

Invasion of bluetongue and other orbivirus infections into Europe: the role of biological and climatic processes

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Summary

The invasion of multiple strains of the midge-borne bluetongue virus into southern Europe since the late 1990s provides a rare example of a clear impact of climate change on a vector-borne disease. However, the subsequent dramatic continent-wide spread and burden of this disease has depended largely on altered biotic interactions with vector and host communities in newly invaded areas. Transmission by Palearctic vectors has facilitated the establishment of the disease in cooler and wetter areas of both northern and southern Europe. This paper discusses the important biological and climatic processes involved in these invasions, and the lessons that must be drawn for effective risk management of bluetongue and other midge-borne viruses in Europe.

Keywords

Bluetongue virus – Climate change – Culicoides – Environmental envelope – Europe – Invasion – Virus-vector interactions.

Introduction

Recent unprecedented climate change is widely predicted to increase the incidence and intensity of vector-borne disease transmission (11, 36), largely through direct effects of climate on vector biology, abundance and distribution. However, there is little direct evidence that recently observed changes in vector-borne diseases have been precipitated by climate change (33, 51, 62) and there is a growing recognition of the influence of other non-climatic abiotic and biotic factors on disease distributions (34, 35, 59, 61). Against this background, the invasion of a midge-borne disease of livestock called bluetongue (BT) into southern Europe constitutes a rare example of a clear impact of climate change on a vector-borne disease (56). However, the subsequent continent-wide spread and burden of this disease has depended largely on its biotic interactions with vector and host communities in newly invaded areas (55).

In this paper, we describe how the pattern (and impact) of BT epidemics has altered in Europe and set out the main strands of evidence linking this invasion to climate change. The biotic factors underlying this response to climate change are discussed. These include a northward shift in the range of the traditional African-Asian vector, *Culicoides imicola*, and, beyond this vector's range, the involvement of indigenous European *Culicoides* vector species (56). We demonstrate that the subsequent spread of bluetongue into cooler and wetter areas of Europe was facilitated by these new vectors that carried infection far beyond the range of the traditional vector (55). Understanding the relative role of biotic and environmental processes in such disease invasions is essential for development of early warning systems for vector-borne diseases. We finally consider how such knowledge is best integrated into risk assessment and early warning systems for bluetongue and other orbiviruses.

Bluetongue virus and its *Culicoides* vectors

Bluetongue virus (BTV) is a double-stranded RNA virus (family Reoviridae: genus *Orbivirus*) that can replicate in all ruminant species. Severe clinical signs are usually restricted to improved breeds of sheep and some species of deer (71) whilst in cattle, BTV usually causes long-lived sub-clinical infections, making these ruminants the main reservoir host. Bluetongue virus is transmitted between its ruminant hosts, primarily by certain species of *Culicoides* biting midges (Diptera: Ceratopogonidae) and is, in turn, restricted to areas where these competent vector species occur – broadly, the tropical and sub-tropical parts of the world, between latitudes 35°S and 40°N. *Culicoides* populations can build up to high abundances under suitable conditions, and adults can be transported by the wind for several kilometres within one night, leading to rapid spread of the diseases they carry (66). In Europe, BTV reaches its northern range margin and until recently this continent contained large populations of naïve and susceptible ruminants (particularly fine wool and mutton breeds of sheep).

The shifting pattern and impact of European bluetongue epidemics

Bluetongue virus has circulated on Europe's fringes for decades – in sub-Saharan Africa, Turkey and the Middle East (19, 24, 60, 72). Throughout this period, these fringe areas have been connected to Europe by synoptic wind systems and by traditional livestock trade routes. The potential for BTV to enter Europe has therefore long existed – either by the movement of infected ruminants or by the wind-dispersal of infected midges. Yet, historically, this disease has made only brief sporadic incursions into Europe. Outbreaks were confined to southern Iberia, Cyprus and some Greek islands and occurred wholly within the range of the major African-Asian vector *Culicoides imicola* Kieffer (Fig. 1, dark red hatched area and blue line). On each of these incursions, only one or two countries were affected at a time and only a single BTV serotype was involved.

Between 1998 and 2005, however, six strains (of five serotypes) of BTV entered Europe more-or-less

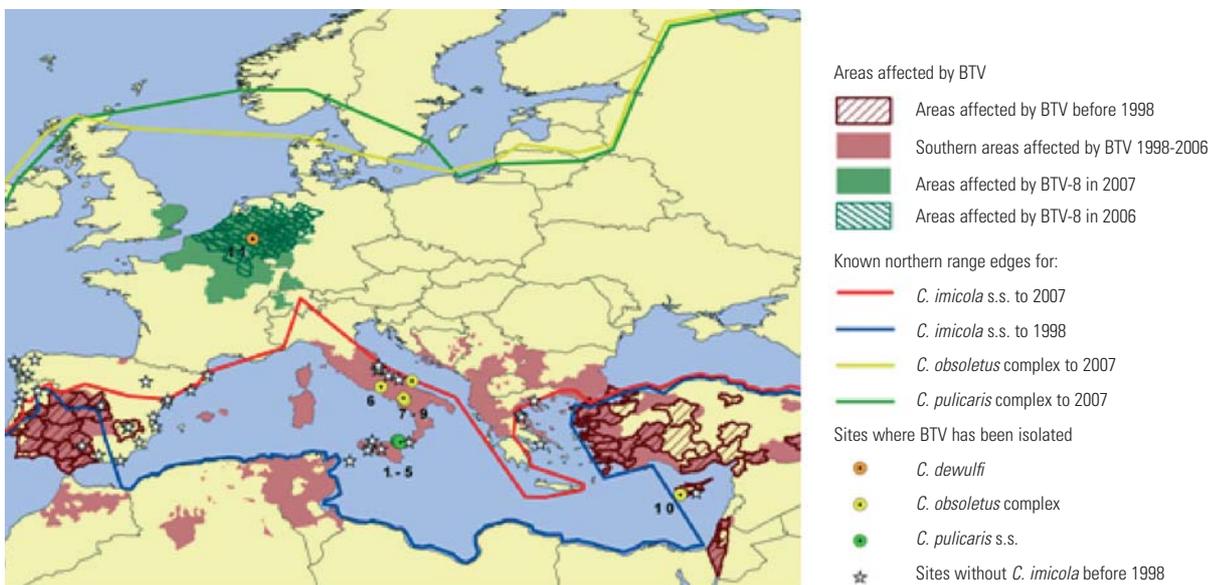


Fig. 1
The changed distribution of bluetongue virus and its vectors in Europe: map showing the distribution of BTV in southern Europe (prior to 1998 and since 1998) and in northern Europe (2006 to 2007)

The distribution of BTV prior to 1998 in North Africa and the Middle East is likely to have been extensive, but much transmission in these endemic areas occurs silently in disease-resistant host animals. The reported outbreaks mapped here, therefore, vastly underestimate the extent of historical transmission in these fringe areas. The green and yellow lines indicate the current known northern range limit of the major indigenous European species complexes. The blue and red lines show the northern range limit of the African-Asian vector midge species, *Culicoides imicola* up to 1998 (blue) and up to the present day (red). Dotted circles indicate sites where BTV has been isolated from wild caught non-engorged individuals from Palearctic vector groups. Mehlhorn *et al.* (37) also made isolations from *C. obsoletus* complex species in Germany at unspecified sites. Stars indicate sites where *Culicoides imicola* was found to be absent before 1998, sites in Bulgaria were surveyed, but not geo-referenced, so are not shown)

simultaneously from at least two origins (Fig. 2, east, via Turkey and Cyprus and west, via north Africa) and spread across 12 countries up to 800 km further north in Europe than ever before (Fig. 1, pink shaded area) (46, 56). This has led to the death of over 1.5 million sheep and has caused major disruption to trade in livestock and livestock products (7, 46). Not only did the distribution of BTV expand dramatically northward, but so too did that of *C. imicola* (i.e. into the Balearic Islands, mainland France, Switzerland, central and eastern Spain, mainland Greece, Sicily and mainland Italy (Fig. 1, red line) (see refs listed in [56]). Furthermore, early in the epidemic, transmission occurred beyond even the expanded range of *C. imicola* (in north-west Greece, Bulgaria and the Balkans [Fig. 1]) – indicating a vector role for indigenous European *Culicoides* species in these areas. Disease burdens have been highly dependent on particular strain–host type (or breed) interactions, with the severity of clinical signs caused by the same BTV serotype varying considerably across wide geographical areas (e.g. BTV-9 high severity in Greece and Croatia, low severity [$<2\%$ sick animals] in Bulgaria, Albania, Bosnia and Herzegovina and eastern Serbia [57]).

In August 2006, an African strain of a new serotype (Fig. 2), BTV-8, arrived in northern Europe by an unknown route (5° latitude further north than any BT outbreaks in the south of the continent and 7° latitude further north than the known range edge of the African-Asian vector – Fig. 1, dark green hatched area). This strain spread rapidly, infecting over 2,000 herds across five countries and unusually caused severe clinical signs and low level mortality in some cattle herds (16). This strain then successfully overwintered (at around 53° N [78]) and reappeared across most of the affected area in 2007, spreading to a further five countries (Fig. 1, green shaded area). By October 2007 it had caused around 25,000 outbreaks (27).

Evidence linking patterns in bluetongue to climate change

Examining responses to recent, unprecedented climate change across a range of biological systems, Walther *et al.*

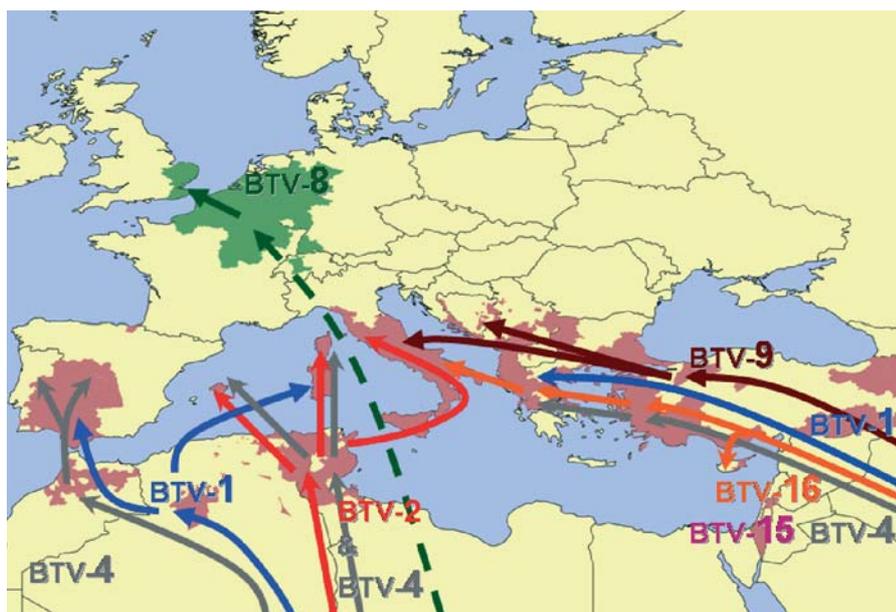


Fig. 2

The molecular epidemiology of bluetongue virus in Europe

Sequence analysis of the 6 European BTV serotypes has identified at least 8 lineages arriving into Europe via at least four distinct routes (47). Two separate introductions of BTV-1 into Europe have occurred. One strain (Greece2001/01) belonging to an 'eastern' group of viruses (being most closely related to Indian isolates) entered Greece from the east whilst another strain, belonging to a 'western' group of viruses, entered via Morocco (MOR2006/01) and Algeria (ALG2006/01) probably from further south in Africa. The European strain of BTV-2, which first appeared in Tunisia in 1998, also belongs to a 'western' group of viruses and is similar to strains from South Africa and Nigeria and probably entered Europe from further south. Both this BTV-2 strain and the 2006 strain of BTV-1 spread further northwards in Europe – into the west Mediterranean islands and mainland Italy (BTV-2) and mainland Spain (BTV-1 in 2007). European BTV-9, which spread extensively in the Balkans, and BTV-16 both belong to 'eastern' groups, while the European type 4, initially isolated in Greece (in 2000), is very similar to viruses that have been periodically isolated in the region (in Cyprus and Turkey) since 1969. However, in late 2003, a distinct western strain of BTV-4 arrived in Corsica and the Balearics, probably from North Africa, and subsequently caused outbreaks in Morocco and Spain. The BTV-8 strain affecting Northern Europe is from a western lineage in sub-Saharan Africa. It did not spread gradually from further south in Europe (it has not been detected there) but 'jumped' into Northern Europe by an unknown mechanism. Importantly, distinct strains are still entering southern Europe on an annual/bi-annual basis, whilst strains from distinct epizootic systems can 'parachute in' and go on to establish in Europe

(76) stated that the 'clearest evidence for a climate trigger occurs where a suite of species, with different histories of introduction, spread *en masse* during periods of climate amelioration' – a situation shown, we suggest, by the near simultaneous entry of six BTV strains into Europe (Fig. 2). Other changes, such as agricultural land use changes, changes in animal health systems, increases in livestock trade, and increases in host density, cannot be shown to follow a similar geographical pattern (56).

Non-climatic (biotic and abiotic) factors unlikely to influence bluetongue distribution in Europe

Alterations in the distribution and movements of susceptible hosts can be ruled out. Although the opening up of trade routes between Europe and the Middle East may have slightly increased the number of host animal movements, the total density of ruminants has actually declined in Europe since the 1980s, particularly in central areas (18). The sudden spread of bluetongue is unlikely to have been due to circulation of new, perhaps more virulent strains of BTV, since the large, naive populations of European sheep were probably highly susceptible to the entry of any BTV strain in the late 1990s – not only novel ones. This high susceptibility also means that any previous incursions would not have gone unreported and that sudden widespread detection of the disease across the region cannot be due to improvements in disease surveillance or changes in control strategies. Other non-climatic, abiotic factors (socio-economy, land use, animal health systems) also appear unlikely to be responsible. Since *Culicoides* are habitat generalists, breeding in a range of moist microhabitats that are ubiquitous across many farmyards (irrigation channels, drainage pipes, dung heaps [40]), any recent changes in agricultural practice or land-use are unlikely to have had a substantial and sudden impact on *Culicoides* vector distributions all across the continent.

Biological sensitivity of bluetongue virus and *Culicoides* to climate

Having discounted competing explanations, a direct causal link between BT emergence and climate change is suggested due to close adherence of the observed ecological response to criteria set out by peers (33, 52, 59, 62), namely:

- research along several axes (theoretical model systems, laboratory experiments, field manipulations and observations) demonstrates the biological sensitivity of both *Culicoides* vectors and BTV to climate (50)
- there is meteorological evidence of climate change with sufficient measurements in the study region

– significant changes in the climatic drivers of infection in Europe have occurred at the same times and in the same places as the changes in the incidence of BT.

In order to pin down the climatic drivers of BTV transmission, we must consider the various (independent and sometimes opposing) responses of the biological processes involved in the life-cycle of *Culicoides* and in the transmission cycle of BTV to climate. In common with vector-borne disease systems, key events in both cycles are modulated by temperature and moisture availability, as reviewed extensively elsewhere (40, 43, 79). Broadly speaking, warm temperatures enhance the recruitment, development, activity and survival rates of *Culicoides* vectors (45, 80). Significantly, the competence of *Culicoides* vectors, both the degree of transmission by 'traditional vectors' and the extension of transmission to historically 'non-vector' species, is enhanced by warm temperatures (53, 80). Within traditional vectors, warm temperatures increase viral replication rates (optimal temperatures 28°C to 29°C [74]) and may reduce the efficiency of heritable barrier mechanisms that constrain virus dissemination through a vector individual at various stages following oral infection. Bluetongue virus can persist at low temperatures (<10°C) for up to 35 days inside adult vectors and later replicate and be transmitted when the temperature increases (45). In a 'non-vector' species, *C. nubeculosus*, competence can be induced when larvae are reared at high temperatures, with 10% of emerging adults being infectable when reared at 33°C to 35°C, compared to 0% at 30°C (45, 80). This phenomenon has been attributed to the leakage of virus directly into the haemocoel, bypassing the midgut barriers, allowing virus replication and dissemination. Considering both vector and non-vector species together then, an increase in the cumulative frequency of either warm or hot periods in summer/autumn or whilst overwintering as larvae or adults will increase their transmission potential for BTV.

Moisture availability is the second most important extrinsic variable affecting *Culicoides* vectors and, in turn, BTV transmission. Precipitation governs the size and persistence of semi-aquatic breeding sites for larvae and the availability and duration of humid microhabitats in summer/autumn where adults can carry out key activities and shelter from desiccation (40, 49). Whether changes in precipitation act as climatic drivers of transmission is likely to vary geographically according to the habitat preferences of the vectors in that region and the average suitability of breeding sites there. For example, *C. imicola* breeds in wet, organically enriched soil and mud, but the pupae cannot survive flooding of these sites (5, 6). Thus, precipitation increases might favour increased breeding in arid areas, but across the Mediterranean, the presence of this species can be matched statistically to areas that are relatively dry in summer (55). For indigenous European species, however, conditions of high humidity may enable adults to resist desiccation during increasingly warm summers.

Overall, we expect increases in temperature (particularly at night-time and in winter) and precipitation (particularly in summer/autumn and in dry areas) to lead to an increased geographical and seasonal incidence of BTV transmission. This will occur as a result of:

- increases in the range, abundance and seasonal activity of vectors
- increases in the proportion of a vector species that is competent
- increases in the development rates of the virus within vectors
- the extension of transmission ability to additional *Culicoides* species.

Spatio-temporal correspondence between changes in European climate and changes in bluetongue virus

Coincident in time and space with the emergence of BTV in Europe in the late 1990s (56), there have been pronounced increases in night-time and winter temperatures (17, 31), fewer frost days, and changes in moisture conditions (25, 32, 31). As shown in Figure 3, BT incidence in the south of Europe has increased most markedly in areas where temperature has increased by at least 1°C since the 1980s (yellow in Fig. 3c) – in Italy, adjacent west Mediterranean islands and the Balkans. Bluetongue incidence in northern Europe increased in areas that have warmed by almost 1.5°C (orange in Fig. 3c), making these areas as warm as infected areas of Italy, Spain and Greece much further south (Fig. 3a).

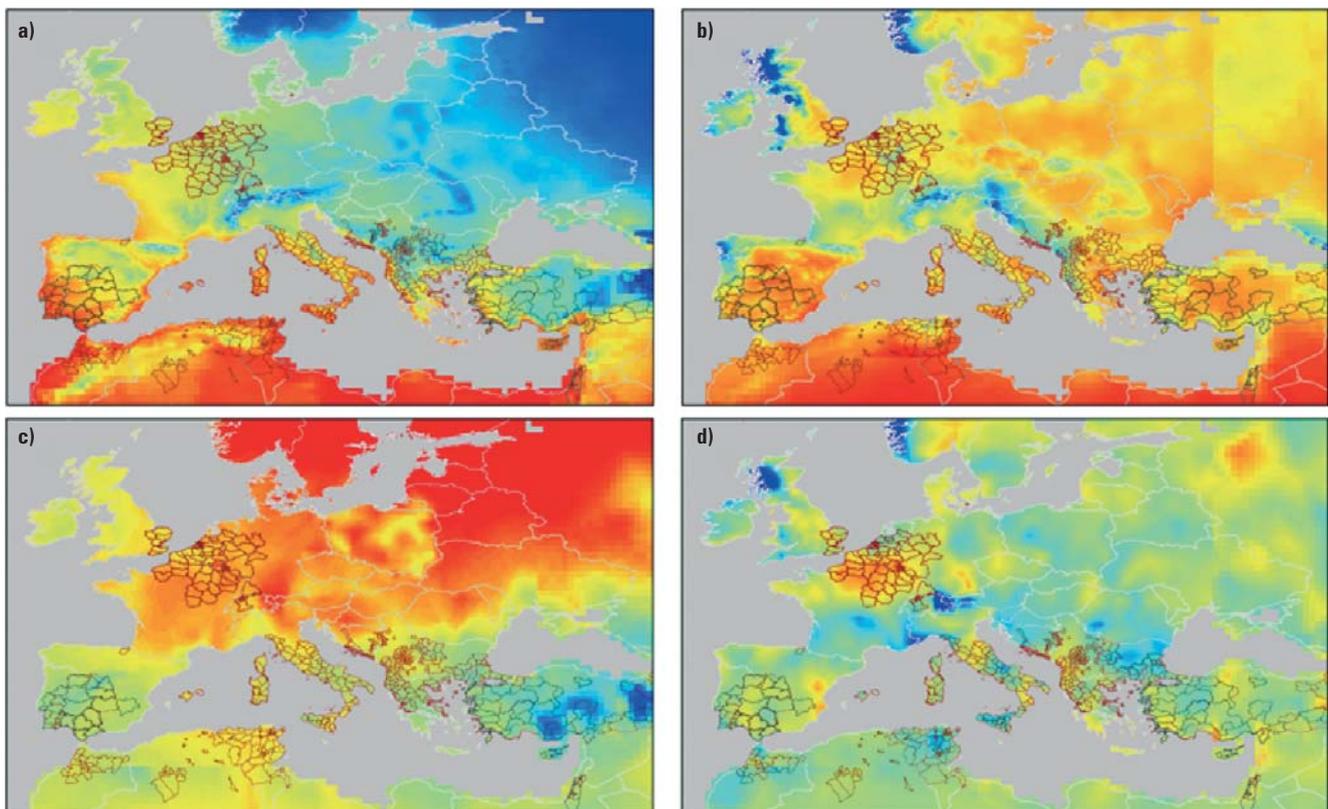


Fig. 3
Spatial variation in recent climate change in Europe

Figs. 3a and 3b show average 1990s conditions of minimum temperature (from -10°C in dark blue to 13°C in dark red) and sum of annual precipitation (from 0 to 2,000 mm) for each sixth of a degree latitude and longitude square in Europe. Figs. 3c and 3d show changes in these conditions between the 1980s and the 1990s. In Fig. 3c temperature changes are shown on a sliding colour scale ranging from a reduction of 2.0°C (dark blue) to an increase of 2.0°C (dark red). Temperature increases are most marked in both central and northern Europe, whilst central Iberia, the border region between Morocco and Algeria, and parts of Turkey have cooled. (Temperature images were produced by temporal Fourier processing the raw time series of data and re-constituting it by summing the annual, bi-annual and tri-annual harmonics – essentially smoothing the data. The minimum values here are the minima of the re-constituted series for the period in question.) In Fig. 3d precipitation changes are shown on a sliding colour scale ranging from an increase of 200 mm a year (dark blue) to a reduction of -200 mm a year (dark red). These are overlaid with the areas historically affected by BT in grey outline and the newly-affected areas in red outline

Areas such as central Iberia, northern Morocco and Algeria – where the distribution of BT has broadly remained stable – have cooled but are still warm on average (Fig. 3a). As expected, the spatial correspondence between changes in BTV and changes in precipitation amounts is less clear, but BTV-affected areas tend to be drier on average (Fig. 3c) and increased BT incidence in northern Europe, north and central bands of mainland Italy, and the Balkans overlaps with areas that have dried since the 1980s.

Biological factors underlying the response of bluetongue virus to climate change

What are the mechanisms that might underlie these responses of BTV to climate change in Europe and what are their consequences for future spread?

Extended distribution of the major African-Asian vector, *C. imicola*

Vector surveillance efforts have been dramatically stepped up in Europe during the recent BT epidemic, such that people are looking for the major African-Asian vector, *C. imicola*, more often and in more places than before. This vastly increased sampling effort might result in an extension of the recorded northern range limit of *C. imicola* regardless of any actual extension on the ground. However, *C. imicola* has now been found in or near sites in which it had been searched for and found to be absent before 1998 (Fig. 1, white stars – see refs listed in [55]), suggesting the actual distribution limit really has extended, at least in places (56).

Have regional climate changes precipitated this extension in *C. imicola*'s northern range limit perhaps by increasing the extent of suitable habitat in Europe? Alternatively, has *C. imicola*, in the absence of climate change, simply been filling suitable habitat in Europe that was always available to it but remained unoccupied due to geographical isolation until recently? Has the environmental envelope of *C. imicola* itself changed over this time period? Without extensive historical and current distribution data for *C. imicola*, these alternatives are extremely difficult to tease apart. However, the most important driver of this species' current distribution across the Mediterranean was recently found to be annual mean temperature, and populations were associated with locations that are warm, not just on average (annual mean 12°C to 20°C), but year-round (55). This leads us to expect that increases in annual mean temperatures and narrowing of daily and annual temperature ranges across Europe (31) would favour range

extension in this species. Broadly speaking, the pattern of *C. imicola*'s range extension during the 1990s mirrors the pattern of warming (compare Fig. 1 and Fig. 3c). This species has expanded most into warmed areas – eastern Spain, northern Italy, southern France and north-eastern parts of Greece – whilst areas where temperatures have remained largely unchanged (European Turkey and eastern Bulgaria) have, as yet, seen no such invasion.

Involvement of Palearctic vectors in bluetongue virus transmission in southern Europe

By the early 2000s, several pieces of evidence pointed to a role for indigenous European vector groups, primarily species from the *C. obsoletus* and *C. pulicaris* complexes, in BTV transmission in southern Europe. These included fine-scale overlap of the distributions of these complexes with outbreaks (13, 57, 73), isolation of virus from wild-caught adults of the *C. pulicaris* and *C. obsoletus* complexes in several sites (Fig. 1, dotted circles) (8, 14, 37, 38, 64, 65) and laboratory studies indicating competence levels for BTV comparable to *C. imicola* in some populations (9). These Palearctic complexes are abundant and widespread in northern Europe, but also extend southward into north Africa (4, 67), Turkey (28) and the Middle East (5, 6) and, as such, overlap with both the major vector *C. imicola* and areas of historical BTV incursions across a wide geographical area. Despite this overlap, there is little evidence, either from the timing or fine-scale spatial distribution of historical outbreaks (41, 42), that these complexes played a major role in transmission before the late 1990s (39).

In turn, it has been hypothesised that the recent warming in Europe may have increased the importance of Palearctic vectors – by increasing their population sizes and survival rates to compensate for their low competence levels and by increasing their individual susceptibility through the developmental temperature effects mentioned above (56). In support of this hypothesis, the areas where these Palearctic vectors have been involved in transmission again coincide with those areas of Europe that have warmed the most (Fig. 3c).

It is important to note however, that a similar temporal pattern in their involvement in transmission could have been produced, in the absence of climate change, given geographical variation in these aspects of their vector capacity – if, for example, the populations of the *C. obsoletus* and *C. pulicaris* complexes in the Balkans, Bulgaria, northern Greece, European Turkey have (or had) higher vectorial capacity than do populations in areas historically affected by outbreaks (Spain, Portugal, Morocco and the Greek Islands). In either scenario, the involvement of these complexes in transmission would have been facilitated by their increased spatial (range

extension) and temporal (prolonged seasonal activity) overlap with *C. imicola*, allowing frequent 'hand-over' events of the virus between the traditional and novel vectors. Evidence for the importance of such hand-over events during the current epidemic is substantial. In both Sicily (73) and Lazio and Tuscany provinces, BTV was transmitted initially in lowland areas by *C. imicola*, but was then handed-over and spread inland by species from the *C. pulicaris* and *C. obsoletus* complexes (13).

Consequences of transmission by Palearctic vectors for bluetongue spread

Whether driven by regional warming or not, what were the consequences of the involvement of Palearctic vectors in BTV transmission for the subsequent continental spread of this virus? As expected when any pathogen moves to a new vector, the distribution of the new vector is likely to extend the kinds of environments (or environmental envelope) in which the pathogen can occur. However, despite the wide distribution and high abundances of the Palearctic vectors and their substantial laboratory competence levels for BTV, they were generally assumed to be of relatively minor importance in transmission, whilst BTV remained in southern Europe. Vector surveillance effort (up to 2004), for example, was directed towards defining *C. imicola* free zones (10) between which vaccinated animals could be legally moved for trade or seasonal transhumance – without regard for the abundance of Palearctic vectors in those zones.

For accurate risk assessment it was essential to test this assumption and to determine the following:

- the relative extent to which the Palearctic vectors versus the African-Asian vector, *C. imicola*, were involved in BTV transmission in southern Europe
- the extent to which the environmental envelope of BTV had been extended by the early 2000s (and into which kinds of environment) due to its transmission by Palearctic vectors.

We took an environmental envelope modelling approach to this investigation (55) – analysing the differential degree of overlap between the environmental envelope of BTV and each of its vectors and assuming that the distribution of BTV in environmental space would be closest to that of the vector(s) playing the greatest role in transmission. We first mapped the current, fine-scale, distributions of BTV (501 presence records), *C. imicola* (395 presence and absence records) and the *C. obsoletus* (428 presence records) and *C. pulicaris* (410 presence records) complexes across southern Europe and north Africa. Secondly, we

determined (statistically) the key climatic factors that best defined the current envelope of *C. imicola* (this was possible because this species, being the target of historical surveillance efforts, is relatively well-recorded along its northern range edge). Thirdly, we compared the overlap of *C. imicola*'s envelope (defined by these climatic factors) and areas of BTV transmission to the overlap between the Palearctic vectors and BTV transmission.

Locations favoured by *C. imicola* across the Mediterranean were not only warm and thermally stable, but were also relatively dry in summer – consistent with this species' susceptibility to flooding of their breeding sites (see above). The Palearctic *C. obsoletus* and *C. pulicaris* complexes, by contrast, were both found to occur in cooler (down to 7°C annual mean), thermally more variable and wetter (up to 700 mm summer precipitation) locations. The overlap of the distribution of BTV and *C. imicola* in environmental space in southern Europe (and North Africa) is shown on the left-hand panel of Figure 4. On the pairs of environmental axes depicted in Figs. 4a and 4c, around 44% of southern BTV records fall outside of the envelope of *C. imicola* (estimated as the 95% confidence ellipse around presence locations for this species), and do so in the directions of much lower annual mean temperatures (to 6°C or 7°C) and greater ranges of annual temperature (>9°C) on Fig. 4a, and wetter as well as cooler areas on Fig. 4c. Superimposing the sampled distributions of the *C. obsoletus* and *C. pulicaris* complexes on the same pairs of axes (right hand panel Figs. 4b and 4d) we can see they overlap much of the space beyond *C. imicola*'s envelope into which BTV transmission has extended. When measured in multivariate space, their distributions are closer to the overall distribution of BTV transmission than is the distribution of *C. imicola* (even when locations inside *C. imicola*'s range limit were considered separately). This indicates that these Palearctic complexes made a significant contribution to the transmission of BTV in southern Europe – not only northward of the range limit of *C. imicola* but also inside this species' range – and have been instrumental in the spread of the virus into cooler and wetter regions of Europe. Furthermore, the Palearctic complexes overlap extensively with the envelope of *C. imicola* (and with each other) affording ample opportunity for the virus to be 'handed over' between traditional and novel vectors. This study also shed light on the seasonal conditions of temperature and precipitation limiting the distribution of *C. imicola* in the north-east/north-central (wetter in summer and low winter temperatures) and north-west Mediterranean (wetter year-round and cooler) and the environmental changes that would be required for further northward spread in different areas.

Overall, these results for southern Europe suggested that further northward spread of bluetongue from the mid-2000s would most likely depend on the portion of the

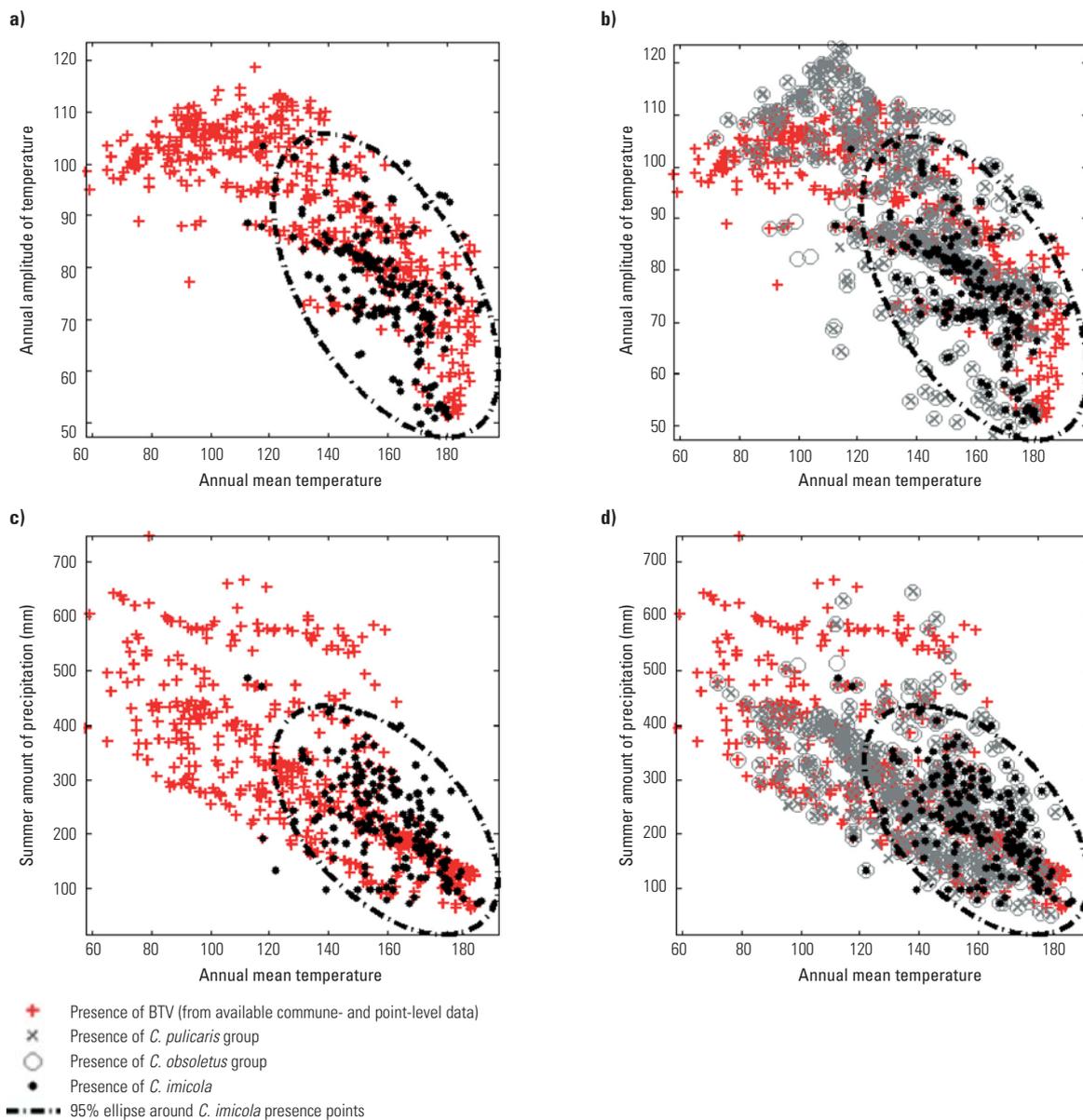


Fig. 4
Climate space occupied by bluetongue virus and its vectors: southern Europe

The axes of bivariate climate space are defined by two pairings of three important determinants of *C. imicola* distribution across Europe: annual mean temperature (in 0.1°C), annual amplitude of temperature (in 0.1°C), and summer amount of precipitation (in mm per summer). In Figs. 4a and 4c the overlap between the presence of BTV and the presence of *C. imicola* in environmental space is shown. In Figs. 4b and 4d their overlap with the presence of other Palearctic *Culicoides* is also shown. Modified with permission from Purse *et al.* (58)

distributions of species within the Palearctic complexes that BTV could occupy (determined by the environmental effects on the viral replication and vectorial capacity of midge populations within these distributions). This was borne out in the summer of 2006, by the appearance of an African strain of BTV in northern Europe (16). The overlap of the distribution of BTV-8 outbreaks in northern Europe in 2006 and 2007 with the distribution of vectors and southern BTV outbreaks in environmental space (defined by the same environmental axes as before) is depicted in Figure 5. Records from the northern portion of these

species' ranges (including *C. dewulfi*) have been included in the estimated distributions of the Palearctic complexes (B.V. Purse, unpublished data). It can be seen that the northern BTV outbreaks (in blue on Fig. 5) lie well outside the envelope of *C. imicola* in Europe, occurring in much cooler and wetter environments than those favoured by this species. Compared to previous southern outbreaks (in red on Fig. 5) they are distinct not in mean levels of temperature (annual) or summer precipitation (Fig. 5b) but in the fact that they are also relatively cool year round (Fig. 5a). The extensive overlap with the distribution of the

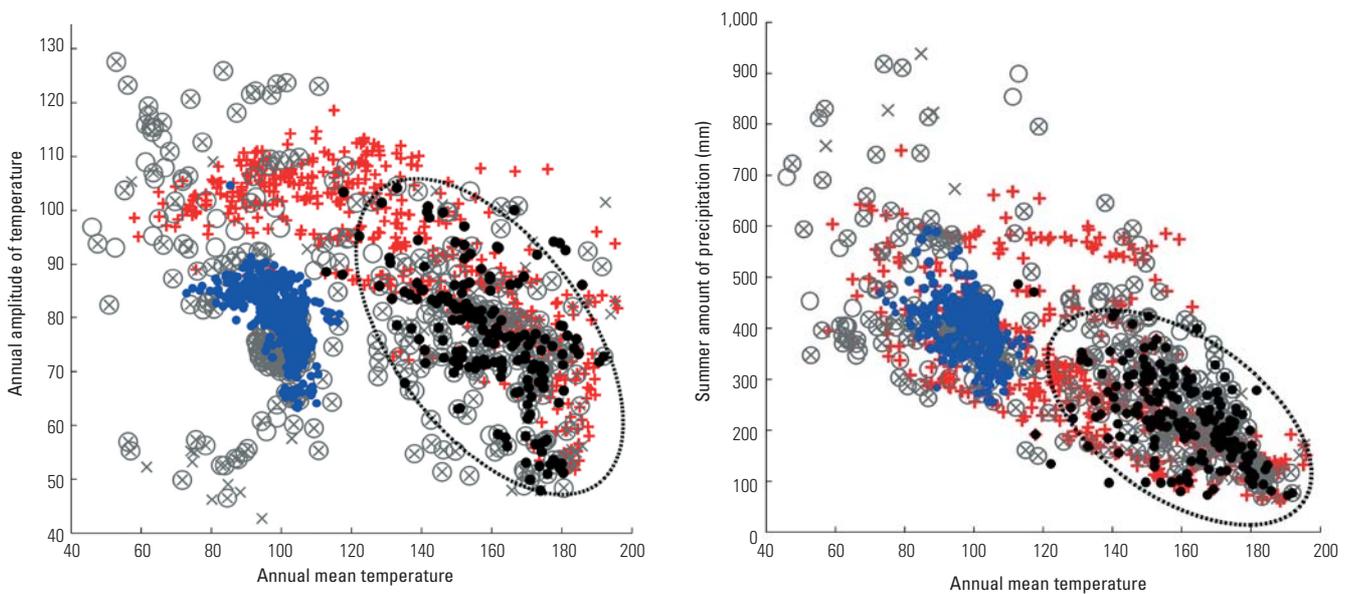


Fig. 5
Climate space occupied by bluetongue virus and its vectors: northern and southern Europe

The axes of bivariate climate space are defined by two pairings of three important determinants of *C. imicola* distribution across Europe: annual mean temperature (in 0.1°C), annual amplitude of temperature (in 0.1°C), and summer amount of precipitation (in mm per summer). The overlap between the presence of BTV (northern in blue circles, southern in red crosses) and the presence of *C. imicola* and Palearctic complexes is shown

Palearctic complexes again indicates a major (if not exclusive) role for these groups as vectors during the northern outbreaks, consistent with virus isolations in the outbreak areas in the field from wild caught adult midges (37, 38). Given that these Palearctic complexes are not widespread in the postulated area of origin of the BTV-8 strain in sub-Saharan Africa, it is unlikely that susceptibility of these vectors and the ability of the virus to replicate inside them gradually evolved in tandem over a long period of co-existence. This is extremely worrying, since it means that some European midge species are capable of transmitting geographically remote strains to which they have not been exposed. In addition, these Palearctic complexes extend far outside the current outbreaks in both geographical (see range limits in Fig. 1) and environmental space (Fig. 5). Further investigation of the distributions, competence and other aspects of vectorial capacity of the species that make up these complexes is essential for prediction of onward spread of bluetongue through Europe.

Vectorial capacity, the number of potentially infectious bites per animal for a particular vector species, is a complex phenomenon for these Palearctic complexes. Geographical variation in vector competence – one aspect of vectorial capacity – has, for example, been noted within the *C. obsoletus* complex in the United Kingdom (UK). Further work is ongoing to pinpoint whether competence is environmentally determined or whether it is heritable – and, if heritable, whether particular species of *C. obsoletus* s.l. and *C. pulicaris* s.l. or genotypes within species are

highly competent. Gathering of these kind of data on geographical and temporal variation in the vectorial capacity of these complexes is currently hampered by the difficulties in routinely distinguishing between species by morphological or molecular taxonomic techniques.

A global view of climate change and bluetongue epidemiology

Worldwide, BTV is thought to have evolved within stable, continental ‘episystems’ where constituent vectors are able to transmit only indigenous viruses despite movements of hosts (due to trade) and vectors between episystems (68). As a consequence, the situation in Europe – of altered vector roles and widespread transmission of ‘foreign’ strains – is deemed unusual. In fact, on some other continents, long periods of BTV faunal stability have been interrupted by the intermittent introduction and establishment of foreign or novel strains. For example, several southeast Asian strains of bluetongue became established in northern Australia during the 1990s (12, 30) and, between 1999 and 2005, six serotypes that were new to the United States of America were isolated from Florida sheep, cattle or deer (29). For the Europe/Africa/Middle East episystem, a period of instability was precipitated by climate change – probably acting on critical determinants of vectorial capacity (the features of the system that made it responsive to climate change [56] are summarised in

Table I
Features of the European bluetongue virus-*Culicoides* episytem precipitating its response to climate change

Feature	Explanation
Wide host preferences	Bluetongue virus (BTV) uses a wide range of wild and domestic ruminant hosts such that susceptible host populations are likely to be spatially continuous across agricultural systems
Wide range of susceptible vectors with different ecologies	Vector populations of <i>Culicoides</i> are widespread and abundant and occupy a wide range of moist soil/dung microhabitats found all across agricultural systems. They are catholic in their biting habits, feeding upon any available large mammal. In Europe, indigenous <i>Culicoides</i> vector complexes (specifically <i>C. pulicaris</i> and <i>C. obsoletus</i>) have a wide zone of overlap with the major Old world vector <i>Culicoides imicola</i> ., providing the opportunity for frequent and widespread 'hand-over' events of the virus between major and novel vector groups. The indigenous vector complexes also extend much further northwards in Europe than <i>C. imicola</i>
Temperature-mediation of vectorial capacity	The temperature effects on the vectorial capacity of both traditional vectors and extension of competence to 'non-vectors'
Sub-clinical infection and 'silent' circulation	Most hosts are sub-clinically infected, most infections are neither identified nor removed rapidly from the population, and so persist as sources of infection for biting vectors
Over-wintering ability	BTV can persist at low titres inside adult vectors for up to 35 days and is later able to replicate and be transmitted when the temperature increases (as would occur in spring). Viral RNA has also recently been recovered from <i>Culicoides</i> larvae (77), calling into question whether trans-ovarial transmission may indeed be possible in some species. In addition, in areas where adult vectors are unable to persist in substantial numbers over winter (such as Bulgaria [57]) it has been hypothesised that the virus can instead persist covertly in the ruminant host itself inside the $\gamma\delta$ T-cells of the immune system (69)

Table I). The major lesson to be drawn from this emergence is that vectorial capacity should be considered as temporally and geographically variable, within and between *Culicoides* vectors, and that the genetic and environmental factors underpinning this variation should be thoroughly investigated. Just because a *Culicoides* species or genotype has been historically refractory to a BTV strain in one area, does not mean that it will remain so in other places or at other times, or even to other strains of the virus. Given the global nature of climate change and the fact that short-term changes in climate can produce short-term changes in vector or virus distributions across most continental bluetongue episytems (54, 75, 81), it should be considered within a suite of other potential abiotic and biotic factors when investigating the mechanisms for dynamism in BT epidemiology worldwide.

Considering future changes in BT epidemiology in Europe, it is conceivable that European livestock may quickly develop immunity to extant strains of BTV in Europe. However, molecular epidemiological evidence indicates that novel strains (to which the population will be naïve) are still entering Europe on an annual basis (47, 48) and, in turn, BTV and related orbiviruses that share the same or similar vectors (e.g. African horse sickness virus and epizootic haemorrhagic disease virus) represent a continuing threat, at least in the short term. Molecular work also indicates that some European strains have re-assorted (i.e. have swapped their genome segments) to create new strains that may potentially have novel biological properties. Thus, even in the absence of entry of

further BTV strains into Europe, it is conceivable that the mixture and re-assortment of eastern and western field and vaccine strains could lead to the emergence of new strains that are better suited to transmission under local conditions. How is knowledge of the environmental and biological factors involved in invasion, establishment and spread of BTV being integrated into risk assessment tools for bluetongue in Europe?

Risk management tools for bluetongue in Europe

Tools for predicting the arrival, establishment and spread of BTV into Europe have developed apace during the recent emergence. Considering the process of arrival, the development and analysis of large nucleotide and amino acid sequence databases (containing geographically and temporally referenced isolates) for BTV have enhanced our ability to identify the origins of new viral strains entering Europe or circulating on the fringes (47, 48). The probability of arrival of new BTV strains via the movements of animals and animal products is often hard to predict, as epitomised by the unknowable entry of BTV-8 into Europe in 2006 (16). Hoar *et al.* (26) have developed Monte-Carlo simulation models to predict the probability of importing a viraemic animal based on the frequency of importation and the countrywide seroprevalence across a range of different exporting countries.

Wind-borne dispersal of *Culicoides* is an important process governing both the arrival of BTV into new land masses and the subsequent spread (66). A range of authors have developed models to better quantify the importance of this process in past incursions (1) and to predict and monitor the likelihood of such movements, their timing and direction – over land as well as over the sea. Ducheyne *et al.* (15) successfully matched wind trajectories (at a pressure level or height thought to permit *Culicoides* survival during movement) with movement patterns inferred from recorded outbreaks in Greece and Bulgaria. Others have taken a more mechanistic approach, borrowing the plume models of atmospheric physicists that predict spread from a point source (20, 21). These incorporate, for example, information on the suitability of local climatic conditions for take-off and landing of adult *Culicoides*, as well as their particle size.

Geographical and temporal variation in the probability of establishment of BTV should ideally be investigated within the framework of the basic reproduction number – R_0 , i.e. the number of new cases that arises when a case is introduced into a naïve population. If climate changes affect vector-borne diseases, they will do so through the parameters and variables of the R_0 equation (63). This approach requires a great deal of detailed knowledge on the rates of biological processes in the host and the vector (and their dependencies on environmental variables) and the ratio of vectors to hosts; this information is often unavailable – necessitating short-cuts. Wilson *et al.* (78), for example, have predicted when and where in the UK BTV might be transmitted under different temperature regimes on the basis of one of the key parameters of the R_0 equation, such as the extrinsic incubation period in the vector, and its relationship with temperature. It is indeed conceivable that the maximum extent of spread across northern Europe, where vectors are ubiquitous and abundant, might eventually be limited by thermal limits on viral replication. Gubbins *et al.* (22), formulated a two host one vector model for R_0 and incorporated information on the temperature dependence of biting rates, the extrinsic incubation period and vector mortality. They found that R_0 was highest between 20°C and 25°C. Below 10°C, vectors were unable to complete the extrinsic incubation period whilst at high temperatures (30°C to 35°C), high vector mortality limits R_0 .

The vector-host ratio is an essential ingredient of the R_0 equation and it is probable that spatial and seasonal variation in vector numbers drive spatial and seasonal patterns in many vector-borne diseases. Many studies have attempted to map the habitat suitability for different midge vectors across Europe. These distribution models have variously incorporated both landscape factors (23) and average seasonal climatic conditions (using both meteorological and remotely-sensed data) as predictors (2, 3, 4, 10, 55, 58, 70). These have been quite successful

in predicting the range limits and regional presence of *C. imicola*, the major African-Asian vector and for teasing apart broad-scale interactions of BTV with different vector groups in Europe (55). Their lack of predictive ability at the farm scale, however, indicates the importance of local-scale factors (farm husbandry, hosts and microclimate) in determining population levels. For the Palearctic complexes, development of models is particularly restricted by current lack of species-specific distributional (and other ecological) data. Scaling up between local and regional-scale predictions of establishment requires that future vector surveillance systems for bluetongue can deliver species-specific information (on breeding habitats and the seasonality of adult *Culicoides* populations) that enables us to relate their demographic rates and carry capacities to environmental variables.

Conclusions

Changes in BT incidence in Europe have been matched by spatio-temporal changes in regional climates, including the specific climatic drivers of BTV infection. However, biotic processes, of changing vector roles and distributions, have been as important as climatic processes in driving the invasion of Europe by multiple bluetongue strains. Enhanced transmission of the virus by indigenous European vectors has been instrumental in the spread and persistence of infection in cooler and wetter areas of both southern and northern Europe following invasion. Vectorial capacity of *Culicoides* species is dynamic and climate-mediated, making it difficult to state unequivocally that particular species cannot or will not be involved in transmission – even of strains that enter Europe unexpectedly from geographically remote regions. There is an urgent need to collect detailed ecological information on indigenous European vector species to support the development and validation of risk tools for bluetongue.

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Les invasions de fièvre catarrhale du mouton et d'autres infections à orbivirus en Europe : le rôle des processus biologiques et climatiques

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Résumé

L'offensive, en Europe méridionale, de nombreuses souches du virus de la fièvre catarrhale du mouton (maladie transmise par les moucheron) depuis la fin des années 1990 est un exemple précieux de l'impact du changement climatique sur les maladies à transmission vectorielle. Toutefois, la propagation de la maladie dans tout le continent et sa gravité s'expliquent surtout par des modifications des interactions biotiques entre les populations des vecteurs et celles des hôtes dans les zones récemment envahies. La transmission par des vecteurs paléarctiques permet à la fièvre catarrhale du mouton de s'établir facilement dans les régions plus fraîches et plus humides d'Europe du Nord et du Sud. Les auteurs examinent les principaux processus biologiques et climatiques associés à ces invasions ainsi que les enseignements que l'on peut en tirer pour gérer plus efficacement les risques liés à la fièvre catarrhale du mouton et à d'autres virus transmis par les moucheron en Europe.

Mots-clés

Changement climatique – Culicoides – Enveloppe écologique – Europe – Interaction virus-vecteur – Invasion – Virus de la fièvre catarrhale du mouton.



Las invasiones de lengua azul y otras infecciones por orbivirus en Europa: papel de los procesos biológicos y climáticos

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Resumen

Desde los años noventa el sur de Europa asiste a la penetración de múltiples cepas del virus de la lengua azul, transmitido por moscas enanas, fenómeno éste que brinda un raro y elocuente ejemplo de la influencia del cambio climático sobre una enfermedad mediada por vectores. No obstante, la subsiguiente y espectacular propagación de esta enfermedad y de la carga que trae consigo ha obedecido sobre todo a la alteración de las relaciones bióticas entre el vector y las comunidades de hospedadores en las zonas recién invadidas. La transmisión por vectores paleárticos facilita el asentamiento de la enfermedad en regiones más frescas y húmedas tanto del sur como del norte de Europa. Los autores examinan los importantes procesos biológicos y climáticos que intervienen en

estas invasiones y exponen las enseñanzas que cabe extraer para afrontar eficazmente en Europa el riesgo de infección por el virus de la lengua azul u otros virus transmitidos por la mosca enana.

Palabras clave

Cambio climático – Culicoides – Envoltura ambiental – Europa – Interacción entre virus y vector – Invasión – Virus de la lengua azul.



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