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The shifting landscape of tick-borne zoonoses: tick-borne encephalitis and Lyme borreliosis in Europe

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The two major vector-borne diseases of northern temperate regions, tick-borne encephalitis (TBE) and Lyme borreliosis (LB), show very different epidemiological patterns, but both have increased significantly in incidence since the 1980s. Insight into the temporal dynamics of TBE, gained from statistical analysis of spatial patterns integrated with biological explanation, suggests that the recent increases in TBE cases in Central Europe and the Baltic States may have arisen largely from changes in human behaviour that have brought more people into contact with infected ticks. Under forecast climate change scenarios, it is predicted that enzootic cycles of TBE virus may not survive along the southern edge of their present range, e.g. in Slovenia, Croatia and Hungary, where case numbers are indeed decreasing. New foci, however, are predicted and have been observed in Scandinavia. At the same time, human impact on the landscape, increasing both the habitat and wildlife hosts of ticks, has allowed tick populations to multiply significantly. This probably accounts for a genuine emergence of LB, with its high potential transmission rate, in both the USA and Europe, although the rate of emergence has been exaggerated by improved surveillance and diagnosis.

Keywords: tick-borne encephalitis; Lyme borreliosis; satellite imagery; climate change; temporal dynamics

1. INTRODUCTION

In temperate zones of the Northern Hemisphere, the overwhelming majority of vector-borne infections of humans are transmitted by ticks rather than insects. In the USA, for example, 99% of all indigenous vector-borne diseases of humans reported annually to the Centers for Disease Control and Prevention (CDC) are tick-borne (http://www.cdc.gov), principally Lyme disease (95%) plus human granulocytic ehrlichiosis (CDC 1999). In Europe, systematic records of human infections are less detailed, but the general pattern is likely to be similar and has probably been so ever since European malaria diminished since the 19th century (Reiter 2000). Yet only over the past one or two decades has the profile of tick-borne zoonoses been raised, largely because of the recognition of the spirochaetes *Borrelia burgdorferi s.l.* as the causative agent of Lyme disease (more correctly Lyme borreliosis). This has given the impression of an 'emergent' problem. The themes of this paper are to establish the extent of any real recent increases in case numbers of tick-borne diseases, and to distinguish between biological and non-biological causes for such increases.

As specific examples, I shall focus on Lyme borreliosis (LB) spirochaetes and tick-borne encephalitis virus (TBEV) because they are most prevalent and widespread. Furthermore, although they are transmitted by the same tick species (*Ixodes ricinus*) and share some of the same reservoir hosts (small rodents), they show very different epidemiological patterns. Explanations for each pattern must therefore be biologically consistent and will be mutually informative. Whereas LB spirochaetes circulate more or less wherever there are competent tick species, TBEV is restricted to distinct foci within Central Europe and the Baltic States, including the south-eastern rim of Scandinavia (Immuno 1997, and see below). In Russia, however, LB and TBE both occur throughout the range of the vector tick species, *I. ricinus* and *Ixodes persulcatus* from the eastern Baltic States to the Ural mountains, and *I. persulcatus* alone eastwards to the Pacific coast (Korenberg 1994). With some exceptions in far east Russia, the infection prevalence of TBEV in unfed, host-questing ticks—typically 0.1–5%—is much lower than that of LB spirochaetes—typically 5–25%. These epidemiological patterns suggest that TBEV circulates within a narrower window of opportunity, with a lower force of infection. Indeed, relative indices of the basic reproduction number, R_0, are an order of magnitude lower for TBEV than for LB spirochaetes (Randolph *et al.* 1996), largely because of the shorter duration of host infectivity to ticks for the virus (a few days) than for the spirochaetes (several months).

Before we can identify the causes of any change in incidence of these two diseases, we must first understand the fundamental determinants of the distribution and risk of infection. For all vector-borne diseases, risk of infection depends on the degree of contact between humans and infected vectors determined by both biological and non-biological factors. Principal amongst the former are the distribution and abundance of vectors. Also, because a tick that acquires an infection at one meal can only transmit it when it feeds as the next stage, after a long period of development off the host, the geographically

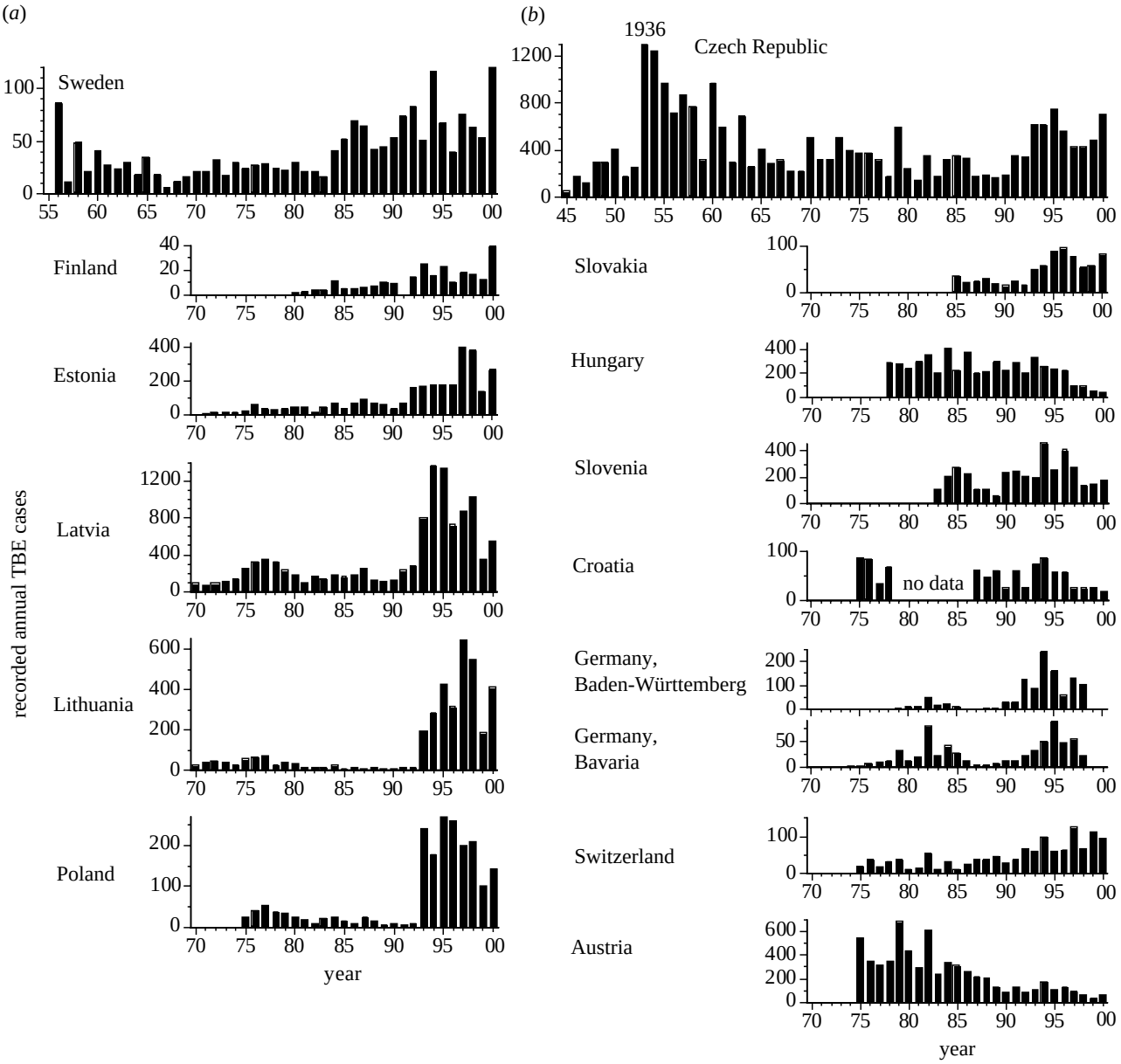

Figure 1. The recorded annual number of cases of tick-borne encephalitis in: (*a*) Scandinavia and the Baltic states; and (*b*) Central Europe (International Scientific Workgroup on Tick-Borne Encephalitis 2000*a*; Holmgren & Forsgren 1990).

variable seasonal population dynamics and natural host relationships of ticks are additional critical risk factors (Randolph 1998). Superimposed on this biology are activities of work and play that take humans into tick habitats, and variable preventive efforts such as avoidance or vaccination. Apart from vaccination, these risk factors appear to be very similar for both infections, but explanations for the contrasting epidemiology of TBE and LB can nevertheless be found from analysis of two factors in relation to the pathogen-specific transmission routes, namely tick seasonal dynamics and relationships with competent vertebrate host species. Any variation in surveillance and diagnosis, however, could give a misleading impression of comparable incidence.

2. THE 'EMERGENCE' OF TICK-BORNE DISEASES IN EUROPE

TBE and LB also differ in their history. Since the 1930s, TBEV has been known in Europe as a tick-borne infection that causes potentially fatal pathology of the central nervous system (case mortality rate typically 1–2%, but up to 24% in parts of Russia; Immuno 1997). Consequently it has a long history of careful reportage going back to 1945 in the Czech Republic, 1956 in Sweden and the 1970s in other affected European countries (International Scientific Workgroup on Tick-Borne Encephalitis 2000*a*). A common trend is a significant rise in the recorded incidence of TBE during the 1990s (figure 1), but there is considerable geographical variation in the occurrence, extent and timing of this increase. It has been especially marked in the Baltic region (figure 1*a*), usually starting in 1992 or 1993, but as early as 1984 in Sweden. Within Central Europe (figure 1*b*), increases in the Czech Republic, Slovakia, Germany and Switzerland from 1992–1994 were not matched in Hungary, Slovenia and Croatia, whilst in Austria the downward trend since the early 1980s (due to vaccination—see below) tended to flatten out through the 1990s. In the Czech Republic, TBE incidence was typically

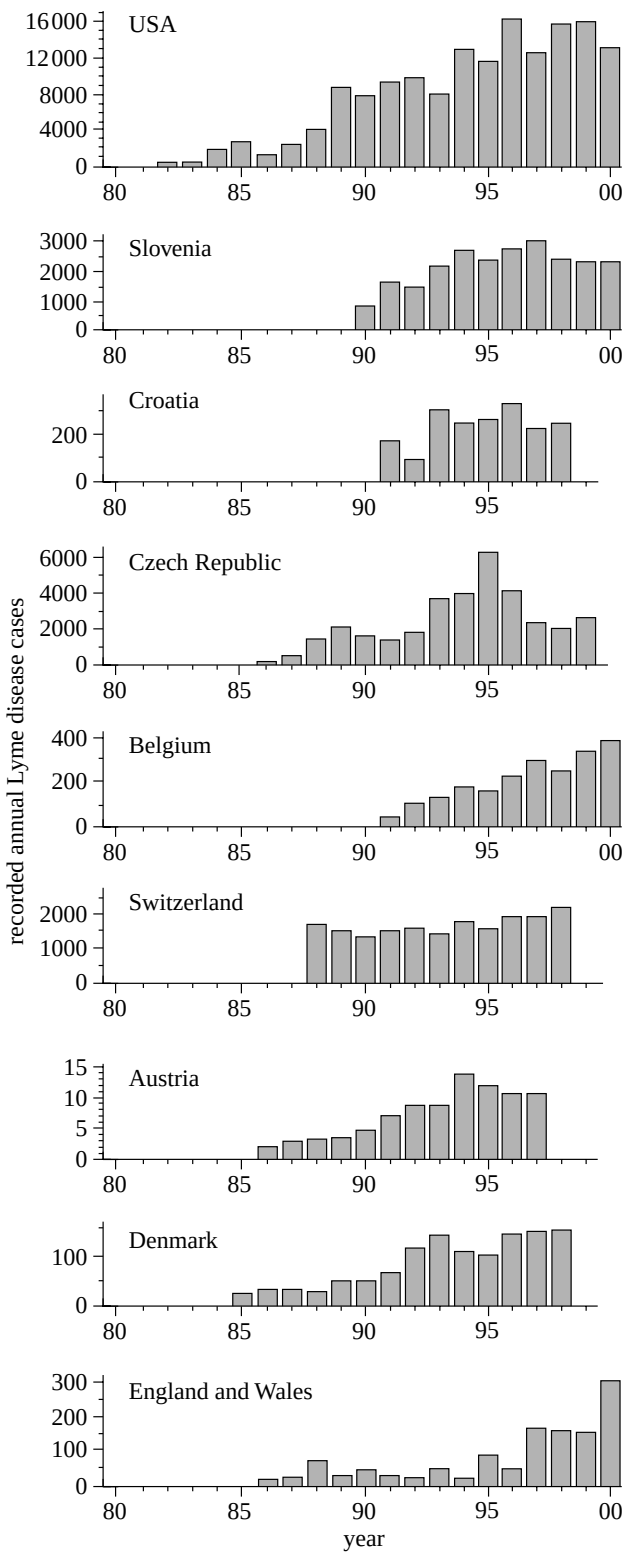

Figure 2. The recorded annual numbers of cases of Lyme borreliosis in the USA (http://www.geocities.com/hotsprings/oasis/6455/international-links.html; http://wonder.cdc.gov/mmwr; Gern & Falco 2000); Slovenia (Stantic-Pavlinic 1996; Strle 1999); Croatia (Borcic *et al*. 1999); Czech Republic (Danielova & Benes 1997; M. Daniel, personal communication); Belgium (http://www.ihe.be/epidemio/epien/index000.htm); Switzerland (http://www.admin.ch/bag/infreporting/index.htm); England and Wales (Subak 1999; R. Smith, personal communication); mean numbers of cases treated per year per practitioner in Austria (Stanek & Kahl 1999); annual cases of neuroborreliosis in Denmark (Jensen & Frandsen 2000).

much higher during the decade 1953–1963 than in the 1990s, which warns us against assuming that all the observed increases in incidence during the 1990s are novel emergences.

In contrast, the aetiology of LB has been known only for the past two decades. Although clinical manifestations, infectivity and treatment of symptoms associated with tick bites were described repeatedly by European clinicians from 1883 to 1955, not until 1977 onwards was Lyme disease named, ticks incriminated as vectors and the causative agents identified, first in the USA and soon afterwards in Europe (reviewed in Gern & Falco 2000). It is now recognized in large parts of the Northern Hemisphere from California to Japan. Not surprisingly, since then the annual recorded case numbers have increased dramatically in all affected countries (figure 2). In the USA, the rate of increase has slowed markedly, from a doubling time of *ca*. 1.5 years in the early 1980s to *ca*. 4.5 years from 1990, and a mean increase of only 1.13 times since 1994. Within Europe, only Slovenia, Croatia, the Czech Republic and Belgium introduced systematic reporting during the late 1980s, with less reliable voluntary reporting in Switzerland, Austria and England and Wales. In Denmark, mandatory reporting since 1984 of only neuroborreliosis (diagnosis confirmed by the Statens Serum Institut) gives a relative index of total LB in the country. Most European countries show a pattern similar to the USA, but in the Czech Republic case numbers have decreased since 1995. Only in UK was there very little increase until 1997. Reasons for these patterns will be discussed below, but it seems intuitively likely that the increase in recorded cases of LB worldwide since the 1980s is at least partially due to raised awareness and better diagnosis.

There is not yet sufficient quantitative biological information on the interacting components of these complex disease systems to allow a process-based analysis of the above changing infection incidence through time, but explanations may be derived from statistical analyses of spatial patterns. If we can identify the environmental determinants, both abiotic and biotic, of the spatial variation in infection risk, we should be able to predict the likely occurrence of foci in uncharted areas and in the future, and, by inference, explain events of the recent past.

3. TICK-BORNE ENCEPHALITIS

(a) *Explanations for observed distribution*

Recent analyses indicate that spatial patterns of TBEV are determined by temporal dynamics on a seasonal scale, offering insight into temporal patterns on a longer timescale. It appears from laboratory experiments (Labuda *et al.* 1993, 1996), from theoretical considerations (Randolph *et al.* 1996), and from analysis of field data (Randolph *et al.* 1999) that enzootic circulation of TBEV depends on amplification of non-systemic infections between infected nymphs and large numbers of infectible larvae co-feeding on rodents. Even though the transmission of non-systemic infections has not been shown definitively to operate in the wild, co-feeding of larvae and nymphs is essential even for the systemic transmission route because viraemia persists in rodents for only around

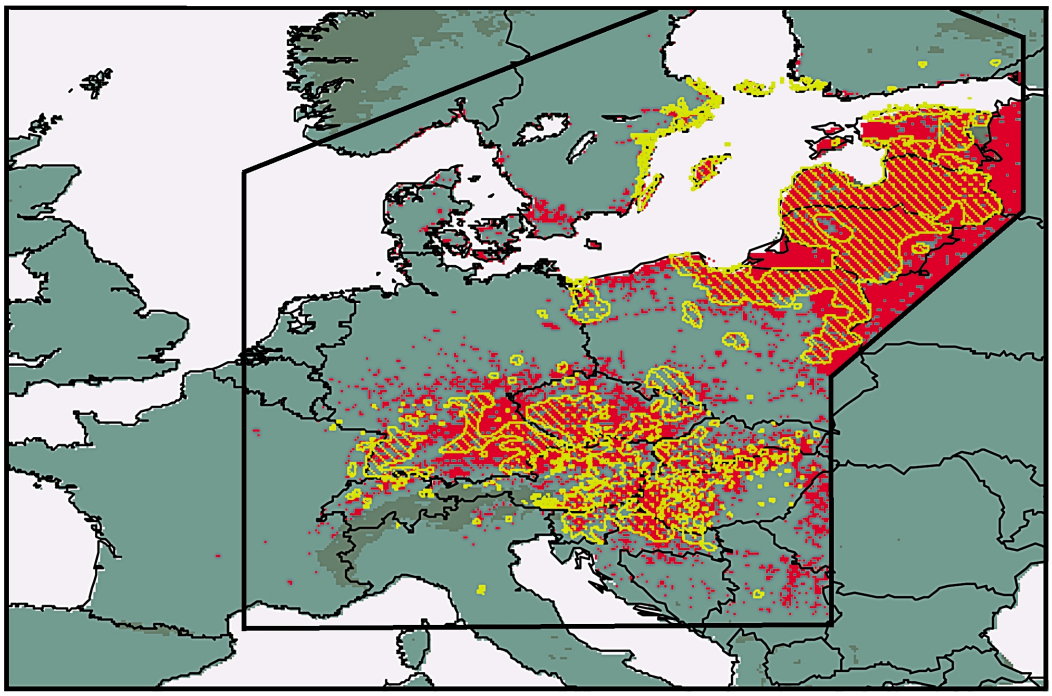

Figure 3. Predicted (red) and observed (yellow hatched) European distribution of tick-borne encephalitis virus (TBEV), based on analysis of remotely sensed environmental variables and elevation within the outlined area. TBEV occurs extensively to the east of this area, in Russia, Belarus, Ukraine and Romania (Immuno 1997), but is not yet mapped in any detail. High mountain areas (darker green), where satellite data are less reliable due to more frequent cloud contamination, were excluded from the analysis. (From Randolph 2000, with permission from Academic Press.)

two days (Kozuch *et al.* 1981). Consistent with this, available data on the feeding seasons of nymphal and larval *I. ricinus* ticks support the prediction that enzootic cycles of TBEV occur only where infectible larvae are active as soon as infected nymphs are feeding. Of 15 sites in France, Switzerland, Austria, Germany, Slovakia, Latvia and Sweden, at those within TBEV foci larvae and nymphs show synchronous feeding periods in the spring/summer, whereas outside foci larvae appear later in the year than nymphs (Randolph *et al.* 2000). Ideally, therefore, places at risk of TBE should be identifiable using a population model to predict the geographically variable tick seasonal dynamics depending on local climatic conditions. Until we have such a model, predictive risk maps must rest on identifying statistical correlations between the spatial patterns of TBEV distribution and of environmental conditions.

For this purpose, multi-temporal information on a variety of environmental conditions at continental scales can be derived from signals from the Advanced Very High Resolution Radiometer (AVHRR) on board the polar-orbiting environmental satellites of the National Oceanic and Atmospheric Administration (NOAA). These signals are processed by temporal Fourier analysis (Rogers *et al.* 1996) to capture summary statistics (mean, amplitude and phase of annual, biannual and triannual cycles) that define the mean seasonal characteristics of each environmental factor, such as temperature, ground-level moisture conditions and rainfall. In this particular case (Randolph 2000), the mapped European foci of TBEV (Immuno 1997) were analysed by logistic regression, using as predictor variables the layers of Fourier-processed 8 km × 8 km resolution imagery from the NASA Pathfinder program (James & Kalluri 1994) and a digital elevation map. The resultant predictive map of TBE risk corresponds closely with the recorded foci, both visually (figure 3) and statistically (82 and 90% correct in Central Europe and the Baltic region, respectively). It captures the overall boundaries of the limited extent of TBEV within the two regions and much of the heterogeneity within Central Europe. Encouragingly, many of the apparently false predictions of TBEV-presence coincide with regions where TBE is known but is currently inadequately mapped, e.g. in the Carpathian foothills in Romania (G. Nicolescu, personal communication), and where new or reactivated infection foci have been recorded over the past two years, e.g. in the far southeast of the Czech Republic and along the Slovak–Hungarian border (M. Labuda, personal communication), in Germany between and north of the major foci (Immuno 1997), on Bornholm Island in the Baltic Sea and at scattered sites in southern Sweden (International Scientific Workgroup on Tick-Borne Encephalitis, 2000*b*).

The particular satellite variables identified (by stepwise inclusion in the logistic regression) as the most significant predictors highlight the biological processes underlying these spatial patterns. The Normalized Difference Vegetation Index (NDVI), an indicator of vegetation type and consequent moisture conditions on the ground, is an important predictor of suitable habitat for *I. ricinus* (Estrada-Peña 1999). This is typically deciduous woodland (Daniel *et al.* 1998) (and the high moorlands of UK), where the ground layer provides the high humidity necessary for the tick's long-term survival and active host-seeking activity. High NDVI is a necessary, but not always sufficient, condition. The second satellite signal, Land Surface Temperature (LST), is more specific. It determines the very existence of the co-feeding transmission route for

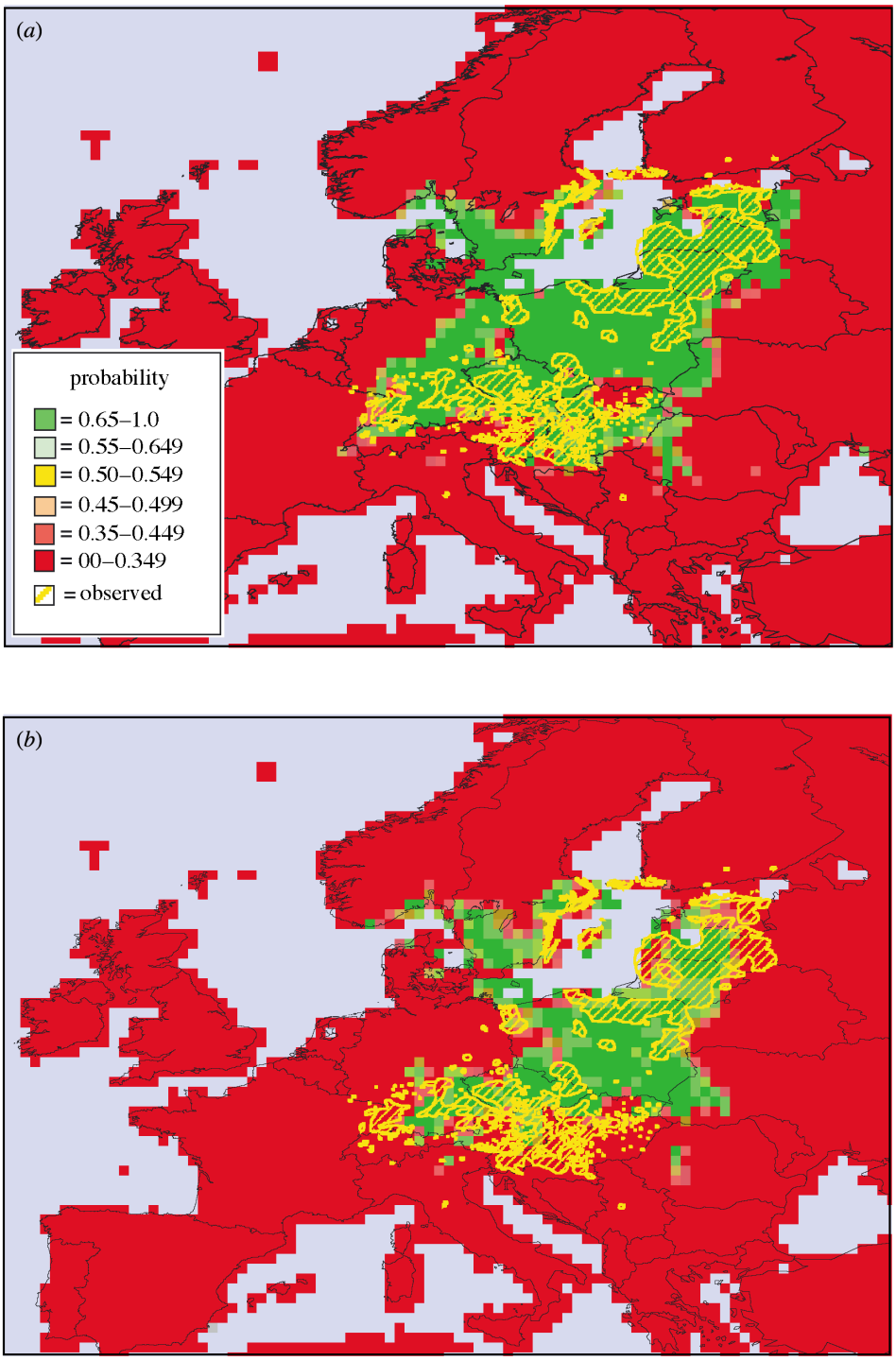

Figure 4. The present-day distribution of tick-borne encephalitis virus in Europe (yellow hatched polygons) with (*a*) present distribution predicted using maximum-likelihood methods based on 1960–1990 average monthly climate surfaces; and (*b*) predicted future distribution based on climate surfaces derived from the Hadley Centre for Climate Prediction and Research (HadCM2) experiment for medium–high scenarios in the 2020s. Red–green posterior probability of TBE presence shown in key. (Redrawn from Randolph & Rogers 2000.)

TBEV because it determines the seasonal population dynamics of *I. ricinus*. The critical feature appears to be the rate at which mean monthly LST cools during the autumn from August to October (Randolph *et al.* 2000). A principal component analysis of approximately 2000 pixels on a grid within the area of analysis (see figure 3) confirmed that TBEV foci are characterized by a higher than average rate of autumnal cooling relative to the midsummer peak LST (Randolph *et al.* 2000, fig. 6). This form of seasonal LST profile also coincides consistently with larval–nymphal synchrony within TBEV foci where appropriate tick data exist. A generic population model for *I. ricinus* will allow the causal link between seasonal LST and tick population dynamics to be explored on a continental basis.

At present it is proposed that rapid autumnal cooling inhibits host-seeking activity of larvae that emerge from eggs laid during the summer, until they are reactivated, together with the nymphs, by rapidly rising temperatures in the spring. Under other temperature regimes, variable combinations of developmental diapause (Belozerov 1982) and temperature-dependent development rates and questing activity evidently result in a delay in larval activity, throwing larvae and nymphs out of synchrony. In Eurasia, where the range of TBEV corresponds closely with that of its tick vectors, the more extreme continental climate may impose a more uniform pattern of seasonal dynamics on ticks that is universally appropriate for TBEV transmission. This remains to be examined.

The conclusion, therefore, is that TBEV is limited by multivariate abiotic factors that drive the population biology of the vector ticks, which can be identified from satellite imagery. There are sufficiently clear links between the critical satellite signals and the biological processes involved in TBEV transmission to provide a firm causal basis for the predictive continental-scale risk map shown in figure 3.

(b) *Predicted impact of forecast climate change*

The above explanation for the spatial pattern of TBEV paves the way for exploring temporal changes in the risk of infection, particularly in the light of climate change that is supposedly already under way (Jenkins *et al.* 1999) and repeatedly invoked as a cause of changing vector-borne disease incidence (Martens 1999). In the absence of a full biological model, geographically coherent conclusions are best produced using a statistical analysis, as described above but using climate surfaces rather than satellite imagery as predictor variables (Randolph & Rogers 2000). First the present-day distribution of TBEV was matched to current climatic variables to establish the multivariate climatic predictors of present-day areas of disease risk. These same variables were then applied to outputs of a General Circulation Model (GCM) that predicts how climatic variables may change in the future (Johns *et al.* 1997). Future TBEV distributions were predicted by identifying places where conditions for TBEV presence or absence will occur in the future. Climate data for these analyses are much cruder than satellite-derived data, both in the range of biologically relevant variables available and in the spatial resolution of the interpolated surfaces (for details see Randolph & Rogers 2000). It nevertheless proved possible to capture the extent, if not the focalization, of the present distribution with 86% accuracy (figure 4*a*) on the basis of five temperature and vapour pressure variables.

The warmer, drier summers forecast under the Hadley Centre for Climate Prediction and Research 'medium–high' scenario (HadCM2) (Johns *et al.* 1997; http://www.met-office.gov.uk/research/hadleycentre/models/HadCM2.html) appear to drive the distribution of TBEV into higher latitude and higher altitude regions progressively through the 2020s, 2050s and 2080s. In the 2020s (figure 4*b*), France, Switzerland, Croatia, Slovenia, Hungary and much of Austria appear to be cleared of TBEV, and the range of this virus (though not necessarily its vector) appears to contract to inland regions of the Baltic states. By the 2050s, TBEV is predicted to move into areas at present free of infection, notably the mountains on the Slovak–Polish border and further northwest 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 (Randolph & Rogers 2000). A similar progressive pattern emerges under the increasingly extreme HadCM2 scenarios; TBEV only remains in Central and Eastern Europe to any extent by the 2050s under the low and medium–low scenarios.

These conclusions, although apparently extreme, are consistent with the inherent fragility of enzootic cycles of TBEV. Climate change may disrupt the rather precise seasonal temperature profile upon which the sustained transmission of TBEV appears to depend. Are they reconcilable with the observed widespread increases in TBE cases during the 1990s?

(c) *Explanations for recent changes in TBE incidence*

Many of the recorded changes in TBE incidence are indeed consistent with the predictions of shifting distributions driven by climate change, although this does not, of course, mean that any climate change to date is the sole cause of change. For example, Croatia, Slovenia and Hungary, where very little change or even a decrease has been recorded (figure 1*b*), are countries at the southern edge of the current distribution that are predicted to lose their foci by the 2020s (figure 4*b*).

At the other latitudinal extreme, the prediction that the distribution of TBEV may expand north and west of Stockholm is consistent with recent appearances of new foci in southwest Sweden (International Scientific Workgroup on Tick-Borne Encephalitis 2000*b*), and with conclusions from local time-series analyses. The northward expansion of the geographical range of *I. ricinus* in Sweden (Talleklint & Jaenson 1998) between the early 1980s and mid 1990s, and increases in tick abundance further south, has been related to milder winters and extended spring and autumn seasons (Lindgren *et al.* 2000). Furthermore, Lindgren (1998) related increased TBE incidence since 1984 in Stockholm County, a region of high endemicity, to higher winter temperatures that permitted a prolonged season of tick activity and hence pathogen transmission. This interpretation would be strengthened by a match between warmer winters and the high incidences in 1956, 1958 and 1960. These purely climatological effects may have been compounded by a marked increase since 1982 in roe deer, the most significant host for adult ticks, due to reduced predation caused by an outbreak of scabies amongst red foxes (Lindgren 1998).

This Swedish analysis provides an example of the general conclusion that the dynamics of any organism at the edge of its range is likely to be determined by a single limiting variable, while at the core of its range an organism is more often subject to multivariate constraints (Rogers & Randolph 1993, 2000; and see above for TBEV). Furthermore, the timing and degree of the recent increases in TBE incidence within well-established foci in Europe (which are indeed predicted to persist over the next two decades) argues against their being explicable by a single climatic factor. They occurred very suddenly, but asynchronously, mostly between 1992 and 1994

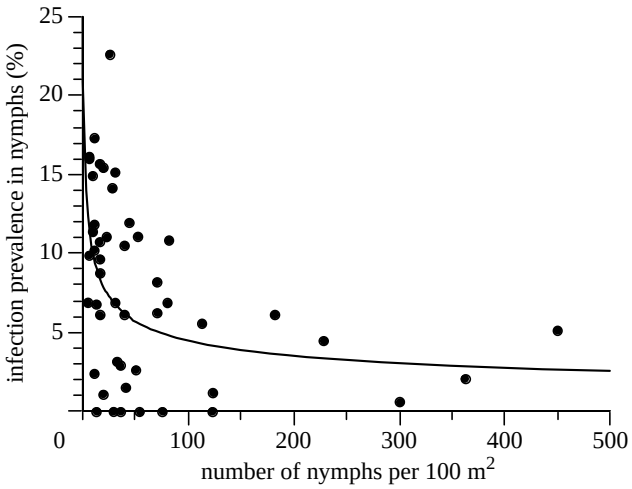

Figure 5. The relationship between the infection prevalence of *Borrelia burgdorferi s.l.* in nymphal *Ixodes ricinus* ticks and the density of unfed nymphal ticks sampled from the vegetation at 48 sites in 16 European countries. $Y = 22.936X^{-0.355}$, $R^2 = 0.24$, $p < 0.001$. (Data from Gray *et al.* 1998.)

(figure 1), indicating that regional climate is not the simple cause. Most striking is the contrast between Finland, with its gradual increase in TBE since 1984 similar to Sweden, and the neighbouring Baltic States, with a 2.4–30-fold increase in 1992 (Estonia) or 1993 (Latvia, Lithuania and Poland). Moreover, in the Czech Republic there was an even more marked increase in 1953 than in 1993, with high case numbers persisting until the early 1960s. All these features suggest that a variety of location-specific non-biological factors may have played a significant role.

The 1990s was a time of great political change in Eastern Europe. The collapse of communism resulted in de-collectivization of agriculture, followed by an increase in individually owned flocks of sheep and goats, often grazed on roadside verges harbouring ticks. TBEV can be passed to humans in the milk of infected animals and clusters of TBE cases have been recorded in the Czech and Slovak Republics within families or villages well known for their cheese making (M. Labuda, personal communication). The increased availability of livestock hosts for adult ticks, leading to higher tick densities in sites accessible to humans, would have added to the transmission potential. 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. Wealthier people increasingly visit such sites for leisure. In effect, a higher percentage of the population is joining the recognized high risk groups, which include agricultural and forestry workers, collectors of mushrooms and berries, and hikers and ramblers (Immuno 1997).

Elsewhere, activities within the medical profession may be responsible for changing numbers of reported TBE cases. In Germany, the disease has been registered by optional questionnaire since 1974, but during the 1990s doctors were questioned more intensively, which is thought to account for the marked increase in cases in the Baden–Württemberg region of southwest Germany (Kaiser 1997; Roggendorf *et al.* 1997). In Bavaria (south-east Germany), there were twice as many reported cases as in Baden–Württemberg before 1990, but a lesser increase in the 1990s, possibly due to a more active vaccination programme there (Roggendorf *et al.* 1997). From 1994, more cases of TBE were reported from the minor foci in other German states, supposedly due to 'reactivation' of old foci, but coincident with special surveys (Fielder *et al.* 1999) and new molecular diagnostic techniques (Süss & Dorn 1997). What is clear, however, is that even these small foci have persisted at fluctuating levels for long periods of time. Only in Austria has there been a marked decline in TBE incidence (figure 1*b*), ascribed to a very thorough vaccination programme targeted particularly at school children (Kunz 1996). As a result, the mean age of infection has shifted from the bimodal pattern typical of the 1970s, with peaks at 7–14 and 21–50 years, to a broad but lower peak at 31–60 years since 1986 (Immuno 1997).

4. LYME BORRELIOSIS

(a) *Spatial variation in risk of infection*

In contrast to TBEV, natural cycles of LB spirochaetes are robust and maintained under a wide variety of conditions, but there is still marked spatial variation in risk across Europe. In the USA, risk of human infection has been related most closely to the density of infected host-questing nymphal ticks (Glass *et al.* 1995; Nicholson & Mather 1996; Dister *et al.* 1997), a product of both tick population density and infection prevalence in unfed nymphs. Across Europe, this latter factor varies from 0 to *ca.* 25% (Gray *et al.* 1998), and is not easily predicted from the density of ticks (figure 5). Within LB foci, over the usual range of tick density (4–100 nymphs 100 m^{-2}) infection prevalence is not significantly related to tick density. Only where tick density is unusually high (100–450 nymphs 100 m^{-2}) is infection prevalence consistently low, varying between 0.6 and 6.1%.

Infection prevalence depends more on the interaction of a genetically diverse array of *B. burgdorferi s.l.* with an even more diverse array of vertebrate host species, both mammalian and avian, operating against a generally permissive abiotic background. Many of the major host species for *I. ricinus* contribute to transmission of spirochaetes, but they do so in different, complementary ways because they feed different fractions of the tick population and they are differentially competent to transmit the different genospecies of *B. burgdorferi s.l.* to ticks (Kurtenbach *et al.* 1998*a*). The known reservoir status of the host species as revealed by xenodiagnosis is mirrored by the species-specific lethality of the host's serum for spirochaetes, mediated via the alternative complement system (Kurtenbach *et al.* 1998*b*). Thus in Western Europe, rodents transmit only *B. afzelii* and *B. burgdorferi s.s.* (Hu *et al.* 1997; Humair & Gern 1998; Humair *et al.* 1995; Kurtenbach *et al.* 1998*a*), while birds transmit *B. garinii* and *B. valaisiana* (Humair *et al.* 1998; Kurtenbach *et al.* 1998*a*). Deer appear to be non-competent for all genospecies (Jaenson & Talleklint 1992; Telford *et al.* 1988) and sheep only support transmission of non-systemic infections (Ogden *et al.* 1997). These interactions determine the infection pattern in tick populations and therefore the risk of infection to humans. Typical of

many European woodlands, where immature ticks feed mostly on mammals but also on birds, 10–25% of unfed nymphs are infected with a mixture of all the above genospecies (Humair & Gern 1998). In parts of England, however, locally abundant pheasants feed such a large proportion of the nymphal population that *B. afzelii* evidently cannot persist (Kurtenbach *et al.* 1998*a*). Because relatively few larvae feed on these birds, most amplification occurs in nymphs feeding on pheasants, yielding a high (16%) mixed infection prevalence of *B. garinii* and *B. valaisiana* only in unfed adult ticks (Kurtenbach *et al.* 1998*a*).

Despite the importance of these biotic interactions in explaining the diversity of LB transmission systems, in foci across Europe the density of infected nymphs depends much more on the density of all nymphs ($R^2 = 0.585$) than on the infection prevalence in nymphs ($R^2 = 0.002$) (derived from figure 5). A similar pattern is seen within Sweden (Talleklint & Jaenson 1996*a*) and Denmark (Jensen 2000). This diminishes any zooprophylactic effect of the presence of non-competent vertebrate species (Matuschka *et al.* 1992, 2000); any host species that feeds enough ticks to reduce the overall infection prevalence in nymphs by diverting them away from transmission-competent host species would be likely to increase the tick population density by improving the chances of successful tick feeding (Pichon *et al.* 1999). Unless the endpoint of $R_0 < 1$ were achieved, thereby eliminating infection, the increased density of nymphs would more than compensate for the reduced infection prevalence. In the English woodlands referred to above, for example, despite the low infection prevalence in nymphs (2.1%), the exceptionally high tick density (on average 362 nymphs $100\,m^{-2}$ through spring and summer), ascribed to the large local deer population, still posed a significant risk of infection with *B. garinii* (7.6 infected nymphs $100\,m^{-2}$ compared with a mean of 2.5 ± 0.74 for the 35 European foci with less than 100 nymphs $100\,m^{-2}$). *B. afzelii*, however, was indeed eliminated by the presence of so many pheasants, non-competent for this genospecies.

(b) *Lessons from the USA*

In common with most insect-borne infections, therefore, in any one place within any one zoonotic system, an increase in vector tick density is likely to lead to an increase in risk of human infection. As confirmed by landscape epidemiological studies in the USA, the incidence of LB is high in areas of high tick densities (Maupin *et al.* 1991; Glass *et al.* 1995; Nicholson & Mather 1996; Dister *et al.* 1997; Kitron & Kazmierczak 1997). Many suitable tick habitats now coincide with human habitation, especially in the northeastern states where residential properties have invaded broad-leaf woodlands, ensuring high contact rates, and consequent spirochaete transmission, between ticks and humans. The necessary wildlife hosts are abundant in the same habitats (Dister *et al.* 1997): deer to support tick populations (Wilson *et al.* 1985), and mice and birds as competent reservoirs (Fish 1995) for the common pathogenic genospecies, *B. burgdorferi s.s.*, found in the USA (Postic *et al.* 1994).

Deer, principally the white-tailed deer (*Odocoileus virginianus*), are generally recognized as an essential host for adult *I. scapularis* ticks in the eastern USA (Spielman *et al.* 1985; Lane *et al.* 1991), accounting for the positive relationship between deer abundance and nymphal tick density (Wilson *et al.* 1985, 1988; Daniels & Fish 1995; Falco *et al.* 1995). There is compelling evidence (reviewed by Spielman *et al.* 1985; Fish *et al.* 1992; Barbour & Fish 1993) that deforestation and the elimination of deer during the 18th and 19th centuries destroyed pre-existing conditions suitable for *I. scapularis* populations and enzootic cycles of *B. burgdorferi*. These conditions were subsequently re-established from 1926 onwards, first with reforestation, then with reintroduction and proliferation of deer, and finally with the spread of ticks from their refuges on certain undisturbed islands. Spielman *et al.* (1985) suggest that *I. muris*, a tick that feeds predominantly on rodents, served as a vector for *B. burgdorferi s.s.*, maintaining cycles not involving humans until *I. scapularis* returned. Hoogstraal (1981) recounts a similar explanation for new epidemics of Kyasanur Fever Disease in India, precipitated by a markedly increased human population during the 1950s: cattle newly introduced into forests, although not hosts for the virus, supported increased populations of ticks that infected humans as they gathered firewood. If these scenarios are correct, both deer and cattle were having exactly the opposite effect to zooprophylaxis, despite their inability to transmit the respective pathogens.

It is therefore impossible to disentangle (human-induced) biological from non-biological causes for the 'emergence' of LB, largely because both sorts of factors changed together. Was the recognition of this tick-borne zoonosis in Lyme, Connecticut at the end of the 1970s a chance event, or did it depend on the re-establishment of a certain level of *B. burgdorferi s.s.* transmission some time after the necessary biotic agents were all in place (Fish *et al.* 1992)? To what extent was the rapid increase in case numbers during the 1980s (figure 2) the product of continuing colonization by, and increasing abundance of, a tick species that bridges the gap between wildlife and humans, or of increased awareness, surveillance and improved diagnosis (Barbour & Fish 1993)? Does the asymptotic pattern of recent years reflect a brake on these processes, either biological or non-biological or both? With increased awareness, are people taking more care to avoid the risk? These questions are currently unanswered.

(c) *Parallels in Europe?*

The same sorts of habitat and wildlife changes have occurred on a more modest scale in Europe. One of the best documented examples comes from Denmark, where roe deer (*Capreolus capreolus*) densities and the incidence of neuroborreliosis are correlated both temporally and spatially (Jensen & Frandsen 2000; Jensen *et al.* 2000). Between 1984 and 1994 deer abundance increased markedly from 31 to 77 per 1000 hectares, and more modestly to 86 per 1000 hectares in 1997, while neuroborreliosis cases increased from 24 in 1985 to 141 in 1993, reaching 150 in 1998 (figure 2). A causal relationship is suggested by the positive correlations between indices of nymphal tick abundance in May–June 1996 and deer kills in the same year (together with soil moisture content) from 35 sites across Denmark ($R^2 = 0.66$) (Jensen *et al.* 2000), and between mean deer density and neuroborreliosis incidence

($R^2 = 0.723$) during 1993–1995 in each of 12 counties of Denmark (Jensen & Frandsen 2000). Jensen (2000) extrapolates back to the start of the 20th century: based on the roe deer population then (14% of the current level), the lesser extent of forests, and a detection rate estimated to have improved from 42% in 1984 to more than 90% since 1993, he suggests an annual incidence of less than five cases of neuroborreliosis 100 years ago. The conclusion is that LB is not a new zoonosis, but a combination of habitat and wildlife management has exacerbated the risk of infection, and did so especially during the latter part of the 20th century.

The effect of fallow deer (*Dama dama*) on *I. ricinus* abundance has also been documented in Ireland, where tick densities were significantly higher inside than outside a fenced deer park (Gray *et al.* 1992). Within lowland Britain, numbers of fallow deer have increased over the past decades, while roe deer, the most widespread species in Europe (Mitchell-Jones *et al.* 1999), have increased in both abundance and distribution (Putman & Moore 1999) due largely to a policy of encouraging agricultural set-aside and planting of broad-leaved woodlands. Within Central Europe, roe deer densities are typically 10–20 per 100 hectares in favourable habitats, but can be even higher in suburban environments (Mitchell-Jones *et al.* 1999). Other habitat changes have facilitated the expansion of *I. ricinus* populations, notably a decrease in the maintenance of heather (*Calluna* spp.) moorlands in upland Britain, allowing invasion by bracken, *Molinia* grass and birch scrub. The build-up of permanently moist mat layers of vegetation turns such moorlands into highly suitable habitats for ticks, where sheep, mountain hares, red deer and colonizing roe deer are hosts for all tick stages, including the reproducing adults (Anonymous 2000). Sheep can maintain enzootic cycles of LB spirochaetes in the virtual absence of other vertebrate hosts (Ogden *et al.* 1997).

Given that the impact of these factors on the potential transmission of LB spirochaetes in the UK will have built up gradually, does the delayed but large increase in LB incidence in 1997/98 in England and Wales indicate a difference in biological or non-biological factors compared with the rest of Europe (figure 2)? As recognition of the disease remained low in UK until the late 1990s (Gray *et al.* 1999), the sudden jump in incidence almost certainly represents a surveillance artefact arising from greater awareness through information increasingly available on the Internet (e.g. http://www.dis.strath.ac.uk/vie/LymeEU/index.htm). There followed greater access to diagnostic facilities, more sensitive diagnostic methods, and more complete reporting to the Communicable Disease Surveillance Centre in the UK (Smith *et al.* 2000). In addition, the real rate of infection may have been raised by the recent influx of British holiday-makers into parks carved out of mature woodlands, where their activities are likely to bring them into close contact with questing ticks.

5. CONCLUSIONS: PARALLELS BETWEEN TBE AND LYME BORRELIOSIS

Real changes in the natural dynamics of the major American and European tick-borne zoonoses appear to have occurred towards the end of the 20th century, largely precipitated by human impact on the habitat and wildlife hosts of ticks. Purely climatic factors may have played some part, but this is only apparent at the northern extreme of *I. ricinus* distribution. At the same time, raised awareness of ticks as vectors triggered by the intense interest in LB, first in the USA and subsequently in Europe, has undoubtedly played its part in stimulating surveillance and protective measures. A comparison between TBE and LB in Europe might help to distinguish changes in real incidence from changes in apparent incidence.

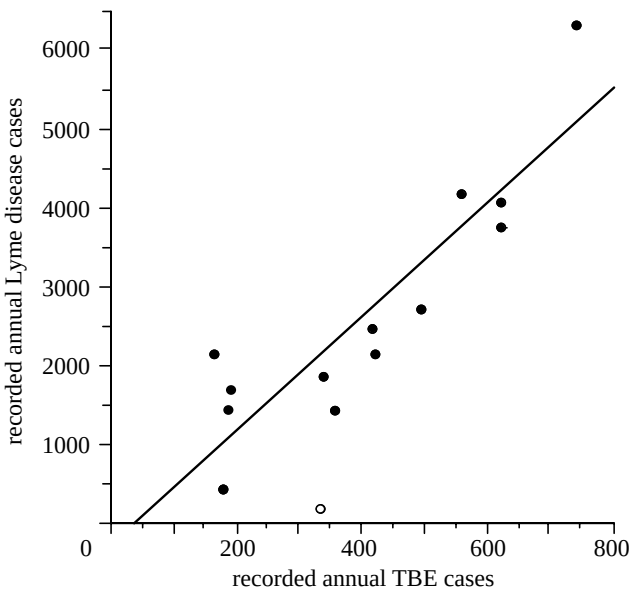

Figure 6. The correlation between the annual number of cases of TBE and Lyme borreliosis from 1986 to 1999 in the Czech Republic. For 1987–1999 (closed circles), $Y = 7.234X - 281.085$, $R^2 = 0.805$, $P < 0.001$). In 1986 (open circle), Lyme borreliosis appears to have been under-reported.

Within their ranges, the frequency of contact between humans and ticks is the common principal determinant of any temporal variation in human infection rates by these tick-borne pathogens, despite differences in the determinants of the spatial patterns of TBEV and *B. burgdorferi s.l.*, abiotic or biotic, respectively. Both human behaviour and tick densities vary seasonally (giving peak infection incidence typically in late spring–early autumn—see Süss & Kahl 1997), from year to year (Talleklint & Jaenson 1996*b*; Dorn & Sunder 1997; S. E. Randolph, unpublished data) and also show longer-term trends. As long as medical records reflect actual incidence rather than surveillance bias, one would therefore expect to see parallel trends in annual case numbers of TBE and LB. In the Czech Republic, where arguably the very long history of systematic registration of TBE should make the records least contaminated by surveillance bias, annual case numbers of TBE and LB are very closely correlated since 1986 (figure 6). In that country, where TBE is widespread, the tenfold higher incidence of LB correctly reflects the much greater force of transmission of LB spirochaetes (Randolph *et al.* 1996) than of TBEV. These data suggest that LB was underreported only in the first year of its records; thereafter the common principal risk factor, tick–human contact, determined annual variations in both infections. If this is true for the Czech Republic,

then the gradual increase in LB elsewhere in Europe may be a genuine 'emergence', despite historical records of symptoms (see Gern & Falco 2000). At the same time, improved surveillance and diagnosis must surely have exaggerated the rate of that emergence. We can only wait and see whether the transmission potential of TBEV really is diminishing in parts of its range, as predicted under developing climate scenarios, just as LB has emerged.

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