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Review

Potential strategies for control of bluetongue, a globally emerging, *Culicoides*-transmitted viral disease of ruminant livestock and wildlife

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ABSTRACT

Bluetongue (BT) is a non-zoonotic arboviral disease of certain wild and domestic species of cloven-hoofed ungulates. The causative agent, bluetongue virus (BTV), is spread through temperate and tropical regions of the world by biting *Culicoides* midges. Control of BTV infection is complicated by the plurality of virus serotypes and the ubiquity and opportunistic feeding behavior of its midge vector. The global distribution of BTV infection has recently altered, perhaps driven in part by climatic influences on midge species resident in different regions. The goal of this review is to evaluate realistic strategies that might be utilized to control or prevent future outbreaks of BT and other *Culicoides*-transmitted diseases. Importantly, optimal control of emerging, rapidly evolving arbovirus diseases such as BT will require integrated countermeasures that mitigate all aspects of the virus's transmission cycle. This will best be accomplished using preventative, rather than purely reactive strategies.

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1. Introduction, history and pathogenesis

Bluetongue (BT) is a non-zoonotic arboviral disease of certain cloven-hoofed ungulates that was first recognized soon after European sheep were introduced to southern Africa over 200 years ago (Henning, 1956; Hutcheon, 1902; Spreull, 1905; Verwoerd, 2012). BT and closely related African horse sickness (AHS) were amongst the first animal diseases recognized to be caused by viruses and to be transmitted by insects (Table 1) (Du Toit, 1944; Spreull, 1905; Verwoerd, 2012). BT was only later recognized to occur outside of Africa, and notable epizootics occurred throughout the world during the 20th and 21st centuries (reviewed: Erasmus and Potgieter, 2009; Maclachlan, 2011; Mellor et al., 2008; Verwoerd and Erasmus, 2004; Wilson and Mellor, 2008; Walton, 2004; Tables 2 and 3). Although bluetongue virus (BTV) infection of animals is

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Table 1
Characteristics of bluetongue virus, its arthropod vector, the disease it produces in animals, its pathogenesis, and related orbiviral diseases of animals.

Virus classification and structure	Bluetongue virus (BTV) is the prototype virus of the genus *Orbivirus*, family *Reoviridae*. Its genome consists of 10 segments of double-stranded RNA. The virions are unenveloped, have icosahederal symmetry, and a double shell particle with an outer capsid of viral proteins VP2 and VP5, and an inner core largely of VP3, VP7 and lesser amounts of VP1, VP4 and VP6. Five nonstructural proteins (NS1, NS 2, NS3, NS3A, NS4) are produced in virus-infected cells. There are currently 26 proposed BTV serotypes, with extensive genetic heterogeneity of field strains, regardless of serotype, which arises through genetic drift and shift
Arthropod vector	*Culicoides* midges are the biological vectors of BTV. Some 30 of >1000 species of midges that occur worldwide are considered vectors. Different midge species are vectors of different constellations of BTV serotypes in distinct global "episystems". Some midge species are voracious blood feeders that will feed on a variety of mammals, humans included
Geographic distribution	BTV infection occurs throughout temperate and tropical regions of the world coincident with the distribution of vector *Culicoides* midges; from approximately latitude 35° S to beyond 50° N but within this range there are groupings of different midge vectors and different constellations of BTV serotypes. The global range of *Culicoides* midges is greater than that of BTV. BT typically occurs at the upper and lower "incursional" areas of the virus' global range, and during the late summer and fall
Clinical syndrome in ruminant livestock and wildlife	Severe BT disease occurs most often in susceptible breeds of sheep, with high fever, hemorrhage and ulceration of the mucosal lining of the upper gastrointestinal tract, coronitis, and multicentric necrosis of both skeletal and cardiac muscle. Edema is characteristic, and pulmonary edema and pleural and pericardial effusion are typical of fatal cases. BT in wild ruminants can present as a peracute hemorrhagic diathesis. Many BTV infections are subclinical, especially in endemic areas and in cattle and wild African ungulates
Pathogenesis	Vascular injury is central to the pathogenesis of BT. BT is similar to other viral hemorrhagic fevers with cellular tropism for dendritic cells, endothelium, and mononuclear leukocytes, capillary leakage and thrombocytopenia, coagulopathy, and hemorrhagic diathesis. Virus is cell-associated during viremia and intimate association of virus with erythrocytes facilitates a prolonged, but not persistent infection of animals and infection of vector hematophagous midges
Other orbiviral diseases	African horse sickness, epizootic hemorrhagic disease of deer, equine encephalosis, Peruvian horse sickness and Elsye disease

frequently subclinical, severe BT disease can be dramatic, particularly in susceptible breeds of sheep and white-tailed deer, with high fever, hemorrhage and ulceration of the mucosal lining of the upper gastrointestinal tract, coronitis, and multicentric necrosis of both skeletal and cardiac muscle (Howerth et al., 1988; Maclachlan et al., 2008, 2009; Moulton, 1961; Spreull, 1905; Verwoerd and Erasmus, 2004). Edema as a consequence of capillary leakage is also characteristic, and pulmonary edema with accompanying pleural and pericardial effusion is typical of fatal cases.

Vascular injury is central to the pathogenesis of BT, thus BT shares many of the characteristic features of the better known viral hemorrhagic fevers such as Ebola, including cellular tropism for dendritic cells, endothelium, and mononuclear leukocytes; capillary leakage; and thrombocytopenia, coagulopathy, and hemorrhagic diathesis (Channappanavar et al., 2012; DeMaula et al., 2001, 2002; Drew et al., 2010a,b; Gowen and Holbrook, 2008; Hemati et al., 2009; Lee et al., 2011; Maclachlan et al., 2009). Although cattle are usually less affected by BTV infection than are sheep, some highly pathogenic virus strains can cause disease in all ruminant livestock, South American camelids, many non-African species of wild ruminants, and even certain carnivores (Darpel et al., 2007; Elbers et al., 2008; Maclachlan et al., 2009; Makoschey et al., 2009; Verwoerd and Erasmus, 2004). BTV infection of ruminants is characterized by a highly cell-associated viremia, and late in the course of infection the virus is associated principally with erythrocytes (Afshar, 1994; Barratt-Boyes and Maclachlan, 1994; Luedke et al., 1969; Maclachlan et al., 1990, 2009). This intimate binding of BTV to the erythrocyte cell membrane leads to prolonged but not persistent infection of animals by protecting the virus from immune clearance, and this interaction also provides an ingenious "Trojan Horse" mechanism for infection of the hematophagous *Culicoides* midges that serve as biological vectors of the virus (Brewer and Maclachlan, 1992, 1994; Maclachlan et al., 1994).

Outbreaks of severe BT can be economically devastating but, because BTV is transmitted by incompletely defined species of a relatively ubiquitous but poorly characterized genus of insect vector (Carpenter et al., 2008; Mellor et al., 2000), elimination of the infection in enzootic areas is difficult or impossible. *Culicoides* biting midges occur throughout most of the inhabited world where they transmit a wide variety (>50) of pathogens of animals and humans, including not only orbiviruses such as BTV, AHS virus and epizootic hemorrhagic disease (EHD) virus, but also rhabdoviruses, reoviruses, and pathogenic bunyaviruses such as Akabane and Schmallenberg viruses (Conraths et al., 2013; Mellor et al., 2000). Of relevance to the possible future emergence of new zoonotic diseases, some *Culicoides* midges have broad host feeding preferences that include humans as well as animals, and animal parasites can be transmitted to humans through the bites of *Culicoides* midges (Calvo et al., 2012; Lassen et al., 2012; Santiago-Alarcon et al., 2012). Thus, in an era of rapid change in global climate, travel, and social structures, strategies to mitigate outbreaks of BT and related animal diseases might someday guide the control of an as yet unknown, newly emergent zoonotic disease of humans that is also transmitted by *Culicoides* biting midges. The goal of this review, therefore, is to evaluate realistic strategies that might be utilized to control or prevent future outbreaks of BT and, potentially, other *Culicoides*-transmitted diseases.

2. Global distribution and recent changes

BTV infection occurs throughout temperate and tropical regions of the world coincident with the distribution of the species of hematophagous *Culicoides* midge that serve as biological vectors of the virus (reviewed: Gibbs and Greiner, 1994; Maclachlan, 2011; Tabachnick, 2004, 2010; Verwoerd and Erasmus, 2004). Although BTV has an extensive global distribution, it is to be stressed that occurrence of BT is more limited and typically occurs only at the northern and southern incursional limits of the virus's range and/or when fully susceptible animals are exposed to virulent strains of the virus. BT is uncommon in regions of the world where enzootic BTV infection occurs year-round, likely because of population immunity or as a result of prolonged co-evolution of the virus and its animal host, as presumably is the case of wild African ungulates that have evolved over the millennia in the continuous presence of the virus throughout much of the continent (Verwoerd, 2012).

The broad global range of BTV extends from approximately latitude 35° S to beyond 50° N. *Culicoides* midges occur even beyond this range, particularly in the northern hemisphere (Mellor et al., 2000). Within this extensive virus-enzootic global zone, different species of *Culicoides* midge transmit different constellations of BTV serotypes in relatively distinct "episystems" (Daniels et al.,