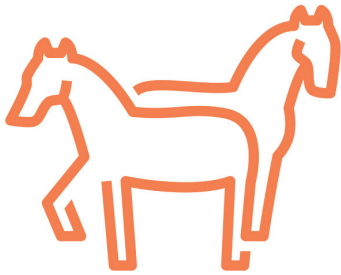


TECHNICAL BULLETIN

August 2015



Equine Leptospirosis: Disease Overview and the Risks and Economic Ramifications of *Leptospira*-Associated Recurrent Uveitis and Leptospiral Abortion

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Key Points

- Leptospirosis in horses is a bacterial disease that is capable of causing serious and costly health problems.
- Leptospire can infect the horse through abraded skin and mucous membranes where they can colonize the kidney and be shed in urine.
- Abortion in pregnant mares and equine recurrent uveitis (ERU) that can lead to blindness are two significant clinical manifestations of equine leptospiral infections.
- Of the more than 250 leptospiral serovars identified, *Leptospira interrogans* serovar Pomona is most often associated with leptospirosis infections in horses in North America.¹
- Wildlife including the striped skunk, raccoon, white tailed deer, and opossum are common maintenance hosts infected with *L. pomona*.
- Whereas diagnosis of *L. pomona* can be challenging and likely represents only the “tip of the iceberg” in terms of number of clinical cases, a 4-fold change in a microscopic agglutination test (MAT) from baseline titer to convalescent titer is strongly suggestive of disease.
- Fetal loss caused by leptospiral abortion and progressive blindness in many horses affected by *Leptospira*-associated uveitis represent substantial financial and emotional burdens for individual owners and the greater equine industry.

EQUINE LEPTOSPIROSIS:

A Serious, Underreported Disease

Relevance

Equine leptospirosis, a disease of worldwide distribution and zoonotic potential, is an acute bacterial infection of horses caused by pathogenic spirochetes belonging to the genus *Leptospira*.² Because clinical signs associated with leptospirosis are nonspecific, disease in horses likely occurs more frequently than it is actually diagnosed. That horses in North America face a threat of exposure to *Leptospira* was demonstrated recently in two serological surveys. In 2012, investigators at the University of Kentucky revealed a leptospirosis seroprevalence of 45% from samples obtained from diagnostic laboratories across 29 states and one Canadian province.³ Similarly, in a 2014 study supported by Zoetis, 75% of 5,261 horses sampled were positive for at least one leptospiral serovar.⁴ Unlike leptospirosis in most other domestic species, leptospirosis in horses is only occasionally diagnosed as causing systemic disease.⁵ Infected horses may go undiagnosed as clinical signs can be mild, including listlessness and low-grade fever of brief duration. Consequently many horses do not appear sick and typically recover quickly without treatment. After penetrating through mucous membranes or abraded skin, *Leptospira* migrate through the blood stream and replicate in the liver, ultimately becoming sequestered in the kidneys, eyes, and reproductive tract.⁶ Leptospire in the kidneys occasionally cause fever and acute renal failure, especially in yearlings.⁷⁻⁹ More importantly, uterine infections account for up to 13% of all bacterial abortions in mares in enzootic regions,⁶ typically without prior clinical signs, and uveitis can result weeks to months after an initial *Leptospira* infection.⁶ Some animals recovering from leptospirosis become asymptomatic carriers that harbor leptospire in the kidneys for

extended periods and shed infectious leptospire into the environment in their urine.^{1,10}

Etiology

Horses can become infected by drinking from standing water contaminated by *Leptospira*-infected urine from infected wildlife or domestic animals, by eating hay or grain that is similarly infected, or by exposure to contaminated soil, bedding, aborted or stillborn fetuses, or vaginal discharges.^{10,11} At least 12 pathogenic and 4 nonpathogenic species, with more than 250 pathogenic serovars of *Leptospira* are currently recognized.¹ Initially, these leptospire were classified into serogroups on the basis of surface antigens, with each serogroup containing one or more serovars.^{2,12} Newer molecular classification schemes dividing the *Leptospira* genus into several species on the basis of DNA relatedness have since been devised.¹²⁻¹⁵ Unfortunately, the correlation between serological typing and genetic classification into species can be poor.¹¹ For this and other practical reasons, the older serovar/serogroup method continues to be used in clinical practice and is routinely used by diagnostic laboratories.¹¹

Leptospira serovars generally are adapted to one or more definitive, or maintenance (see box, right), hosts that maintain the organisms and are vital to their dissemination. Maintenance hosts usually become infected at a young age,¹⁶ harbor *Leptospira* in their kidneys, and shed the organisms in their urine without developing clinical disease.^{6,10,16,17} Horses, however, are incidental (i.e., accidental) hosts for leptospire shed by other species. Incidental host infections (see box) tend to result in more severe disease and clinical signs, strong immune responses, and a short period of bacterial shedding.¹⁸ Leptospire shed by infected

animals into the environment have been shown to survive for periods ranging from 2 to 7 weeks, with survivability depending upon moisture, pH, temperature, and the presence of inhibiting compounds.^{10,19} Serovar Pomona was shown to retain viability, pathogenicity, and antigenicity up to 74 days when recovered from soil with a pH of 6.7 to 7.2, and a moisture content of 15.2 to 31.4%.¹⁶ During periods of heavy precipitation or flooding, leptospires are released from the soil and are brought to the surface in standing water.¹⁸ Leptospiral seasonality in many parts of North

America is associated with rainfall, with reports of disease outbreaks occurring during or immediately after periods of flooding.^{10,20}

Although there is regional variability in the specific leptospiral serovar causing the majority of leptospirosis cases in horses worldwide, in North American horses, *L. interrogans* serovar Pomona is the prominent incidental serovar.⁶ Wildlife including the striped skunk, raccoon, white tailed deer, and opossum are common maintenance hosts infected with *L. pomona*.²¹

The Language of Leptospirosis

Maintenance host: Either wildlife or domestic species, including livestock, that serve as reservoirs of *Leptospira*. Disease in maintenance hosts is characterized by: direct, efficient spread; high incidence of infection; inapparent clinical signs; chronic disease; infertility and reproductive failure; extended period of leptospiral shedding, and low or undetectable antibody titers to the infecting serovar. In maintenance hosts, the infecting serovar resides in the kidneys and genital tract and remains a source of infection for other animals. Despite the long-term nature of the infection, antibody titers do not remain high for an extended period, significantly increasing the difficulty of diagnosing the disease.

Incidental host: Species that typically become infected by indirect transmission from animals of another species. Although the infection is usually of short duration, it is characterized by acute severe disease, a marked antibody response, and a relatively short period of shedding.

Microscopic agglutination test (MAT): The reference test for serological diagnosis of leptospirosis. In the test, animal sera (serial dilutions) are reacted with live antigen suspensions of leptospiral serovars. After an appropriate incubation period, the serum-antigen mixtures are examined by dark-field microscopy, and the titers are determined. Success with the test is enhanced when the range of antigens used includes serovars representative of all serogroups and locally common serovars. Acute infection is indicated by a single elevated titer detected in association with an elevated temperature. A 4-fold or greater rise in titer between paired serum samples confirms a diagnosis, regardless of the interval between samples. Typically, a titer ≥ 100 is indicative of past exposure.¹⁰

Pathogenesis of Leptospirosis

As incidental (i.e., accidental) hosts, horses typically become infected when they drink contaminated water containing urine shed from a maintenance host species. Leptospire penetrate mucous membranes or abraded skin and begin replicating in the bloodstream for about 8 days,¹⁸ depending on the virulence of the organism and the immune response of the host. Nonspecific clinical signs associated with this leptospiremic stage of infection include fever, depression, anorexia, and generalized pain.¹⁸ Antibodies to the leptospire become detectable in serum 4 to 8 days after exposure and may persist for up to 7 years.²²⁻²⁵ By way of the bloodstream, leptospire invade such immunologically privileged sites as the renal tubules, placenta, and anterior and posterior chambers of the eyes during the immune phase of infection.¹⁸ Damage to internal organs is dependent upon virulence of the infecting serovar and host susceptibility. The lack of pathognomonic clinical signs makes an early diagnosis difficult.¹⁸ Occasionally, during the immune phase of infection, *Leptospira* cause fever and acute renal failure. Kidneys become swollen due to tubulointerstitial nephritis, and the urine may have pyuria without visible bacteria.⁶ Infected horses may shed pathogenic leptospire in their urine for up to 4 to 5 months and can potentially transmit the disease to in-contact horses.¹⁸

Leptospiral-Associated Equine Recurrent Uveitis (ERU)

Equine recurrent uveitis (moon blindness or periodic ophthalmia) (**Figures 1 and 2**) is the most common cause of blindness in horses,²⁶ and leptospire are the most commonly identified etiologic agent.^{6,27,28} Based on studies conducted in the U.S. and Germany, it is estimated that up to 70% of all ERU cases are associated with *Leptospira*.^{29,30} ERU is currently thought to be an immune-mediated disease; however, the exact mechanism is a topic of ongoing research. One theory is that after the first episode of uveitis and a subsequent delayed hypersensitivity reaction, memory T cells remain in the uveal tract. Subsequent exposure to the same antigen or a self-protein that is similar to the original antigen triggers a strong immunological response within the uveal tract and results in an acute episode of inflammation.^{26,31} A second theory is that inciting antigens (including leptospiral antigens) become established in ocular tissues and their ongoing presence causes periodic episodes of inflammation.³² A painful condition that develops weeks to months after systemic leptospirosis, ERU is characterized by bouts of inflammation of the vascular tunic or uvea of the eye alternating with symptom-free intervals of low or no inflammation.³³ The recurrences of inflammation are marked with severe inflammatory responses that result in serious injury to ocular components, as cataracts, vitreous exudates and retinal

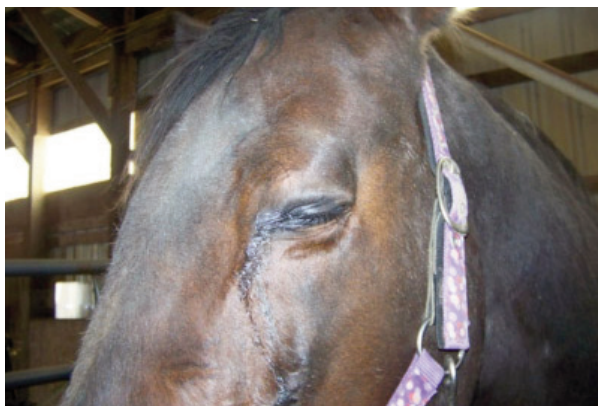


Figure 1. Horse with blepharospasm secondary to uveitis. Photo courtesy of Ann Dwyer, DVM.



Figure 2. Equine eye with signs of uveitis. Photo courtesy of Brian Gilger, DVM, MS, ACVO.

detachment are evident.^{33–36} Recurrent bouts of uveitis many times lead to impaired vision and blindness in the affected eye(s) during the life of the horse.²⁸ Genetic factors also appear to be involved in the etiology of ERU as Appaloosa and some Warmblood breeds are more frequently and more severely affected than other breeds.^{28,37}

Leptospiral Abortion in Mares

Fetal infection with *Leptospira* spp. sometimes follows localization of the organisms in the uterus of pregnant mares, with most abortions occurring late in gestation. On rare occasions, a live foal may be born emaciated and icteric from infection with leptospires, and neonatal death usually ensues.¹¹ Infected fetuses have been shown to have leptospires present in the placenta, umbilical cord, kidney, and liver. Pathology of the placenta does not involve the cervical star. Macroscopically, edema and areas of necrosis are evident in the chorion, whereas microscopic lesions include necrosis and calcification of the placenta. A diffuse yellow discoloration of the umbilical cord likely is indicative of funisitis. Currently, it has not yet been determined whether abortion can be attributed to fetal infection, placentitis, or funiculitis, or a combination of all three conditions. Aborting mares have been reported to shed leptospires in their urine for periods ranging up to three months and can potentially transmit the disease to in-contact animals as well as pose a potential zoonotic risk to humans.^{6,10} Some horses aborting due to a leptospiral infection develop uveitis several weeks to months later.^{6,35}

Diagnosis

The microscopic agglutination test (MAT; see box above) is the most frequently used method of diagnosing leptospirosis in horses, just as it is in other domestic species, including cattle and dogs.³⁸ With the MAT, dilutions of serum are incubated with suspensions of live leptospiral serovars and are then

examined by dark-field microscopy for agglutination. The highest dilution of serum in which 50% of the agglutination occurs is reported as the titer.¹⁸ The usual requirement for unequivocal diagnosis is a 4-fold rise from baseline titer to convalescent titer.³⁷ Unless convalescent serum is obtained, the test does not differentiate between infected and exposed animals.³⁹ Although other diagnostic tests for leptospirosis—fluorescent antibody test (FAT), immunohistochemistry, and dark-field examination of fetal fluids—are available, they may have low sensitivity and specificity on frozen/thawed or autolysed specimens.³⁹ Additionally, testing using PCR analysis has of late become a more common modality for early identification of leptospirosis, but limited information is available on the validity, sensitivity, specificity, and positive predictive value of the various PCR assays.^{38–41}

With the MAT, significant increases in serum antibody titers often occur in cases of leptospiral abortion or acute renal failure; however, in cases of ERU, serum titers may be low—or even negative—because of the chronic and localized nature of the infection.^{6,39} In cases of leptospiral abortion, MAT on fetal fluids and maternal serum usually is diagnostic because the titers are very high.⁶ It is critical, though, that prevalent regional serovars be included as test antigens.^{38,39} The MAT also is used to diagnose leptospiral uveitis in cases where classic signs of ERU (miosis, blepharospasm, lacrimation, photophobia, edema of the eyelid, swollen conjunctiva, corneal edema, and a history of recurrence) are evident. According to one research report, the MAT provides more reliable results when used to determine antibody titers in ocular fluids than in serum.²⁹ Because of the difficulties associated with diagnosing *Leptospira*-associated uveitis, confirmation may require serology, culture, and PCR of aqueous fluid and serum.⁶ Board-certified veterinary ophthalmologist B.C. Gilger, DVM, MS,

recently noted that in suspected cases of *Leptospira*-associated uveitis, it may be advantageous to combine the results of MATs from aqueous humor and serum and PCR to provide the most reliable indications of infection.*

Treatment and Prevention of Leptospirosis

Because treatment regimens for leptospirosis in horses have been largely extrapolated from other species, very little information specific to horses is available.³⁸ The current standard treatment for ERU consists of administering anti-inflammatory agents and mydriatics to decrease pain and inflammation, minimize chronic changes, and prolong

*Personal conversation on June 24, 2015.

vision. Two newer therapies—an intra-ocular device containing cyclosporine to block transcription of interleukin-2 and pars plana vitrectomy—are also available.⁴² Both therapies are invasive and expensive and require specialized skill and equipment.^{18,42}

No leptospirosis vaccines are currently approved for use in horses for either leptospirosis, ERU, or abortions. Prevention should involve good husbandry and hygiene practices, vaccination of other animals on a farm, and minimizing contact with wildlife carriers (especially skunks) and other infected horses. Acutely affected horses and especially mares that abort should be isolated for 14 to 16 weeks and assumed to be shedding leptospires during this time. Affected horses can have their urine tested by FAT to

Table 1.
EQUINE RECURRENT UVEITIS PROBABILITIES AND PERCENTAGE DEPRECIATIONS ESTIMATED FROM PUBLISHED SOURCES

Measurement	Valid for	Value	Reference
Risk of ERU	U.S. horse population	8%	(27)
Percentage of ERU associated with leptospires	U.S. horse population	70%	(46)
Risk of ERU, split into breeds	Thoroughbred Standardbred Appaloosa Other horses	3.77% 1.36% 23.52% 7.69%	(27,44,47)
Ocular involvement split into breeds	One eye affected, still visual: Appaloosa Non-Appaloosa One eye affected, blind: Appaloosa Non-Appaloosa Bilaterally affected, still visual: Appaloosa Non-Appaloosa Bilaterally affected, blind: Appaloosa Non-Appaloosa	19% 58% 45.24% 32.20% 81% 42% 35.71% 14.41%	(48)
Depreciation with vision impairments	One eye affected, still visual One eye affected, blind Bilaterally affected, still visual Bilaterally affected, blind	20% 75% 75% 100%	(49)

determine when the animals stop shedding leptospores. Providing clean drinking water, reducing exposure to stagnant water, and feeding horses off the ground are other management practices that can further help reduce the risk of infection. Because such bio-security measures are challenging to implement and maintain, all newly acquired livestock and new horses should be quarantined and tested before being introduced to resident herds.^{6,18,38}

ERU Prevalence and Associated Loss of Value

Summarized in **Tables 1** and **2** are the results of a recent study conducted in the U.S. to estimate the prevalence of ERU and to approximate the associated depreciation in horse value resulting from visual impairment.⁴³ The U.S. horse population in 2014 was determined by market research.⁴⁴ Published sources permitted the estimation of ERU risk, associated visual impairments, accounting for breed differences, and the loss of value in function of different ocular involvements and the various uses

of a horse.^{27,45-49} Considering the U.S. horse breeds and use distributions, investigators calculated the number of horses allocated to different levels of vision impairment and associated relative depreciations. The average value of horses (\$2,140) was derived from official sources,⁵⁰ conservatively excluding very high-priced competition and racing horses. On the basis of a population of 7.2 million horses and an ERU overall risk factor of 8%, the number of horses in the U.S. calculated to be currently affected by ERU is 576,000. Because 70% of all ERU cases have been reported to be associated with leptospores, the total number of horses affected with *Leptospira*-associated ERU was estimated to be 400,000 in the U.S. Of the total population of horses affected with ERU, 198,513 and 104,269 are or are expected to become blind in one or both eyes, respectively, over the course of 11 years. On the basis of the average value of horses and the loss of value with different degrees of ocular involvements, depreciation was conservatively calculated to be approximately \$800 million over all horses in the U.S., with

Table 2.
NUMBER OF HORSES CURRENTLY AFFECTED BY ERU IN THE U.S., PERCENTAGE DEPRECIATIONS BY OCULAR INVOLVEMENT, AND CALCULATED LOSS OF VALUES OF HORSES WITH ERU DUE TO VISION IMPAIRMENTS

Breed	Horses still visual		Horses blind		Total
	Unilaterally affected	Bilaterally affected	In one eye	In both eyes	
Number of horses in the U.S.					
Thoroughbred	8,574	6,209	8,917	3,989	27,689
Standardbred	1,060	768	1,102	493	3,423
Appaloosa	3,615	15,413	45,193	35,678	99,899
Other horses	137,796	99,783	143,301	64,109	444,989
Total	151,046	122,172	198,513	104,269	576,000
Percentage loss of value (depreciation) by ocular involvement					
All	20.0%	75.0%	75.0%	100.0%	65.1%
Loss of value calculated, considering an average value of horses of \$2,140					
All	\$64,647,688	\$196,086,060	\$318,613,365	\$223,135,660	\$802,482,773

\$560 million depreciation calculated due to *Leptospira* ERU. This figure does not include the costs of diagnosis and treatment of horses, which can amount to thousands of dollars during the course of disease.²⁸

Leptospiral Abortion and Associated Loss of Value

The overall relative risk of leptospiral abortion occurring in mares in the U.S. and the estimated economic losses associated with the abortions were determined in a study conducted by Zoetis. The relative risk of leptospiral abortion was calculated using prevalence data from the University of Kentucky Veterinary Diagnostic Laboratory to represent regions of the country at higher risk of leptospiral abortions during

both average and heavy rainfall seasons.^{3,39} and data from the University of Michigan and the University of Guelph Animal Health Laboratory were used to represent regions of the country at low risk of leptospiral abortion.^{51,52} An additional factor considered in the study was the relative risk of abortions occurring with a worst-case scenario during the course of a leptospirosis-associated abortion storm.²⁰ Cost figures for breeding Thoroughbreds in Kentucky, as reported in 2002, 2006, and 2009,⁵³⁻⁵⁵ were used to calculate costs in the case of no abortion and abortion, whereas the values of Thoroughbreds were those reported for 2013 in *The Jockey Club Fact Book 2014*.⁵⁶ All costs and revenues were inflation adjusted to 2013 values using the U.S. inflation calculator (<http://www.usinflationcalculator.com>. Accessed May 28, 2015).

Table 3.
COST DATA FOR BREEDING THOROUGHBREDS IN KENTUCKY

Cost data	No abortion	Abortion	Reference/Comments
Broodmare value	\$122,155	\$122, 155	(54,55)
Costs associated with the mare			
Maintenance cost	\$12,526	\$12,526	(54,55); inflation adjusted
Annual depreciation (replacement costs)	\$17,451	\$17,451	1/7 of broodmare value as reported in references 54 and 55
Breeding costs (stud fees)	\$30,539		1/4 of broodmare value as reported in references 54 and 55; assumes stud fees with a live foal guarantee (53)
Other breeding costs	\$1,435	\$1,435	(54); inflation adjusted
Veterinary costs related to abortion		\$921	(53); inflation adjusted
Costs associated with the foal			
Yearling cost	\$15,904		(55)
Sum costs yearling	\$77,855	\$32,333	
Yearling revenue	\$89,488		(56); value for 2013
Total net profit*	\$11,633	-\$32,333	
Net profit with abortion compared to no abortion		-\$43,966*	

*Negative values correspond to losses.

Table 4.
COST DATA FOR BREEDING THOROUGHBREDS IN STATES OTHER THAN KENTUCKY

Cost data	No abortion	Abortion	Reference/Comments
Broodmare value	\$81,937	\$81,937	(56); value for 2013
Costs associated with the mare			
Maintenance cost	\$12,526	\$12,526	(54,55); inflation adjusted
Annual depreciation (replacement costs)	\$11,705	\$11,705	1/7 of broodmare value as reported in references 54 and 55
Breeding costs (stud fees)	\$20,484		1/4 of broodmare value as reported in references 54 and 55; assumes stud fees with a live foal guarantee (53)
Other breeding costs	\$1,435	\$1,435	(54); inflation adjusted
Veterinary costs related to abortion		\$921	(53); inflation adjusted
Costs associated with the foal			
Yearling cost	\$15,904		(55)
Sum costs yearling	\$62,054	\$26,587	
Yearling revenue	\$60,025		(56); value for 2013
Total net profit*	-\$2,029	-\$26,587	
Net profit with abortion compared to no abortion		-\$24,558	

*Negative values correspond to losses.

In an average rainfall season in Kentucky, 0.15% of all pregnant Thoroughbred mares are diagnosed to abort due to leptospirosis.³ In these broodmares, costs of \$32,333 accumulate over pregnancy without having a live foal (**Table 3**). Based on absolute figures, on average 21 abortions occur in Kentucky Thoroughbreds due to leptospirosis at an average net loss per abortion of \$43,966 (costs associated with the mare plus missed profit from the foal). Thus, the average total loss in all Thoroughbred mares in Kentucky due to diagnosed leptospirosis abortion totals \$923,286. In a heavy rainfall season when on average 0.55% of all pregnant Thoroughbred mares are diagnosed to abort due to leptospirosis, a 3.7 times greater risk exists in Kentucky for an average total loss in all Thoroughbreds of \$3,341,416. In the case of an

abortion storm (e.g., following a flooding incident), costs could be higher still as 80% of pregnant mares aborted and the losses were attributed to leptospirosis.²⁰

Cost figures for breeding Thoroughbreds in the rest of the U.S. are summarized in **Table 4**. The overall net loss in these states in case of abortion compared with a live foal was calculated to be \$24,588.

Based on these cost data, the calculated total annual loss in Thoroughbred mares in the U.S. totals \$1,168,866 during an average rainfall season, escalating to \$4,231,267 in a heavy rainfall season. Also worthy of special mention is that with each brood mare pregnancy, horse owners have approximately \$13,000 invested in the mare, regardless of geographic location and regardless if the mare delivers a healthy foal.

SUMMARY

Leptospirosis in horses is likely an underdiagnosed disease that is capable of causing substantial economic and emotional impact to horse owners and the horse industry. Two economically important diseases of horses caused by infections with pathogenic *Leptospira* spp. are recurrent uveitis and placentitis/abortion. Estimates indicate that as many as 400,000 horses in the U.S. are affected with ERU caused by leptospires and that of this total 198,513 and 104,269 will develop blindness in one or both eyes, respectively, at a calculated loss in horse value of more than half a billion dollars, exclusive of the costs of diagnosis or treatment. Analysis of published data on leptospiral-associated abortions indicates that annually in an average rainfall year 31 pregnant Thoroughbred mares abort in the U.S. due to diagnosed leptospires, resulting in an overall loss of approximately \$1.3 million. Because reliable abortion data is available only on Thoroughbreds and Standardbreds, which represent fewer than 15% of all horses in the U.S., the actual number of leptospiral abortions might be 5 to 10 times higher according to Craig Carter, DVM, PhD, Director of the University of Kentucky Veterinary Diagnostic Laboratory and professor of

epidemiology.⁵⁷ Additionally, in seasons with heavy rainfall, the risk of abortion associated with leptospiral infections has been estimated to be as much as 3.7 times higher with losses rising to \$4.2 million in the Thoroughbred breed alone. In areas where leptospirosis is enzootic, the value of a single high MAT titer is limited; therefore, the usual requirement for diagnosis is a 4-fold rise in titer in paired serum samples for an accurate diagnosis. In cases of leptospiral abortion, a very high titer on fetal fluids and maternal serum is diagnostic, providing that prevalent serovars are included as test antigens. No specific test is available to exclusively diagnose leptospiral uveitis. There is no equine-labeled *Leptospira* vaccine available, so current prevention relies upon instilling effective biosecurity measures, education, and creating awareness in horse owners.

ACKNOWLEDGEMENTS

Zoetis thanks Dr. Brian Gilger of North Carolina State University and Drs. Barbara Nautrop and Ilse Van Vlaenderen of EAH Consulting for conducting the economic impact study, and Gary Svatos of SVATOS COMMUNICATIONS INC for his contribution in the preparation of this Technical Bulletin.

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