infections in horses forces treatment to rely solely on antibiotics. This reliance on antibiotics is precarious, as *R. equi* has demonstrated a remarkable ability to adapt and develop resistance against antibiotics. Moreover, antibiotic use can induce adverse side effects in foals, including antibiotic-associated diarrhea and hyperthermia. These concerns highlight the pressing need to develop antibiotic-alternative strategies to treat *R. equi* infections and reduce the risk of antibiotic resistance.

The Helmy Laboratory at the University of Kentucky Maxwell H. Gluck Equine Research Center is dedicated to developing novel drugs as antibiotic alternatives to improve foal health and welfare through better control of *R. equi*. We have identified novel drug candidates that show promising efficacy when evaluated in the laboratory against *R. equi's* growth, biofilm formation, virulence, colonization and survivability in the alveolar macrophages (the bacteria's target cells within the foal). These pharmacologically active compounds, identified using innovative technologies, offer a multifaceted approach to infection control.

The identified drugs originated from two different sources: small molecules extracted from natural products isolated from subterranean environments in Appalachian Kentucky by the UK's Center for Pharmaceutical Research and Innovation and novel probiotic strains that had not been previously tested for their effect against pathogenic bacteria. Probiotics are well known for their beneficial effects on the host, enhancing gut health and immunity and directly impacting bacterial growth. As a result, these newly discovered small molecules and probiotics could potentially treat *R. equi*-associated pneumonia in foals and control bacterial contamination of the environment by fecal shedding. The next step is to continue the evaluation of the efficacy and potential toxicity of these drug candidates in the laboratory. Once these potential treatments are deemed safe, we will translate these laboratory findings into real-life using foals as animal models and evaluate the efficacy of the identified drug candidates in protecting foals from infection and stopping the shedding of bacteria to the environment.

The Helmy Lab's goal is to continue developing novel drugs that benefit the entire equine industry by controlling *R. equi* and other bacterial infections in foals, as well as the spread of diseases within the farm environment. By decreasing the use of antibiotics and preventing their adverse effects, we can help prevent the spread of multi-drug resistant *R. equi*, promote sustainable horse agriculture and health and reduce economic losses by the equine industry in the U.S. and worldwide.

This project is a collaboration between the Helmy Lab, the UK Martin-Gatton College of Agriculture, Food and Environment and the Thorson Lab at the UK College of Pharmacy. The evaluation of the selected new drug candidates in vitro is supported by the American Quarter Horse Foundation and the Center of Biomedical Research Excellence for Translational Chemical Biology.

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INTERNATIONAL

Second Quarter 2024

International report on equine infectious diseases

This report collates information provided by diagnostic laboratories in Lexington, Kentucky, University of Kentucky Veterinary Diagnostic Laboratory (UKVDL) and Equine Diagnostic Solutions, Inc. We also want to thank IDEXX laboratories providing data for Germany. We have further included information from the International Thoroughbred Breeders' Federation, the International Collating Centre (ICC) in Newmarket/Cambridge, United Kingdom, and information from the American Association of Equine Practitioners' Equine Disease Communication Center (EDCC). This report summarizes heightened activity of several relevant contagious or environment-linked diseases among equids. We encourage everyone to report laboratory-confirmed (toxico)infectious disease of *Equidae* to the ICC in Cambridge, UK, or EDCC, USA. With few exceptions (Ecuador and Chile), reports are from Europe and North America.

Information from all our sources again for the second quarter shows *Strep. equi spp. equi* (Strangles) as the most frequently and consistently diagnosed equine pathogen. Reports from various sources reflect 'newly diagnosed' infection from North America and Europe. There have been sporadic reports of equine influenza virus, both from Europe (UK and NL) and North America (mainly from the Pacific Northwest).

Many mares are in or entering their third trimester of pregnancies. Not surprisingly, the numbers for EHV-1 (and incidental EHV-4) abortions are up for this quarter. Kentucky reports incidental cases.

Continuing into the second quarter of 2024, there have been more cases of EHV-1 neurologic disease (EHM) cases/outbreaks, both in North America and Northern Europe.

We report three cases of Coital exanthema (EHV-3) from France.

USA reports a small outbreak of CEM (*Taylorella equigenitalis*) in central Florida. CEM was diagnosed in a pony mare after natural cover. Subsequently, the stallion, but also a gelding and a separate pony stallion, tested positive. Germany reports four positive cases of CEM for this quarter.

A cluster of Equine Infectious Anemia (EIA) cases was detected in Texas; and single cases in a few other states or provinces in North America. A single case of EIA was identified in Chile.

The Southeast United States reports a number of Eastern Encephalitis virus cases, which is early in the season. In addition, there was one report of Eastern Encephalitis from Ecuador.

Last, but not least, it is the season for grass sickness (equine dysautonomia) with almost 20 cases reported from the United Kingdom.

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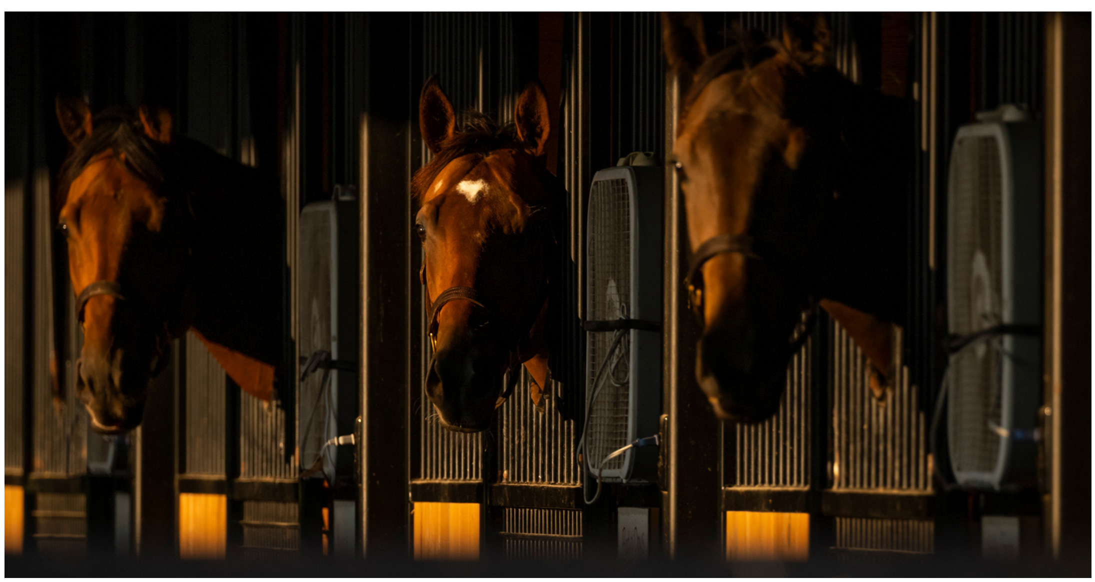

Photo Courtesy Mark Pearson Photography.

Hendra virus: Australia's contribution to equine zoonoses

In 1994, an outbreak of respiratory and neurological disease was reported in a racing stable in the Brisbane suburb of Hendra. Of the 20 horses affected, 14 died or were euthanized, seven of these within 12 hours of the onset of clinical signs.

African horse sickness was quickly ruled out as the cause, which left veterinary authorities with another problem. What was causing these deaths? To make the situation more serious, two of the people looking after the horses were also hospitalized, and one of these people died.

After a significant collaborative effort between veterinary virologists, a novel Paramyxovirus, subsequently named Hendra virus (HeV), was identified as the causal organism. Since the first recognised occurrence in 1994, HeV infections have been identified sporadically in horses showing clinical signs of respiratory disease, neurological disease or sudden death. More than 100 horses have been infected in this time, mostly occurring as single cases, but all of these horses have died or were euthanized. Significantly, seven people have been reported to have been infected with HeV, and four of these people have died because of the infection. To date, all of the people infected with HeV have contracted the infection through exposure to an infected horse.

Extensive investigations led to the identification of Pteropid fruit bats, also called flying foxes, as the natural host of HeV. There are four species of Pteropid bats that inhabit the Australian mainland, and antibodies to HeV have been detected in all species. Extensive epidemiological investigations have identified a greater likelihood of equine cases of HeV infection associated with Black flying foxes (*Pteropus alecto*) and Spectacled flying foxes (*P. conspicillatus*), although a recent report has identified a new HeV variant in Greyheaded flying foxes (*P. poliocephalus*).

No evidence of HeV infection has been reported in other wildlife species, although dogs have been found to be infected in both outbreaks and in experimental studies. There is no evidence of direct, bat-to-human HeV infection. There is experimental evidence that HeV can infect horses, ferrets, pigs, cats, monkeys, mice, guinea pigs and hamsters, however, only bats, horses, humans and dogs have been identified as hosts in an outbreak situation. To date, Hendra virus infections have only been reported on the Australian mainland, although a closely related virus, Nipah virus, has been reported as a significant cause of human mortality in South-East and South Asia.

Hendra virus infection has been identified in many different organs in bats, however, it is present in highest concentrations in kidney tissue and urine, and it is thought that contamination of the environment with HeV-laden bat urine is the mechanism by which horses are infected with HeV. Subsequent horse-to-horse transmission has been reported. Risk factors associated with an increased likelihood of equine HeV infection are the presence of fruiting or flowering plants and trees in the yards or paddocks where horses are housed, lack of stables and feeding of horses outside where feeding stations are exposed to bat urine. There is considerable season-to-season variation in the occurrence of equine HeV infections and it is likely that this is associated with seasonal conditions that affect the availability of flying fox food sources and roosting sites. Additionally, equine HeV cases have only been identified in Queensland and coastal areas of NSW north of Sydney, despite the virus being detected in flying foxes in a much broader geographical range, around the coast from Adelaide to Cairns.

Experimental challenge studies in horses have identified a wide range of clinical signs associated HeV infection, from the severe respiratory and neurological conditions identified in early outbreaks, to less obvious signs such as discomfort, increased heart rate and fever, all of which could be confused with other diseases, such as colic. This poses a significant workplace safety problem for veterinarians who see sick horses routinely. Two veterinarians and a veterinary assistant have died and a vet nurse was seriously affected as a result of occupational exposure to HeV. There are no HeV vaccines registered for use in humans, however, since all human cases are associated with equine infections, the risk of human infection has been moderated by vaccination of horses with the available equine HeV vaccine. Hendra virus vaccine has been shown to protect horses from challenge doses of HeV that were previously demonstrated to be lethal in unvaccinated horses. To date, HeV vaccination has been extremely effective in preventing equine HeV disease. Since the vaccine was commercially released in 2012, there have been no HeV cases reported in vaccinated horses. All cases since 2012 have been in unvaccinated horses.

Hendra virus is a significant zoonotic risk to Australian horses, horse owners and handlers and especially to equine veterinarians practicing in Australia. Vaccination is the most effective means of protecting horses from HeV infection and consequently protecting the people who look after them from being exposed to a potentially life-threatening disease.

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Anthelmintic treatment failure against equine tapeworms

While drug resistance has been known to be common in equine gastrointestinal parasites for several decades, this has been restricted to three parasite categories: the small strongyles (cyathostomins), the ascarids (*Parascaris* spp.) and the pinworms (*Oxyuris equi*), all of which belong to the nematode family. However, in the past two years, we have seen mounting evidence suggesting that anthelmintic resistance could be emerging in the equine tapeworm species, *Anoplocephala perfoliata*, which belongs to the flatworm family, and is a well-documented cause of colic in horses.

Starting in early 2022, local veterinarians in Central Kentucky were reporting that they were observing tapeworm eggs in routine fecal samples analyzed two weeks post-deworming with products containing praziquantel. Given that this is one of two currently available anthelmintics with documented efficacy against tapeworms, this was a concerning finding. Our laboratory received some of these samples and we were able to confirm the findings. Since this finding, we have evaluated the efficacy of different praziquantel products as well as the only available treatment alternative – a double dose of pyrantel pamoate – and documented a lack of clearance of tapeworm eggs in all cases. These observations were primarily made in groups of yearlings on two farms; we were also able to evaluate a praziquantel product in one group of mares with a similar apparent lack of efficacy.

Historic field efficacy trials with these anthelmintic products had all demonstrated complete or near complete clearance of tapeworm eggs from fecal samples in treated horses, so these findings are strongly suggesting emergence of multidrug resistant equine tapeworms. Our findings have been documented in two different peer-reviewed publications, and local veterinarians have made similar observations in other equine operations in the area. This is very concerning given that there are no treatment alternatives currently available with documented efficacy against tapeworms.

These findings emphasize the importance of routine anthelmintic efficacy testing. The veterinarians discovered this lack of treatment efficacy because of having systematic testing protocols in place on these farms. Since praziquantel and pyrantel products are very commonly used around the world, and routine efficacy testing is still rarely implemented, it is likely that a similar, yet undetected, development could be occurring elsewhere. One aspect that separates the tapeworms from all the nematode gastrointestinal parasites is that horses do not develop immunity to the tapeworms. Thus, any age group can harbor these parasites and the occurrence and infection intensity does not decline with age. We, therefore, strongly recommend the implementation of routine anthelmintic treatment efficacy testing procedures in all horse operations.

It is remarkable that these findings were made using routine standard fecal egg counting techniques that were not optimized for tapeworm detection. While it is well described that these techniques can substantially underdiagnose tapeworm infection in horses, it should be noted that they, nonetheless, were able to detect this lack of treatment efficacy because of the tendency to underestimate and not overestimate tapeworm presence. Provided that the evaluator is experienced in identifying tapeworm eggs, the finding of tapeworm eggs post deworming is suggestive of treatment failure. While work is currently underway to develop refined testing protocols for measuring anthelmintic treatment efficacy against equine tapeworms, the current recommendation is to make sure to count and record the number of equine tapeworm eggs present both pre- and post-deworming.

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Equine Tapeworms. Photo courtesy Dr. Martin Nielsen.

Ergopeptine alkaloid toxicosis in horses

Ergopeptine alkaloids (EPAs) are toxic compounds produced by fungal organisms including *Epichloë coenophiala* and *Claviceps purpurea*. The first is an endophyte, a microscopic fungus that lives within the intercellular spaces of leaf sheaths, stems and seeds of certain types of tall fescue grass (*Schedonorus arundinaceus* (Schreb.) (Dumort.)), especially the infamous variety Kentucky-31. Endophyte-infected tall fescue is indistinguishable from endophyte-free varieties without microscopic examination and special staining. The tall fescue endophyte produces primarily ergovaline and much smaller amounts of other EPAs. The highest concentrations are typically in the seedheads and the bottom-most parts of the plant. The alkaloids confer increased vigor to the plant by increasing resistance to drought, insects and other plant stressors. In return, the plant provides nutrients to the endophyte.

Claviceps purpurea (ergot fungus) is a plant pathogen and can infect the seeds and grains of a wide variety of small-grain forages (including oats, barley, wheat, rye and triticale) and grasses, including tall fescue grass. Other commonly affected pasture grasses include bluegrasses, bentgrasses and redtops, bromegrasses, canary grasses, cocksfoot and orchard grasses, June grasses, love grasses, quackgrasses and wheatgrasses, ryegrasses, timothy and wild barleys, oats and ryes. Ergot-infected (ergotized) seeds form dark brown/black ergot bodies – also called sclerotia – in place of individual seeds. Affected plants are easily identified by direct examination of the seedheads. Ergot fungus produces a wide variety of EPAs, predominately ergotamine, ergocristine, ergosine, ergocornine and ergocryptine. Ergot bodies/sclerotia generally contain much higher EPA concentrations than toxigenic endophyte-infected tall fescue.

Horses and other livestock can be exposed to EPAs via contaminated pastures or hay, processed feeds (especially pelleted formulations) and screenings from ergotized grains. It is important to note that although most mammals are susceptible to EPAs, the effects vary dramatically depending on the species. Effects in horses (and probably other equids) are dose dependent and primarily affect reproduction. The most consistent signs are lactation abnormalities in late-term pregnant mares. Markedly decreased or absent mammary development and milk production can occur at relatively low EPA doses and may be the only clinical signs observed. Common indicators of impending foaling, including rapid udder development ("bagging up"), colostrum accumulation at teat orifices ("waxing") and increasing calcium concentrations of mammary secretions, are often absent or minimal with EPA exposure. This can lead to unexpected/unattended deliveries and consequently higher foal morbidity and mortality. Additionally, the lack of colostrum production can lead to failure of passive transfer and potentially sepsis in these foals.

At higher EPA doses, other effects can include prolonged gestation, placental thickening and edema, premature placental separation ("red bag"), dystocia, retained placenta, metritis and other reproductive abnormalities. Foals continue to grow during prolonged gestation but fail to develop normally. They are typically large and gangly, with poorly developed muscle mass, an abnormally long, fine haircoat, overgrown hooves and sometimes prematurely erupted central incisors. The suckling reflex is often decreased or absent.

Nonpregnant mares exposed to sufficient concentrations of EPAs may not respond normally to seasonal photoperiod changes, leading to long spring transitional periods. These mares can experience irregular or prolonged estrus without ovulation. Increased incidence of early embryonic death has been reported following experimental EPA exposures. Therefore, it is recommended to withdraw any potential EPA sources from the diet of mares with a history of abnormalities in seasonal cyclicity, early embryonic loss and/or other reproductive abnormalities.

Unfortunately, there are no blood, urine, tissue or other tests in horses to diagnose excessive EPA exposure. Currently, the only reliable diagnostic test for EPA toxicosis is measurement of dietary concentrations. Feeds and forages can be analyzed for ergopeptine alkaloids; however, "safe" or "nontoxic" concentrations have not been established in mares. Additionally, EPAs can have effects long after dietary exposure has ceased, and ergovaline concentrations in toxigenic endophyte-infected tall fescue can fluctuate week-to-week; therefore, by the time a problem is identified and samples are collected, measured concentrations may not truly reflect exposures. Also, different laboratories use different analytical methods and may report in different units, which makes comparisons between results from different labs impossible. The same is true for interpreting "relevant" concentrations reported in the literature. Finally, some mares appear more sensitive than others. Lactation abnormalities have been reported in individual mares at relatively low dietary EPA concentrations. There are very few other causes of lactation abnormalities; EPA toxicosis should always be considered in these cases and the diet evaluated carefully. If tall fescue is not a component of the diet, particular attention should be paid to potential sources of ergot fungus.

Ergopeptine alkaloids, regardless of source, can cause various reproductive problems in horses, especially late-gestation mares. Dietary EPA concentrations in these animals should be kept as low as possible by minimizing exposure to potential sources including toxigenic endophyte-infected tall fescue and ergotized pasture grasses, hay and grain.

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