Hemorrhagic Disease (HD) in USA

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Overlapping clinical signs and lesions make it challenging to distinguish between epizootic hemorrhagic disease (EHD) and Bluetongue (BT) affecting wild ruminants in the USA. Therefore, the syndrome caused by EHD and BT viruses is referred to as Hemorrhagic Disease (HD).

BTV EHDV epidemiology orbiviruses reassortment serotypes surveillance white-tailed deer Bluetongue Epizootic Hemorrhagic Disease

1. Introduction

Bluetongue disease (BT) and epizootic hemorrhagic disease (EHD) are vector-borne viral diseases caused by closely related orbiviruses (Family *Reoviridae*) that affect domestic and wild ruminants and are transmitted by insect vectors of the genus *Culicoides* [1][2]. *Culicoides* biting midges are hematophagous flies that inflict painful bites on animals and humans. Although *Culicoides* can be significant pests of humans, no pathogens are known to be transmitted to humans by *Culicoides* midges in the USA. However, multiple vector-borne diseases that affect mammal species and birds occur in the USA [3][4].

Because ruminant livestock is notably affected by BTV, while EHDV primarily impacts ruminant wildlife—in particular white-tailed deer (*Odocoileus virginianus*)—, BTV has been known longer than EHDV [5]. Bluetongue disease was first recognized in the 17th century when European sheep were introduced in South Africa [6]. However, recent phylodynamic models suggest that BTV has circulated among ruminant populations for more than 1000 years [7].

Both BTV and EHDV are closely related and genetically diverse, with multiple serotypes and distinct strains [8][9][10][11]. Epidemiological differences between these two related, but different viruses, are due to the geographic distribution of the virus serotypes and differences in the distribution of ruminant hosts and *Culicoides* spp. Worldwide, there are currently seven EHDV serotypes (EHDV-1,2, and 4 to 8) and 27 BTV serotypes (BTV-1 to 27) [12][13][14], although the number of BTV serotypes may increase as putative new BTV serotypes and strains have been described (e.g., BTV-36-CH2019 and a vaccine-derived putative BTV-28 strain) [15][16]. While vector/host interactions are impacted by climate and habitat suitability, our understanding of the proportion of wild ruminants affected by BTV or EHDV in the USA is also limited to mostly syndromic based reporting of hemorrhagic disease rather than virus isolation in a targeted population [17]. Similar knowledge gaps exist in the USA regarding the insect vectors' geographic distribution and which *Culicoides* spp. are competent vectors; thus, the variation in vector susceptibility to serotypes and variations in their *Orbivirus* vector capacity is not well investigated. As such, there are remaining unknowns related to our understanding of the virus, vector, and host dynamics for BT and EHD [5][18][13][19].

Both BT and EHD are listed in the USA's National List of Reportable Animal Diseases and the OIE list of notifiable terrestrial and aquatic animal diseases [20][21]. They have a negative impact not only on the local economies of regions and countries but also on the ecology and health of threatened or endangered wild ruminant populations [22][23][24]. The potential to identify the viruses responsible for EHD/BT outbreaks depends on understanding when and where ruminants are at risk of exposure to the different *Culicoides* midges that participate in the transmission of their viruses [25].

2. Animal Health Impact of BT and EHD

To date, seven serotypes for EHDV and 27 serotypes for BTV have been confirmed [12][26][27][28][29] including two genetically distinct BTVs identified from healthy goats in Italy (X ITL2015) [30] and goats and sheep in China (XJ1407) [31]. There are genetically different strains of the virus throughout the world, and the field strains may differ on phenotypic properties like

virulence and transmission potential [32]. Mutation (a change in DNA sequence) and reassortment (the genetic recombination between different virus serotypes/ strains co-infecting a host cell) of RNA viruses contribute to the genetic diversity among field strains, changing transmissibility, pathogenicity, and causing altered virulence in susceptible ruminant hosts [13][33].

Moreover, the diversity of EHDV/BTV is associated with the reassortment of segments of the viral gene during the co-infections (with more than one virus strain) in either ruminant or vector host cells that lead to genetic change [32]. Furthermore, the appearance of antigenically new viruses or genetic variants through mutations in either insect or animal hosts can develop due to genetic drift (mutation of individual genes) during virus replication [5][34]. Worldwide, the evolution of different field strains is driven by genetic drift, genetic reassortment between viruses within each genus or serogroup, intragenic recombination, and the selective evolutionary pressure to establish genetically distinct virus strains in diverse epidemiological systems [34][32].

For livestock, mortality rates for BT and EHD may range between 0–100% depending on the ruminant host and prior infection, affecting the regions and countries' economies depending on the severity of the outbreak [35][36]. However, morbidity cost is related to the care for sick animals (e.g., veterinary cost and animal support) and reduced productivity of affected animals in livestock operations (e.g., weight loss, reduced milk yield, and abortion).

There is no cure or treatment for BTV and EHDV; therefore, the goal of BT and EHD management is to prevent virus spread into unaffected areas and clinical disease in ruminant hosts [4]. For example, BT has been listed as a notifiable animal disease by the Office of International Epizootics [35][36][21]. Restrictions in the trading and movement from enzootic regions of livestock and their products—including those that could be vertically transmitted, such as fetal bovine serum and fetal tissue—are suggested to avoid introducing the viruses to new places [37].

3. Prevalence and Distribution of BT and EHD in the USA

Historically, EHDV/BTV has occurred in the southeastern, central, and western USA. However, during the last 20 years, these viruses have spread northward within the USA territories, with cases reported across the upper Midwest and the northeastern USA [19][38]. The distribution of EHD/BT depends on the occurrence of competent *Culicoides* vector species. The home range of *Culicoides* midges was historically maintained between latitude 35° S and 40° N [39], however, changes in the global range of vectors and distribution of BT and EHD have shown a northward expansion where the diseases are maintained between latitudes 35° S and 50° N [39][40].

Wittmann et al. (2002) found that increasing temperatures reduced the extrinsic incubation period for both BTV and EHDV, which can, in turn, facilitate the transmission of orbiviruses; although, rising temperatures also reduce vector survival [41][42]. In addition, differences in vector competence between EHDV and BTV were described as higher temperatures (e.g., 27–30 °C) increase vector competence for EHDV (serotype 1) but not for BTV (serotypes 10 and 16) [42]. When temperature and humidity were evaluated together, both high humidity/temperature and low humidity/temperature were detrimental for vector longevity [42].

While *C. sonorensis* and *C. insignis* are confirmed competent vectors for EHDV/BTV in the USA, there is strong evidence that suggests that other species can be involved in the transmission of EHDV/BTV viruses. However, in order to elevate other *Culicoides* spp. to confirmed vectors, a set of criteria needs to be fulfilled. There are four criteria defined by the World Health Organization (WHO 1967) [43] that are used as guidelines for incriminating an insect as a vector of a disease agent or pathogen: (1) repeated recovery of the pathogen from blood free, wild-caught insects; (2) demonstration in a control environment that the insect can become infected via a blood meal from a viremic vertebrate host or an artificial substitute; (3) demonstrate the transmission of the pathogen to a susceptible vertebrate host after the bite of an infected insect vector; and (4) demonstration on the field of the contact of the insect vector and susceptible vertebrate host populations [44][45]. In North America, *C. sonorensis* has been reported as the primary vector of EHDV and BTV, as studies have demonstrated its implication as a vector in the field (via isolation of the pathogen from field-collected vectors and demonstrated contact between vector-ruminant host) and the laboratory (by the demonstration of vector infection after a blood meal from an infected host and subsequent transmission of the pathogen to a susceptible host) [44]. Moreover, *C. sonorensis* complies with the four criteria that demonstrate its status as the primary insect vector for BTV/EHDV in the USA.

Vector competence studies are essential to establish the presence of primary vectors (critical to maintenance of the viruses in the host population) and secondary vectors (candidate vectors that may contribute to virus dissemination, helping to explain changes in distribution/geographic expansion of BT and EHD). Based on the four guidelines defined by WHO, vector competence—the capability of an insect vector species to become infected after a blood meal from a viremic/infected vertebrate host—can be estimated by using the vector implication criteria 2 and 3 of the of the World Health Organization [45]. In search of other potential *Culicoides* vectors, accurate verification of ruminant host–*Culicoides* vector contact and subsequent blood meal analysis of the vector is needed. For example, *C. debilipalpis* (formerly *C. lahillei*) are considered candidate vectors for EHDV as laboratory studies have demonstrated that they can become infected after a blood meal and do come in contact with susceptible host ruminants in the field [44]. Furthermore, laboratory studies have shown that *C. venustus* can get infected with the pathogen after a blood meal, while isolates of the pathogen from blood-free field-collected C. mohave have also been reported [44]. Other *Culicoides* species regarded as potential vectors in Florida include *C. stellifer, C. debilipalpis, C. venustus, C. pallidicornis,* and *C. biguttatus*, as these species have been demonstrated to come into contact with susceptible ruminant species in the field [46]. However, all four criteria from the World Health Organization need to be met to elevate vector species to competent vectors of BTV and EHDV.

4. Conclusions

Current and accurate information on when and where animals are at risk of exposure to EHD/BT viruses helps target research efforts toward understanding different determinants of serotype occurrence in several USA regions. It also offers the opportunity to evaluate virus, vector, host, and environmental condition that allows different EHDV or BTV serotypes to become established in a geographic region. In addition, advances in the pathogenesis of the viruses, immune response in the host, vector competence, impact of weather, and changes in habitats on the vectors' survival may influence the epidemiology of EHDV and BTV. Over time, these advances may contribute to the development of mechanisms to manage disease outbreaks. The disease distribution maps have been generated based on agency reports and previous peer-reviewed literature. However, the lack of ongoing and systematic BTV and EHDV surveillance efforts and the limited understanding of which *Culicoides* serve as competent vectors makes it challenging to develop accurate distribution and risk-associated maps. A systematic sustained, and comprehensive disease-virus-vector surveillance program for EHDV and BTV in wildlife and livestock would help to fill in research gaps.

All in all, national *Culicoides* and EHDV/BTV surveillance efforts can improve our understanding of geographic variation in risk factors for EHDV/BTV, and efforts to build such a program have increased in recent years. Nonetheless, the sustainability of BTV, EHDV, and *Culicoides* midge surveillance programs depends on improving their financial/fiscal support and coordination and efficiency to render them cost-effective. In addition, the final results of implementing systematic animal and vector surveillance can provide the necessary data for more extensive coordination among local, state, federal agencies and universities as well as agricultural agencies involved in assessing animal diseases and animal well-being.

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