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Culicoides and the global epidemiology of bluetongue virus infection

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Summary

The distribution of the bluetongue viruses (BTV) is limited to geographic areas containing competent vector species. All BTV-competent species belong to the genus *Culicoides*. In the New World, two different BTV epidemiological systems (episystems) occur. *Culicoides sonorensis* is responsible for transmitting BTV serotypes in North America that differ from South American serotypes transmitted by *C. insignis*. There are other episystems in the world. The role of different *Culicoides* vector species and the underlying mechanisms governing their vector capacity for BTV are unknown. It is likely that these vary between *Culicoides* species and episystems. As a result, our ability to predict and/or mitigate BTV in different episystems will remain problematic. Several complex issues need to be resolved to provide risk assessment and mitigation for BTV. This will require a substantial investment in new research paradigms that investigate details of underlying controlling mechanisms in several species of *Culicoides*.

Keywords

Bluetongue virus – *Culicoides* – Epidemiology – Episystem – Genetic control – Vector capacity.

Since the first report of bluetongue (BT) disease as malarial catarrhal fever in South African sheep in 1902 (3), the role of BT virus (BTV) and its impact on animal health and animal economies worldwide has become increasingly important. BTVs are distributed worldwide, and indeed the distribution of the viruses has been described as 'limited to geographic areas containing competent vector species' (13).

The major issues that have impeded efforts to reduce the impact of BTV on animal health and the economics of animal industries continue to be as follows:

- to develop the capability to predict regions of the world with high risk for BTV transmission to livestock
- to develop the capability to predict temporal periods in at-risk regions in advance of a BT outbreak
- to develop strategies to reduce the potential for a BT epidemic in at-risk regions, reduce the risk of introducing BTV or new BTV serotypes to BTV-free regions, and strategies that will interrupt and mitigate the impact of ongoing BTV transmission in a region.

It is clear that the ability to predict and mitigate BT outbreaks in animals is at a very rudimentary stage. In particular, a major difficulty is that the ability to define potential regions that are at risk for BT epidemics is primarily based on the identification of 'geographic areas containing competent vector species'. Although it is well established that the vectors of the BTVs are all biting midges in the genus *Culicoides*, the identification of suitable *Culicoides* vector species is fraught with uncertainties and unknowns. There is now a large body of research on several species of *Culicoides* and their role in BTV endemic regions (7, 10). This information has been obtained largely due to substantial BTV epidemiological history in a specific region, coupled with intensive field and laboratory confirmation on vector capacity. This has enabled identification of the major *Culicoides* vector species in some areas. Figure 1 shows major *Culicoides* BTV vector species in different regions of the world, based on information reviewed elsewhere (7, 10).

The information depicted in Figure 1 is very superficial and not of much specific use in predicting or mitigating the risk for BTV transmission on a regional or local level. It is important to note that there are many localities where populations of many of these known vector species can be found, yet there is no evidence of BT. Alternatively, livestock producers in regions that have yet to experience BT are concerned that their local *Culicoides* species place them at risk for a BT epidemic. The distribution of known vector species and BTV serotypes is only a first cursory level for predicting and mitigating the risk for a BT epidemic. It is very likely that a good portion of the ability of various species of *Culicoides* to serve as effective epidemic BTV vectors is associated with the large population sizes that can be achieved under appropriate weather conditions. Therefore, weather and climatic conditions are very important (7, 15). Climate and weather models can provide a measure to predict vector distribution and epidemic risk that is discussed elsewhere in these Proceedings. However, these models are usually based on data from one *Culicoides* species, and extrapolation to other species may not be appropriate.

Weather and climate conditions can provide indications of the risk for BT though there are many additional factors that need to be evaluated to improve risk assessment. It is essential to understand the details of the influence of many other factors on the vector capacity of a species in order to provide accurate prediction and mitigation of potential epidemic risk beyond the cursory prediction based on suitable weather conditions for the presence of a vector species. Unfortunately not much progress has been achieved in obtaining this type of information since recommendations for research on *Culicoides* vector species were made at the Second International Symposium on bluetongue (13). There is little information about the details of the mechanisms contributing to the role of any of the known *Culicoides* vector species, little to no information on intraspecies or population differences within any species of *Culicoides* for BTV transmission and the consequent effects on the epidemiology of BTV infection, and little information to assess the potential role of any species of *Culicoides* in BTV transmission in advance of a BT outbreak.

The current status of information on the *Culicoides* species vectors of BTV worldwide requires study, as does the information needed to enable greater predictability and mitigation for BTV transmission and the risk for epidemics.

Episystem concept

The concept of an episystem is used here, consisting of the species and environmental aspects of an epidemiological system in a particular ecosystem which affects the distribution and dynamics of a pathogen and disease. This concept will be particularly valuable in considering complex systems such as the BTVs.

Figure 1 shows that the major vector species for BTV transmission differ in different broad geographic regions of the world, namely: *C. sonorensis* (formerly *C. variipennis)* (2) in North America, *C. insignis* in Central and South America, *C. imicola* in Africa and *C. wadai* and *C. brevitarsis* in Australia. Certainly other species, particularly in Africa, Asia and Australia play a role in BTV transmission in specific regions and at specific times, such as *C. fulvus* and *C. schultzei* in Asia and *C. bolitinos* in South

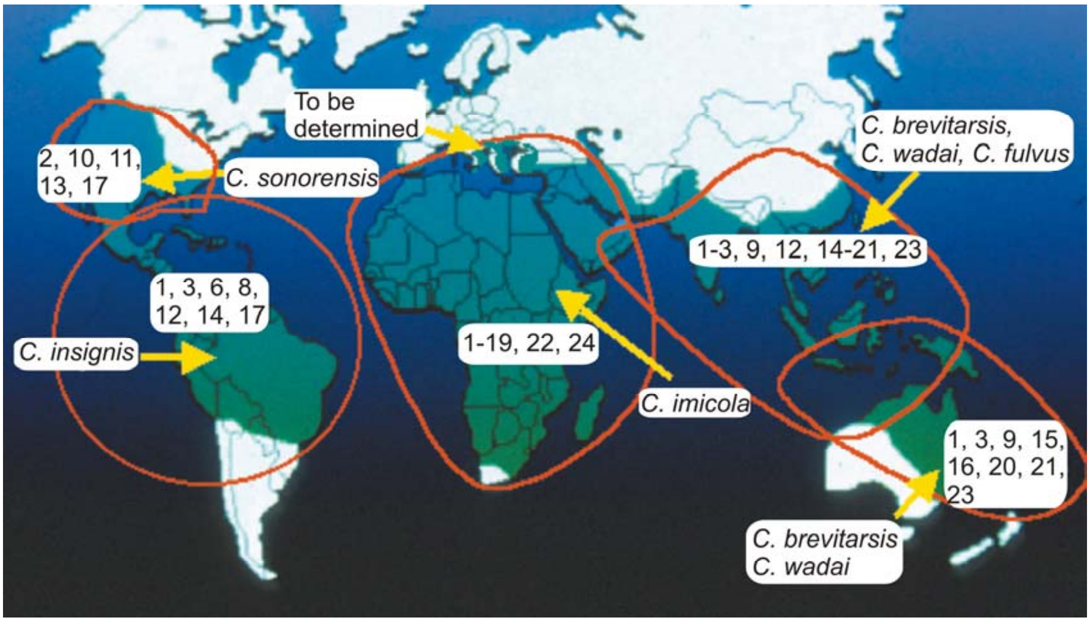

Figure 1
Worldwide distribution of the bluetongue viruses and the major *Culicoides* vectors

Africa, among others. The role of these and other species, i.e. *C. nubeculosus*, *C. obsoletus*, *C. pulicaris*, *C. actoni*, *C. fulvus* needs to be defined and, specifically, it is important to understand how populations of these species contribute to BTV epidemiology in the presence or absence of populations of the major vector species. As a first step, accurate species descriptions, taxonomy and systematic relationships of the species in the genus *Culicoides* will be an essential step in addressing these issues. Information on the phylogenetic relationships in the genus *Culicoides* can provide clues to understanding the evolution of vector capacity for the BTVs. Phylogenetic relationships among *Culicoides* are only beginning to be explored using molecular phylogenetics (4, 5).

The different broad geographic regions of the world contain different suitable *Culicoides* vector species and it is interesting to note that particularly in the New World, there are associated BTV serotypes that are apparently confined to specific regions. In the New World, two broad episystems can be defined for the BTVs. In the North American system *C. sonorensis* is the vector of BTV serotypes 2, 10, 11, 13 and 17, while in the South American ecosystem *C. insignis* is the vector of BTV serotypes 1, 3, 6, 8, 12 and 14. The factors that govern these ecosystems are unknown and are likely to be a combination of vector-virus and host interactions and differences that have yet to be explored. However, the New World does suggest that there are two BT ecosystems with different viruses and vector species. The epidemiologically significant factors that contribute to the maintenance of the two systems are unknown, possibly the result of a complex interaction between environment and all the biological components existing in each region. The result is different epidemiological systems or 'episystems'. The term 'episystem' is used here to include all those aspects of the ecosystem specifically relevant to the epidemiological distribution of the BTVs.

New World bluetongue episystems

The New World BTV episystems provide a useful illustration of the complexities in providing information to predict and mitigate vector borne animal disease like BT. The North American BTV episystem is perhaps the best understood of the BTV episystems. Tabachnick (10) reviewed the substantial information collected over the past 50 years on this system. North American BTV epidemiology, field and laboratory assessments of vector competence, and studies on genetic differentiation have shown that *C. sonorensis* is the primary North American vector. Close relatives of *C. sonorensis* in the North American Variipennis Complex, i.e. *C. variipennis* and *C. occidentalis* have not been implicated in BTV transmission. Indeed, the absence of *C. sonorensis* and the presence of only *C. variipennis* populations with lower vector competence in the north-east United States has been the basis for recommendations that the north-east United States be recognised as a BTV-free region (14).

The question of whether the information from the New World episystems might be useful in understanding other episystems, and enable predictions and mitigation of BT elsewhere in the world should be examined. One might assume that *C. insignis* and *C. sonorensis* share certain characteristics that enable them to be efficient BTV vectors – they both are indeed vectors of these viruses. However, it is unlikely that these two species share similar vector capacity control mechanisms. *C. insignis* in the subgenus *Hoffmania* and *C. sonorensis* in the subgenus *Monoculicoides* are not closely related phylogenetically. Since the close North American neighbours of *C. sonorensis* in *Monoculicoides*, i.e. *C. occidentalis*, *C. variipennis* and *C. gigas*, are not BTV vectors, and there are no close neighbours in New World *Hoffmania* that are BTV vectors, it is difficult to imagine that these two distantly related species (*C. insignis* and *C. sonorensis*) share vector characteristics due to a shared common ancestry. This would require that the ancestral characteristics have been maintained in two distantly related species while being lost in all other close neighbours. It is more likely that *C. insignis* is capable of fulfilling its BTV transmission role in the BTV South American episystem due to either different mechanisms and/or adaptations to this ecosystem that also have an impact on vector capacity. This may be related to different ancestral hosts or pathways evolved during the adaptation to cattle as hosts, which occurred under different conditions in North and South America. These secondary traits might be considered exaptations (1) or traits that evolved originally for a particular function, but were later recruited to fulfil new functions, i.e. vector capacity in the BTV episystem of South America. Similarly, *C. sonorensis* vector capacity traits possibly evolved independently in the North American ecosystem. BTV vector capacity traits may be exaptations that evolved in the North American episystem. What characteristics and mechanisms, whether homologous or completely different, allowing each species to fulfil the role of BTV vectors in their respective episystems are unknown.

It is important to note that the previous discussion illustrates the significance of having an appreciation of the phylogenetic relationships in the genus *Culicoides* and using this information to obtain information on the evolution of vector capacity. Many *Culicoides* vectors are distantly related, yet have close relatives that are not vectors. The distribution of vector capacity in species complexes needs to be resolved. Only *C. sonorensis* in the Variipennis Complex is a BTV vector. When considering the Imicola, Shultzei and Pulicaris Complexes (16), it would appear that it is unlikely that there will be shared mechanisms between the disparate *Culicoides* vectors for the BTVs, and that there are likely many different mechanisms capable of producing the same phenotypes contributing to vector capacity for BTV. For example, genetic studies with *C. sonorensis* identified a single locus controlling susceptibility to *C. sonorensis* infection with BTV (8). There is no reason to suspect that this locus is the controlling locus that causes resistance in the close neighbour *C. variipennis*. Furthermore, there is no evidence or reason to assume that this locus is largely responsible for intraspecies variation or the differences observed in BTV susceptibility between populations of *C. sonorensis*. The identified locus contributed to the differences between individuals in a *C. sonorensis* laboratory colony. The extent of its significance in nature is unknown.

There is no reason to expect that the North American and South American BTV episystems exist because there are similar mechanisms in each system. If *C. sonorensis* vector capacity is contingent on its presence and evolution in the North American ecosystem, it is problematic that *C. sonorensis* would even be a BTV vector if somehow transported to South America, or if it had evolved in the South American episystem. The same could be said of the entry of *C. insignis* into North America. Unfortunately, with the limited understanding of these complex episystems, our ability to predict the behaviour of a vector species in a different episystem, or the behaviour of any species of *Culicoides* encountering BTV for the first time, i.e. in a new potential episystem, is problematic. Unfortunately, the ability to predict the potential *Culicoides* BTV vectors in Italy, the United Kingdom, or anywhere else is equally rudimentary. The BTV episystems in each of these new regions simply do not exist so there is little information available to provide critical parameters of the system. Similarly, the information to predict the consequences of introducing different strains of BTV into an existing episystem is lacking. Although laboratory experiments and evaluations as currently undertaken, i.e. studies of vector competence and capacity, with colonies or even field collected populations may provide clues, these efforts may also be uninformative. In the absence of information about the episystem and the details of the mechanisms controlling vector ability for a particular species, such laboratory experiments provide little information about natural situations. The long-term history of the epidemiology of BTV infection in North America was essential to the interpretation of laboratory vector capacity information that resulted in understanding the role of *C. sonorensis* populations in BTV transmission. However, even in this situation, there is no understanding of the details of any controlling mechanisms of *C. sonorensis* capacity to transmit the BTVs. Hence, although there are some populations of *C. sonorensis* with low vector competence to infection for BTV there is no ability to assess whether these populations actually pose less of a risk for BTV transmission in an episystem. For example, there are populations of *C. sonorensis* in Weld County (Colorado) with approximately 1-2% susceptibility to infection for BTV in the laboratory. This is similar to the susceptibility of all *C. variipennis* populations tested to date (10) but whether there is less risk of BTV transmission in the Colorado episystem as a result cannot be predicted. There may be episystem factors that influence these populations and would support BTV transmission. Information on the intraspecies variation or population variation in vector capacity traits is virtually non-existent for other *Culicoides* species.

Requirements for bluetongue risk prediction and risk mitigation

It is essential to identify the critical factors governing a BTV episystem that have an impact on various geographic areas containing competent vector species. A competent *Culicoides* vector species must be capable of being infected with BTV, must be capable of transmitting BTV, must bite susceptible animal hosts, and must occur in numbers sufficient to sustain epidemic transmission. What is missing is information on the details of the specific underlying biological-genetic controlling mechanisms for vector capacity in each of the known BTV vector species. The following questions need clarification:

1) What specific genes govern BTV vector competence and capacity in each *Culicoides* vector species?
2) Are there BTV vector capacity genes that are homologous between distantly related *Culicoides* vector species?
3) What are shared vector capacity mechanisms between vector species and how have they evolved? Common ancestry? Convergent evolution?
4) What is the nature of intraspecies variation for vector capacity traits and how does this variation influence the risk for BTV transmission?

5) What are common and different features of the major BTV episystems?
6) What are potential new BTV episystems?
7) What critical features of particular BTV episystems can be targeted to reduce the risk of the establishment of BTV in the system or the risk of a BT epidemic in the system?

The ability to predict and mitigate an arthropod-borne disease such as BT is fundamentally a very difficult issue. Similar difficulties have been raised elsewhere for understanding other arthropod-borne diseases, such as West Nile virus in North America, malaria in Africa, and other emerging arthropod-borne diseases in general (10, 11, 12). There are genetic factors that control *Culicoides* vector competence and capacity and environmental influences (9, 10). The dynamics of the interactions probably vary according to the different species and ecologies. It is naive to believe that the same genetic factors, environmental factors and interactions between them are the same in different *Culicoides* species in different ecologies, particularly when species are phylogenetically disparate. The mechanisms allowing *C. sonorensis* to be effective as a vector of BTV serotype 11 may be absent and completely different from the mechanisms influencing *C. insignis* as a vector of BTV serotype 6. In *C. sonorensis*, the reaction of a colony to infection with one BTV serotype does not even predict the susceptibility of this colony to a different BTV serotype (6). There is little ability to predict interspecies abilities for the BTVs in northern Europe, and there is even less information to use to gauge intraspecies or population vector potential. Even in the best evaluated BTV episystem, the North American episystem, *C. sonorensis* interpopulation variation is virtually ignored in assessing the potential for sustaining BTV and epidemic transmission.

The ability to predict and mitigate BT epidemics will require a substantial investment to obtain essential information on the mechanisms controlling vector capacity in different vector species. This will require a change in the research focus from evaluating vector capacity phenotypes in laboratory experiments with no understanding of underlying mechanisms, to elucidating the fundamental genetic and environmental factors governing vector capacity traits in several different species of *Culicoides*. A well documented phylogeny for the genus *Culicoides* is essential to understand the evolution of vector capacity and for use to predict potential vector species. Genetic, environmental and phylogenetic information will make it possible to identify with assurance the competent *Culicoides* vector species in specific geographic areas in different episystems. Such information will also provide opportunities to develop new strategies to interrupt introduction of the BTVs into new regions, and to reduce the impact of epidemic BT.

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