THE ROYAL SOCIETY

Fragile transmission cycles of tick-borne encephalitis virus may be disrupted by predicted climate change

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Repeated predictions that vector-borne disease prevalence will increase with global warming are usually based on univariate models. To accommodate the full range of constraints, the present-day distribution of tick-borne encephalitis virus (TBEv) was matched statistically to current climatic variables, to provide a multivariate description of present-day areas of disease risk. This was then applied to outputs of a general circulation model that predicts how climatic variables may change in the future, and future distributions of TBEv were predicted for them. The expected summer rise in temperature and decrease in moisture appears to drive the distribution of TBEv into higher-latitude and higher-altitude regions progressively through the 2020s, 2050s and 2080s. The final toe-hold in the 2080s may be confined to a small part of Scandinavia, including new foci in southern Finland. The reason for this apparent contraction of the range of TBEv is that its transmission cycles depend on a particular pattern of tick seasonal dynamics, which may be disrupted by climate change. The observed marked increase in incidence of tick-borne encephalitis in most parts of Europe since 1993 may be due to non-biological causes, such as political and sociological changes.

Keywords: ticks; tick-borne encephalitis; global warming; climate matching; risk maps

1. INTRODUCTION

Tick-borne encephalitis (TBE), caused by two subtypes of flavivirus (TBEv) transmitted by the ticks *Ixodes ricinus* and *I. persulcatus*, is the most significant vector-borne disease in Europe and Eurasia. Central nervous system pathology causes a case morbidity rate of 10–30% and a case mortality rate of typically 1–2% but as high as 24% in the Far East (Immuno Ag 1997). Prior to 1992, infection incidence was typically 2–40% in endemic areas but since 1993 TBE cases have increased two- to 17-fold in many parts of Europe (Immuno Ag 1997; Süss & Kahl 1997; S. Dittman and W. Jilg, unpublished data) and new foci have been identified. TBE is a typical zoonosis, with enzootic cycles maintained in natural rodent–tick cycles (Labuda & Randolph 1999); humans may be infected if accidentally bitten by an infected tick or by drinking untreated milk from infected sheep or goats (which cannot themselves pass the virus to ticks) (Labuda *et al*. 1997). Increased risk to humans may therefore arise in three ways: (i) improved conditions for natural transmission cycles resulting in higher densities of infected ticks; (ii) changed human behaviour resulting in greater exposure to ticks; and (iii) changed agricultural practices resulting in a higher consumption of raw milk. As both of the first two factors are climate dependent, TBEv is included in the list of vector-borne pathogens anticipated to become more of a threat to humans in a predicted warmer world (Lindgren 1998*a*; Martens 1999).

Only in Sweden has this prediction been explicitly tested for TBEv. Lindgren *et al*. (2000) showed that the northward expansion of the geographical range of *I. ricinus* (Talleklint & Jaenson 1998) between the early 1980s and the mid-1990s was related to fewer days during

the winter with minimum temperatures below $-12\,^{\circ}$C. Further south, in areas with medium to high tick densities, further increases in tick abundance were related to a combination of milder winters (fewer days with minimum temperatures below $-7\,^{\circ}$C) and extended spring and autumn seasons (more days with minimum temperatures of 5–$8\,^{\circ}$C). Using the excellent national registration of TBE cases in Sweden since the 1950s, Lindgren (1998*b*) related the increase in TBE incidence from 1960 to 1995 in Stockholm County, a high-endemic region, to higher winter temperatures permitting a prolonged season of tick activity and hence pathogen transmission. Here the major increase occurred from 1984 onwards: 1960–1983, mean annual cases 18.6 (range 6–36); 1984–1995, mean annual cases 45.1 (range 33–74).

Events at the extreme limit of an organism's distribution, however, may not reflect future events at the core of the range. In Europe, TBEv is highly focal in its distribution, limited to a well-defined region in central Europe, where the distribution is very patchy, and a quasi-separate region covering the Baltic states and the south-eastern rim of Scandinavia, where the distribution is more continuous (figure 1). This pattern has been predicted with 85% accuracy from satellite-derived data on environmental conditions (Randolph 2000) and its biological basis is now clearly understood. The reason TBEv occurs in only a narrow subset of suitable tick habitats is because its cycles are maintained by transmission of non-systemic infections between infected nymphs and uninfected larval ticks co-feeding on small rodent hosts, principally murids (Labuda *et al*. 1993). The force of transmission is sufficiently high only when there is a high degree of coincident feeding of larval and nymphal ticks (Randolph *et al*. 1999). This depends on a particular pattern of seasonal tick-population dynamics determined by rather precise climatic conditions, specifically the

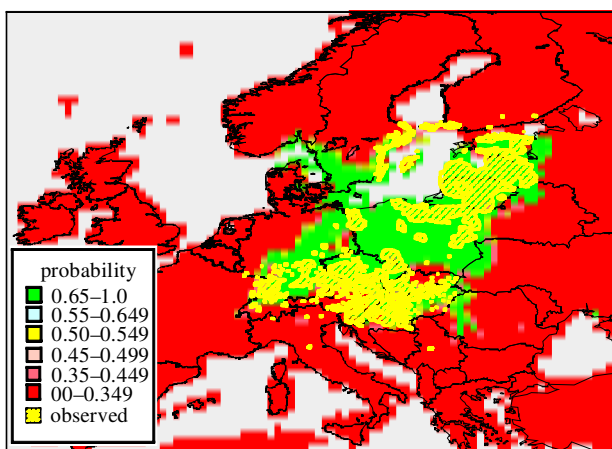[*]Author for correspondence (sarah.randolph@zoology.ox.ac.uk)

Figure 1. The present-day distribution of tick-borne encephalitis virus in Europe (yellow hatched polygons) and distribution predicted using maximum-likelihood methods based on 1960–1990 average monthly climate surfaces (red to green posterior probability scale in key). Training-set predictions (> 0.5 probability) 86% correct, 12% false positives and 2% false negatives.

seasonal land-surface temperature profile (Randolph 2000; Randolph *et al.* 2000). It must be hot enough in the summer to allow rapid tick development, especially of the eggs, but cool down rapidly in the autumn to send the emergent larvae into behavioural diapause over the winter. In this way, larvae and nymphs become active in synchrony in the spring and efficient virus transmission is achieved. At the same time, moisture availability to ticks on the ground, as measured by a remotely sensed vegetation index, must be sufficient to ensure good tick survival.

Like many vector-borne pathogen cycles that depend on the interaction of so many biotic agents with each other and with their abiotic environment, enzootic cycles of TBEv have an inherent fragility. Their continuing survival or expansion cannot be predicted from simple univariate correlations. Ideally, robust biological models are needed to capture the complexity of such systems. The quantitative biological information needed to give an accurate description of even the current situation is not yet available, however, so this approach cannot yet be used to give reliable predictions about the future. Instead, we here adopt a two-step statistical approach to matching TBEv distributions to present and future climatic conditions.

2. METHODS

This analysis is confined to Europe where western-type TBEv is transmitted by *I. ricinus*. First, the present-day distribution of TBEv (Immuno Ag 1997) is matched statistically to current climatic variables, to provide a multivariate description of present-day areas of disease risk. This understanding is then applied to outputs of a general circulation model (GCM) that predicts how climatic variables may change in the future (Johns *et al.* 1997), and future TBEv distributions are predicted for them. The approach, therefore, is essentially a 'pattern-matching' exercise, from which conclusions may also be drawn about the likely climatic sensitivity of vectors and/or diseases.

Obtaining a good fit of the present-day distributions to present-day climates is a necessary first step in this modelling exercise. The analysis randomly selected a training set of 200

points within the mapped limits of TBEv (Immuno Ag 1997) and 600 points outside, but within 8° of longitude or latitude of, the limits. Data for each point were derived from 30-year (1960–1990) average monthly climate surfaces at 0.5° longitude and latitude resolution (New *et al.* 1999) for the mean (T_M), maximum (T_X) and minimum (T_N) temperature, rainfall (R) and saturation vapour pressure (SVP) variables. These surfaces were pre-processed by temporal Fourier analysis (Rogers *et al.* 1996) of the monthly data (essentially smoothing the data), from which the mean, maximum and minimum of each variable were extracted for each training-set location. Data were first clustered using the '*k*-means cluster' option of SPSS (SPSS, Inc., IL, USA), producing three clusters each for presence (p) and absence (a) sites. Stepwise discriminant analysis (Rogers *et al.* 1996) of the resulting six clusters, using the criterion of maximizing the Mahalanobis distance between all pairs of dissimilar (i.e. p to a and a to p) clusters, chose the minimum T_N, minimum T_X, mean T_X, maximum T_M and maximum SVP as the five most important discriminating variables for describing the current western-type TBEv situation (figure 1). Only these, which are all consistent with the results of the predictive mapping based on satellite-derived data (Randolph 2000), were used to make the predictive maps of posterior probabilities (Rogers *et al.* 1996) on a scale of 0.0 (red in figure 1) to 1.0 (green).

The results of the above exercise were applied to GCM scenarios (Johns *et al.* 1997) to produce predictions for the future, i.e. the covariance matrices from the present-day climate-matching exercise were used to identify places where conditions for TBEv presence or absence will occur in the future. The future climate scenarios have been constructed for low, medium–low, medium–high and high degrees of change projected to the 2020s, 2050s and 2080s, at an original spatial resolution of 3.75° longitude and 2.5° latitude, but then spatially interpolated using cubic splines to give the same resolution as the long-term past climate data sets. GCM predictions are given as the change from the modelled present to the modelled future climate and, following standard practice, these values are added to the present observed climate averages to predict the future. For example, the 2050s 'high' scenario from the HadCM2 experiment (http://www.met-office.gov.uk/sec5/sec5pgl.html) predicts mean global land surface changes of + 3.45, + 3.63 and + 3.29 °C in mean, minimum and maximum temperatures, + 1.87 hpa for SVP and + 0.127 mm day^{-1} for precipitation by 2050. These figures take account of the greater rise in temperature over the land than over the sea, but not the differential seasonal changes: temperatures rise by more than the average in the summer, while rainfall levels drop.

3. RESULTS

The extent, although not the focalization, of the present distribution can be predicted very well (86% accuracy) from the above five climatic variables (figure 1). The major inaccuracy is the false prediction of TBEv presence through southern Poland and in south-western Sweden.

The rise in temperature and decrease in moisture in the summer predicted under the 'medium–high' scenario appears to drive the distribution of TBEv into higher-latitude and higher-altitude regions progressively through the 2020s, 2050s and 2080s (figure 2*a–c*). The Alps, however, are always too high to become a region of risk. In the 2020s, France, Switzerland, Slovenia, Hungary
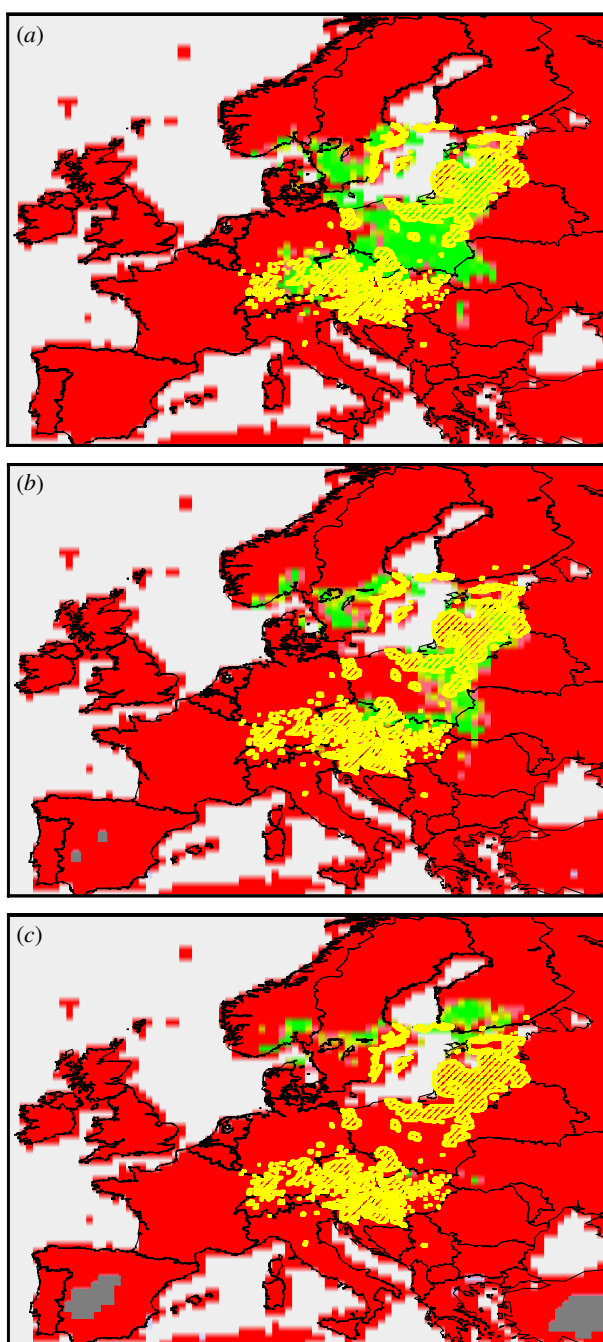
Figure 2. Predicted future distribution of tick-borne encephalitis virus based on climate surfaces derived from the HadCM2 experiment for 'medium–high' scenarios in (*a*) 2020s, (*b*) 2050s and (*c*) 2080s. The yellow overlay and the probability scale are the same as in figure 1. Grey stipple: no predictions possible.

and much of Austria are cleared of TBEv, and the range of this virus (though not necessarily its vector) has contracted to inland regions of the Baltic states. By the 2050s, TBEv has moved into areas at present free of infection, notably the mountains on the Slovak–Polish border and further north-west in Scandinavia, but central Europe is virtually cleared of TBEv. The final toe-hold in the 2080s is confined to a small part of Scandinavia, including new foci in southern Finland.

A very similar progressive pattern emerges under the increasingly extreme scenarios (not shown): from low to high degrees of change, TBEv is pushed further north-east of its present range, only moving westwards in southern Scandinavia. Only under the 'low' and 'medium–low' scenarios does TBEv remain in central and eastern Europe to any extent by the 2050s.

4. DISCUSSION

Climate matching is well able to capture the rather subtle interactions between predictor variables (many of which covary) that are often important in shaping distributions. The drawback of the pattern-matching approach is that it is essentially a statistical inference method, based on the past, and may not be a reliable guide to distributions in a climatically changed world where covariation between climate variables may be different. It is also possible that the variable selection method will identify biologically spurious variables, so it is important to select the variables submitted to the analysis on the basis of prior biological understanding. In the case of TBEv, this understanding, both qualitative and quantitative, exists (Randolph 2000; Randolph *et al*. 1999, 2000): the rate of autumnal cooling, which would be captured reasonably well by relative annual minimum and maximum temperatures, and moisture conditions on the ground, monitored as SVP, are key factors in determining the current focal distribution of TBEv. The focalization of the present distribution, however, is not predicted as well by the standard GCM variables as it is by using surrogates of a wider range of climatic variables derived from satellite imagery (Randolph 2000), resulting in the large area of false-positive predictions in southern Poland and southwest Sweden. This climate-matching approach cannot take into account the possibility of genetic change permitting the virus to use subtly different transmission routes.

The prediction that the distribution of TBEv may expand north and west of Stockholm is consistent with the conclusion that increased temperatures have already allowed the limit of *I. ricinus* to be extended both northwards and westwards in Sweden (Talleklint & Jaenson 1998; Lindgren *et al*. 2000). Elsewhere, however, fears for increased extent of risk from TBEv caused by global climate change appear to be unfounded. Rather, the precise conditions required for enzootic cycles of TBEv are predicted to be disrupted. It is impossible to distinguish between the effects of a changed seasonal temperature profile, with its impact on tick development rates and therefore seasonal activity patterns, and reduced summer rainfall, with its negative impact on tick survival rates, but the combination appears to be lethal for TBEv.

Although the predictions can only be as good as the climate scenarios upon which they are based, this analysis gives the lie to the common perception that a warmer world will necessarily be a world under greater threat from vector-borne diseases. It is true that, given the sensitivity of transmission cycles of vector-borne pathogens to environmental variables, these, rather than directly transmitted pathogens, are likely to be affected by climatic change (Rogers & Packer 1993) but in the case of TBEv that change appears to be to our advantage, while for malaria there may be very little alteration to the current situation (Rogers & Randolph 2000).

What, therefore, may have caused the widespread increase in TBE cases since 1993? This was a time of great political change in Eastern Europe. The collapse of communism resulted in de-collectivization of agriculture, with active governmental encouragement of individuals to keep flocks of sheep and goats, often grazed on roadside verges harbouring ticks, and to use their milk products. Clusters of TBE cases have been recorded in the Czech and Slovak Republics within families or villages well known for their cheese making (M. Daniel and M. Labuda, personal communication). At the same time, increased poverty arising from the collapse of centralized welfare has forced many poor people to supplement their diet with fruits gathered from tick-infested forests. Other wealthier people increasingly visit such sites for leisure. This would not account for the approximately eightfold rise in cases in the Baden-Württemberg region of south-west Germany (Roggendorf *et al*. 1997). Here, however, systematic registering of TBE cases was introduced in 1994 (Kaiser 1997), while vaccination was targeted more in Bavaria, south-east Germany, where no increase in cases has occurred (Roggendorf *et al*. 1997). It is clear that there are a variety of location-specific non-biological potential causes for the observed changes in TBE epidemiology over the past decade. It is also possible that the modest global warming to date may have increased tick–human contact, through both changes in human behaviour and prolonged seasons of tick activity, without yet disrupting the particular pattern of tick seasonal dynamics necessary for enzootic transmission cycles.

Ultimately, when we have a complete process-based model for this complex vector-borne disease system, the non-biological variables can be incorporated to predict rates of incidence of infection. Until then, the climate-matching approach presented here is the best, most inclusive, way of identifying the likely impact of multivariate climatic conditions on the potential geographical range of TBEv.

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