CHAPTER 14

ECOLOGY OF TICK-BORNE DISEASE AND THE ROLE OF CLIMATE

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14.1. INTRODUCTION: ECOLOGY UNDERPINS EPIDEMIOLOGY

Crimean-Congo hemorrhagic Fever (CCHF) is unusual among vector-borne zoonoses in that, as well as the virus being transmitted to humans if they accidentally intrude on the natural transmission cycle by being bitten by ticks, the virus is also commonly transmitted directly to humans from its natural wildlife and livestock hosts (and even human patients) via contact or contamination with infected tissue or blood. The epidemiology of human disease therefore follows a pattern that is greatly influenced by employment practices that bring humans into close contact with livestock, whether alive or, even more riskily, dead. In tanneries, for example, ticks that detach from hides may reattach to humans, potentially transferring the infection much more rapidly than via the conventional transmission route that involves a long delay between the engorged infected tick of one stage and the feeding tick of the next stage. Nevertheless, like all other vector-borne diseases, the presence and persistence of zoonotic foci of infection depend on biological and ecological relationships between three very different kinds of organisms: virus, ticks, and vertebrates. These three must interact not only physically and biologically to permit each complete act of transmission, but also ecologically to permit continuing cycles of transmission. Although the focus of epidemiological interest is on the pattern of human cases, explanations for the described distribution and abundance of infections must come from understanding the underlying ecological processes.

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14.2. ECOLOGICAL HURDLES TO PERSISTENT TRANSMISSION CYCLES OF TICK-BORNE DISEASES

14.2.1. Biotic specificity

14.2.1.1. Vector competence

The first task is to identify the key players. In the CCHF disease system, the main unresolved question concerns the identity of any significant vectors in addition to *Hyalomma* spp., particularly *Hyalomma marginatum, Hyalomma truncatum*, and *Hyalomma anatolicum*, the three most widely recognized vector tick species [3, 15, 56] (See also Chapter 12). It is not sufficient to base conclusions on the coincidence in distributions of CCHF and certain tick genera or species, because other ticks may be competent but not yet "active" vectors, ready to play a more significant role if abiotic or biotic environmental conditions change. We need to identify the factors that limit the competence of each potential vector, and assess their flexibility relative to likely environmental changes.

In addition to the genus *Hyalomma*, ticks of other genera (*Dermacentor*, *Rhipicephalus*, *Ixodes*, *Amblyomma*, *Boophilus*) are biologically competent in the laboratory and can even become infected under natural conditions [3]. The prevalence of virus in unfed ticks questing for hosts reveals whether or not these additional species can play a significant role in nature. Such ticks can only have become infected from an infected host during feeding by previous tick stages as long as they maintain sufficient viral load during interstadial development and molting. They must then be able to develop mature infections in the salivary glands for onward transmission to the next host. Each of these steps depends on the ability of a microbe to overcome the many intrinsic biological (molecular, cellular, physiological, and physical) barriers during its passage from host to host via the vector (Fig. 14-1). Even then, although biologically possible, this cycle may not proceed with sufficient force to support persistent transmission cycles. That depends on the quantitative balance of the rates of all the processes involved in each complete transmission cycle. The majority of these rates are affected by extrinsic environmental factors, both biotic and abiotic (Fig. 14-1), although host-acquired immunity also plays a significant role. Wherever the basic reproductive number, R_0 (defined as the number of new infections that arise over each transmission cycle from a single index case introduced into a wholly susceptible population [1]) falls below the absolute threshold value of 1, the infection is not sustainable. This may be due to a shortfall in any one of the followingfactors: (1) tick abundance; (2) tick contact rates with competent hosts; (3) tick survival rates; (4) tick interstadial development rates; and (5) transmission coefficients from host to tick, interstadially between ticks, or from tick to host.

This concept of ecological specificity, highlighting the distinction between biological and ecological competence, is well illustrated by tick-borne encephalitis (TBE) virus (TBEV). As with CCHFV, many tick species have been shown to be competent vectors in the laboratory, but in the field only *Ixodes ricinus* seems

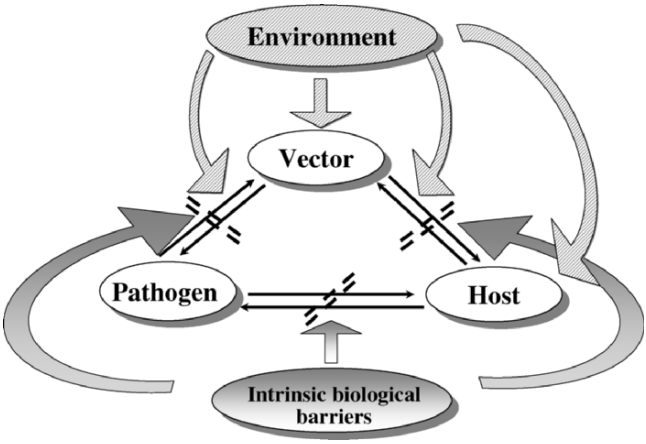

Fig. 14-1. The triangle of host–vector–pathogen interactions, showing the points of action of the intrinsic biological barriers to transmission and the extrinsic environmental factors.

to play a significant role in Europe [22]. Within TBE foci in Slovakia, a second biologically competent tick species, *Dermacentor reticulatus*, feeds on rodents alongside *I. ricinus*, but *D. reticulatus* develops very rapidly so that larvae molt and give rise to feeding nymphs within a month. Each immature stage therefore feeds sequentially within the summer on the competent rodent hosts, with very little overlap and therefore little co-feeding by larvae and nymphs on the same host [37]. Co-feeding is a necessary condition for the transmission of virus from infected nymphs to infectible larvae for any tick-borne virus that remains infective within the host for only a few days (as is true of CCHFV) [32]. Our understanding of the ecology of TBEV transmission tells us that *D. reticulatus* is unlikely to assume a significant role as vector of this virus under changing environmental conditions, because the timing of its developmental cycle is entirely wrong. Furthermore, in this region at least, *D. reticulatus* feeds to a significantly lesser extent on mice, *Apodemus flavicollis*, than on voles, *Clethrionomys glareolus*; the former rodents are quantitatively superior as transmission hosts because they support nonviremic transmission better [21], and also do not acquire immunological resistance to feeding ticks [5].

Not enough is known quantitatively about the necessary biotic conditions for the maintenance of CCHFV cycles in nature to allow a firm conclusion on the relative roles, potential, or realized, of the various biologically competent tick species. This is a significant gap, limiting our ability to assess the potential for epidemiological change in the future (see below).

14.2.1.2. Vertebrate amplification hosts

The edge of the distribution of any tick-borne disease system (i.e. where $R_0 < 1$) is defined by the product of all the factors within the R_0 equation [32]. The closer the value is to 1, the more fragile are the transmission cycles and the

greater the likelihood that the distribution will be focal, occurring only in well-defined places where all the conditions are satisfied quantitatively. Conversely, robust systems will be more widespread. Many of the most widespread tick-borne pathogens utilize a wide range of ubiquitous hosts; *Borrelia burgdorferi* sensu lato is an obvious example, whose long period of infectivity within its hosts makes this system even more robust. In the case of CCHF virus, both wild and domesticated ruminants appear to be commonly infected hosts, with a variety of small mammals (e.g. susliks, hares, hedgehogs, rodents) [3, 15, 50, 52, 56] and possibly some birds (e.g. ostriches and guinea fowl) [3, 51, 60] also warranting full experimental investigation of their exact transmission potential.

Just as with ticks, however, infection or even transmission competence per se are not necessarily sufficient for persistent cycles if the pattern of attachment by different tick stages does not allow sufficient amplification. In order to overcome the inevitable high mortality between each tick stage, transmission must occur "backwards" through the tick's life cycle, from one infected nymph to many larvae, or from one infected adult to many larvae and/or nymphs. Only if transovarial transmission is efficient, from one infected female to a large proportion of her progeny, does pathogen amplification run in the same direction as the tick's life cycle. For this reason, for CCHFV, for which transovarial transmission does occur but is not very efficient [59], at least two tick stages must feed on any one host. Immature stages of *Hyalomma* species, or indeed most other tick species from which CCHFV has been isolated, are much more commonly recorded on small mammals and birds than on ruminants [41, 54, 57]. In a national park in Cape Province, South Africa, there was a complete separation between immature stages of *H. marginatum turanicum* and *H. truncatum* on hares (the most highly infested host species), ground-feeding birds or small rodents, and adult ticks on zebra and eland [16]. This pattern of tick biology raises the distinct possibility that, while ruminants may be vital in feeding adult ticks and therefore supporting tick populations, and domestic livestock infected by these adult ticks may be instrumental in bringing CCHFV to humans, smaller vertebrates may be the principle maintenance hosts. This "division of labor" among the vertebrate components of tick-borne disease systems is not uncommon and has been well documented for Lyme borreliosis, TBE and Louping ill [11, 19, 22, 34], all transmitted by *I. ricinus*, a tick with an exceptionally catholic host range. An additional complication for CCHF, unquantified in nature, is the variability shown by *H. truncatum* and *H. marginatum rufipes* between a two-host feeding pattern (i.e. both larvae and nymphs feeding from the same host and adults from a second) and three-host feeding pattern (each stage feeding on a different host), apparently depending on the species of larval hosts [23, 41]. For two-hosts ticks showing distinct host relations as immature stages and adults (above), the sustainability of natural virus transmission cycles depends on the efficiency of complete vertical transmission, including transovarial transmission, and the degree of amplification amongst immature stages feeding together on the same host individual. This latter factor is augmented by the commonly observed aggregated distribution of ticks

amongst their hosts, with the few hosts that carry many ticks making an essential, disproportionately large, contribution [37]. All these factors need to be quantified before natural transmission cycles can be fully understood.

14.2.2. Abiotic specificity

Because of the ubiquity of the putative vertebrate hosts of CCHFV, and their common infestation by ticks of many genera including *Hyalomma*, host availability is unlikely to be a limiting ecological factor in the distribution, or even the prevalence, of this virus. Moreover, a nonviremic route has been indicated by reports of transmission among co-feeding ticks via hosts that do not develop viremia above a notional threshold level [60]. This may add both qualitatively (more species than conventionally recognized acting as hosts) and quantitatively to the transmission potential [35].

Rather, abiotic factors are more likely to determine patterns of epidemiological risk, because they affect the rates of many of the tick population processes critical to the dynamics of tick-borne disease systems. The most obvious outcomes that vary with climatic conditions are tick abundance and patterns of seasonal tick population dynamics; these are the product of interstadial development rates and the timing of questing activity. Microclimate may also have a direct impact on tick behavior, in particular the height on the vegetation at which they quest for hosts, affecting tick–host contact rates and therefore pathogen transmission potential [40]. Adult ticks, which typically quest at higher levels in the vegetation than do immature stages, will be unavailable to smaller hosts species moving about at ground level. At the same time, host dynamics and behavior vary independently, also determining contacts rates. Any seasonal variation in the differential availability of each host species results in different tick–host ratios in different places. Smaller hosts show stronger seasonal cycles of abundance wherever the climate dictates seasonal breeding, but even among larger hosts exposure to ticks may vary with, for example, livestock husbandry practices or changes in behavior (e.g. squirrels shifting from ground- to tree-based foraging in the summer [4]).

It is one thing to argue in principal for the likely importance of abiotic limiting factors, and quite another to identify those factors precisely and define the necessary conditions for CCHF presence. Yet without such knowledge we can neither explain the present situation nor predict any future changes.

14.3. METHODS FOR IDENTIFYING THE LIMITING CONDITIONS FOR CCHF PRESENCE

14.3.1. The biological approach

The fuller and more quantitative the description of any system, the better our understanding of the causes of the observed patterns and the more reliable our predictions of possible change will be. Patterns are simply the product of the

underlying processes. Even in the case of complex vector-borne disease systems these include the same small handful of principal events, namely vector birth, death, and feeding, pathogen developmental cycles within the vector, and vertebrate host recovery from infection. The myriad of patterns, different for each system and varying in both time and space for any single system, is simply the outcome of interactions of the variable rates of these processes. These rates are typically driven by environmental factors. If we could quantify the relationship between each process rate and its environmental drivers, we could build full biological, process-driven models (Fig. 14-2). Unfortunately this exceeds our current knowledge; there is no single fully functional biological model for any vector-borne disease system.

The most variable term in such a model is vector abundance, which commonly varies by up to several orders of magnitude seasonally, annually, or geographically. Yet our ability to model vector population dynamics is the biggest single gap in our biological toolbox. For ticks, this exercise is particularly demanding as the changing abundance of all three tick stages must be predicted simultaneously, because at least two stages are required for pathogen transmission (see above). Indeed, for *Hyalomma* ticks, it seems that we do not even have good descriptions of vector abundance, as these ticks are typically counted on cattle, upon which typically only the adults feed [56], leaving the all-important immature stages out of the equation (but see the exemplary work of Ivan Horak as an exception to this, e.g. [16]). While the framework necessary to direct new empirical measures of input data is relatively simple [33], and a variety of tick population models has been proposed [26, 38, 49], there has been limited success in using these models to predict tick abundance at locations independent of the input data [33, 38].

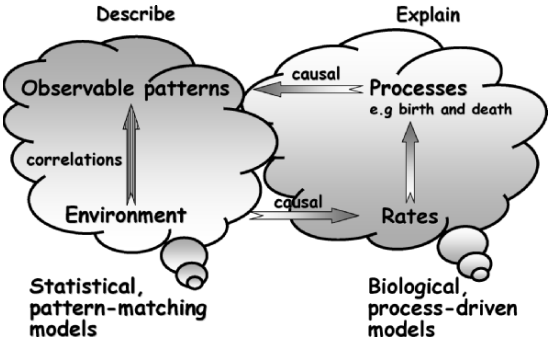

Fig. 14-2. The causal links between the environment, rates of processes and resultant patterns inform biological, process-based models. This offers an explanation of the system. Alternatively, the correlations between the environment and the described patterns allow the creation of statistical, pattern-matching models.

14.3.2. The statistical approach

14.3.2.1. Basic principles

Nil desperandum: because of the causal link between the environment, process rates, and resultant patterns, the shortcut correlational link between environmental conditions and patterns can be exploited (Fig. 14-2). By identifying the best environmental correlates of the known presence or absence of any organism (whether an elephant, a cactus, or a tick-borne virus), the relative significance of each environmental variable can be quantified by determining its distribution. The multivariate correlation can then be extrapolated beyond existing observations, to fill in the gaps in our knowledge and so create predictive risk maps for the full potential global distribution of the organism. This has all been made much easier by the development of geographical information systems (GIS), software programs that collate, analyze, and display spatially explicit data. The reliability of such predictive risk maps depends, of course, on the quality of the input data used to train the correlations, the quality and spatial resolution of the environmental data, the statistical handling of these data to take account of multivariate nonnormality across wide heterogeneous areas, and the particular statistical pattern-matching program chosen. Detailed considerations of these points can be found in several reviews [12, 13, 31, 47]. Moreover, the reliability of these maps, expressed as percentage correct matches between the predictions and the test data, can appear misleadingly good if, for example, the latter are inflated by a disproportionately large sample of absence points taken from far outside the observed distributional limits. Predicting the absence of tsetse flies outside sub-Saharan Africa, for example, or of *Amblyomma hebraeum* outside southern Africa, carries very little merit. It is not the production of such maps that is now the challenge, but the intelligent use to which they are put.

14.3.2.2. Data sources: the environment

There is now a major disparity between the availability of environmental data and of useful spatially explicit epidemiological data. The era of satellites ushered in an abundance of information about conditions on the earth's surface, albeit measured remotely as surrogates of ground-based conditions. Data in 3–7 wavebands (channels) within 0.3–14 μm of the electromagnetic spectrum are usually processed to produce indices related to the following ground-based variables: (1) thermal conditions (land surface temperature – Price LST, near-surface air temperature – TvX, and middle infrared band – MIR); (2) moisture conditions (normalized difference vegetation index – NDVI, actually an index of plant photosynthetic activity); and (3) rainfall (cold cloud duration – CCD) [14, 47].

Any approximation in absolute measures of temperature and moisture conditions is offset by the benefit of the near-global coverage. Whereas ground meteorological stations are unevenly, and commonly sparsely, distributed around the

globe, satellites provide blanket-cover information on continental scales at spatial and temporal resolutions to match our epidemiological questions. There are, however, inevitable trade-offs between the spectral, spatial, and temporal resolutions, with different satellites designed for different purposes and suitable for different epidemiological uses [13, 47].

At one extreme, earth-observing satellites produce data with high spatial resolutions (i.e. pixel sizes) of between 1 and 4 m (Ikonos-2) and between 30 and 120 m (Landsats 1–5), but low repeat frequencies of only 2–3 weeks. As clouds commonly obscure images, however, these low-frequency images provide only occasional snapshots. In contrast, orbiting oceanographic, or geostationary meteorological satellites have lower spatial resolutions, down to 1.1 km (National Oceanographic and Atmospheric Administration Advanced Very High Resolution Radiometer [NOAA AVHRR]), but they produce two or more images per day of the entire earth's surface. These high-frequency images can be combined to produce relatively cloud-free monthly "maximum value composites" (MVCs). Because many of the dynamical processes within vector-borne disease systems follow seasonal ecological patterns, the high-frequency images are of the much greater use. The more recent Terra (EOS AM-1) and Aqua (EOS PM-2) spacecraft include a moderate resolution imaging spectroradiometer (MODIS) with 36 spectral channels and spatial resolutions of between 250 and 1,000 m. This instrument has a 2-day repeat frequency and the images it produces have much greater geolocational accuracy than those of the AVHRR instrument, giving better quality MVCs of seasonal processes.

The problem now is one of a superabundance of environmental data, with a high degree of inherent redundancy in serial monthly imagery. Temporal Fourier processing offers a method of overcoming this, without losing the biologically meaningful signals [42, 43]. The French mathematician Joseph Fourier (1768–1830) showed that any complex time series can always be expressed as the sum of a series of sine and cosine curves with different amplitudes, frequencies, and phases (i.e. timings) around a characteristic mean. Multitemporal satellite data can be processed to yield information about the annual, biannual, and triannual cycles of rainfall, temperature, etc. that characterize the natural environments of diseases (Fig. 14-3). In temperate and tropical environments with a dominant annual cycle, the biannual and triannual Fourier cycles modulate the simple annual Fourier cycle (i.e. a sine curve with a period of 1 year) to characterize the particular shape of the rising and falling curves between the annual minima and maxima. The output of temporal Fourier analysis is a set of orthogonal (i.e. uncorrelated) variables that capture the seasonality that is of vital interest in epidemiology [42, 43, 45], and these variables may therefore be used to classify habitats in ways that are relevant to arthropod vectors and transmitted pathogens [44]. For disease systems, Fourier variables are the environmental equivalent of the genes of individual pathogens, and whole Fourier-processed images [48], that capture all the interactive space–time features of a habitat, may be likened to the organismal genome.

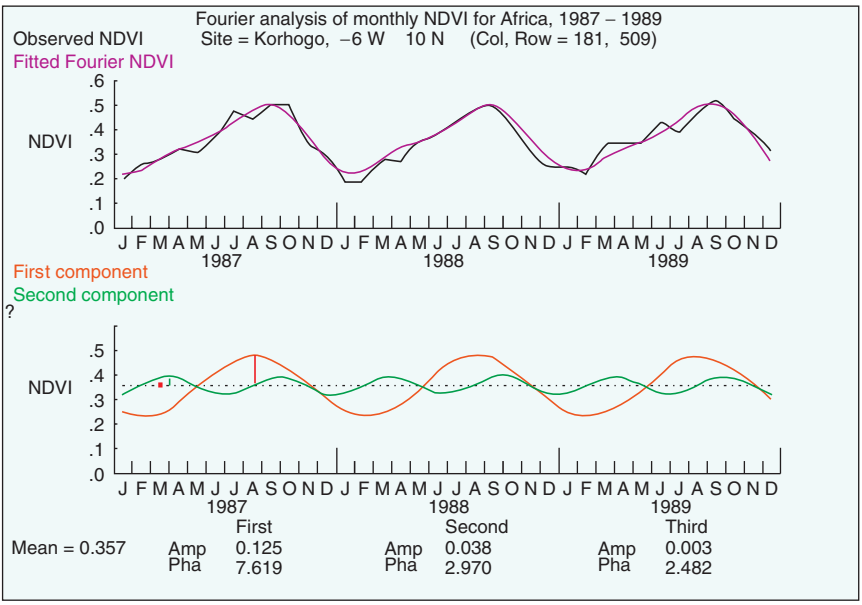

Fig. 14-3. Any regular seasonal cycle (black line), in this case of the remotely sensed normalized difference vegetation index (NDVI) at Khorogo, Côte d'Ivoire, Africa may be deconstructed by temporal Fourier analysis into its component harmonic sine waves with annual (red line), biannual (blue line), and triannual (green line) periodicities. Each sine wave (rescaled here to fluctuate around zero) has its characteristic amplitude (variation around the mean) and phase (timing of peak). The component cycles may be reconstructed to the fitted Fourier mean (purple line) to give the smoothed seasonal signal characteristic of each location over the period of observation.

14.3.2.3. Data sources: CCHF

The statistical prediction exercise must always start with some baseline knowledge that is expected to be incomplete (hence the need for the exercise). CCHF has the largest geographic distribution of any tick-borne viral disease, so it is not surprising that its full range is described in broad brush-strokes with little subnational precision. In addition to much of sub-Saharan Africa and a belt from the Balkans and Ukraine throughout southern central Asia including Kazakhstan, the map based on human cases [2] shows foci in Portugal and southern France. An alternative map based on both human disease and viral isolates [58] shows a much more extensive range to the east across all of China and Mongolia, and includes the Arabian land mass but not India. Recently, more spatially explicit data were acquired by extracting 622 unique case records of CCHF from the literature (1920–2006), as part of a major project on risk mapping for a variety of infectious diseases. This database was reduced to 378 positive records after the elimination of duplicates and insufficiently exact locations (such as when cases are reported only to the level of large administrative

regions). This database does not, however, include the hitherto unpublished records of several hundred cases in Turkey each year since 2002. Records of definite absence were too scarce to be useful in defining the disease's geographical limits. Instead, 5,000 locations, randomly selected between 0.5° and 10° away from the nearest site for CCHF presence, were taken as negative locations. Satellite data were then extracted for each positive and negative location. Details of the precise procedure and the model building methods are given in Hay et al. [12]. In brief, 100 bootstrap samples (400 each of presence and absence points) were selected at random (with replacement) from the training data set. Nonlinear, maximum likelihood discriminant analysis was used to select the best set of descriptor variables for each bootstrap sample, using the information-theoretic approach of stepwise selection of variables that minimized Akaike's information criterion (AIC), corrected for the number of variables in the model (i.e. the AICc). Each resulting model was then applied to the full extent of the satellite image data to make global predictions of the posterior probabilities of habitat suitability for CCHF.

14.4. USES AND INTERPRETATIONS OF PREDICTIVE RISK MAPS FOR CCHF

14.4.1. Risk maps as blueprints

The most immediate use of a risk map is as a blueprint to inform people about the full potential extent of the risk of infection. If the training data comprise human case records, as here, the predicted distribution will also refer to human risk, the tip of the zoonotic iceberg, but almost certainly not the full range of natural enzootic cycles, the whole iceberg. A variety of factors may cause the iceberg to emerge further above the surface without necessarily any change in enzootic transmission potential, i.e. greater human exposure to risk without any change in that intrinsic risk (see below).

The risk map for CCHF (Fig. 14-4) shows a greater than 0.5 probability of human disease not only where cases have indeed been recorded, but also extensively in other parts of the world: notably in large parts of North America, south, western and eastern parts of South America (Argentina, Chile, Bolivia, Peru, Brazil), eastern China, Australia, Spain and Italy, and the northern edge of Morocco, Tunisia, and Libya. At the same time, only the southeastern edge of Kazakhstan is predicted as highly suitable, even though a few positive records come from central and northern Kazakhstan. Most of India and central Africa have little or no predicted habitat suitability, despite recent records from these areas. While the very few false negative predictions obviously arise from errors or inadequacies in this modeling procedure, the much more extensive false positive predictions are far more interesting. They could also be dismissed as errors, as any prediction of West Nile virus in the Americas would have been prior to 1999 (when this virus arrived in the New World for the first time). Alternatively,

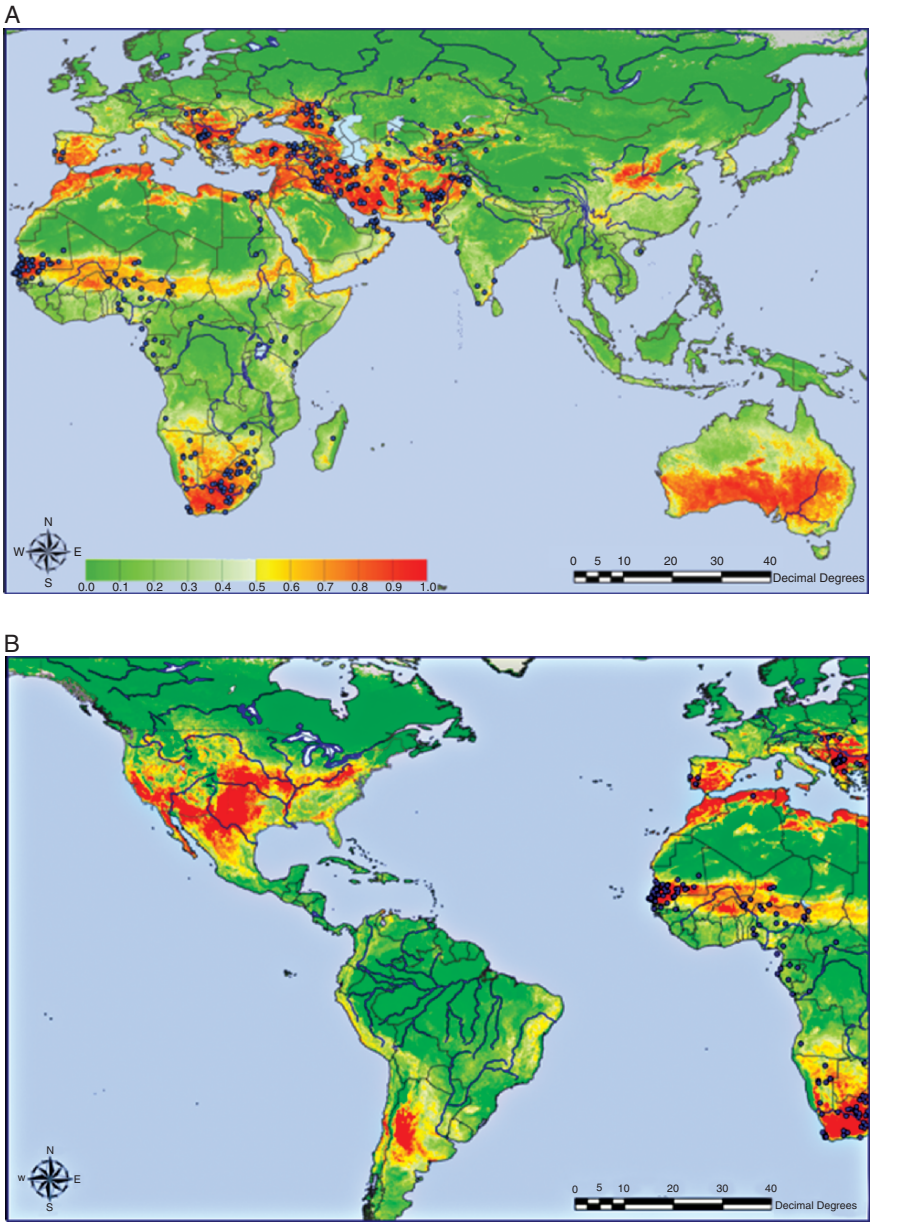

Fig. 14-4. Predictive risk map for CCHF (A) Old World and (B) New World. The data source and methods of creation are summarily described in the text (further methodological details in [12]). The mean posterior probabilities of environmental suitability for CCHF from 100 bootstrapped models are here shown on a color scale from green (low probability) to red (high probability). The original literature records of CCHF presence, on which the models were based, are shown as blue points on the map(s). (*See Color Plates*)

they can be taken as a wake-up call, alerting public health authorities to regions potentially at risk of invasion if the virus were to be introduced across the current oceanic barriers. Such an invasion would depend on the virus finding permissive biotic conditions (i.e. competent vector species and vertebrate transmission hosts) within the apparently abiotically hospitable regions. Within the previously well-recognized broad-brush range of CCHF, predictions at this much finer spatial scale (here down to 0.10° longitude/latitude, ~10 km^2 pixel size at the equator) allow intervention strategies to be targeted much more precisely, achieving greater cost-effectiveness.

14.4.2. Risk maps to throw spotlights on the underlying biology

For scientists, an equally valuable and far more interesting use of risk maps is as spotlights on the biological processes underlying the observed patterns, seeking explanations upon which to base more versatile, robust predictions. For this, the critical information lies in the key predictor variables: which abiotic factors best define the necessary conditions for CCHF presence, what are these conditions, what do they tell us about the virus transmission dynamics, and are these conditions changing to account for past epidemiological changes and warn of any future changes?

Table 14-1 shows the top ten variables in ranked order from the best of the 100 bootstrap models (i.e. minimum AICc value across all models). Many of the other models had similar, but not identical, combinations of predictor variables. All the evidence points to the importance of seasonal thermal conditions in determining suitable conditions for CCHF risk: it appears that the specific form of the seasonal thermal profiles, as indicated by the phases and amplitudes of the harmonic cycles, is significant. In addition, the presence of CCHF cases is

Table 14-1. The key predictor variables (shown in ranked order of selection) for the presence of CCHF identified by stepwise forward selection for the best of the 100 bootstrap models

Variable	Mean values CCHF present	Mean values CCHF absent
Price LST minimum (°C)	18.91	18.16
MIR variance	78.47	78.79
MIR mean (°C)	36.42	34.89
NDVI triannual phase, decimal months	1.80	2.05
Price LST annual amplitude (°C)	13.49	13.04
Price LST biannual amplitude (°C)	2.60	2.58
NDVI maximum	0.36	0.39
Digital elevation model	7.85	7.08
MIR biannual amplitude (°C)	2.41	2.23
Price LST maximum (°C)	46.91	45.00

LST, land surface temperature; MIR, middle infrared; NDVI, normalized difference vegetation index. Not all models selected the same top ten variables.

consistently associated with warmer temperatures. In particular, minimum LST was selected as the top ranked variable by the best individual model, and had by far the highest mean rank across the various bootstrap models, while mean middle infrared was also highly ranked.

Until a great deal more is known about the specific biotic interactions involved, such as the necessary tick infestation patterns (both qualitative and quantitative) on the key transmission hosts, it is impossible to progress from identifying the key predictor variables to interpreting their relevance for CCHF virus transmission. Even for TBE virus, whose biotic interactions are well established and whose ecology has therefore been quantitatively analyzed in detail by an integrated biological and statistical approach, there remains a major gap in the story: there is a clear biological link between the cellular transmission route amongst co-feeding ticks via rodent hosts [20] and the climate-driven seasonal dynamics of the ticks to ensure a high degree of co-feeding between larval and nymphal *I. ricinus* [22]; there is a strong statistical correlation between a particular feature of the remotely sensed autumnal thermal conditions (a higher than average rate of cooling) and both the seasonal synchrony of these tick stage and the presence of TBE cases [36]; but biologically it seems more likely that rates of increasing temperature in the spring would determine the degree of seasonal synchrony as larvae have a higher temperature threshold for activity than do nymphs [33]. Nevertheless, identifying the key predictor variables for TBE presence, by creating a risk map, was an important step in the (hitherto incomplete) analytical process, and so it could be for CCHF.

14.5. POTENTIAL FOR EPIDEMIOLOGICAL CHANGE OF CCHF

14.5.1. Predicting future change

It is clear that we do not yet have sufficient quantitative knowledge of either the biotic or the abiotic factors limiting the distribution of CCHF foci to predict whether, as environmental factors change, the disease will emerge more widely in human populations. For any tick-borne disease whose existing foci depend on a delicate balance of factors and rates, the system may equally well be disrupted by environmental change, leading to retrenchment rather than emergence. Predictions must rest on system-specific analyses, taking into account the particular ecology of the major tick vectors and wildlife hosts. The wide geographical distribution of CCHF, wider than for any other tick-borne disease, indicates an ecological robustness in the system, which may therefore confer considerable potential for epidemiological expansion in the future. This potential may be enhanced by the wide range of biologically competent tick species if those that are not yet ecologically competent are rendered so by changing environmental conditions. There is no evidence that *I. ricinus*, for example, currently plays a major role in the transmission of CCHF virus; its biological competence in the laboratory and widespread distribution

throughout Europe, however, are sufficient reasons to place CCHF on the UK Health Protection Agency's "at risk" list of potential invaders (http://www.hpa.org.uk).

Just as there are two complementary methods for predicting the present distribution of any organism, the biological process-based approach and the statistical pattern-matching approach, so these two methods may be applied to predictions of future change. Ideally, if we had a full biological model for the CCHF system driven by environmental variables, we could apply the environmental conditions forecast under the scenarios of climate change to predict new process rates and therefore distribution patterns at specified points in the future. Failing that, for with an incomplete, not to say nonexistent, biological model this approach is doomed to fail, we can extrapolate the identified correlations between present environmental and epidemiological patterns into the future according to forecast climate scenarios. This latter approach depends very much on the assumption that all other nonclimatic factors will stay the same so that the shape and structure of the underpinning correlations do not change. In reality, climate change will have an impact on all sorts of human behavioral factors, which in turn may alter livestock and wildlife host availability for ticks and CCHF virus. Past exercises of this sort, taking into account changes in both temperature and moisture conditions, have suggested that vector-borne diseases may appear in some new places but disappear from parts of their current range, mostly around the distributional edges, with little net change for malaria [46] but considerable decrease in range for TBE [39]. This is entirely consistent with the complexity of these disease systems and the greater quantitative fragility of TBE. Nevertheless, such conclusions, however plausible, are not scientific because they are inherently untestable until the future arrives.

14.5.2. Explaining past changes

A more rigorous approach is to seek explanations for the past. Specifically, we should search for key changes in abiotic, biotic, or socioeconomic factors associated with specific epidemiological events. We may then warn of potential future changes if conditions continue to change in the same way. The danger is that correlations between recent epidemiological phenomena and recent climate changes are almost inevitable, given that climate change is the general backdrop to all recent and current events, but this does not necessarily indicate causality. Only if disease emergence in new places or increases in incidence, for example, are strictly consistent in time and space with environmental changes may we impute causality. This is analogous to Koch's postulates, which demand absolutely consistent associations between the presence of a pathogen and evidence of infection. The present task, however, is beset not by the technical microbiological hurdles of the 19th century, but the analytical problems of dealing with a complex network of environmental and human factors, operating over large heterogeneous regions and each changing independently yet indirectly

linked, which may act synergistically or antagonistically on the enzootic transmission cycles and/or degree of human exposure.

The last 5 years have witnessed notable increases in reports of CCHF, including first reports of cases in Kenya [6], Iran [24], Albania [29], Kosovo [30], and Turkey [9]. As ticks are obviously subject to seasonal climate effects, it is reasonable to suggest that recent climate change may have promoted these outbreaks of CCHF. As is typical of arthropods, tick development rates and activity increase with temperature, while *Hyalomma* ticks are better adapted to surviving in dry conditions than are many other ticks. This is consistent with the mean values of the key predictor variables for the presence of CCHF (Table 14-1), which indicate that CCHF occurs where average conditions are warmer. In the northern hemisphere, *H. marginatum marginatum* is usually activated by increasing temperature in the spring, with adults appearing as average daily temperatures reach 5–9°C in April or May, and the immature stages appearing somewhat later from May onwards; tick activity continues throughout the summer to early autumn [7, 15, 55]. Hoogstraal (1979) attributes the reduction in case numbers of CCHF in the Astrakhan Oblast of Russia in the late 1960s to a reduction in tick densities due to the severe winter of 1968–1969 in that region.

Conversely, Ergönül et al. [8] examined trends in April temperatures and annual rainfall to test for a climatic cause for the emergence of CCHF in Turkey. CCHF infection was first recognized in 2002 in Turkey [9, 18], with marked increases in the numbers and spread of cases recorded through to 2006. Cases were mainly from three provinces of central Turkey, namely Tokat, Sivas, and Yozgat, for which meteorological records were available over the last 40, 70, and 60 years, respectively. Significant increasing trends in monthly mean and minimum temperatures, and in the number of days in April with temperatures of >5°C, were detected only for Sivas, but not for Tokat or Yozgat. Likewise, a significant increase in annual rainfall was detected only in Tokat [8]. Changing climate does not, therefore, provide a sufficiently consistent explanation for this CCHF emergence in Turkey. Although shorter-term variation in climate, not detectable as statistically significant trends, might still indicate an abiotic contribution, other possible human-induced biotic changes have been suggested [7]: because of terrorist activities in the region, hunting and pastoral activities had been abandoned between 1995 and 2001, allowing an increase in populations of mammals such as hares and wild boar. After 2001, hunting resumed and the fields became available again, exposing cattle and sheep to increased populations of virus-carrying ticks. Similar environmental changes due to wartime events have been held responsible for an outbreak of CCHF in Crimea in 1944–1945 [15]: after the occupation of Crimea during World War II, disruption of normal agricultural activities and the abandonment of hare hunting allowed fields to become overgrown with weeds and occupied by high densities of hares, thereby improving both the abiotic and biotic conditions for ticks. When susceptible Soviet troops reoccupied the region in 1944, a major epidemic occurred (200 cases, 10% mortality [7]).

Such considerations confirm the conclusion, obvious from first biological principles, that CCHF, like all other vector-borne disease systems, is potentially highly dynamic in response to a wide range of disparate factors, of which climate change per se is only one and not necessarily the most influential. Changes in human factors can be very abrupt, perhaps matching the abrupt outbreaks of large numbers of cases of CCHF over the last 60 years [7].

14.5.3. Vehicles of invasion

The predictive risk map (Fig. 14-4) shows far-flung areas of apparent habitat suitability for CCHF, many at considerable distance, even on different continents, from any records of presence to date. Are we to consider these as areas at real, rather than merely theoretical, risk of invasion? Such an invasion depends primarily on the introduction of the virus. The source of any newly arrived pathogen can now be identified by molecular epidemiology, allowing appropriate suspected vehicles to be investigated. The movement of livestock is now more carefully regulated than in the past, although illegal trade is still common (and the centralization of abattoirs in the UK following the bovine spongiform encephalopathy [BSE] crisis has resulted in increased animal traffic). The movement of humans and undetected arthropod stowaways in planes and ships, however, continues to grow inexorably and has been associated with the introduction of exotic vector-borne microbes [*inter alia* 10, 53].

Migrating birds are largely outside legislative control and have been held responsible for the dispersal of a large range of infectious agents (and are assumed to be so now and in the future [25] even if there is evidence against their involvement [28]). These events are either well established and account for the disjunct global distribution of closely related microbes [27], or occur rarely through exceptional random events [17], or may become newly established through changing patterns of migration in response to climate change (virtually all reports of the impact of climate change on bird migration refer to the timing, not direction, of migration – http://wok.mimas.ac.uk – which could be equally critical for any seasonal disease system). With tick-borne diseases, ticks will only be introduced if they do not complete their feeding and drop off before the birds complete their migration (although transport over part of the migration route is still possible if birds feed on the ground *en route*). Birds most commonly feed immature tick stages, which have feeding periods of a few days, and which must be introduced in sufficiently large numbers to offset the normal 80–90% interstadial tick mortality if breeding populations are to become established. Any introduced ticks would only be infected if the birds were competent to permit pathogen transmission to ticks, or allowed the maintenance of pre-existing infections in ticks as they fed on birds. Alternatively, the birds themselves must transport the pathogens, retaining the infection during the course of their migration. For CCHF virus, none of these alternatives has been demonstrated, and none seems likely on the basis of current knowledge, even though CCHF

virus has been transmitted experimentally from birds to *H. marginatum rufipes* ticks [60].

The predictive risk map at least helps to direct future investigations into the potential for long-range introductions of CCHF virus, by focusing attention on transport networks between known foci and areas identified as environmentally suitable for continuing transmission once all the key biotic elements are in place.

14.6. CONCLUSIONS

The principles behind the ecology of tick-borne disease systems are increasingly well understood and the likely significant impact of climate on CCHF enzootic cycles may be argued from first principles. The devil of any system, however, lies in the detail of each specific tripartite network of hosts, vectors, and pathogen. While increasing interest in CCHF is evident (see the front cover illustration on the April 2006 issue of *The Lancet Infectious Diseases*), greater emphasis has so far been on clinical and epidemiological features rather than on the basic biology and ecology of the system. Until the biotic interactions have been fully identified and subjected to detailed quantitative analysis, the impact of geographically, not to mention temporally, variable climate on the risk of infection must remain speculative. The creation of the first predictive risk map for CCHF offers a step towards identifying critical environmental factors, and provides a framework for intensive field work to validate the predicted fine-scale distribution. With such a widespread recorded distribution, CCHF is an ideal subject for a major international research initiative lest it turns into a major story of international emergence.

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