

# THEILERIOSIS

Aetiology Epidemiology Diagnosis Prevention and Control References

## AETIOLOGY

### **Classification of the causative agent**

Theileriae are obligate intracellular protozoan parasites phylum *Apicomplexa*, order *Piroplasmida*, family *Theileriidae*, genus *Theileria*. They are most closely related to *Babesia*, from which they differ by having a developmental stage in leukocytes prior to infection of erythrocytes.

This agent infects both wild and domestic *Bovidae* throughout much of the world and some species also infect small ruminants. There are several identified *Theileria* spp. that infect cattle; the most pathogenic and economically important are *T. parva*, which causes East Coast fever (ECF), *T. annulata*, which causes Tropical theileriosis (TT) or Mediterranean theileriosis and *T. orientalis* (*T. orientalis/buffeli* group), which causes Oriental theileriosis (OT) or *Theileria*-associated bovine anaemia (TABA). *Theileria lestoquardi* (*T. hirci*), which causes Malignant ovine theileriosis (MOT), *Theileria uilenbergi* and *Theileria luwenshuni* are the most pathogenic species of economic significance infecting small ruminants.

### **Resistance to physical and chemical action**

Temperature:	Not applicable.
pH:	Not applicable.
Disinfectants:	Not applicable.
Survival:	Theileriae are obligate intracellular protozoan parasites

## EPIDEMIOLOGY

### **Hosts**

- Theileriae are transmitted by ixodid ticks, and have complex life cycles in both vertebrate and invertebrate hosts
- Theileriae infect both domestic and wild *Bovidae*
  - *Theileria parva* infects cattle, African buffalo (*Syncerus caffer*), Indian water buffalo (*Bubalus bubalis*), and waterbuck (*Kobus* spp.)
  - Taurine breeds of cattle are generally more susceptible to ECF than zebu (*Bos indicus*) or sanga breeds. In addition, introduced cattle, whether of a taurine, zebu, or sanga breed, are much more susceptible to theileriosis than cattle from endemic areas
  - Subclinical infections are common only in cattle and water buffalo; African buffalo and waterbuck are reservoirs for the infection
  - *Theileria annulata* infects cattle and yak (*Bos grunniens*), milder infections are usually seen in water buffalo; the water buffalo is considered to be the natural host in which the parasite evolved. The taurine breeds of cattle, introduced into endemic areas, have a much more severe form of the disease than do indigenous zebu cattle
  - *Theileria orientalis* (*T. orientalis/buffeli* group) has different genotypes able to infect cattle, water buffaloes (*Bubalus bubalis*), yaks (*Bos grunniens*), and sheep
  - *Theileria lestoquardi*, *T. luwenshuni* and *T. uilenbergi* affect sheep and goats. *T. uilenbergi* have also been found in subclinically infected sika deer (*Cervus nippon*) and red deer (*Cervus elaphus*), and *T. luwenshuni* was detected in asymptomatic roe deer (*Capreolus pygargus*) and Mongolian gazelles (*Procapra gutturosa*)

### **Transmission**

- *Theileria* species are spread by ticks
- The most important vector for *T. parva* is *Rhipicephalus appendiculatus*. *R. zambeziensis* in southern Africa and *R. duttoni* in Angola can also spread ECF
- *Theileria annulata* is transmitted by ticks of the genus *Hyalomma*
- Ticks can remain infected on the pasture for up to 2 years depending on the climatic conditions

- Disease is not maintained in the absence of these field vectors
- *Theileria* sporozoites are transmitted to susceptible animals in the saliva of the feeding tick
- Ordinarily, *Theileria* only mature and enter the saliva after the tick attaches to a host; usually, a tick must be attached for 48–72 hours before it becomes infective; however, if environmental temperatures are high, infective sporozoites can develop in ticks on the ground and may enter the host within hours of attachment
- Transovarial transmission does not occur
- Inside the host, *Theileria* sporozoites undergo a complex life cycle involving the replication of schizonts in leukocytes and piroplasms in erythrocytes
- Cattle that recover from *Theileria* infections usually become carriers
- *Theileria orientalis* is transmitted by *Haemaphysalis* spp., or other genera of ixodid ticks. *H. longicornis* is the vector in Australia, New Zealand and Japan
- Mechanical transmission through routine husbandry practices is another potential method for *T. orientalis* transmission
- When a *T. orientalis* infects nymph feeding on a naïve cow, the cow can become infective to ticks in 10 days
- *Theileria lestoquardi* is transmitted by ticks of the genus *Hyalomma*
- *Theileria luwenshuni* and *T. uilenbergi* are transmitted by ticks of the genus *Haemaphysalis*

### Sources of the agent

- *Theileria parva*/East Coast fever (ECF):
  - Sporozoites in salivary glands of infected *Rhipicephalus appendiculatus* ticks
  - Schizonts occur in spleen, lymph nodes and whole blood (lymphoblasts) from ECF-infected animals; experimental transmission to cattle is erratic
- *Theileria annulata*/Tropical theileriosis (TT):
  - Sporozoites in salivary glands of infected *Hyalomma* spp. ticks
  - Schizonts occur in spleen, lymph nodes, liver and whole blood (mononuclear cells) from TT infected animals; transmission by inoculated schizonts occurs readily to cattle
- *Theileria orientalis*/Oriental theileriosis (OT)-*Theileria*-associated bovine anaemia (TABO)
  - Sporozoites in salivary glands of infected *Haemaphysalis* spp. ticks
  - Schizonts can be detected transiently in the lymph nodes, spleen and liver. Piroplasms can be detected in the erythrocytes at approximately 10 days post inoculation.
- *Theileria lestoquardi*/Malignant ovine theileriosis (MOT)
  - Sporozoites in salivary glands of infected *Hyalomma* spp. ticks
  - Schizonts occur in lymph nodes, spleen and liver. The schizonts produce many merozoites that are released after lymphocyte disruption, enter the erythrocytes and transform to piroplasms with ring, dot and rod forms
- *Theileria uilenbergi* and *Theileria luwenshuni*
  - Sporozoites in salivary glands of infected *Haemaphysalis* spp. ticks
  - Schizonts can be detected in lymph nodes, spleen and liver. Piroplasms can be detected in the erythrocytes

### Occurrence

- *Theileria parva* (ECF) occurs in 13 countries in sub-Saharan Africa. The tick vectors can be found from sea level to over 8000 feet in any area where the annual rainfall exceeds 20 inches
- *Theileria annulata* (TT) occurs in southern Europe, North Africa, the Middle East and Asia
- Endemic regions of *T. annulata* and *T. parva* do not overlap. However, tick distribution might change because of changes in climatic conditions
- *Theileria orientalis* is a blood-borne parasite with eleven genotypes identified (named: Chitose or type 1, Ikeda or type 2, buffeli or type 3, types 4 to 8, and N1 to N3). Genotypes Chitose and Ikeda are associated with severe disease. *Theileria orientalis* is globally spread but countries impacted by clinical OT are Australia, New Zealand, Japan, Korea, China and Vietnam
- Cattle are thought to become infected within three weeks of being placed on pasture harbouring infected vectors. Disease is more frequently seen when naïve animals are introduced into an endemic area or when infected animals are introduced to a herd where a competent vector is present but *Theileria* species are not present or only at a low prevalence
- *Theileria lestoquardi* (*T. hirci*), infects small ruminants and it occurs in Middle East, East and North Africa, India, China, Central Asia and Eastern and Southern Europe
- *Theileria* species vary widely in virulence, ranging from production of severe disease, resulting in high levels of mortality, to completely benign forms

For more recent, detailed information on the occurrence of this disease worldwide, see the OIE World Animal Health Information Database (WAHID) Interface [<http://www.oie.int/wahis/public.php?page=home>]

## DIAGNOSIS

- A definitive diagnosis is achieved by the combination of clinical examinations and appropriate laboratory testing
- The incubation period for ECF is 8–12 days on average and for TT is 10–25 days
- In the field, diagnosis is usually achieved by finding *Theileria* parasites in Giemsa-stained blood smears and lymph node needle biopsy smears, but species-specific diagnosis is difficult as most theilerial piroplasms are morphological identical except for *T. velifera*. Schizonts are not always present in the superficial lymph nodes during the disease course
- Morbidity and mortality vary with the host's susceptibility and the strain of the parasite
- The mortality rate from ECF can be up to 100% in cattle from non-endemic areas, however, in indigenous zebu cattle in endemic areas, mortality is usually low even with a morbidity of approximately 100%
- Tropical theileriosis is more severe in European breeds, with a mortality rate of 40–90%, while the mortality rate in indigenous breeds of cattle from endemic areas can be as low as 3%. The mortality rate for tropical theileriosis vary depending on the strain of parasite and the susceptibility of the animals
- Oriental theileriosis has been reported to cause mortality in up to 5% of infected cattle. OT can occur in cattle depending on a number of epidemiological factors (including previous exposure to Theileriae, stress or health status, and genotype). Pregnant heifers and calves are particularly susceptible to the infection. In endemic areas, the mortality rate may be high only in calves
- The morbidity rate in small ruminants infected with *T. lestoquardi* can rise up to 100%, with reported mortality rates of 46–100% in the most susceptible breeds. Clinical cases seem to be more severe in sheep than goats
- Limited information is available for *T. luwenshuni* and *T. uilenbergi*, but morbidity rates in sheep and goats ranged from 19% to 65% in different regions of China (People's Rep. of), with mortality rates of 18–65%

## Clinical diagnosis

- The first clinical sign of ECF is usually a swelling of the draining lymph node, usually the parotid, for the ear is the preferred feeding site of the vector; this is followed by a generalised lymphadenopathy in which superficial lymph nodes such as the parotid, prescapular, and prefemoral lymph nodes, can easily be seen and palpated
- Fever ensues and continues throughout the course of infection; this rise in temperature is rapid and may reach 42°C
- There is marked petechial and ecchymotic haemorrhage on most mucous membranes of the conjunctiva and the buccal cavity
- Anorexia develops, and loss of condition follows
- Other clinical signs may include lacrimation, corneal opacity, nasal discharge, terminal dyspnoea, and diarrhoea
- Before death the animal is usually recumbent, the temperature falls, and there is a severe dyspnoea due to pulmonary oedema that is frequently seen as a frothy nasal discharge
- The severity and time course of the disease depend on, among other factors, the magnitude of the infected tick challenge (ECF is a dose-dependent disease), and on the strain of parasites
- Some stocks of parasites cause a chronic wasting disease
- In recovered cattle, chronic disease problems can occur that result in stunted growth in calves and lack of productivity in adult cattle, however, this syndrome tends to be in the minority of recovered clinical cases
- In a majority of cases, subclinical carriers can be recognised with apparently little or no effect on their productivity

- A fatal condition called 'turning sickness' is associated with the blocking of brain capillaries by infected cells and results in neurological signs
- TT resembles ECF, but jaundice and anaemia may also occur. In its acute form, death occurs 15–25 days after infection. Clinical signs might include pale mucous membranes (anaemia) or jaundice, as the piroplasms will cause destruction of red blood cells
- During the stage with great production of macroschizonts within macrophages, there could be enlarged lymph nodes, and a generalised loss of condition and muscle wasting due to massive release of cytokines from infected cells
- Haemorrhagic diarrhoea may be present in the terminal stages
- In the early stages of clinical OT, signs of muscle weakness, ataxia, and abortion are observed in infected animals. A variety of clinical findings such as lack of appetite, pyrexia, elevated heart rate, abnormal breathing, pale mucous membranes have been reported, all non-specific signs of infection with *T. orientalis*, particularly if accompanied by a history of cattle being moved. Physical examination may reveal pallor (pale eyes, vaginal mucosa), pyrexia, and elevated heart and respiratory rates. Blood samples in EDTA can be collected for laboratory analysis.
- The major clinical manifestations of the disease are haemolytic anaemia, jaundice, lethargy, tachycardia and late-term abortion in pregnant animals. *Theileria orientalis* infections can remain subclinical, although stress may cause the disease to recrudesce and animals are infected long-term, perhaps for life
- Identification of anaemia in *T. orientalis* infections can be achieved by measuring haematocrit (packed cell volume), which in severely infected cattle can be as low as 8%
- The most prominent clinical signs of *T. lestoquardi* infections include generalised enlargement of the superficial lymph nodes, high fever, listlessness, anorexia, emaciation, intermittent diarrhoea or constipation, respiratory signs (coughing, nasal discharge, dyspnoea), icterus and loss of weight. Reproductive losses including abortions may be seen
- Sheep infected with *T. lestoquardi* also display anaemia due to erythrocyte destruction
- Similar signs have been reported in sheep infected with *T. luwenshuni* or *T. uilenbergi*

## **Lesions**

- A frothy exudate is frequently seen around the nostrils of an ECF-infected animal
- Signs of diarrhoea, emaciation, and dehydration may be seen
- Lymph nodes are greatly enlarged and may be hyperplastic, haemorrhagic, and oedematous
- In acute cases of ECF, lymph nodes are oedematous and hyperaemic, but often become necrotic and shrunken in more chronic disease
- Generally, muscles and fat appear normal, but depending on relative acuteness of infection, fat may become greatly depleted
- Serosal surfaces have extensive petechial and ecchymotic haemorrhages, and serous fluids may be present in body cavities
- Haemorrhages and ulceration may be seen throughout the gastrointestinal tract – particularly in the pylorus part of the abomasum, where necrosis of Peyer's patches can be observed
- Lymphoid cellular infiltrations appear in the liver and kidney as white foci
- The most striking changes are seen in the lungs; in most cases of ECF, interlobular emphysema and severe pulmonary oedema appear, the lungs are reddened and filled with fluid and the trachea and bronchi are filled with fluid and froth
- There are no specific lesions associated with tropical theileriosis
- Shortly after infection, the lymph node draining the site of the tick bite will be enlarged
- At the time of severe clinical disease or death, anaemia, jaundice, enlarged lymph nodes, muscle wasting, pulmonary oedema, and haemorrhagic enterocolitis may all be present
- Several authors have reported cutaneous lesions including nodular, haemorrhagic and/or necrotic lesions

- Unlike ECF, which is characterised by a marked lymph proliferative response due to massive infection of lymphocytes, TT is primarily a macrophage infection
  - It is thought that extensive infection of macrophages stimulates a huge outpouring of cytokines, predominantly TNF $\alpha$ , which accounts for many of the lesions seen
  - Macroschizonts may be seen in infected macrophage type cells within various organs

### **Differential diagnosis**

- Heartwater
- Trypanosomosis
- Babesiosis
- Anaplasmosis
- Malignant catarrhal fever
- Contagious bovine pleuropneumonia
- The parasites must also be differentiated from other species of *Theileria*

### **Laboratory diagnosis**

- Diagnosis of acute theileriosis is based on clinical signs, knowledge of disease situation, and vector distribution as well as examination of Giemsa-stained blood, lymph node and tissue impression smears. At necropsy, schizonts may be found in impression smears from most internal organs
- *Theileria parva* and *T. annulata* are diagnosed by the detection of schizonts in white blood cells or piroplasms in erythrocytes. The piroplasmic stage follows the schizont stage and, in both *T. parva* and *T. annulata*, it is usually less pathogenic and is thus often found in recovering or less acute cases. Polymerase chain reaction (PCR) tests and DNA probes are sometimes used to detect and identify *Theileria* species
- Antibodies to *T. parva* and *T. annulata* can be detected with an enzyme-linked immunosorbent assay (ELISA) (not commercially available anymore) or an IFA (indirect fluorescence antibody) test
- Serological tests may be not sensitive enough to detect all infected cattle, and cross-reactions can occur with other species of *Theileria*
- Animals acutely infected with *T. orientalis* seroconverted 2–3 weeks after the parasite was detectable via qPCR (34 days post-introduction to the affected herd)
- It is hoped that a combination of enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR) and DNA probes will greatly enhance our present capacity to identify infected animals, thus making possible accurate surveys of *Theileria* species

### **Samples:**

The schizont is the pathogenic stage of *T. parva* and *T. annulata*. It initially causes lymphoid proliferation, and later lymphoid destruction. In *T. annulata*, both the schizont and piroplasm stages may be pathogenic. Schizonts are scarce in the peripheral blood of acutely sick animals and their presence in blood smears indicates a poor prognosis.

The major pathogenic effect caused by *T. orientalis* is through the destruction of host erythrocytes and subsequent anaemia. Schizonts can be detected transiently in the lymph nodes, spleen and liver of infected cattle approximately 10 days post-inoculation with sporozoites. However, schizonts in *T. orientalis* are rarely associated with major pathogenic effects as the schizont-infected cells are not commonly found in the peripheral blood

*Theileria*-parasitised cells may be found in:

- Blood or buffy coat smears air-dried and fixed in methanol for demonstration of schizonts
- Lymph node for demonstration of schizonts
- Impression smears from lung, spleen, kidney and lymph node, air-dried and fixed in methanol, for demonstration of schizonts
- Lung, kidney, brain, liver, spleen, and lymph nodes for histopathology: demonstration of schizonts and infiltrations of immature lymphocytes

- A nervous syndrome called 'turning sickness' is sometimes observed and intravascular and extra vascular aggregations of schizont-infected lymphocytes are observed, causing thrombosis and ischemic necrosis throughout the brain
- Serum for antibody detection

## Procedures

### *Identification of the agent*

#### Microscopic examination

- The presence of multinucleate intracytoplasmic and free schizonts, in lymph node biopsy smears, is a characteristic diagnostic feature of acute infections with *T. parva* and *T. annulata*
- The demonstration of schizont-infected cells in Giemsa-stained blood smears, lymph node impression smears, or histological sections, is diagnostic of ECF
- Small piroplasms in erythrocytes are suggestive of ECF, but diagnosis must be confirmed by the detection of schizonts
- Schizonts can be detected in sections but are best seen in smears of lymph node biopsies as there is considerable similarity between schizonts of other theileria parasites (*T. mutans*, *T. vellifera*, *T. taurotragi* and *T. orientalis*), which may co-infect an animal, it is important to differentiate the infecting species; this can be done by using serological and DNA-based assays
- In *T. annulata*, both the schizont and piroplasm stages may be pathogenic. Anaemia and jaundice are features of both schizont and piroplasm pathology
- Piroplasms of most species of *Theileria* may persist for months or years in recovered animals, and may be detected intermittently in subsequent examinations, however, negative results of microscopic examination of blood films do not exclude latent infection
- Relapse parasitemia can be induced with some *Theileria* species by splenectomy
- Piroplasms are also seen in prepared smears at post-mortem, but the parasites appear shrunken and their cytoplasm is barely visible
- Light microscopy is unable to differentiate between pathogenic and apathogenic genotypes of *T. orientalis*. Light microscopy lacks the sensitivity to adequately detect clinically benign carrier animals

#### Molecular methods

- A number of PCR methods (targeting sequences TpR, p104, p67, PIM) can be used to detect *T. parva* and *T. annulata*
- A reverse line blot (RLB) assay, a high sensitive test to detect carrier animals, for simultaneous detection of different *Theileria* species that are known to infect domestic and wild animals, based on hybridisation of PCR products target V4 18S ribosomal RNA region to specific oligonucleotide probes, is available
- PCR is currently use for the detection of *T. orientalis*. PCR can detect infection in cattle up to 2 weeks before the infected erythrocytes can be observed under a light microscope. To distinguish between clinically infected and subclinical animals a number of real time semi-quantitative and quantitative PCRs have been developed for the detection of *T. orientalis*. Genotype discrimination has been most successfully achieved using assays targeting the MPSP p32 gene or p33/34 genes of the *T. orientalis/buffeli* complex, followed by restriction enzyme analysis

### *Serological tests*

#### Indirect fluorescent antibody test (IFA)

- The most widely used diagnostic test for *Theileria* species is the IFA test; both schizont and piroplasm antigens may be used
- The sensitivity of the IFA test depends on the period of time that has elapsed since the onset of infection. Following infection with sporozoites, antibodies to *T. parva* and *T. annulata* are first detected between days 10 and 14 using the schizont antigen. Using the piroplasm antigen, antibodies are first detected between days 15 and 21. High levels of antibody are generally detected for 30–60 days. The antibody levels gradually decline and low antibody titres are still

detectable 4–6 months after recovery. Later, antibody may become undetectable at a serum dilution of 1/40, but may persist for more than 1 year following a single challenge

- In an endemic area where a seasonal transmission cycle of ECF occurs, IFA has been shown to lack sensitivity.
- The IFA test is useful for identifying herds that contain carriers of *T. annulata*, but is not always sufficiently sensitive to detect all infected individuals
- the IFA test is usually easy to perform
- because of the problems of cross-reactivity among some *Theileria* species, the test has limitations for large-scale surveys in areas where species distribution overlaps
- the IFA test for *T. parva*, does not distinguish among the different immunogenic stocks

#### Enzyme-linked immunosorbent assay (ELISA)

- The new indirect ELISAs for *T. parva*, and *T. mutans*, based on recombinant parasite-specific antigens, have demonstrated higher sensitivity and specificity and have largely replaced the IFA tests previously used in Africa
- Serological tests based on the ELISAs are being used increasingly for the detection of parasite-specific antibodies
- ELISAs have been successfully adapted for the detection of antibodies to *T. annulata* and have been shown to detect antibodies for a longer period of time than the IFA. Indirect ELISAs for *T. parva* and *T. mutans* have been extensively evaluated in the laboratory and the field, and are now being used in large parts of Africa
  - these tests provide higher (over 95%) sensitivity and specificity than IFA tests but are not commercially available

For more detailed information regarding laboratory diagnostic methodologies, please refer to Chapter 3.4.14 Theileriosis in the latest edition of the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* under the heading “Diagnostic Techniques”.

## **PREVENTION AND CONTROL**

### **Sanitary prophylaxis**

- Bovine theileriosis is generally controlled by the use of acaricides to kill ticks, but this method is not sustainable
- Acaricides are expensive, they cause environmental damage, and over time ticks develop resistance to them requiring newer acaricides to be developed
- An alternate method to control *Theileria* transmission by ticks would be the development of a vaccine that targets exposed antigens of the tick. The immunised animals when exposed to ticks, display interference that reduce tick growth and increase mortality of the ticks. Besides controlling the tick vectors, proper management of animals can also reduce infection or re-infection with *Theileria*
- More sustainable and reliable methods for the control of theileriosis that deploy a combination of strategic tick control and vaccination are desirable, however, these are yet to be successfully applied on a large scale in endemic areas
- Animals that recover from Theileriosis may suffer from weight loss, reduced milk production and delayed maturity. These animals also remain a carrier and may contribute to disseminating infection. Consequently, these losses have a major impact on animal welfare and stock-holder prosperity worldwide
- knowledge of tick distribution, knowledge of pathogen distribution, knowledge of the main impact risk factors on cattle farms are the bases for the application of appropriate containment and control plans of theileriosis

### **Medical prophylaxis**

- Chemotherapeutic agents such as buparvaquone are available to treat *T. parva* and *T. annulata* infections

- Buparvaquone treats *Theileria* infections with great efficacy when used in the early stages of disease
- Imidocarb and oxytetracyclines are chemicals which in some studies, appeared to have a positive response on cattle with low parasitaemia, but a poor response in severely infected cattle
- Treatments with these agents do not completely eradicate theilerial infections and lead to the development of carrier states in their hosts
- Recovery from one strain of *T. annulata* confers cross-protection against most other strains
- Complete cross-protection does not occur with *T. parva*

#### *Inactivated vaccines*

- None available

#### *Live attenuated vaccines*

- Reliable vaccines of known efficacy have been developed for *T. parva* and *T. annulata*
- For *T. annulata*, the vaccine is prepared from schizont-infected cell lines that have been isolated from cattle and attenuated during *in-vitro* culture
- The vaccine must remain frozen until shortly before administration
- Vaccination against *T. parva* is based on a method of infection and treatment in which cattle are given a subcutaneous dose of tick-derived sporozoites and a simultaneous treatment with a long-acting tetracycline formulation
  - this treatment results in a mild or inapparent ECF reaction followed by recovery
  - recovered animals demonstrate a robust immunity to homologous challenge, which usually lasts for the lifetime of an animal
- Immunisation of animals with a stock(s) engendering a broad-spectrum immunity is desirable to cover a range of immunological *T. parva* strains that exist in the field
- Immunised animals usually become carriers of the immunising parasite stock(s)
- Consideration should be given to the risk of introducing new isolates into an area where they may then become established through a carrier state

#### *Recombinant vaccines*

- Experimental subunit vaccines are being developed for ECF, and ideally will contain antigens from both sporozoite (as the p67 protein) and schizont stages. An improved p67 vaccine has been tested in the field and might be available soon

There is no evidence that *T. parva* or *T. annulata* are hazards to humans.

For more detailed information regarding vaccines, please refer to Chapter 3.4.14 Theileriosis in the latest edition of the *OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* under the heading “Requirements for Vaccines”.

For more detailed information regarding safe international trade in terrestrial animals and their products, please refer to the latest edition of the *OIE Terrestrial Animal Health Code*.

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