

Bluetongue: a review

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ABSTRACT: Bluetongue is a non-contagious disease of domestic and wild ruminants caused by a virus within the *Orbivirus* genus of the family *Reoviridae* and transmitted by *Culicoides* biting midges. It is a reportable disease of considerable socioeconomic concern and of major importance for the international trade of animals and animal products. In the past, bluetongue endemic areas were found between latitudes 40°N and 35°S; however, bluetongue has recently spread far beyond this traditional range. This is in accordance with the extension of areas in which the biting midge *Culicoides imicola*, the major vector of the virus in the “Old World”, is active. After 1998 new serotypes of bluetongue virus (BTV) were discovered in Southern European and Mediterranean countries. Since 2006 BTV-serotype 8 has also been reported from the countries in Northern and Western Europe where *Culicoides imicola* has not been found. In such cases, BTV is transmitted by Palearctic biting midges, such as *C. obsoletus* or *C. dewulfi*, and the disease has thus spread much further north than BTV has ever previously been detected. New BTV serotypes have recently been identified also in Israel, Australia and the USA. This review presents comprehensive information on this dangerous disease including its history, spread, routes of transmission and host range, as well as the causative agent and pathogenesis and diagnosis of the disease. It also deals with relevant preventive and control measures to be implemented in areas with bluetongue outbreaks.

Keywords: *Orbivirus*; ruminants, *Culicoides* spp.; pathogenesis; control; prevention

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1. Introduction

Bluetongue is an infectious, non-contagious disease of ruminants and camelids transmitted by *Culicoides* biting midges. It is caused by the bluetongue virus (BTV) and is placed in the Office International des Epizooties list of diseases. The manifestations of bluetongue range from an inapparent to a fatal outcome depending on the serotype and strain of the virus and the species, breed and age of the infected animal; older animals are generally more susceptible (Elbers et al., 2008b). Clinical signs are usually detected in fine-wool breeds of sheep and the white-tailed deer (*Odocoileus virginianus*) and include fever, facial oedema, haemorrhages into, and ulceration on, the oral mucosa and coronitis. Bluetongue typically occurs when susceptible animal species are introduced into areas with circulating virulent BTV strains, or when virulent BTV strains extend their range to previously unexposed populations of ruminants (Zientara et al., 2010). The worldwide economic losses due to bluetongue have not been expressed in exact numbers, but the estimate is 3 billion US\$ a year (Tabachnick, 1996). The losses are both direct (death, abortions, weight loss or reduced milk yield and meat efficiency) and, what is more important, indirect as a result of export restrictions for live animals, their semen and some products such as foetal bovine serum. The costs of preventive and control measures should also be taken into account. In cases of a wider spread of bluetongue, these measures could have a serious impact on the quantity of meat and animal products available for the consumer market; therefore, bluetongue is considered a potential biological weapon (Blancou and Pearson, 2003; Zendulkova and Pospisil, 2007).

2. History and distribution

Bluetongue was first recorded at the end of the 18th century in South Africa after an import of fine-wool sheep from Europe (Spreull, 1905). It was first referred to as fever, malarial catarrhal fever of sheep or epizootic malignant catarrhal fever of sheep (Hutcheon, 1902; Spreull, 1905). In 1933 it was first diagnosed in cattle (Bekker et al., 1934) and, because its clinical signs were similar to those of foot-and-mouth disease, it was called pseudo-foot-and-mouth disease, seerbeck or sore-mouth

(Vellema, 2008). “Bluetongue”, the name used today, has been derived from the African “bloutong”, which was coined by South-African farmers who noticed tongue cyanosis in seriously diseased animals (MacLachlan et al., 2009). In 1906 Theiler was the first to report that the infecting agent was a filtrable virus (Mehlhorn, 2008; Vellema, 2008).

Bluetongue can develop and spread when susceptible hosts, BTV and competent insect vectors are all present at the same time. Traditionally, the virus was present in a geographic band between the latitudes 40°N and 35°S where its vectors, certain species of biting midges, were living (Rodriguez-Sanchez et al., 2008; Vellema, 2008; Wilson and Mellor, 2009). In North America and China the virus spread even further, up to 50°N (Mellor et al., 2000). Before the 1940s the occurrence of bluetongue was limited to South Africa (MacLachlan et al., 2009). The first well recorded epidemic beyond the African continent dates back to 1943 in sheep in Cyprus (Gambles, 1949; MacLachlan, 2004), but there are indications that bluetongue had been there since 1924 (Polydorou, 1978; Rodriguez-Sanchez et al., 2008). In 1943–1944 bluetongue was found in Israel (Shimshony, 2004), in 1948 it was reported in Texas, USA (Hardy and Price, 1952), between 1956 and 1957 a large epidemic broke out on the Iberian peninsula, and subsequently bluetongue was also found in the Middle East, Asia and Southern European countries (Gibbs and Greiner, 1994; Mellor and Wittmann, 2002; MacLachlan, 2004). In Australia it first appeared in 1977 (Gibbs and Greiner, 1994), and in South America it was found in the 1980s (Rosadio et al., 1984; Lopez et al., 1985; Tamayo et al., 1985; Clavijo et al., 2002). Bluetongue is also present in Central America and Mexico, Papua New Guinea, Thailand, China, Japan, the Indian subcontinent, Mediterranean countries (Greece, Spain, Italy, Corsica), Portugal, Bulgaria and other countries (Baylis and Mellor, 2001; Mellor and Wittmann, 2002; Tweedle and Mellor, 2002; Anonymous, 2007; Mehlihorn et al., 2007; Mellor et al., 2008).

2.1. Bluetongue epidemiology after 1998

2.1.1. Southern Europe

During the 20th century, only short outbreaks of bluetongue were occasionally recorded in Southern European countries (Spain, Portugal, Greece and

Cyprus) (Mellor and Boorman, 1995; Hendrickx, 2009). However, since 1998 BTV has been present in Southern European and Mediterranean countries from which it has gradually spread to areas previously free of the virus. This finding of BTV in the countries north of the Alps is considered to be associated with recent global climatic changes and the related spread of the main BTV vector *Culicoides imicola* (Purse et al., 2005; Randolph and Rogers, 2010). In 1998 the disease was recorded in Greece, in 1999 in Turkey and Bulgaria, then also in Serbia, Montenegro, Kosovo and Macedonia. In 2000 bluetongue was found in Sardinia, Sicily, mainland Italy, and in Corsica, Menorca and Mallorca. In 2001 it was first found in Croatia and the following year in Bosnia and Albania. Up to now serotypes 1, 2, 4, 9 and 16 have been isolated in the region of Southern Europe (Mellor and Wittmann, 2002; Anonymous, 2007; Mellor et al., 2008; Saegerman et al., 2008).

2.1.2. Northern Europe

In August 2006 bluetongue epidemics broke out suddenly and unexpectedly in Northern Europe – first in The Netherlands and shortly afterwards in Belgium, Germany and the north of France (Thiry et al., 2006; Carpenter et al., 2009; Wilson and Mellor, 2009). They were caused by the BTV serotype 8 (Elbers et al., 2008a; Mintiens et al., 2008) that is common in Kenya (Davies, 1978), Nigeria (Sellers, 1984), Sudan (Mohammed and Taylor, 1987), Malawi (Haresnape et al., 1988), South African Republic (Nevill et al., 1992), India (Prasad et al., 1992b) and Central America and the Caribbean (Gibbs and Greiner, 1994; Mo et al., 1994). This serotype had never been reported in Europe before 2006 (Mehlhorn et al., 2007; Mintiens et al., 2008) and up to now its origin has not been traced (Mintiens et al., 2008; Wilson and Mellor, 2009). There are several theories explaining its introduction, for instance, import of animals at a viraemic stage of the disease, infected semen or embryos, inadvertent shipment of infected biting midges together with animals or plants, or the introduction of biting midges either through their own flight over long distances or with the aid of wind (Saegerman et al., 2008).

By the end of 2006, BTV-8 had further been discovered in Luxembourg (Carpenter et al., 2009; Wilson and Mellor, 2009). Owing to survival over the winter, the BTV-8 appeared in these countries again the next year, and even spread to Great Britain,

Switzerland, Denmark and the Czech Republic (Saegerman et al., 2008; Schwartz-Cornil et al., 2008; Hendrickx, 2009). New outbreaks of bluetongue were reported in Hungary, Austria and Sweden in 2008 (Carpenter et al., 2009; Agren et al., 2010; Kampen and Werner, 2010; Lewerin et al., 2010) and in Norway at the beginning of 2009 (Anonymous, 2009b). The BTV-8 strain that has invaded Northern Europe is highly virulent not for only sheep, but also cattle or South American camelids and, in addition, it can cross the placenta, which was not typical of the field strains of BTV in the past (MacLachlan, 2010). The BTV-8 epidemic in Northern Europe has probably caused greater economic damage than any previous single-serotype bluetongue outbreak (Wilson and Mellor, 2008).

In 2008 BTV-6 was identified in the Netherlands and Germany and BTV-11 in Belgium. Both viruses were derived from the vaccine strains (De Clercq et al., 2009; Eschbaumer et al., 2010) most likely introduced to Europe through the illegal use of attenuated vaccines (MacLachlan, 2010).

A new virus, similar to BTV, and infecting goats was discovered in Switzerland in early 2008. It was named *Toggenburg orbivirus* (Hofmann et al., 2008), and is a so far unknown orbivirus with low pathogenicity and a potential BTV serotype 25 (Hofmann et al., 2008; Chaignat et al., 2009). And similarly in the Arab countries, in 2010, a potential serotype 26 of BTV was identified in sheep and goats in Kuwait (Maan et al., 2011).

2.1.3. USA, Australia, Israel

As in Southern Europe, new BTV serotypes were identified in the USA, Australia and Israel during the last decade. In the USA, in addition to the serotypes 2, 10, 11, 13 and 17 found in enzootic outbreaks before 1999, BTV serotypes 1, 3, 5, 6, 9, 12, 14, 19, 22 and 24 were newly isolated. In Australia serotypes 2 and 7 were newly identified in 2007 and 2008. The situation was similar in Israel where, in addition to the previously recorded BTV serotypes 2, 4, 6, 10 and 16, serotypes 8, 15 and 24 were discovered after 2006 (MacLachlan, 2010).

3. Aetiology

Bluetongue virus is a member of the genus *Orbivirus* in the family *Reoviridae*. It is similar in mor-

phology to other orbiviruses, such as epizootic hemorrhagic disease virus, African horse sickness virus or equine encephalosis virus. So far 24 BTV serotypes have been identified world-wide (Roy and Noad, 2006; Schwartz-Cornil et al., 2008) with the already mentioned potential serotypes 25 and 26 recently isolated in Switzerland and Kuwait, respectively (Hofmann et al., 2008; Chaignat et al., 2009; Maan et al., 2011). Bluetongue virus is a non-enveloped virus, 90 nm in diameter, with a triple-layered icosahedral protein capsid (Huismans and Erasmus, 1981; Prasad et al., 1992a; Grimes et al., 1998; Mertens and Diprose, 2004; Nason et al., 2004; Roy and Noad, 2006). Its genome consists of ten double-stranded (ds) RNA segments coding for seven structural proteins (VP1–VP7) and four non-structural proteins (NS1–NS3 and NS3A) (Kar et al., 2007; Roy, 2008). The outer layer consists of two major proteins, VP2 and VP5 (Verwoerd et al., 1970, 1972; Nason et al., 2004; Roy and Noad, 2006). The VP2 protein determines the serotype, is responsible for receptor binding, haemagglutination and eliciting host-specific immunity (Huismans and Erasmus, 1981; Cowley and Gorman, 1987; Mertens et al., 1989; Hassan and Roy, 1999; Roy, 1992, 2008). The VP5 protein interacts with the host cell endosomal membrane and plays a minor role in eliciting an antibody response (Hassan et al., 2001; Roy, 2008).

The middle layer or inner capsid (core) is formed by the VP7 protein (Prasad et al., 1992a; Roy, 1992; Nason et al., 2004) which is the main determinant of serotype specificity (Inumaru et al., 1987; Oldfield et al., 1990; Anthony et al., 2007) and provides an epitope in ELISA tests for detection of antibodies against BTV. The innermost layer (subcore) consists of the VP3 protein (Grimes et al., 1998) and three smaller structural proteins, VP1, VP4 and VP6, involved in transcription and replication of viral RNA (Prasad et al., 1992a; Nason et al., 2004; Schwartz-Cornil et al., 2008).

The role of the NS1 non-structural protein is not yet clear; the present data indicate an involvement in viral morphogenesis (Brookes et al., 1993; Owens et al., 2004). The NS2 protein is the major component of viral inclusion bodies (Brookes et al., 1993; Owens et al., 2004; Lymperopoulos et al., 2006; Schwartz-Cornil et al., 2008) and is also involved in recruitment of BTV mRNA for replication (Fukusho et al., 1989; Kar, 2007; Roy, 2008). The NS3 protein acts as a viroporin, which enhances permeability of the cytoplasmic membrane

and thus facilitates virus release from mammalian or insect cells (Hyat et al., 1991; Roy, 1992, 2008; Han and Harty, 2004). In addition, NS3 also allows BTV particles to leave host cells by a budding mechanism (Wirblich et al., 2006). This probably operates in insect cells where no cytopathic effect is induced by BTV (Schwartz-Cornil et al., 2008).

The segmented nature of the BTV genome allows for reassortment of ds-RNA segments if the host cell is concurrently infected by several different serotypes or strains (Oberst et al., 1987; Samal et al., 1987; Stott et al., 1987; Belyaev and Roy, 1993; Batten et al., 2008). The reassortment event plays an important role in the development of viral diversity (Carpi et al., 2010) and gives rise to changes in virulence and serological characteristics of the virus (Cowley and Gorman, 1989; Mertens et al., 1989; Nuttall et al., 1992; O'Hara et al., 1998; Batten et al., 2008).

BTV remains stable in the presence of proteins and can survive for years, for instance, in blood stored at 20 °C (Anonymous, 2009a). It is sensitive to 3% NaOH, organic iodine complex, phenol and b-propiolactone (Radostits, 1994; Anonymous, 2009a).

4. Transmission

4.1. *Culicoides* biting midges

Bluetongue is almost always transmitted by biting midges of the genus *Culicoides* (Diptera: *Ceratopogonidae*) and therefore outbreaks depend on the concomitant presence of competent insect vectors and susceptible ruminants. The genus *Culicoides* at present includes 1300 to 1400 species (Mellor et al., 2000; Borkent, 2005), but only about 30 of them are BTV vectors (Meiswinkel, 2004). Although biting midges are ubiquitous (Mellor et al., 2000), they are most frequently present in warm, damp and muddy areas which are rich in organic matter, and plentiful in animal hosts they can feed on. They are most active from about one hour before sunset until one hour after sunrise (Mellor et al., 2000).

The midge life cycle lasts for two to six weeks (Veronesi et al., 2009), is direct and involves an egg, four larval instars, a pupa and an adult (Mellor et al., 2000). Adults usually live for only ten to 20 days, but can survive for up to 90 days in colder conditions (Mellor, 2000; Lysyk and Danyk, 2007). Females of

some midge species need to take a blood meal three to four days prior to egg laying and feed at roughly four-day intervals; males feed on plant juices (Birley and Boorman, 1982; Mellor et al., 2000). By sucking the blood of infected ruminants, midges acquire BTV which then replicates in their digestive tract. Progeny virus is then released into the haemocoel from where the secondary target organs, including the salivary glands, are infected. Subsequent to virus replication in the salivary glands, transmission can take place. The whole cycle from infection to transmission takes between ten to 15 days at 25 °C and individual vectors once infected usually remain so for life (Chandler et al., 1985; Eaton et al., 1990; Mellor, 1990, 2000, 2004).

The ability of biting midges to transmit BTV is markedly influenced by ambient temperature, air humidity and total seasonal rainfall (Mullens et al., 1995; Wellby et al., 1996; Mellor, 2000). The virus in vectors can replicate at a temperature above 15 °C (Mellor et al., 2000), with the intensity of replication growing with increasing temperature (Van Dijk and Huismans, 1982). The recent “global warming” has allowed for longer activity of biting midges and thus longer periods during which they are capable of BTV transmission (Tweedle and Mellor, 2002). In addition, the higher temperatures recently experienced in northern Europe have increased the competence of indigenous *Culicoides* species to transmit BTV (Gale et al., 2009; MacLachlan, 2010). In the temperate zone the adults of biting midges usually do not survive the first frost and bluetongue thus has a seasonal nature (Radostits et al., 1994), with peaks of activity in spring and autumn (Purse et al., 2005).

Biting midges are regarded as exophagic and exophilic insects (i.e., feeding on animals outdoors and remaining outside, respectively), but some species, such as *C. dewulfi* and *C. obsoletus*, have shown endophagic behaviour (i.e., feeding inside) which increases in intensity with decreasing ambient temperatures (Baldet et al., 2008).

Biting midges can fly over a maximum distance of two km, but because of their small size (one mm to three mm) they can easily be carried on the wind; their passive transport up to a distance of 700 km has been reported (Ducheyne et al., 2007).

In the “Old World” the species *Culicoides imicola*, the most widely spread midge on the globe, is regarded as the major BTV vector. It is a thermophilic species requiring an average ambient temperature of above 12 °C to survive and over 15 °C for virus replication in the organism. It shows

the highest activity in the temperature range from 13 °C to 35 °C (Tweedle and Mellor, 2002). It reproduces in damp or wet soils fertilised with manure (Meiswinkel et al., 1994) and feeds on cattle, sheep and horses (Mellor and Wittmann, 2002). *Culicoides imicola* has been found in Africa, the south of Asia, Portugal, Spain, Greece, Cyprus, Corsica, Italy, Israel, Turkey, Yemen, Oman and other countries (Mellor, 1990). It does not live in Northern and Central Europe. Here, psychrophilic species of biting midges are found, such as *C. obsoletus*, *C. pulicaris* and other species, which are potential BTV vectors (Mehlhorn et al., 2007).

In the epidemic caused by BTV-8 in Germany in 2006–2007, bluetongue was transmitted by *C. obsoletus* (Mehlhorn et al., 2007), the species from which BTV was isolated as early as 1977 during the Cyprus epidemic (Mellor and Pitzolis, 1979) and later in outbreaks in Italy (Savini et al., 2005), The Netherlands (Meiswinkel et al., 2008), and again in Germany (Hoffmann et al., 2009). In Sicily and Germany BTV was isolated from the species *C. pulicaris* (Caracappa et al., 2003; Hoffmann et al., 2009) and in the Netherlands from *C. dewulfi* (Meiswinkel et al., 2007) and *C. chiopterus* (Dijkstra et al., 2008).

The species *C. obsoletus* is one of the commonest species in Central and Northern Europe (Tweedle and Mellor, 2002) and together with *C. scoticus* is included in the *Obsoletus* complex (Savini et al., 2003; Meiswinkel et al., 2004). The females of these two species are very similar in morphology, which makes their differentiation hard (Campbell and Pelham-Clinton, 1960; Meiswinkel et al., 2004; Savini et al., 2005), but species identification is possible with the use of molecular methods (Nolan et al., 2007; Balczun et al., 2009; Stephan et al., 2009). *C. obsoletus* midges proliferate among wet decaying leaves, in water-filled tree cavities or manure heaps (Anonymous, 2007). *C. pulicaris* and *C. punctatus* midges are members of the *Pulicaris* complex (Carpenter et al., 2006; Dijkstra et al., 2008; Hoffmann et al., 2009). *C. pulicaris* midges go to rain-pools on peat moorland for reproduction (Anonymous, 2007). Similarly to *C. obsoletus*, they are widespread in Northern and Central Europe, but probably play only a minor role in BTV transmission (Mehlhorn et al., 2009). The females of species included in the *Pulicaris* and *Obsoletus* complexes preferably attack cattle (Bartsch et al., 2009; Ninio et al., 2011). The occurrence of *C. dewulfi* biting midges is closely related to the rearing of cattle

and horses whose manure heaps are ideal breeding sites for the insects (Kettle and Lawson, 1952; Campbell and Pelham-Clinton, 1960; Meiswinkel et al., 2007). *C. chiopterus* midges are also coprophilic and preferably feed on cattle and horses (Kettle and Lawson, 1952; Campbell and Pelham-Clinton, 1960; Dijkstra et al., 2008; Zimmer et al., 2008). Both species exhibit strong endophagic behaviour (Baldet et al., 2008).

In North America the species *C. sonorensis* is known as the major BTV vector (Mellor, 1990); *C. insignis* is considered to be less important (Tanya et al., 1992). The species *C. insignis* and *C. pusillus* act as BTV vectors in South and Central America (Kramer et al., 1985; Mo et al., 1994) and *C. brevitaris*, *C. fulvus*, *C. wadai* and *C. actoni* in Australia (Mellor et al., 2000).

4.2. Other ways of transmission

Biting midges are responsible for BTV transmission in the majority of cases, but occasionally some other vectors can be involved. In addition to biting midges, BTV has been isolated from some arthropods, e.g., sheep ked (*Melophagus ovinus*) (Luedke et al., 1965) or some species of ticks (Stott et al., 1985; Bouwknegt et al., 2010) and mosquitoes (Brown et al., 1992). However, these are mechanical vectors with only a negligible role in disease epidemiology (Radostits et al., 1994).

Bull semen can also transfer the virus, but it can be infected only when the bull is viraemic (Bowen and Howard, 1984; Howard et al., 1985; Osburn, 1994; Kirkland et al., 2004) and when semen contains red or white blood cells with which the virus is associated (Osburn, 1994; Wilson et al., 2008).

The passage of BTV across the placenta is another mode of transmission. It has been recorded in cattle (Gibbs et al., 1979; Thomas et al., 1986; De Clercq et al., 2008; Desmecht et al., 2008; Menzies et al., 2008; Backx et al., 2009; Darpel et al., 2009; Lewerin et al., 2010; Santman-Berends et al., 2010), sheep (Richardson et al., 1985; Flanagan and Johnson, 1995; Saegerman et al., 2011) and in dogs (Wilbur et al., 1994).

Recently, an until now unique route of transmission was described in ruminants. This involved ingestion of the placenta of a BTV-infected bovine foetus (Menzies et al., 2008). In an experimental study it was possible to infect a newborn calf with BTV-contaminated colostrum (Backx et al., 2009).

Transmission with colostrum has also been reported by Mayo et al. (2010). This is the first report of BTV or its nucleic acids naturally occurring in colostrum. Oral transmission has been described in carnivores (Alexander et al., 1994; Jauniaux et al., 2008) and has recently been experimentally confirmed in type1 interferon receptor-deficient mice (Calvo-Pinilla et al., 2010).

Bluetongue can also be spread by live attenuated vaccines against BTV, or even by vaccines against other antigens contaminated with BTV (Wilbur et al., 1994; Evermann, 2008).

5. Host range

All ruminants are susceptible to infection with bluetongue, but clinical disease is most often manifested in sheep; a serious disease also develops in white-tailed deer (*Odocoileus virginianus*) (Howerth and Tyler, 1988; Parsonson, 1990; Johnson et al., 2006). In cattle, which play an important role in the epidemiology of BTV mainly because of prolonged viraemia, the disease has in the past mostly been reported to have a subclinical course (Tweedle and Mellor, 2002). However, in the epidemics caused by BTV-8 in Western and Central Europe, even cattle showed clinical disease (Thiry et al., 2006; Darpel et al., 2007; Elbers et al., 2008a). Under natural conditions the disease may also be present in wapiti (*Cervus elaphus canadensis*), proghorn (*Antilocapra americana*), African antelopes and other wild ruminants (Howerth et al., 2001), but it can also affect camelids (Rivera et al., 1987; Henrich et al., 2007; Meyer et al., 2009) and elephants (Erasmus, 1990; Mushi et al., 1990). Bluetongue has also been recorded in axis deer (*Axis axis*), fallow deer (*Dama dama*), sika deer (*Cervus nippon*), red deer (*Cervus elaphus*), roe deer (*Capreolus capreolus*), mouflon (*Ovis orientalis musimon*), Spanish ibex (*Capra pyrenaica*) and captive yak (*Bos grunniens grunniens*) (Murray and Trainer, 1970; Corn et al., 1990; Fernandez-Pacheco et al., 2008; Linden et al., 2008; Mauroy et al., 2008; Ruiz-Fons et al., 2008; Garcia et al., 2009; Rodriguez-Sanchez et al., 2010a,b).

Although bluetongue is a disease found in ruminants and camelids, under certain circumstances it can also be transmitted to carnivores. In dogs, for instance, bluetongue has been reported following the use of a BTV-contaminated vaccine (Wilbur et al., 1994; Evermann, 2008). Bluetongue has also

been recorded in Eurasian lynxes (*Lynx lynx*) kept in a Belgian zoo; the cats were fed on aborted or still-born fetuses of ruminants raised on neighbouring farms (Jauniaux et al., 2008). Specific antibodies to BTV were also identified in African carnivores including lions, cheetahs, wild dogs, jackals, hyenas and large-spotted genets (Alexander et al., 1994). These findings can also be explained by ingestion of flesh and organs of BTV-infected animals. In the USA antibodies against BTV have been found in Florida black bears (*Ursus americanus floridanus*), Florida panthers (*Puma concolor coryi*) (Dunbar et al., 1998) and domestic dogs (*Canis familiaris*) (Howerth et al., 1995).

6. Overwintering

The survival of virus from one “vector season” to the next is called “overwintering”, but the mechanism involved is still poorly understood. However, BTV can survive in the absence of adult vectors for nine to 12 months of cold weather in an infected host with no detectable viraemia, disease or sero-conversion (Taylor and Mellor, 1994; Takamatsu et al., 2003; Osmani et al., 2006; Wilson et al., 2007). One way in which overwintering may be achieved is by the infection of adult vectors (Wilson et al., 2008). Although the average life span of these is usually ten to 20 days (Mellor, 2000), they can occasionally live for up to three months (Lysyk and Danyk, 2007). During the winter of 2006–2007, which was exceptionally mild in Europe (Wilson et al., 2008), some small numbers of adult *Culicoides* midges were recorded in Belgium (Losson et al., 2007). This suggests that under favourable conditions some biting midges can live long enough to survive the period between two vector seasons (Wilson et al., 2008). Possibilities for BTV to survive at different stages of the *Culicoides* life cycle have also been investigated. It has previously been shown that, in biting midges, small RNA fragments, but not the whole virus, can pass through pores of vitelline membrane (Nunamaker et al., 1990). Further evidence was provided by White et al. (2005) who detected BTV RNA in midge larval stages; however, transfer of virus in larvae has not been demonstrated. Takamatsu et al. (2003) have shown in an *in vitro* study that BTV can persistently infect ovine T-cells, a process that may also occur during infection and viraemia in mammalian hosts, thus providing a mechanism for virus persistence.

This hypothesis, however, has not been confirmed (Lunt et al., 2006; Wilson et al., 2008). In some instances, the virus could overwinter in cattle owing to prolonged BTV viraemia, which can occasionally last up to 100 days (Sellers and Taylor, 1980), or due to latent BTV infection (Luedke et al., 1977). Another mechanism suggested for BTV overwintering is transplacental infection (De Clercq et al., 2008; Menzies et al., 2008; Backx et al., 2009; Darpel et al., 2009; Lewerin et al., 2010; Santman-Berends et al., 2010). Pregnancy in cattle is long enough for BTV to survive during a period free of competent insect vectors (Wilson et al., 2008). Mechanical vectors may also be involved in virus overwintering; BTV has been isolated from the sheep ked (Luedke et al., 1965) and some tick species (Stott et al., 1985; Bouwknecht et al., 2010), which are arthropod species living much longer than *Culicoides* midges. In addition, the trans-stadial passage found in hard ticks and trans-ovarial passage in soft ticks suggests their role in virus transmission (Bouwknegt et al., 2010). Mechanical vectors should therefore be regarded as potential reservoirs for BTV (Wilson et al., 2008; Bouwknecht et al., 2010).

7. Pathogenesis

After introduction through the bite of an infected midge, the virus is transported by the host dendritic cells from the skin to the local lymph nodes (Hemati et al., 2009), the sites of initial virus replication (MacLachlan, 2004). Subsequently, it spreads to the blood circulation inducing a primary viraemia which seeds secondary organs, i.e., lymph nodes, spleen and lungs (Barratt-Boyes and MacLachlan, 1994; Sanchez-Cordon et al., 2010). The virus replicates in vascular endothelial cells, macrophages and lymphocytes (MacLachlan et al., 1990, 2009; Barratt-Boyes and MacLachlan, 1994; MacLachlan, 2004; Drew et al., 2010a). In early viraemia virus is associated with all blood elements, while at later stages of viraemia it exclusively associates with erythrocytes (MacLachlan et al., 1990, 2009; MacLachlan, 2004). Virus particles appear to be sequestered in invaginations of the erythrocyte membrane (Brewer and MacLachlan, 1994; MacLachlan, 2004), allowing prolonged viraemia in the presence of neutralizing antibodies (Richards et al., 1988; Brewer and MacLachlan, 1994). Free virus in low titres is found in blood plasma only at the initial stages of infection (MacLachlan et

al., 1990; MacLachlan, 1994; Barratt-Boyes and MacLachlan, 1994).

Infection with BTV results in cell necrosis and apoptosis (Barratt-Boyes et al., 1992; DeMaula et al., 2001; Mortola et al., 2004) and, by activating the p38MAP kinase, the virus increases vascular permeability (Chiang et al., 2006; Drew et al., 2010b). In addition, it induces the production of TNF α , IL-1, IL-8, IL-6, IFN-I and cyclooxygenase-2, and enhances plasma concentration of prostacyclin and thromboxane, which frequently leads to an excessive inflammatory response and subsequent damage to the cells and tissues of the infected animal (MacLachlan and Thompson, 1985; DeMaula et al., 2001, 2002; Schwartz-Cornil et al., 2008; Drew et al., 2010a). The pathogenesis of bluetongue is characterised by injury to small blood vessels in target tissue, resulting in vascular occlusion and tissue infarction. Virus-induced vasoactive mediators produced by thrombocytes, dendritic cells, macrophages and BTV-infected endothelial cells increase damage to the endothelium, interfere with its function and increase vascular permeability; this leads to the development of oedema and effusions (MacLachlan et al., 2009; Drew et al., 2010a).

7.1. Viraemia and immune response

Viraemia in infected animals has a prolonged course, but is not persistent (Barratt-Boyes and MacLachlan, 1995; Bonneau et al., 2002; Melville et al., 2004). Its duration depends on the longevity of erythrocytes to which virus is bound, in contrast to the other blood cells, even at the late stage of infection (MacLachlan et al., 2009). It is also related to the species and breed of the infected animal. Viraemia lasts 14 to 54 days in sheep and 19 to 54 days in goats (Barzilai and Tadmor, 1971; Luedke and Anakwenze, 1972; Koumbati et al., 1999). In cattle, viraemia may last as long as 60 or, even 100 days (Sellers and Taylor, 1980), which makes this animal an important host from the epidemiological point of view.

The infected animals react to BTV with interferon production and humoral and cell-mediated immune responses (MacLachlan and Thomson, 1985; MacLachlan, 1994). Serotype-specific neutralising antibodies against the VP2 protein confer protection against homologous strain reinfection (Cowley and Gorman, 1987; Hassan and Roy, 1999; Roy, 1992; Schwartz-Cornil et al., 2008). Neutralising antibodies are also induced, to a lesser degree, by

the VP5 protein (Roy, 1992; Lobato et al., 1997). The sera of infected ruminants also contain sero-group-specific antibodies induced by the VP7 protein, as well as antibodies against other structural and non-structural proteins (MacLachlan et al., 1987; Richards et al., 1988; MacLachlan, 2004). The cell-mediated immune response to BTV can probably reduce the spread of virus in the organism early after infection, but cannot eliminate the virus completely (MacLachlan, 1994; Barratt-Boyes et al., 1995). By producing a cytotoxic effect in infected cells, CD8 $^{+}$ T-lymphocytes play the most important role (MacLachlan, 1994; Barratt-Boyes et al., 1995; Schwartz-Cornil et al., 2008).

8. Clinical signs

Bluetongue in sheep is manifested as an acute, chronic or subclinical condition; fine wool breeds are most susceptible. An incubation period of four to eight days (Tweedle and Mellor, 2002) is followed by fever, apathy, tachypnea, and hyperaemia of the lips and nostrils with excessive salivation and serous nasal discharge that is initially clear, then becomes mucopurulent and upon drying may form a crust around the nostrils. Oedema of the tongue, lips, submandibulum and sometimes ears appears, petechiae develop on the conjunctiva and ulcers on the oral mucosa. Cyanotic tongues are found in rare cases. In some cases, dyspnoea, profuse haemorrhagic diarrhoea or vomiting that can cause aspiration pneumonia is recorded. At the end of the pyrexia stage, affected sheep may have coronitis, laminitis or paresis and necrosis of striated muscles and, as a result, stand with an arched back and are reluctant to move. Torticollis, dermatitis and breaks in the wool may also develop (Brewer and MacLachlan, 1994; Tweedle and Mellor, 2002; Anonymous, 2004; Darpel et al., 2007; Elbers et al., 2008a, 2009; Kirschvink et al., 2009). Infection in pregnant ewes may lead to abortion, foetal mummification and the birth of weak calves with potential congenital defects (hydrocephalus, cerebral cysts, retinal dysplasia, etc.) (Osburn et al., 1971; Osburn, 1994; MacLachlan et al., 2000; Tweedle and Mellor, 2002; Saegerman et al., 2011). Chronically affected sheep may succumb to other diseases such as bacterial pneumonia (MacLachlan and Gard, 2009).

Goats are less frequently infected with BTV, and rarely show any signs of clinical disease. If they do, the signs are similar to but less severe than in sheep.

In the 2006 epidemic in the Netherlands, the diseased goats showed a sudden drop in milk production, high temperature, oedema of the lips and head, nasal discharge and scabs on the nose and lips, erythema of the skin of the udder and small subcutaneous haemorrhagic lesions (Dercksen et al., 2007).

In cattle clinical disease is rare (Tweedle and Mellor, 2002) with the exception of BTV-8 infection in which clinical signs are manifested in large numbers of animals (Elbers et al., 2008b). Clinical infection is considered a hypersensitivity reaction mediated by the IgE antibody (Anderson et al., 1987). The early stages are characterised by fever, apathy and depression followed by erosion and necrosis of the oral and nasal mucosae, nasal discharge, excessive salivation, conjunctivitis, lameness and stiffness, ulcerative dermatitis, corinitis, occasional bloody diarrhoea, oedema and hyperaemia. The skin of teats is often inflamed and may crack and peel (Tweedle and Mellor, 2002; Thiry et al., 2006; Williamson et al., 2008; Elbers et al., 2008a, 2009). Milking cows show reduced milk production (Thiry et al., 2006; Mehlhorn et al., 2008; Elbers et al., 2009). Infection of dams in early stages of pregnancy can result in early death and resorption of the embryo; other consequences involve abortion or the birth of malformed and weak calves (MacLachlan et al., 2000; Tweedle and Mellor, 2002; Elbers et al., 2008a; Desmecht et al., 2008). If dams survive, the foetuses infected between 70 and 130 days of gestation develop serious CNS malformations (hydrocephalus, cerebral defects) while those infected a few weeks before delivery usually have only mild encephalitis (Waldvogel et al., 1992; MacLachlan et al., 2000).

In white-tailed deer bluetongue has, similarly to epizootic haemorrhagic disease of deer, an acute course manifested as haemorrhagic diathesis as a sequela to disseminated intravascular coagulation (Waldvogel et al., 1992; MacLachlan et al., 2000). It is characterised by widespread haemorrhages throughout the body, swelling of the head and neck, hypersalivation, blood-stained nasal discharge and bloody diarrhoea (Radostits et al., 1994; Howerth et al., 2001).

9. Pathology

Necropsy findings in affected animals reveal subcutaneous tissues infiltrated with gelatinous fluid

in the head, haemorrhages in the tunica media of the pulmonary artery or even aorta, hyperaemia, or occasionally cyanosis, of the oral mucosa with petechiae and ecchymoses. Erosions with coats of necrotic tissue may be present in the lips, tongue and cheeks. There may be hyperaemia of the ruminal pillars and reticular folds. The spleen, lymphatic nodes and tonsils are enlarged and haemorrhagic, occasionally with petechiae. The tongue root, pericardial sac, kidney, gut (particularly at the iliocaecal junction) and subcutaneous tissues may have petechiae. The skeletal and heart musculature shows light necrotic areas. In addition, inflammation of the upper respiratory tract, pulmonary oedema, pleuritis, pericarditis or enteritis may be present (Tweedle and Mellor, 2002; Darpel et al., 2007; Mauroy et al., 2008; MacLachlan et al., 2009).

Histological findings include hypertrophy of endothelial capillaries, perivascular oedema and infiltration of skeletal and cardiac muscle with macrophages and lymphocytes, vascular congestion with subsequent tissue infarction leading to epithelial tissue hypoxia and cell desquamation. In acute cases heart and skeletal muscles have haemorrhage and necrosis which, in chronic cases, results in fibrosis and infiltration with mononuclear cells (Brodie et al., 1998; Tweedle and Mellor, 2002; MacLachlan et al., 2009).

10. Diagnosis

A preliminary diagnosis based on clinical signs, post-mortem findings and epidemiological assessment should be confirmed by laboratory examination (Afshar, 1994).

Samples to be examined in the laboratory should include non-coagulated blood (use of ethylenediaminetetraacetic acid or heparin is preferred), blood serum, post-mortem tissue samples of spleen, lymph nodes, lungs, liver, bone marrow and, when indicated, heart and skeletal muscles; in addition, brain tissue is collected in foetuses (Stott et al., 1983; Parsonson, 1990; Afshar, 1994; Tweedle and Mellor, 2002).

For transport, blood serum samples should be frozen at -20°C and the other samples should be kept on ice (Tweedle and Mellor, 2002). Full blood samples can be stored at $+4^{\circ}\text{C}$ for a long time; isolated blood cells in 10% dimethyl sulphoxide require storage at a temperature of -70°C (Thomas, 1984).

10.1. Bluetongue virus isolation

Bluetongue virus can be propagated in embryonated chicken eggs, cell cultures or in sheep.

Embryonated eggs, nine to 12 days old, are used for BTV isolation (Anonymous, 2004) and intravenously inoculated with the material examined. This method is 100- to 1000-fold more sensitive than yolk sac inoculation (Goldsmid and Barzilai, 1985), but is demanding in terms of technical skills and experience (Clavijo et al., 2000). The material obtained from embryonated eggs can either be further propagated in cell culture or directly examined using molecular methods (PCR or *in situ* hybridisation) (Schoepp et al., 1991; Katz et al., 1994; Wang et al., 1988; Clavijo et al., 2000).

Bluetongue virus can also be isolated in cell lines of insect origin, such as the KC line derived from *Culicoides sonorensis* cells or the C6/36 line from *Aedes albopictus* (AA) cells; the mammalian BHK-21, CPAE or Vero cell lines can also be used (Wechsler and McHolland, 1988; Anonymous, 2004; Mecham, 2006). The cytopathic effect produced by BTV is observed only on cell lines of mammalian origin at three to five days after inoculation and appears as foci of rounded and refractile cells (Clavijo et al., 2000). The isolation of virus in cell culture is usually preceded by its passage in embryonated chicken eggs which are more susceptible to BTV than cell lines (Afshar, 1994; Clavijo et al., 2000).

Sheep can provide a sensitive and reliable system for BTV isolation; however, today they are used only occasionally, e.g., in cases when a sample contains a very low virus titre (Afshar, 1994; Anonymous, 2004).

10.2. Antigen identification

A direct identification of BTV in blood or tissue samples is possible with use of the reverse transcription-polymerase chain reaction (RT-PCR) method that allows for serotyping and can detect BTV RNA in samples as late as six months after infection (Katz et al., 1994; MacLachlan et al., 1994). A quantitative assessment of RNA in an examined sample is possible by real time-RT-PCR (Shaw et al., 2007; Toussaint et al., 2007). The identification of a BTV serotype is carried out in the virus neutralisation test. Other available diagnostic methods include antigen-capture ELISA, immunospot and immunofluorescence tests (Anonymous, 2004), but they are rarely used.

10.3. Antibody identification

Serogroup-specific antibodies against BTV can be detected by a competitive ELISA test targeted to the VP7 protein. This is a rapid method permitting determination of serum or plasma antibody as early as the 6th post-infection day (Koumbati et al., 1999). There are other commercial ELISA kits developed recently by which early antibodies or antibodies against BTV in individual or bulk milk samples can be detected (Mars et al., 2010). In addition, serogroup-specific antibodies can be identified by an agar-gel immunodiffusion test, which, however, may produce cross-reactions with other orbiviruses (Afshar et al., 1989), a complement-fixation test and a haemagglutination-inhibition test (Anonymous, 2004). The serum neutralisation test has the highest specificity and sensitivity of all the tests, but is also most expensive and time-consuming (Reddington et al., 1991; Hamblin, 2004).

11. Differential diagnosis

The clinical signs of bluetongue can easily be mistaken for those of other ruminant diseases such as orf (contagious pustular dermatitis), foot-and-mouth disease, acute photosensitisation, acute haemonchosis (with depression and submandibular oedema), facial eczema, *Oestrus ovis* infestation, pneumonia, plant poisoning, salmonellosis, sheep pox, peste des petits ruminants (Tweedle and Mellor, 2002; Williamson et al., 2008), malignant catarrhal fever, pododermatitis, rinderpest, infectious bovine rhinotracheitis, bovine viral diarrhoea, bovine popular stomatitis, bovine herpes mamillitis and epizootic haemorrhagic disease (Frank and Willis 1975; Mehlhorn et al., 2008; Williamson et al., 2008; Savini et al., 2011).

12. Prevention and control

There is no specific therapy for animals with bluetongue. Symptomatic therapy includes gentle handling of affected animals, their stabling and, if indicated, administration of non-steroidal anti-inflammatory drugs (Radostits et al., 1994; Tweedle and Mellor, 2002).

An immediate ban on animal import from countries with bluetongue is the priority measure, followed by the monitoring of farms raising domestic ruminants which include clinical examination and

serological and virological testing, and a monitoring of insect vectors. Prophylactic immunisation and the removal of vectors or prevention of vector attacks can also be used.

12.1. Prophylactic immunisation

Vaccination can prevent clinical bluetongue or at least mitigate its course by interrupting the BTV cycle in the environment; it thus reduces the economic losses due to animal infection and makes transfer and trading of animals from BTV enzootic regions possible (Savini et al., 2008; Bhanuprakash et al., 2009; Caporale and Giovannini, 2010). Bluetongue vaccines are serotype-specific (Bhanuprakash et al., 2009) and therefore, before use in a given area, the serotypes present in the environment should be taken into account. Two types of vaccines, inactivated and live attenuated, are currently available.

12.1.1. Live attenuated vaccines

Live attenuated vaccines were until recently the only bluetongue vaccines commercially available (Caporale and Giovannini, 2010), and were originally used in endemic situations where multiple serotypes of virus are common (e.g., South Africa). In these regions multivalent live attenuated vaccines against the serotypes present there are still used (Veronesi et al., 2005). One dose of attenuated vaccine is enough to provide good protection for at least one year. Their production is inexpensive, which is another advantage (Savini et al., 2008; Bhanuprakash et al., 2009), but they may lose efficiency at temperatures over 35 °C (Hammoumi et al., 2003) and may provide poor protection against infection with a heterologous BTV serotype (Tweedle and Mellor, 2002). However, there are growing concerns about the use of BTV attenuated commercial vaccines (Veronesi et al., 2005) which can result in clinical signs of bluetongue, abortion, reduced milk production, temporary poor semen quality in rams (Breard et al., 2007; Savini et al., 2008) and foetal malformation if pregnant ewes are vaccinated (Flanagan and Johnson, 1995; Tweedle and Mellor, 2002; Bhanuprakash et al., 2009). For these reasons it is recommended to vaccinate ewes nine to 15 weeks before mating, and rams after the mating

period (Bhanuprakash et al., 2009) but at least six weeks before the beginning of the following period (Savini et al., 2008). Attenuated vaccine virus can also produce viraemia lasting over two weeks in vaccinated sheep (Veronesi et al., 2005). There is a possibility that vaccine virus will infect vectors and revert to virulence, or will produce a recombinant progeny virus with novel properties after the reassortment of genes from wild and vaccine virus in the vaccinated animal or the vector (de Mattos et al., 1994; Tweedle and Mellor, 2002; Veronesi et al., 2005; Savini et al., 2008). However, Caporale and Giovannini (2010) consider these possibilities as only hypothetical and they remain unsupported by factual scientific data.

12.1.2. Inactivated vaccine

If properly produced, inactivated vaccines can induce reliable and protective immunity that, for a good and lasting effect, requires re-vaccination (Savini et al., 2008, 2009). Although their production is rather expensive, at present they are the best compromise in terms of safety and efficiency (Schwartz-Cornil et al., 2008; Bhanuprakash et al., 2009). Well inactivated vaccines can prevent the development of clinical disease in susceptible hosts, reduce direct economic losses due to infection, facilitate safe trading in animals and prevent the development of viraemia, or make it less severe, following infection with a homologous BTV serotype (Tweedle and Mellor, 2002; Bhanuprakash et al., 2009). After the 1998 outbreaks of bluetongue in Southern Europe, monovalent inactivated vaccines were first prepared against BTV-2, then against BTV-4; bivalent vaccines were made against BTV-2 and BTV-4 (Savini et al., 2008). Today monovalent vaccines against BTV-1, BTV-8 and BTV-9 are available (Zientara et al., 2010). Strategies for differentiating infected from vaccinated animals (DIVA) are theoretically possible with inactivated vaccines, but have not yet been developed (Bhanuprakash et al., 2009).

12.1.3. New-generation vaccines

At the present moment new types of vaccines are being developed; they include, for instance, recombinant vector vaccines, sub-unit vaccines and others which would offer advantages such as no risk of

virus transmission, rapid onset of immune response or options to make them polyvalent or as DIVA vaccines (Savini et al., 2008; Bhanuprakash et al., 2009; Roy et al., 2009). However, they are expected to have a considerably higher price, which would be a disadvantage (Bhanuprakash et al., 2009).

12.2. Vector control

Understandably, it is impossible to completely eliminate *Culicoides* midges in the natural environment. It is possible, however, to reduce midge populations to ineffective levels, or to prevent vector attacks by stabling susceptible animals overnight since midges have nocturnal feeding habits. In addition, the protection of animals in stables can be improved by door and window screens made of a fine mesh or a coarse fabric impregnated with insecticide (Radostits et al., 1994; Calvete et al., 2010). Alternative approaches involve moving the animals from insect resting and breeding sites or complete elimination of such sites. The species *C. imicola*, *C. obsoletus* and *C. pulicaris* breed in wet soils rich in organic matter and such grounds should be drained and dried.

The control of adult midges can be carried out by use of approved insecticides (Schmahl et al., 2009a,b) applied outside or inside (in areas with *C. dewulfi* occurrence) the stable or directly to the susceptible animals. The latter approach is allowed only with agents of low toxicity to mammals such as synthetic pyrethroids (deltamethrin, cyfluthrin, permethrin and fenvalerate); these agents provide protection for three to five weeks (Mehlhorn et al., 2009; Schmahl et al., 2009a,b) and can be used in the form of insecticide-impregnated ear tags. Animals can also be protected by systemic avermectins administered intradermally or subcutaneously. The larvicide Abate (5% temephos granulated with gypsum) can be applied to midge breeding grounds. Insect repellents can also be used for direct protection of animals; diethyl toluamide (DEET), for instance, is effective for up to four hours (Tweedle and Mellor, 2002).

12.3. Measures for bluetongue control

In accordance with European Union Council Directive No 2000/75/EC, in the case of bluetongue, three zones of restriction are defined, namely, a zone

of 20-km radius around the infected premises, and a protection zone and a surveillance zone together of at least 150-km radius around the infected premises (Caporale and Giovannini, 2010). In the European Union, Commission Regulation (EC) No 1266/2007, as amended, lays down rules for the control, monitoring, surveillance and restrictions on movements of animals, in relation to bluetongue, in and from the restricted zones. Veterinary investigations are carried out, suspect animals are examined and samples are taken for laboratory tests. The reference laboratory for bluetongue in the European Union is the Pirbright Laboratory of the AFRC Institute for Animal Health in the United Kingdom.

13. Situation in the Czech Republic

A total of 14 bluetongue outbreaks have so far been reported in the Czech Republic and all occurred in cattle herds. In contrast to Western Europe, the disease had a mild course and only one out of 25 affected animals showed clinical signs. Similarly to other European countries (Caporale and Giovannini, 2010), the compulsory vaccination of all domestic ruminants all over the country, with an inactivated vaccine against BTV-8, was started in 2008. Currently, due to favourable bluetongue status, the vaccination is only voluntary for all domestic ruminants, since April 2011. Monitoring of insect vectors and other measures are implemented in accordance with Commission Regulation (EC) No. 1266/2007. The State Veterinary Institute in Jihlava serves as the Czech national reference laboratory for bluetongue. The Department of Parasitology, Faculty of Science, Charles University in Prague, is responsible for insect vector monitoring and examination.

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