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Impact of bluetongue virus infection on the international movement and trade of ruminants

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Bluetongue is a noncontagious disease of some species of wild and domestic ruminants that develops as a result of insect-transmitted BTV infection.[1-7] The pathogenesis of BTV infection of cattle and sheep is similar,[4,7] but bluetongue typically affects only sheep, whereas cattle and a variety of other ruminants are amplifying reservoir hosts of the virus that rarely manifest obvious signs of disease. In sheep, bluetongue is characterized by hemorrhage and ulceration of the mucous membranes of the upper portion of the gastrointestinal tract, coronitis, laminitis, and facial edema and is associated with high rates of morbidity and mortality in some outbreaks.

Bluetongue was first referred to as malarial catarrhal fever and epizootic catarrh of sheep in the original descriptions[8,9] of the disease written by investigators in South Africa in the late 19th and early 20th centuries. The disease was identified by farmers in South Africa soon after the introduction of fine-wooled European breeds of sheep to that region and became known as bluetongue because of the distinctive cyanosis of the tongue that develops in some severely affected sheep. Prior to the 1940s, bluetongue was thought to be confined to southern Africa, and the first well-documented epizootic of bluetongue outside of Africa occurred among sheep on Cyprus in 1943, although outbreaks of bluetongue likely had occurred in the region long before that date.[1] The disease was identified in Texas soon thereafter, and an extensive epizootic occurred on the Iberian Peninsula during 1956 and 1957. Bluetongue was subsequently detected in the Middle East, Asia, and southern Europe. In the second half of the 20th century, the sequential appearance of these epizootics was interpreted as the emergence of bluetongue disease from its presumed ancestral origin in Africa; this lead to so-called doomsday scenarios regarding putative global spread of bluetongue that justified its inclusion in the former List A of the OIE (World Organisation for Animal Health).[10]

Bluetongue virus has now been isolated from ruminants and vector insects from all continents except Antarctica.[1,3,11,12] Hematophagous *Culicoides* insects are biological vectors that transmit BTV from infected to susceptible ruminants, and because BTV infection of ruminants is not contagious, the global distribution of BTV coincides with the distribution of competent *Culicoides* insect vectors and warm or hot climatic conditions. Thus, the virus exists in an extensive band that includes tropical, subtropical, and temperate regions of the world between latitudes of approximately 40° North and 35° South. Exceptions are Asia and western North America, where BTV infection of ruminants occurs as far as latitude 50° North. The virus also recently has expanded its range in the Mediterranean Basin to a latitude of at least 45° North, affecting increasingly extensive portions of Italy, Greece, Spain, France (Corsica), and the Balkan countries.[13,14]

Abbreviations

BTV	Bluetongue virus
OIE	Office International des Épizooties

Although > 1,000 species of *Culicoides* are known worldwide, few have been incriminated as vectors of BTV.[15] Species of vector insects that transmit BTV differ among regions and are especially poorly characterized in Europe and Asia.[12,15-18] Ambient temperature has a profound effect on the feeding activity and survival of vector insects and on the replication efficiency of BTV in the insect vector.[19] Thus, temperature-dependent control of BTV virogenesis potentially limits the expansion of BTV into regions outside of its current range, even into areas inhabited by apparently competent vector insects. The continuation of global warming would be predicted to extend the northern and southern extremes of BTV distribution by expanding the range of competent insect vectors, as has occurred recently in the Mediterranean Basin where viruses from adjacent regions of North Africa and the Middle East have now become established.[3,12-14,20-22]

It is increasingly evident that BTV has not recently been spread globally through international trade of ruminants or their germ plasm. Rather, BTV exists in distinct ecosystems in different regions of the world and specific virus strains have likely coevolved with different species of insect vector (**Figure 1**).[3,12] Thus, the serotypes

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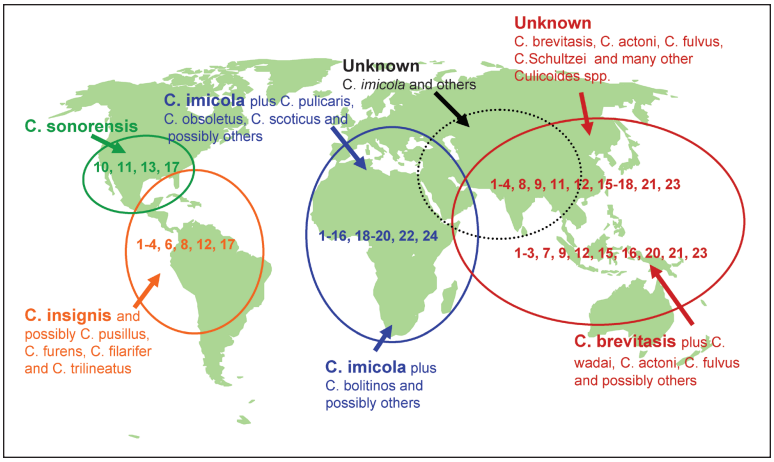

Figure 1—Global ecosystems of BTV. Virus serotypes and (known) *Culicoides* vector species in each ecosystem are identified. (Courtesy of UB Balasuriya. Adapted from Tabachnick WJ. *Culicoides* and the global epidemiology of bluetongue virus infection, in *Proceedings*. 3rd Int Symp Bluetongue. *Vet Ital* 2004;40:145–150. Reprinted with permission.)

of BTV that circulate in North America are different from those in adjacent regions of the Caribbean and Central America, despite the lack of any substantial geographic barrier between the ecosystems. The essential difference lies in the different species of vector insects in those geographic regions: *Culicoides sonorensis* is the vector of BTV serotypes 10, 11, 13, and 17 in North America, whereas *Culicoides insignis* is the vector of BTV serotypes 1, 2, 3, 4, 6, 8, 11, 12, 13, 14, and 17 in the Caribbean and Central and South America. Extensive movement of animals among these regions without any testing for BTV infection has not altered the different constellations of BTV serotypes that occur in each.[11,12,23]

Impact of Bluetongue on Animal Movement and Trade

It is now clear that BTV infection of domestic and wild ruminants occurs throughout much of the world with minimal development of disease,[3,11,24] but aspects of the epidemiology of BTV infection remain poorly defined. Whereas BTV may be transmitted year-round in tropical and subtropical areas of the world, infection is seasonal in temperate areas.[1,3,25,26] Thus, BTV infection is rarely detected for much of the year (winter, spring, and early summer) in temperate regions, and the mechanism that is responsible for this phenomenon of overwintering of BTV remains uncertain. In an effort to better define the phenomenon of BTV overwintering, Luedke et al[27-29] conducted laboratory studies more than 30 years ago; from those data, they concluded that infection of cattle during early gestation lead to the birth of progeny that were persistently infected and immunologically tolerant to BTV and that these animals then would remain clinically unaffected reservoirs of the virus. Obviously, if cattle were to become persistently infected, they would provide an ideal natural virus reservoir; therefore, at the time of its proposal, this hypothesis was readily accepted as a logical explanation for both the overwintering and putative global spread of BTV. Restrictive nontariff trade barriers that were subsequently instituted by some BTV-free countries were justified in part by these uncertainties regarding the epidemiology of BTV infection and the putative role of persistently infected (carrier) cattle in the perceived global dissemination of BTV in particular.[11,30,31] The export of live ruminants from the United States to the countries of the European Union, for example, was terminated in the early 1980s because of the presence of BTV in the United States. By 1998, 66 countries had imposed 159 import measures on ruminants and germ plasm from the United States because of bluetongue.[31]

Nontariff trade barriers are those that impose limits on the free flow of commodities internationally, without use of tariffs that countries also apply to protect specific industries against the rational progression of market forces. Thus, although the direct economic impact of bluetongue is minimal in the United States, nontariff trade barriers pertaining to bluetongue have caused substantial economic loss because of their adverse impact on animal movement and trade, particularly that of cattle and germ plasm.[11,23,31,32] These nontariff trade barriers may also have contributed to the relocation of extensive portions of the bovine germ plasm industry from states in which BTV is endemic, such as Texas and California, to the BTV-free regions of the upper Midwest as a means of facilitating the export of cattle semen and embryos. An additional illogical consequence is that animal movement between BTV-endemic areas also can be impacted. For example, the trade of cattle and germ plasm from the southwestern United States to Central and South America sometimes is affected by bluetongue, despite the fact that BTV is present throughout extensive areas of all of these regions and that the movement of millions of cattle in the reverse direction has not altered the distribution of the 2 BTV ecosystems in the Americas (Figure 1). Specifically, substantial numbers of cattle have been imported into the United States from Mexico for many years without any testing for BTV infection, even from the portions of Mexico that lie within the Caribbean and Central American ecosystem.[11,12,23] Similarly, cattle may now be imported into Canada from the United States without testing for BTV infection provided that they are moved during winter months when vector insects are not active.[23] Despite the fact that the distribution of competent insect vectors, and not animal trade, is clearly responsible for the current global distribution of BTV, countries and regions in which the virus is endemic continue to be impacted by restrictive and protectionist nontariff trade barriers.[23,33]

The Role of International Symposia

By the early 1980s, there was increasing evidence that the concept of long-term persistence of BTV in cattle was not consistent with field observations, and efforts to reproduce the experimental results obtained by Luedke et al[27-29] were not successful.[11,34-37] In an effort to address this disconcerting paradox, the First OIE

International Symposium on Bluetongue and related orbiviruses was held in Asilomar, Calif, in 1984. In his summation of the meeting, the external reviewer, Dr. W. C. Reeves,[38] concluded that "I see no alternative but to recommend that confirmation of the presence or absence of chronic infections with BTV in cattle and sheep if they occur, and the factors that might lead to such infections, must receive the highest priority and be the subject of intensive research by several independent laboratories. Furthermore, this research is so important that the research must be designed by and subjected to serious and continuous peer review at an international level. Biological phenomena that assume such a high economic significance should be clearly documented, reproducible experimentally and be the target for effective control." This challenge served as the catalyst for a concerted and substantial international research effort, and the topic was revisited at the Second International Symposium on Bluetongue that was coordinated by the OIE and held in Paris in 1991. Results of studies[11,37] in several countries had indicated that BTV infection of the bovine fetus in early gestation was teratogenic, and investigators conducting field studies had failed to identify persistently infected cattle. Thus, at that meeting, the OIE's working team on germ plasm concluded that "reassessment of previously published studies in the light of recent work, both published and unpublished, indicates that viremia resulting from natural infection with 1 BTV serotype is transient, lasting up to 3 months, but usually of shorter duration," thereby dispelling the myth of persistent BTV infection.[39]

Despite the consensus achieved at the Paris symposium that persistent BTV infection of ruminants was unproven and the duration of viremia in infected ruminants was finite, there was little change in international regulatory policies pertaining to bluetongue. Some BTV-free regions and even some countries in which BTV was endemic (eg, the People's Republic of China) continued to selectively restrict the importation of ruminants because of the uncertain maximal duration of viremia after BTV infection and the perceived threat of introducing the virus via animal trade. Furthermore, efforts made in 1998 and 1999 to revise the bluetongue chapter of the OIE Terrestrial Animal Health Code[40] in light of conclusions of the Paris symposium were met with resistance by representatives of BTV-free countries, who stressed the uncertain duration of viremia in ruminants and the possible existence of persistently infected cattle.[11,41] However, the massive bluetongue pandemic that began in 1999 and subsequently spread throughout the Mediterranean Basin had enormous repercussions because of the devastating impact of the disease on some affected sheep populations and the animal movement restrictions that were immediately imposed on affected European countries, especially Italy. Specifically, because bluetongue was an OIE List A disease at the time, the animal movement controls prescribed by the existing OIE code prevented the centuries-old practices of animal movement with potentially catastrophic consequences to the entire cattle and small ruminant production sector in Italy.[13] In response to this most recent bluetongue pandemic, the Third OIE International Symposium on Bluetongue was held in Taormina, Sicily, in 2003,[24] and on the basis of the conclusions of that meeting, the bluetongue chapter of the OIE Terrestrial Animal Health Code[40] was thoroughly revised and adopted by the member countries of OIE in May 2005.

The bluetongue chapter in the OIE Terrestrial Animal Health Code now lists the maximum infective period for BTV infection of ruminants as 60 days,[40] reflective of results of extensive research[4,7,11,42-45] that has confirmed prolonged but not persistent infection of ruminant erythrocytes. In recognition of the central role of competent vector insects in the global epidemiology of BTV infection, the chapter stresses the need for surveillance programs that target areas at highest risk based on historical, geographic, and climatic factors. Furthermore, because BTV infection of ruminants is frequently subclinical or inapparent, the BTV status of a country or region can only be established by ongoing surveillance. Thus, surveillance guidelines consistent with the new chapter on bluetongue in the OIE Terrestrial Animal Health Code were also developed as a guide for member countries.

Summary and Lessons Learned

The history of international regulatory policy pertaining to bluetongue graphically confirms Darwin's insightful observation that "false facts are highly injurious to the progress of science for they often endure long, but false views, if supported by some evidence, do little harm for everyone takes a salutary pleasure in proving their falseness."[46] In hindsight, the scientific community too readily accepted unfounded claims that bluetongue was spread throughout the world through animal trade and failed to challenge the initial data of Luedke et al[27-29] that provided a plausible but erroneous explanation for the complex biological process of overwintering of BTV.[11] Unfortunately, these uncertainties regarding the epidemiology of BTV were used to justify protectionist nontariff trade barriers that were imposed by some BTV-free countries. These regulatory barriers continue to adversely impact animal trade,[23,33] despite the fact that bluetongue is emerging only in areas such as the Mediterranean Basin where expansion of the virus' range likely reflects incursion from adjacent ecosystems (perhaps as the result of climate change).[3,12,14,15,20-22]

Although critical aspects of the epidemiology of BTV infection remain to be thoroughly characterized, there clearly is little scientific justification for the restrictive and protectionist nontariff trade barriers pertaining to bluetongue that continue to be used by some countries to restrict animal movement and trade. The Sanitary and Phytosanitary Agreement of the World Trade Organization requires that member countries not apply sanitary and phytosanitary regulations in an arbitrary or discriminatory "zero-risk" manner as a means of protecting their domestic animal industries.[47] Rather, regulation of the international movement and trade of animals must be based on objective risk assessment, equivalency between countries, and scientific transparency. In the case of bluetongue, 3 international symposia have provided a venue for the exchange and discussion of relevant scientific data pertaining to the virus and disease and for the identification and resolution of specific issues that potentially complicate the movement and trade of domestic ruminant livestock.

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