**Research gaps in understanding how climate change will affect arboviral diseases**

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Abstract

Climate change is widely expected to cause the emergence and spread of vector-borne diseases, and predictive models are needed so that we can be prepared. We developed a climate-sensitive, predictive, model that describes the risk of an arboviral disease of ruminants called bluetongue (BT) which has emerged dramatically in Europe. Developing the predictive BT model led to the identification of numerous gaps in both understanding, and the availability of data. These mostly pertain to the vectors and their interaction with hosts. These gaps should be closed, to allow better models, with more precise predictions, to be produced. These research gaps apply to many other arboviral diseases as well. As a consequence, there needs to be an increase in research on the vectors that transmit arboviral diseases. Priorities are the training of a new generation of taxonomists, studies on the field biology of potential vectors, increased coordination of vector surveillance and recording between countries facing similar threats.

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*He was distressed, however, at having to part with his sheep, which he gave to the Bordeaux Academy of the Sciences. The Academy proposed as the theme for its yearly prize competition an investigation into the reason for the redness of the sheep’s wool. The prize was won by a scholar from the north, who demonstrated by A + B – C / Z that the sheep must of necessity be red, and furthermore that it would die of the rot*.

From Voltaire’s *Candide*, 1759

This quotation describes one of the earliest attempts to use mathematical modelling to solve disease problems, and must surely be the first such example concerning diseases of sheep. It is personally disappointing that Voltaire chose the colour red as, for many years, I have used mathematical modelling to address a disease that turns sheep – well, their tongues at least – blue. This disease is ‘bluetongue’, an insect-borne viral disease of ruminants which causes fever, swelling, inflammation and haemorrhage, leading sometimes to death.

Bluetongue (BT) has emerged dramatically in Europe in the last fifteen years, causing the deaths of millions of sheep and many cattle ([Mellor et al., 2008](#_ENREF_13)). Before this outbreak, the disease had never occurred in Europe north of Madrid but, in 2006, there were cases in northern Europe, in 2007 it occurred for the first time ever in the UK and in 2008 it reached southern Scandinavia. This remarkable spread has led to questions about the role of climate change in BT’s emergence.

BT is caused by an arthropod-borne virus (ar-bo-virus) called bluetongue virus (BTV) ([Mellor et al., 2000](#_ENREF_12)). It is transmitted to its ruminant hosts by *Culicoides* biting midges, tiny flies which are often hugely abundant. Other important vectors of arboviruses are mosquitoes (which transmit Japanese encephalitis, West Nile, dengue, Yellow fever and many more) and ticks (which transmit tick-borne encephalitis, louping ill, Crimean-Congo haemorrhagic fever and others). Arthropods are usually extremely sensitive to climate and diseases spread by them, including arboviral diseases, have therefore long been identified as those most likely to respond to climate change. Given this threat, it is sensible to ask: as our climate changes, how will vector-borne diseases respond? Which ones will spread, and how fast? Where will they spread to? Answering such questions will help with climate change mitigation or adaptation.

Despite widespread concern about climate change, and recognition that one of its impacts could be the spread of vector-borne diseases ([I.P.C.C., 2007](#_ENREF_7)), until recently there had been relatively little effort expended on exploring what those effects might be. Indeed, only 12 years ago researchers concluded that there was a lack of strong evidence for an effect of climate change on vector-borne diseases ([Kovats et al., 2001](#_ENREF_8)).

The recent BT outbreak was first linked to climate change by demonstrating that its early emergence in southern-central Europe coincided approximately, in space and time, with the area of the continent that warmed the most between the 1990s and 2000s ([Purse et al., 2005](#_ENREF_15)). The strength of evidence was limited, however, because it did not explain the spread to northern Europe which followed; and it was only a correlation in space and time, with no mechanistic processes involved.

Stronger evidence for the role of climate change would be a mechanistic model for BT which successfully predicts the disease’s emergence when run at warmer - observed - temperatures. This rationale led us, recently to build a climate-driven model for the disease ([Guis et al., 2012](#_ENREF_4)). Our aim was a model with which we could explore how predicted changes in climate would affect the risk of BT, expressed through the epidemiological concept of the basic reproduction number or R0. The model demonstrates that many aspects of BT’s recent emergence can be explained by the effects of increased temperature in the last two decades on the risk of disease transmission. The model was also driven with future climate scenarios, leading to predictions of further increases in the risk of BT in Europe up to at least 2050. While broadly successful, this exercise led us to discover gaps in arboviral (and other disease vector) research that need to be closed to improve the accuracy of predictive models for vector-borne diseases under scenarios of climate change..

In the case of BT there is one particularly obvious gap: what are the vectors? The occurrence of the disease outside of areas where the Afrotropical species, *Culicoides imicola*, was found, first in the Balkans from 2000 ([Purse et al., 2006](#_ENREF_16)), and then in northern Europe from 2006 ([Mellor et al., 2008](#_ENREF_13)), indicated that there must be other vectors in Europe. Indigenous *obsoletus* and *pulicaris* group midges were soon implicated ([Caracappa et al., 2003](#_ENREF_2); [Meiswinkel et al., 2007](#_ENREF_11); [Mehlhorn et al., 2007](#_ENREF_10); [Balenghien, 2008](#_ENREF_1); [Dijkstra et al., 2008](#_ENREF_3)), but there is still debate about which of the different species play the most important roles. In our model we focused on *C. imicola* and the *obsoletus* group only.

Secondly, there is poor information about where these vectors occur. Prior to the European BT outbreak the only published distributions in Europe were from Spain and Portugal, as surveys were undertaken following an earlier African horse sickness (AHS) outbreak. AHS is also transmitted by *Culicoides*. Since the start of the European BT outbreak, several countries have undertaken *Culicoides* surveys, but often with different trap types or protocols. Even today the UK has not published any national distributions; and there are no Europe-wide distribution maps in existence. And yet, BT readily crosses frontiers and Europe-wide information is required for an international approach to prevention and control.

Light traps are used for *Culicoides* surveillance and we used light trap data from Spain to model vector distributions across western Europe. However, this led us to a major gap in understanding that is pervasive in vector-borne disease studies. Models of vector-borne diseases utilise the number of vectors per host (often calling this ratio *m*), but how does the number of vectors caught in a trap relate to the number per host? One approach is to use arbitrary multipliers of trap catches (such as 100x; ([Hartemink et al., 2009](#_ENREF_5))), without evidence, to estimate the number of vectors in a region, which can then be divided by the host density to estimate *m*. This causes various difficulties however: estimates of R0 then scale with the arbitrary multiplier, introducing huge subjectivity; and very high estimates of R0 arise where host density is very low or zero (in large cities, for example) and where the risk of an outbreak is, intuitively, low. In our work, we made the assumption that trap catches are estimates of *m* itself, and do not need to be multiplied and divided by host number. After all, a light trap may be a proxy for a host; and as the number of vectors that comes to a host should, by definition, be proportional to *m*, so the number that come to a trap may also be proportional to *m*. While the argument is interesting, the real point is that while we use insect traps for surveillance, we have poor understanding of what the contents of the trap mean in terms of the risk of disease transmission.

Three additional variables required for estimating R0 are the mean lifespan of vectors, their feeding interval, and the extrinsic incubation period (EIP) - the length of time between a vector taking an infected blood meal and becoming infectious. These variables combine to tell us how many times, on average, avector will feed on a suitable host in its remaining life after becoming infectious. While these variables are very important for understanding transmission risk, we have poor knowledge of them in Europe. First, there are no colonies of European indigenous *Culicoides* vectors or *C. imicola*, and so data on the EIP (which must be obtained in high containment facilities) are misappropriated from other species. Mortality rates and feeding intervals can be obtained for the correct species in the field, but remarkably little research has been undertaken on the species present in Europe.

The above discussion makes two important points regarding our understanding of the epidemiology of BT in Europe. Most of the required information (to understand the epidemiology, model disease spread or predict the effect of climate change, for example) pertains to the vectors; and much of it does not exist or is inadequate.

Similar cases can be made for many other arboviral diseases in Europe; and yet, Europe’s people and animals have never seemed at higher risk. A second *Culicoides*-transmitted viral disease of ruminants, Schmallenberg, has followed hot on the heels of BT ([Hoffmann et al., 2012](#_ENREF_6)). It is believed to have first emerged in mid-2011, it was only identified in late 2011 and by late 2012 it had spread over much of western Europe. Its full impact remains to be seen. Meanwhile, mosquito-borne viruses are affecting people: nearly 200 people were reported with Chikungunya in Italy in 2007 ([Rezza et al., 2007](#_ENREF_17)); West Nile is occurring over a large area of Europe (more than ten countries in 2012); dengue occurred in France in 2010 ([La Ruche et al., 2010](#_ENREF_9)) and there have been more than two thousand cases on the Portuguese island of Madeira since October 2012. A woman died of CCHF in Greece in 2008 ([Papa et al., 2010](#_ENREF_14)).

The recent emergence of these arboviral diseases in Europe, the predominance of vector-related variables in epidemiological models, and the paucity of vector-data in Europe, points to the need for an overhaul of arboviral research. We need significant investment in the training of a new generation of taxonomists, fluent in both morphological and molecular methods of insect identification. This field is ‘unsexy’ to many, but so important, that it should perhaps be achieved with a dedicated funding stream. We need more basic research on the biology of our vectors or potential vectors. And European researchers need to work more closely together, not just to learn from each other, but to start integrating vector surveillance efforts. We tend to share arboviruses and the vectors that spread them; we now also need to share sampling methods and the data so-obtained.

The relevant authorities should reappraise the value of restricting much arboviral research to high containment facilities. In the UK, access to highly contagious, devastating viral diseases of livestock, such as foot-and-mouth virus and rinderpest virus, are restricted to a single high-containment facility, the Pirbright Laboratory. Some decades ago virologists at Pirbright added BT and AHS to the portfolio, and restrictions designed for viruses that spread by direct contact or aerosol were applied to arboviruses that require a vector. Elsewhere in the UK, interested scientists were not permitted to work on live BT or AHS viruses, even outside of the vectors. The rationale was’ biosecurity’ but, really, the risk of BT or AHS viruses escaping from a laboratory and going on to cause an outbreak was virtually nil, unless *Culicoides* themselves were infected and released.

The end result of the restrictions was that the research-base for such diseases was, and has remained, small; and to some extent left the UK poorly prepared for BT when it arrived.

Of course, not all research gaps pertain to vectors: some relate to hosts. Important variables like host mortality and recovery rates can often be estimated from a number of laboratory studies, if not always for the right serotype of arbovirus. In the case of BT there is good information on the density of farmed ruminants in the UK (and Europe) with which to model spatial spread. However, were the UK or continental Europe to be invaded by AHS virus, which could be devastating for our horse populations as AHS has a fatality rate of up to 95%, our ability to model, explain or predict the outbreak, and test the efficacy of interventions, would be limited by the remarkable paucity of information on the distribution of equids. A database of equids in the UK, for example, began in 2008, was discontinued 4 years later, and was voluntary and therefore, probably, incomplete.

Conclusion

No one can predict what will be the next arboviral disease to enter the UK, but that does not mean we should not prepare for it. In the event of an arbovirus outbreak, be it African horse sickness, African swine fever, West Nile, dengue, Chikungunya or any one of many others, we know already what sort of information will be required to deal with it, and also to answer questions posed by ministers, media or the public. We will need to know what and where the vectors are, and how or whether the vectors can be controlled. We will need to know whether hosts, be they human or animal, can be protected from vector bites. We will need to know if and how the arbovirus can survive the vector-free period. Much of this information can be obtained inexpensively because entomology tends to come cheap, like many of its practitioners. However, the work is slow, laborious and often seasonal, and almost certainly cannot be delivered in a useful time-frame during an outbreak. With climate change seemingly being behind the emergence of BT, and other arboviral diseases emerging in Europe for this or other causes, we need a significant upturn in arboviral disease research, with a primary focus on the vectors.

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