Bluetongue

Sore Muzzle,
Pseudo Foot-and-Mouth Disease,
Muzzle Disease,
Malarial Catarrhal Fever,
Epizootic Catarrh, Beksiekte

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the Center for Food Security & Public Health
IOWA STATE UNIVERSITY®
College of Veterinary Medicine
Iowa State University
Ames, Iowa 50011
Phone: 515.294.7189
Fax: 515.294.8259
cfsph@iastate.edu
www.cfsph.iastate.edu

INSTITUTE FOR INTERNATIONAL COOPERATION IN ANIMAL BIOLOGICS
Iowa State University
College of Veterinary Medicine
www.cfsph.iastate.edu/IICAB/

Importance

Bluetongue is a viral disease of ruminants transmitted by midges in the genus *Culicoides*. Bluetongue virus is very diverse: there are more than two dozen serotypes, and viruses can reassort to form new variants. This virus is endemic in a broad, worldwide band of tropical and subtropical regions from approximately 35°S to 40°N; however, outbreaks also occur outside this area, and it may persist long-term if the climate and vectors are suitable. While overwintering in regions with cold winters is unusual, bluetongue virus recently demonstrated the ability to survive from year to year in central and northern Europe.

Bluetongue virus can replicate in many species of ruminants, often asymptomatically. Clinical cases tend to occur mainly in sheep, but cattle, goats, South American camelids, wild or zoo ruminants, farmed cervids and some carnivores are occasionally affected. Cases range in severity from mild to rapidly fatal, and animals that survive may be debilitated. Additional economic costs result from reproductive losses, damaged wool and decreased milk production. Control of this vector-borne disease is difficult, except by vaccination. The existence of multiple serotypes complicates control, as immunity to one serotype may not be cross-protective against others.

Etiology

Bluetongue results from infection by bluetongue virus, a member of the genus *Orbivirus* and family Reoviridae. At least 26 serotypes have been identified worldwide. A few bluetongue viruses have additional names (e.g., Toggenburg orbivirus for the prototype strain of serotype 25). Isolates differ in virulence, and some strains seem to cause few clinical signs. Like some other viruses such as influenza virus, bluetongue viruses can reassort and recombine to produce new variants.

Bluetongue viruses are closely related to the viruses in the epizootic hemorrhagic disease (EHD) serogroup, a factor that can influence the development and/or selection of some diagnostic tests.

Species Affected

Bluetongue virus can infect many domesticated and wild ruminants including sheep, goats, cattle, water buffalo, African buffalo (*Syncerus caffer*), bison (*Bison* spp.), various cervids, wild relatives of sheep and goats, wildebeest (*Connochaetes* spp.) and other species. Both domesticated ruminants (especially cattle) and wild ruminants can be maintenance hosts. Infections are often subclinical. The virus can also infect camelids, and antibodies have been detected in some nonruminant wildlife including African elephant (*Loxodonta africana*), black and white rhinoceros (*Diceros bicornis* and *Ceratotherium simum*) and giraffe (*Giraffa camelopardalis*) in Africa, and collared peccaries (*Pecari tajacu*) in South America.

Among domesticated animals, clinical cases mainly occur in sheep; however, cattle, goats, yaks (*Bos grunniens*), llamas and alpacas were also affected in some outbreaks. In North America, cases of bluetongue have been documented in wild white-tailed deer (*Odocoileus virginianus*), pronghorn (*Antilocapra americana*) and bighorn sheep (*Ovis canadensis*), and captive Reeve's muntjac (*Muntiacus reevesi*) and greater kudu (*Tragelaphus cupensis*). There are no published reports of outbreaks among wild ruminants in Africa or Europe; however, clinical cases were reported in some zoo animals during serotype 8 outbreaks in Europe. Affected species included North American bison (*Bison bison)*, European bison/ wisents (*Bison bonasus*), yaks, musk ox (*Ovibos moschatus*), Alpine ibex (*Capra ibex*), Siberian ibex (*Capra sibirica*) mouflon (*Ovis aries musimon*), blackbuck (*Antilope cervicapra*), fallow deer (*Dama dama*) and a Bactrian camel (*Camelus bactrianus*).

Accumulating evidence suggests that carnivores can also be infected by bluetongue virus. Antibodies to this virus have been detected in dogs, cats, cheetahs (*Acinonyx jubutus*), lions (*Panthera leo*), wild dogs (*Lycaon pictus*), jackals (*Canis* spp.) spotted hyenas (*Crocuta crocuta*) and large-spotted genets (*Genetta maculata*). Clinical signs have been reported in pregnant dogs infected by serotype 11, and nonpregnant Eurasian lynx (*Lynx lynx*) infected by serotype 8.

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Zoonotic potential

Bluetongue virus is not zoonotic.

Geographic Distribution

Bluetongue virus can be found worldwide within tropical and subtropical climates from approximately 35° S to 40° N, and in some areas outside this region (e.g., in parts of California). Endemic areas exist in Africa, Europe, the Middle East, North and South America and Asia, as well as on numerous islands (e.g., Australia, the South Pacific, the Caribbean). Multiple serotypes can be found in many regions.

Outbreaks can occur outside endemic areas, but in most cases, the virus does not persist once cold weather kills the *Culicoides* vectors. Unusually, a serotype 8 virus overwintered for multiple years in central and northern Europe.

Transmission

Bluetongue virus is mainly transmitted by biting midges in the genus *Culicoides*, which are biological vectors. These midges can fly short distances of 1- 2 km, but they can be blown much farther by wind. Some species known to be effective vectors include *Culicoides sonorensis* in the United States; *C. brevitarsis* in Australia and parts of Asia; *C. imicola* in Africa, the Middle East, southern Europe and parts of Asia; *C. bolitinos* in some cooler regions of Africa; and *C. insignis* in the Caribbean, Central and South America and parts of the U.S. Additional species (e.g., members of the *C. obsoletus-dewulfi* complex in northern Europe) may be important locally. Other biting arthropods such as sheep keds (*Melophagus ovinus*), cattle lice (*Haematopinus eurysternus*), ticks and mosquitoes might be capable of transmitting the virus mechanically, but their role, if any, is thought to be minor. Bluetongue virus can also be spread mechanically on surgical equipment and needles. Some field strains and attenuated vaccine strains can infect the fetus *in utero*. Some of these animals can be born infected, and may introduce the virus to new areas if the dam is transported. Bluetongue virus can overwinter in some cold regions, by unknown mechanisms.

Bluetongue virus can persist in the blood of some animals for relatively long periods, facilitating transmission to *Culicoides*. Live virus has been isolated from some cattle for as long as 5 to 9 weeks, and viral RNA has been found much longer. Prolonged viremia has also been reported in other species, such as red deer (*Cervus elaphus*). However, animals eventually clear the virus, and there is no evidence that they remain persistently infected, even when infected *in utero*. Serotype 25 (Toggenburg orbivirus) in goats might be an exception. In one report, serotype 25 viral RNA was found for at least 2 years in individual animals, and the blood of some goats was infectious at 12-19 months.

At least some bluetongue strains (including members of serotypes 1, 8 and 26) can be transmitted directly between ruminants in close contact. This is a newly recognized route, and is generally thought to be of little epidemiological significance compared to transmission by midges. Serotypes 25 and/or 26 might be exceptions, as these viruses do not seem to replicate readily in some *Culicoides* vectors or in cell lines derived from these midges. The mechanisms of contact transmission are still uncertain. Suggestions have included shared feed and water troughs, contamination of wounds with blood during fighting among red deer, and contact with infected placentas in a case in cattle. Oral transmission of bluetongue virus has been demonstrated in colostrum, and experimentally via cultured viruses or urine from an experimentally infected sheep. Serotype 26 nucleic acids were found at low levels in nasal and ocular secretions of goats, and this virus was isolated from ocular swabs. Bluetongue virus can also be shed in semen.

How bluetongue virus infects carnivores is still uncertain. Seropositive dogs, cats and wild carnivores in Africa were thought to have eaten tissues from infected animals, and Eurasian lynx in a zoo had been fed ruminant fetuses and stillborn animals from outbreak areas. However, seropositive dogs in Morocco had not been fed raw diets, suggesting that they were infected by *Culicoides*. Bites from midges were also thought to have been responsible for some clinical cases among pregnant dogs in the U.S., although other routes (e.g., infection via semen or a contaminated semen extender) could not be entirely ruled out. Other dogs became infected when they accidentally received a bluetongue virus-contaminated vaccine. Transplacental transmission has been demonstrated in dogs, at least for serotype 11.

Disinfection

Disinfectants reported to be effective against bluetongue virus include sodium hypochlorite and 3% sodium hydroxide. Sodium hypochlorite, iodine (potassium tetraglicine triiodide) and a quaternary ammonium disinfectant (didecyldimethylammonium chloride) could inactivate another orbivirus, African horse sickness virus, and may also be active against bluetongue.

Incubation Period

The incubation period is estimated to be approximately a week, with a range of 2-10 days.

Clinical Signs

Clinical cases of bluetongue occur mainly in sheep, while subclinical infections seem to predominate in most other species.

Sheep

Sheep infected with bluetongue virus may remain asymptomatic, or become mildly to severely ill. Common clinical signs include fever and depression; serous to mucopurulent nasal discharge, which may crust around the nostrils; and hyperemia of the muzzle, oral and nasal

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mucous membranes, conjunctiva and coronary band of the hooves. The muzzle, periocular region and face often become edematous; in some cases the swelling may also involve the ear and/or submandibular region, and occasionally even extends as far as the axillae. The lips and tongue may be very swollen in some animals; the tongue is occasionally cyanotic in severe cases, and may protrude from the mouth. Petechiae and ecchymoses can also develop on the muzzle, oral mucous membranes and coronary band. The oral lesions, which often include erosions and ulcerations, can result in drooling, soreness during eating, or anorexia. Involvement of the coronary bands leads to lameness, with hot and painful hooves; sloughing of the hooves is possible. The udder and teats may also have lesions, and muscle damage can result in torticollis. Some sheep with bluetongue develop pulmonary edema and die rapidly, with clinical signs of dyspnea.

Pregnant ewes can abort or give birth to lambs that are stillborn or have CNS lesions, retinal lesions and/or skeletal malformations. CNS lesions can result in neurological signs or "dummy" lambs that cannot nurse or follow the ewe. The specific syndromes vary with the stage of gestation, and lambs infected later in the pregnancy can be born normal.

Deaths are often the result of pulmonary edema in acute cases, or secondary bacterial complications and exhaustion when the course is more prolonged. In animals that survive, sequelae may include general loss of condition and hoof deformities. Some surviving sheep have abnormal wool growth, or lose some or all of their wool a few weeks after the illness, and poor quality semen has been reported transiently in rams. Mildly affected sheep usually recover rapidly.

Wild relatives of sheep and goats

Some bighorn sheep in North America or European mouflon affected by serotype 8 outbreaks in Europe had clinical signs resembling classical bluetongue in sheep, while other animals died suddenly without preceding signs. Hemorrhages were also reported. Nasal discharge and sudden death were seen in Alpine ibex in European zoos during the serotype 8 outbreaks. A Siberian ibex developed swelling of the head and neck, but survived.

Cattle and goats

Infections in cattle and goats are usually subclinical in endemic areas. These species are more likely to be affected when a naive population is first exposed to bluetongue virus, such as during recent serotype 8 outbreaks in Europe. Clinical cases resemble the disease in sheep, but tend to be milder. Reported signs in cattle include inappetence, lethargy, facial edema, submandibular edema, oral inflammation with vesicles or ulcers in the mouth, excess salivation, nasal discharge, an elevated respiratory rate, edema of the distal limbs, and hyperemia of the coronary band with lameness. The muzzle of some cattle was reported to have a “burned” cracked appearance. Body temperature was sometimes normal. Cattle can also develop various skin lesions including vesicular and ulcerative dermatitis, periocular dermatitis, necrotic lesions, sloughing of affected skin and photodermatitis. In some cases, the skin may develop thick folds and cracks, particularly around the withers and neck. Udder and teat lesions, such as erythema, ulcers, cracking and necrotic lesions, have been reported in both cattle and goats, and milk production can be decreased. In some goats, a high fever and drop in milk production were reported to be the only sign. Abortions and stillbirths have been reported in both species, and congenital abnormalities including CNS lesions have been observed in newborn calves. Temporary sterility may be seen in bulls. Deaths are possible, but uncommon.

Camelids

Only a few cases have been described in llamas and alpacas. Several fulminant, fatal infections were characterized by brief (< 24 hour) histories of severe respiratory distress, with recumbency or reluctance to rise, followed rapidly by death. Additional signs in some of these animals included coughing, foaming at the mouth, abnormal lung sounds, abortion, paresis and disorientation. Some reports described isolated cases; in others, a few additional llamas also had dyspnea, or were reported to have developed respiratory signs but recovered. In two studies, small numbers of experimentally infected llamas or alpacas had only mild signs (anorexia, mild conjunctivitis, periods of recumbency/ signs of discomfort, low grade lung sounds) or remained asymptomatic.

Sudden death was reported in one Bactrian camel at a European zoo during serotype 8 outbreaks. Three dromedary camels experimentally infected with a serotype 1 virus remained asymptomatic.

Yaks, bison and musk ox

During serotype 8 outbreaks in Europe, some yaks, North American bison and European bison in zoos developed clinical signs resembling the illness in sheep. Corneal edema as well as conjunctivitis was reported in all three species, and some yaks had udder erythema with papules and crusts. Dyspnea occurred in some yaks and European bison, and sudden death was reported in all three species. Fever, lethargy, conjunctivitis and abortion were seen in a musk ox during this outbreak. North American bison inoculated with a serotype 11 isolate remained asymptomatic.

Cervids

While subclinical infections appear to be common in some species of cervids, a number of bluetongue cases have been reported in white-tailed deer. Syndromes reported in naturally- or experimentally-infected white-tailed deer include nonspecific signs such as fever, severe depression, anorexia and loss of normal fear responses, as well as signs similar to classical bluetongue in sheep. Some animals had severe respiratory distress, and others developed hemorrhagic signs including multifocal hemorrhages in the

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skin and mucosa, severe bloody diarrhea, or excessive bleeding and hematoma formation at venipuncture sites. Peracute disease characterized by head and neck edema, or acute cases mainly characterized by hemorrhages throughout the body, predominated in some epidemics, and were often fatal, Rumen and hoof lesions have been reported in white-tailed deer from areas where the disease was endemic. Lameness can persist after other signs have resolved. Syndromes reported in free-ranging pronghorn antelope in the U.S. include sudden death after the animals were disturbed, or a more prolonged illness (1-6 days), with signs of anorexia, decreased activity, recumbency and reluctance to move. Two pronghorn inoculated with a serotype 8 virus became depressed and inappetent, with labored breathing, and were able to stand only with extreme difficulty. Both cases were fatal

There is limited information other cervids. Although fatal illness associated with bluetongue infection has been reported in wild mule deer (*Odocoileus hemionus*) in the U.S., fever of a few days' duration was the only sign in experimentally infected black-tailed deer (*Odocoileus hemionus columbianus*). There are no reports of outbreaks or clinical cases among wild cervids in Europe, despite evidence of widespread exposure, particularly among red deer. Fallow deer and blackbuck (*Antilope cervicapra*) became ill during serotype 8 outbreaks at European zoos. The clinical signs in fallow deer included oral ulcers, excess salivation, difficulty eating and lameness in some animals, and sudden death in others. Sudden death was reported in blackbuck. Experimentally infected red deer (*Cervus elaphus*) and North American elk (*Cervus elaphus canadensis*), which are closely related, remained asymptomatic or only had mild clinical signs consisting of transient fever, mild conjunctivitis and diarrhea with small amounts of blood and mucus.

Carnivores

Bluetongue virus can cause abortions, sometimes accompanied by fatal illness, in dogs. Serotype 11 was involved in all cases to date. Four experimentally infected pregnant dogs died 5-10 days after aborting, or were euthanized with dyspnea. Some naturally infected dogs also died after an abortion, with respiratory distress and signs of heart failure in some cases. One dog was found dead after apparent recovery from a caesarean section the previous day. Other dogs aborted, but did not become ill. A few nonpregnant dogs inoculated with serotype 1 or 11 viruses remained well. The existence of healthy seropositive dogs in some endemic regions also suggests that some infections are asymptomatic.

Lethargy was the only clinical sign reported in 2 bluetongue virus-infected Eurasian lynx. One of these animals died after 2 days with a virologically confirmed infection. The other animal died several months later, and had only serological evidence of exposure at this time.

Post Mortem Lesions

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In addition to the external lesions seen in living animals, such as facial edema and coronary band lesions, sheep may have hyperemia, hemorrhages, erosions and/or ulcers in the mucosa of the gastrointestinal tract from the mouth to the forestomachs, particularly where mechanical abrasion occurs (e.g., the buccal surface of the cheek and the mucosa of the esophageal groove and omasal fold). The heart may contain petechiae, ecchymoses and necrotic foci; in bluetongue, focal necrosis is particularly common in the papillary muscle of the left ventricle. Subintimal hemorrhage at the base of the pulmonary artery is also characteristic. Pulmonary edema, which may be accompanied by pleural and pericardial effusion, is a common cause of death in fatal cases, and may be a prominent finding. Hyperemia, hemorrhages and/or edema may also be detected in other internal organs. In addition, the skeletal muscles may have focal hemorrhages or necrosis, and the intermuscular fascial planes may be expanded by edema fluid. Lesions in fetuses and newborn lambs can include cavitating lesions in the brain, hydranencephaly, porencephaly, retinal dysplasia and skeletal abnormalities.

Similar signs may be seen in other species. Pulmonary edema was the most prominent finding in llamas, alpacas, and experimentally infected pregnant dogs. Widespread petechial to ecchymotic hemorrhages were common in some animals, including some white-tailed deer. A Eurasian lynx that died with virologically confirmed bluetongue virus infection had gross lesions of petechial hemorrhages, subcutaneous hematomas, anemia and lung congestion with edema. A second lynx that died several months later was emaciated, with anemia, enlarged and gelatinous lymph nodes, petechial hemorrhages and pneumonia.

Diagnostic Tests

Bluetongue virus can be found in blood from living animals, and in spleen, lymph node or bone marrow samples collected at necropsy. Reverse transcriptase-polymerase chain reaction (RT-PCR) tests are widely used to identify viral RNA in clinical samples, and can also identify the serotype. Bluetongue virus can be isolated in embryonated chicken eggs or various mammalian or insect cell lines (e.g., KC [*Culicoides variipennis*] cells). Animal inoculation in sheep or suckling mice is not usually employed, except where cell culture facilities are unavailable; however, it is reported to be more sensitive than isolation in cell culture. Blood samples for virus isolation should be collected as early as possible after infection. Bluetongue viruses are usually identified (i.e., to the bluetongue serogroup level) by RT-PCR. Immunofluorescence/immunoperoxidase staining, or group-specific antigen-capture ELISAs may also be used. Viruses can be serotyped by RT-PCR, gene sequencing or virus neutralization tests. Serotyping by virus neutralization can be difficult to interpret, as some serotypes cross-react in this assay.

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Serology can be used to identify animals that have been infected or exposed to bluetongue virus. Antibodies typically appear 7 to 14 days after infection and are usually persistent. ELISAs are often used, but agar gel immunodiffusion (AGID) or virus neutralization can also be employed. AGID cannot reliably distinguish whether the animal was infected by bluetongue virus or epizootic hemorrhagic disease (EHD) virus; however, monoclonal antibody-based competitive ELISAs can distinguish antibodies to these two viruses. An indirect ELISA can detect antibodies to bluetongue virus in bulk milk samples. Complement fixation has largely been replaced by other tests, although it may still be used in some countries.

Treatment

No specific treatment is available, other than supportive care.

Control

Disease reporting

Bluetongue is difficult to control once it has been transmitted to its vectors, and infections should be reported quickly in countries where this virus is not endemic. Reporting requirements in endemic areas may vary, depending on factors such as the existence of a control program. Appropriate sources (e.g., state authorities in the U.S.) should be consulted for the most current information.

Prevention

Bluetongue is mainly controlled by vaccination. Vaccines should be matched to the viral serotype; protection against other serotypes can be limited or nonexistent. Both attenuated and killed vaccines are currently made (although not necessarily sold in all regions), and multivalent vaccines are available. Attenuated vaccines are considered to be more effective than killed vaccines; however, midges may transmit these vaccine strains to unvaccinated animals during the vector season. Such vaccine strains could reassort with field strains, although how often this happens is currently unclear. Attenuated vaccine strains can also cause fetal malformations in pregnant ewes, and in some cases, may be able to cause systemic disease in highly susceptible animals.

Surveillance of sentinel animals may detect bluetongue viruses before outbreaks occur, and allow vaccination campaigns or other controls to be implemented early. Movement controls for infected animals (including pregnant, seropositive animals) may help limit virus introduction into new areas. Measures to reduce exposure to the *Culicoides* vectors may also be helpful during outbreaks or in endemic regions, although they are unlikely to be effective as the sole control measure. Such measures can include avoidance of environments where midges are more prevalent (e.g., low-lying, damp pastures), stabling animals from dusk to dawn, and/or the use of insecticides or insect repellents (e.g., insecticide-impregnated nets in stables) to help protect groups of animals. Effective vector control is challenging, due to factors such as the extensive breeding sites and large populations of *Culicoides*, and there are also environmental concerns with widespread use of pesticides. Some species of *Culicoides* are now known to enter barns and stables, especially late in the season when temperatures are becoming colder. Direct contact transmission is thought to have only a minor role in most outbreaks; however, disinfection and other infection control measures might be considered in some situations.

Morbidity and Mortality

Bluetongue is a seasonal disease in many areas, due to fluctuations in vector populations caused by cold temperatures or other factors such as rainfall. In regions where multiple serotypes circulate, the dominant serotypes may differ between years. Seroprevalence rates vary widely in endemic regions, ranging from 1% to more than 80% in domesticated and wild ruminants such as sheep, goats, cattle and cervids, as well as in some other species such as camels. In Europe, red deer seem to be the most important wildlife species; during serotype 8 outbreaks, more than half the red deer surveyed in some areas were seropositive. Some studies in endemic areas have not detected antibodies in South American camelids; however, 14% of these animals were seropositive during serotype 8 outbreaks in Germany, with rates varying from <1% to 43% in different parts of the country. Infections in carnivores are still poorly understood, but antibodies were found in 21% of dogs sampled in an endemic region of Morocco, as well as in some dogs, cats and wild carnivores in Africa. A few seropositive dogs have been reported in the U.S.

Sheep are usually the most severely affected species, and in endemic regions, they are often the only domesticated animal with obvious clinical signs. Morbidity rates in sheep range from < 5% to 50-75% (or higher), and are usually at their highest when the virus is first introduced. The case fatality rate is typically < 30%, but can reach 50-90% in highly susceptible populations. Once a virus has become endemic, morbidity may decrease to low levels (e.g., 1-2%), with very few deaths. Outbreaks are uncommon where a virus circulates year-round. Other species such as cattle and goats can also be affected when a bluetongue virus is introduced into a naive population. Many cattle became ill during recent serotype 8 outbreaks in Europe. Generally, cases in cattle and goats are milder than in sheep, and the mortality rate is lower. However, the case fatality rate was reported to be 26% in some goats infected with serotype 8 in Germany. Few cases have been documented in llamas and alpacas, and they were generally fatal. Among wildlife, whitetail deer and pronghorn antelope can be severely affected, with morbidity rates reported to be as high as 100% and case fatality rates up to 80-90%. Disease severity can also be influenced by factors such as the virus strain, host factors (e.g., immunity, general health, genetic factors, age and possibly breed) and environmental stressors.

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Internet Resources

European Commission. Bluetongue
http://ec.europa.eu/food/animal/diseases/controlmeasures/bluetongue_en.htm

The Merck Veterinary Manual
http://www.merckvetmanual.com/mvm/index.jsp

United States Animal Health Association. Foreign Animal Diseases
http://www.aphis.usda.gov/emergency_response/downloads/nahems/fad.pdf

United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS). Bluetongue
http://www.aphis.usda.gov/animal_health/animal_diseases/bluetongue/

Wildpro. Literature Reports of Clinical Signs for Bluetongue (includes zoo animals)
http://wildpro.twycrosszoo.org/S/00dis/viral/Bluetongue/08Bluetongueclinical.htm

World Organization for Animal Health (OIE)
http://www.oie.int

OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals
http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/

OIE Terrestrial Animal Health Code
http://www.oie.int/international-standard-setting/terrestrial-code/access-online/

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