

Climate change and mosquito-borne disease: knowing the horse before hitching the cart

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Summary

Speculations on the potential impacts of climate change on human health often focus on the mosquito-borne diseases but ignore the complex interplay of the multitude of factors that are generally dominant in the dynamics of their transmission. A holistic view of this complexity – particularly the ecology and behaviour of the host and the ecology and behaviour of the vector – is the only valid starting point for assessing the significance of climate in the prevalence and incidence of these diseases.

Keywords

Arbovirus – Chikungunya – Climate change – Dengue – Emerging disease – Mosquito – Saint Louis encephalitis – West Nile virus – Yellow fever.

Introduction

Man-made climate change has become a defining moral and political issue of our age. Speculations on its potential impact often focus on infectious diseases and on mosquito-borne pathogens in particular. Predictions are common that malaria will move to higher latitudes and altitudes, dengue is increasing its range and incidence in the tropics, mild winters enabled West Nile virus to become enzootic in the United States of America (USA), recent epidemics of chikungunya on islands in the Indian Ocean are due to changes in temperature, and so on. Animal diseases receive relatively little attention. For this reason, part of this article deals with malaria and mosquito-borne zoonoses that affect humans. The principles involved, however, are equally applicable to the veterinary field.

Multiple depths of complexity

A large number of review publications, and the enormous media attention they generate, have had a major impact on public perceptions of the issue. In most cases, these publications name a disease, where it occurs and how it is transmitted, followed by a succession of statements on the

action of temperature, rainfall and other climate variables on specific components of the transmission cycle. Disquieting predictions that are persuasive because they are intuitive follow these statements. Some are based on mathematical models that select a climate variable (usually temperature), propose a direct interaction with a transmission parameter (e.g. multiplication of pathogen, survival of vector), and inevitably arrive at the same conclusions. Many focus on the vulnerability of people in poorer countries, and place the blame squarely on the activities of the industrial nations. A deplorable trend in the scientific press is the inclusion of a political message, much as in the popular media.

The great majority of these publications ignore two factors that are key to the transmission and epidemiology of all infectious diseases: host ecology and host behaviour. When the cycle of transmission includes mosquitoes, ticks, rodents or other intermediaries, their ecology and behaviour are also critical. When multiple species are involved, the levels of complexity are even greater. Lastly, the virulence of the pathogen, the susceptibility of its hosts, the immunity of the host and the host populations can be critical at all levels.

The role of climate in the dynamics of transmission can only be assessed in the perspective of this daunting

complexity. Moreover, the key parameters – temperature, rainfall and humidity – cannot be viewed independently. The effects of temperature are modified by humidity. The daily range of each may be more significant than the daily mean. Brief periods of atypical heat or cold can be more significant than long-term averages. Heavy storms can have a different impact than light, prolonged rainfall. One year's events may have a significant impact on subsequent years.

In summary, a holistic view of the role of host behaviour and host ecology in the natural history of an infectious disease is the only valid starting point for a study of the significance of climate parameters in its transmission. Having established what we understand and do not understand about the system as a whole, we can begin to speculate on future scenarios in the context of changing climates.

A common misconception

There is a widespread misconception that mosquito-borne diseases require tropical temperatures, or at least the temperatures of the warmer temperate regions (31). A glance at a map of global isotherms reveals that summer temperatures in many temperate regions are at least as high as in the warmest seasons of many regions in the tropics. The crucial difference is that the tropics do not have cold winters. Moreover, if tropical mosquito-borne pathogens are introduced to temperate regions in the right season, they can be transmitted if suitable vectors are present (32).

There is also a misconception that mosquitoes die in winter, and that more die in colder winters, but it is obvious that mosquitoes, and indeed all life-forms that are native to temperate regions, have evolved strategies to survive low temperatures. In the tropics, comparable adaptations are necessary for surviving unfavourable dry periods. In both cases, such adaptations merely impose seasonality on transmission. In southern Europe, for example, *Plasmodium falciparum* (the most dangerous species of malarial pathogen) was transmitted from July to September (4). In Mali, where the disease is still endemic, most transmission occurs during the same three months, the wet season (6).

The physical environment is an important modifier of local climate. *Anopheles arabiensis*, an important vector of malaria in Africa, can survive in the Sudan when outdoor temperatures are above 55°C. It hides in the thatch of buildings during the day, feeds after midnight, and oviposits at dawn or dusk (28). In Lapland, *Anopheles* species survive the winter in houses and stables, feeding occasionally, and even (in the past) transmitting malaria when outdoor temperatures were below –40°C (19). *Culex pipiens*, a vector of West Nile virus in the northern hemisphere, is common as far north as Nova Scotia and

Finland. It overwinters in the adult stage; the author has collected live specimens in Tennessee that were sheltering at –18°C. *Aedes aegypti*, the principal urban vector of dengue and yellow fever, is a tropical species for which temperatures below 0°C are fatal, but its range extends from Texas to South Carolina and it survives the sub-zero winter temperatures in niches protected from the cold.

In conclusion, meteorological variables alone are of limited value as a guide to the ecology, behaviour and geographic range of vector species. The same is true for the pathogens they transmit.

Malaria: a paradigm of the mosquito-borne diseases

'Everything about malaria is so moulded and altered by local conditions that it becomes a thousand different diseases and epidemiological puzzles. Like chess, it is played with a few pieces, but is capable of an infinite variety of situations' (14).

Malaria is the most important of all mosquito-borne diseases. Each year, 350 million to 500 million cases of malaria occur worldwide, and over a million people die, most of them young children in sub-Saharan Africa (44). This appalling toll is mainly restricted to the tropics, and is the most commonly cited disease in the climate change debate, yet few people are aware that it is less than forty years since the final eradication of the disease from Europe. Indeed, the disease was common in the period from the 16th to 18th Centuries that climatologists term the Little Ice Age, and data from burial records around the Thames estuary reveal that mortality in 'marsh parishes' of England was comparable to that in areas of transmission in sub-Saharan Africa today (8, 9, 31).

Malaria in temperate regions

In the mid-19th Century, the northern limit of transmission, which had roughly been defined by the present 15°C July isotherm, began to decline in many countries (14). Denmark and parts of Sweden suffered major epidemics until the 1860s. Thereafter, the number of cases diminished and the disease had essentially disappeared around the turn of the 20th Century. In England, there was a gradual decrease in transmission until the 1880s, after which it dropped precipitously and became relatively rare except in a short period following World War I. In Germany, transmission also diminished rapidly; after World War I it was mainly confined to a few marshy localities (4).

The decline of malaria in western countries of Europe is attributed to a combination of factors, each of which is described below.

Ecological changes

Improved drainage, reclamation of swampy land for cultivation and the adoption of new farming methods (there is an old Italian adage: 'malaria flees before the plough') all served to eliminate mosquito habitat.

New farm crops

New root crops, such as turnips and mangel-wurzels were adopted as winter fodder. These enabled farmers to maintain larger numbers of animals, particularly cattle, throughout the year. European vectors of malaria readily bite cattle, so the increasing size of herds diverted mosquitoes from feeding on humans. Human malaria parasites cannot infect cattle, so this diversion reduced the number of infected mosquitoes, and thus the exposure of humans to infection.

New rearing practices

Selective breeding of cattle, and new introductions (e.g. the Chinese domestic pig), in combination with the new fodder crops, enabled farmers to keep large populations of stock in farm buildings rather than in open fields and woodland. These buildings provided attractive sites for adult mosquitoes to rest and feed, diverting them from human habitation.

Urbanisation and mechanisation

Rural populations declined as industrialisation drew people to urban areas. The increased ratio of cattle to people further reduced the attack rates of mosquitoes on humans.

Human living conditions

New building materials and improvements in construction methods made houses more mosquito-proof, especially in winter, another factor that reduced contact with the vector.

Medical care

Greater access to medical care, and wider use of quinine (in part due to a major reduction in price) reduced the survival rate of the malaria parasite in its human host, thus limiting the infection rate of mosquitoes.

These factors are a classic illustration of the role of human behaviour, human ecology, vector behaviour and vector ecology in the prevalence and incidence of a mosquito-borne disease. Moreover, the decline cannot be attributed to climate change, for it occurred at the start of the current warming phase. Nor can it be attributed, as is often stated,

to deliberate mosquito control, for it came before recognition of the role of the vector.

In contrast, malaria did not decline 'spontaneously' in countries where there was limited urbanisation and few changes in crop production and stock rearing. In the Soviet-bloc countries, for example, from Poland to eastern Siberia, major epidemics occurred throughout the 19th Century, and the disease remained one of the principal public health problems for the first half of the 20th Century. Indeed, in the 1920s, in the wake of massive social and economic disruption, a pandemic swept through the entire Soviet Union. Official figures for 1923 to 1925 listed 16.5 million cases, of which at least 600,000 were fatal (4). Tens of thousands of infections, many caused by *P. falciparum*, occurred as far north as the Arctic seaport of Archangel (61° 30'N).

The advent of dichlorodiphenyltrichloroethane (DDT) revolutionised malaria control. Cheap, safe, effective applications of the chemical could be targeted at the site where most infections occur – in the home – by treating indoor walls. Initial efforts in Italy, Cyprus and Greece were so successful that a decision was made to eradicate the disease from all of Europe. The entire continent was finally declared free of endemic malaria in 1975. One of the last affected countries was the Netherlands.

Malaria vectors are, of course, still widespread in Europe, and malaria cases in European travellers are increasing steadily due both to an increase in the volume of international tourism to endemic areas, and to migration of people from these areas to Europe. For example, in 2004, United Kingdom residents made a total of 1.2 million visits to the Indian sub-continent alone. In these circumstances, it is inevitable that there are occasional cases of autochthonous transmission. Given the efficacy of anti-malaria therapy, however, and the increasing sophistication of disease surveillance, it is safe to say that there is no chance of significant transmission arising from such cases, and certainly no chance of the disease becoming endemic, at least under current economic circumstances.

Malaria in the tropics

Ninety percent of the estimated 300 million to 500 million cases of malaria worldwide occur each year in sub-Saharan Africa. Statements on climate change and human health often focus on this region, with predictions that as many as 100 million more cases will occur as a direct result of increasing temperatures by the mid-21st Century.

The epidemiology of malaria is extremely complicated; what follows is a gross simplification. A critical aspect is the concept of *stability*. In much of equatorial Africa, parts of northern India, Indonesia, South America and

elsewhere, transmission is termed *stable* because it is fairly constant from year to year. The disease is endemic, but epidemics are uncommon. In other regions, including much of India, Southeast Asia, Central and South America, the disease is also endemic but is termed *unstable* because transmission can vary greatly from year to year, and the potential for epidemics is high. These terms are, of course, a simplification; there is a wide range of degrees of stability, depending on complex factors in local circumstances.

Stable endemic malaria

In regions where the anophelines are anthropophilic (prefer to feed on humans) and have a high survival rate, transmission is usually stable. Temperature and humidity are generally high, and there is relatively little seasonal variation. The disease is hard to control because transmission is efficient, and transmission rates are so high that most people experience many infective bites per year. Severe illness and mortality occurs mainly among 'new arrivals', i.e. children and non-immune immigrants. Older inhabitants have survived multiple infections and maintain a degree of immunity by repeated re-infection. They can have bouts of illness that are usually relatively mild, but can be life threatening.

Unstable endemic malaria

This generally occurs in regions where the anophelines are zoophilic (bite animals as well as humans), or their survival rates are low, or where both apply. Transmission can vary greatly from year to year, with epidemics separated by many years of relatively low activity, during which the overall immunity of the population declines. The factors that precipitate such epidemics are often difficult to identify. The disease may appear suddenly, for no apparent reason, only to disappear again without obvious cause. In general, transmission is relatively inefficient, and therefore requires high mosquito populations. In theory, this implies that the disease is easier to control. In practice, such outbreaks are often catastrophic, not least because the attack rate is not restricted to 'new arrivals'.

Figure 1 shows an approximate distribution of regions of stable endemic transmission in sub-Saharan Africa. The vast majority of people live in these regions. In other words, throughout their lives, they are regularly exposed to multiple bites from infective mosquitoes; in some regions they may suffer as many as 300 infective bites per year. Under such circumstances, just as it is impossible to pour more water into a glass that is already full, it is illogical to suggest that increased temperatures will result in an increased incidence of infections. On the other hand, changes in rainfall patterns could alter the distribution; a decrease in rainfall could shift transmission towards a less stable pattern.

Behavioural and ecological factors that affect transmission

As in temperate regions, the behaviour and ecology of vector and host are the dominant factors in transmission in tropical areas, and many can be attributed to poverty and explosive population growth.

Birth rate

The world's population has grown from 2.5 billion in 1950 to 6.7 billion in 2007. In sub-Saharan Africa, there are now nearly five times as many people (c.790 million) as there were in 1955. In some countries, more than half the population is under 15 years of age. A high birth rate supplies a large population of non-immunes and thus of new infections. Clinical studies in some parts of Africa quote 998 infections per 1,000 infants.

Forest clearance

Many malaria vectors breed in open sunlit pools. Forest clearance provides abundant new habitat for these species, a classic cause of the emergence of malaria problems (42).

Agriculture

Irrigation creates an ideal habitat for mass-production of mosquitoes, as can construction of dams for hydroelectric power. Rice cultivation provides an environment for many of the most efficient malaria vectors. Conversely, the drainage and cultivation of marshlands can suppress such vectors and thereby reduce transmission (25).

Movement of people

Infected people in pursuit of work can introduce malaria to areas where it is rare. Non-immune people are at high risk if they move to areas of transmission. Extensive road building and modern transportation have greatly exacerbated this factor.

Urbanisation

Water storage and inadequate water disposal can provide habitat for mosquitoes, particularly in rapidly expanding urban areas. The absence of cattle can promote stable transmission by forcing zoophilic species to feed on people. Moreover, many tropical cities are surrounded by densely populated satellite settlements that are essentially rural in nature.

Insecticide resistance

Physiological resistance to insecticides is common in many regions. Behavioural resistance can also be a problem: treatment of indoor surfaces is effective against species that prefer to feed and rest indoors (endophilic), but such treatments can select for strains with outdoor (exophilic) activity.



Fig. 1
Distribution of endemic malaria: current suitability of local climatic conditions for stable transmission of malaria in sub-Saharan Africa, i.e. regions where significant transmission occurs every year

Epidemic transmission is mainly limited to narrow bands to the north and south of the shaded area

Source: Adapted from a map based on available long-term climate data published by Mapping Malaria Risk in Africa (<http://www.mara.org.za>), a major international project supported by the International Development Research Centre, Canada; the Wellcome Trust, UK; and the South African Medical Research Council

Drug resistance

In many parts of the world, the malaria parasite has evolved resistance to commonly used anti-malarial drugs. Substitutes are available, but are much more expensive.

Degradation of the health infrastructure

Lack of funding, institutional difficulties, rapid urbanisation and other problems associated with rapid development have eroded the public health sector of many countries. In addition, the AIDS pandemic has overwhelmed the ability of authorities to deal with other diseases.

War and civil strife

In times of conflict, mass movements of people, e.g. soldiers and refugees, often promote malaria transmission. The breakdown of public health services, damage to water distribution and drainage systems, and the destruction of homes often exacerbate the situation. High concentrations of people in camps for displaced persons can also be disastrous.

Climatic factors that affect transmission

As already mentioned, the relationship between climate, weather and transmission is complex.

Temperature

High temperatures may increase the likelihood of transmission because they reduce the extrinsic incubation period, but the frequency of biting, egg laying and other behaviours are also likely to be accelerated. These are high-risk activities, so survival rate – and thus transmission rate – may also be affected.

Humidity

Survival rate may be reduced when hot weather is accompanied by low humidity, but in areas where such conditions are normal, local species are adapted to cope with them. For example, in the severe drought and extreme heat of the dry season in semi-arid parts of the Sudan, female *An. gambiae* survive for up to eleven months of the year by resting in dwelling huts, wells and other sheltered places (28). Blood feeding continues, so transmission is not interrupted, but eggs do not develop until the rains return. This gonotrophic dissociation is remarkably similar to the winter survival of *An. atroparvus* in the Netherlands and other parts of Europe in the past (4). In both cases, inactivity leads to a high vector survival rate and continued transmission of malaria, even under adverse climatic conditions.

Rainfall

Rainfall can promote transmission by creating ground pools and other breeding sites, but heavy rains can have a flushing effect, cleansing such sites of their mosquitoes. Drought may eliminate standing water, but cause flowing water to stagnate. Thus, in arid areas, prolonged drought may cause malaria to decline, whereas in areas where rainfall is normally abundant, vast numbers of mosquitoes can be produced and 'drought malaria' may follow. The same applies to artificial streams in irrigated regions and storm drains and sewers in urban areas. Drought may also stimulate people to store water in cisterns, drums and other man-made containers that serve as breeding sites for vectors of other diseases.

Sri Lanka: a counter-intuitive case

The complexity of the influence of climate on malaria transmission in the tropics is illustrated by the history of epidemics in Sri Lanka (20). In the 1930s, the disease was common. In a 'normal' year, 1.5 million cases, about a quarter of the total population, were treated in hospitals and dispensaries. However, in the years 1934 and 1935 there was a catastrophic epidemic that is estimated to have killed 100,000 people. Worst hit was the south-western quadrant of the country, a region with an average annual rainfall of more than 250 cm. The dominant vector in that part of the country is *An. culicifacies*, a species that breeds along the banks of rivers. In normal years, it was not

abundant. Malaria was endemic, but the stability index was low; in most years, the disease was relatively unimportant.

The monsoons in the preceding five years had been exceptionally favourable, with abundant heavy rainfall leading to excellent rice crops. Under such conditions, river-flow was high, *An. culicifacies* was rare, and the population was exceptionally healthy. However, when two successive monsoons failed, the rice crops were lost and there was widespread hunger. Colossal numbers of *An. culicifacies* were produced in the drying rivers and irrigation ditches. The epidemic that followed was exacerbated by the weakened condition of the people. In addition, the immunity of the population was especially low because the previous five years had been wet and therefore relatively free of malaria. By contrast, in the drier parts of the island, where *An. culicifacies* was dominant but the stability index was higher, immunity protected the population from the worst ravages of the epidemic.

Malaria was almost eradicated from all of Sri Lanka in the 1960s, but in recent years, lack of effective control has allowed the disease to return as a public health problem.

Highland malaria

A topic that is repeatedly cited in the climate change debate, in both the scientific and the popular press, is that warmer temperatures will drive malaria transmission to higher altitudes in the Highlands of Africa, particularly East Africa.

It is certainly true that, just as in lowland regions, the incidence of malaria has increased in highland areas, and it is perfectly acceptable to cite temperature as a limiting factor at altitude; vectors such as *An. gambiae* are commonly found as high as 3,000 m above sea level, but endemic malaria disappears above 1,800 m to 2,000 m. What is rarely mentioned is that less than 2% of the African continent (including North Africa) is above 2,000 m, and that much of this is so arid that it offers little opportunity for human settlement. Moreover, the history of malaria in highland areas is a compelling example of the dominant role of human behaviour and human ecology, not climate, as the driving factors in the dynamics of transmission. A useful example is the history of malaria in Kenya.

The city of Nairobi, capital of Kenya, was founded in 1899 during the construction of a railway from Mombassa, on the coast, to Lake Victoria. The site was chosen because it was on the last stretch of level ground before the steep descent into the Rift Valley. It was a swampy area, and had always been known as an unhealthy locality 'swarming with mosquitoes' (23). Indeed, in 1904, when the town had already grown substantially, a committee of doctors

petitioned the Colonial government to relocate the entire municipality because it was such a 'spawning ground for disease'. Problems with the disease began to appear at higher altitudes after the clearance of forests for the development of tea estates and the importation of infected labourers (11). The first sizeable epidemic (1918 to 1919) was attributed to the return of local soldiers from Tanzania. A major epidemic in 1926 led to recognition that economic development was a key factor in the proliferation of mosquito breeding sites, and hence the source of the increasingly serious problem:

'That there have been no notable general alterations in the domestic environment of the natives of these reserves during recent years is true, but on the other hand it is to be remembered that in every direction roads, and to a lesser extent, railways, have been carried into and through these areas, and always where there are roads, artificial and undrained excavations are to be found' (12).

The following year, the Municipal Corporation of Nairobi agreed to match a grant of £20,000 (close to US\$ 785,000 in today's money) from the Colonial government for eradication of anopheline breeding sites in the Nairobi area. Nevertheless, there were six major epidemics in the city between the two World Wars, with serious rates of transmission extending to the Londiani district (2,250 m to 2,490 m above sea level) and even at a farm near Mount Timboroa, at altitudes of 2,490 m to 2,550 m (10). Nairobi is at 1,680 m.

The fundamental cause of the upward advance of malaria was widespread deforestation and development, as the areas were opened up for large farming ventures. As described in a report by J. Gilks (Kenya's Principal Medical Officer at that time) (12), the construction of roads and railways generated innumerable flooded 'borrow pits', – depressions left by excavation for materials. These provided perfect breeding grounds for *An. gambiae*, and also contributed to the dispersal of the mosquito. The introduction of the ox wagon caused a proliferation of rough cart roads; water in the wheel ruts provided a prolific breeding site for vectors. Milldams on rivers interfered with natural drainage (10). These factors, along with many others, were components of a drastic ecological change that, coupled with a rapid increase in the human population, brought transmission to the Highlands. The disease continued to be a serious public health problem until the 1950s, when the colonial government organised an extensive control programme, mainly based on DDT, after which the area was essentially malaria-free until the 1970s.

The tea-growing estates (1,780 m to 2,225 m above sea level) in the Kericho district have an extensive medical service for employees and their dependents that was initiated in the 1920s. Health care at the central hospital of

Brooke-Bond Kenya Ltd is extended to some 100,000 inhabitants of the region. However, mosquito control efforts have declined, and malaria has re-emerged as a serious problem, with epidemics in almost every year from 1990 to 1997, and a mean annual attack rate of around 50% (21). Peak transmission is from May to July, i.e. after the principal rainy season and before mean monthly temperatures drop below 18°C. A questionnaire survey (June 1997) indicated that only 8% of patients had travelled to areas with known malaria transmission in the previous 30 days.

The main factor in this recrudescence may be increased resistance to anti-malarial drugs and/or the unsupervised use of ineffective medications, but the picture is not entirely clear (40). Whatever the cause, the history of multiple epidemics in the earlier part of the century, including many at higher altitudes, makes it unnecessary to infer climate change as a contributory factor. Moreover, a set of well-maintained meteorological records on the tea estates shows no significant change in temperature over recent decades (16). Indeed, in a detailed report to the World Health Organization, a group of malaria specialists based in Nairobi dismissed those who claim a global warming link as 'scientific Nostradamus' (41).

The arboviruses

Travel and transportation have been an important activity since the earliest societies. Trade in useful materials, such as flints, amber and gold involved movement over long distances, even in prehistoric times. This mobility and the range of goods transported have increased exponentially in recent times, and with this increase has come an increase in the transportation of vectors and pathogens. If global temperatures continue to rise, their impact on disease transmission must be viewed in the context of this quantum leap in the globalisation of disease.

Yellow fever

An early example of globalisation was the introduction of yellow fever and the yellow fever mosquito, *Aedes aegypti*, to the New World during the slave trade. Slave ships generally made the passage from Africa to the Americas in four to six weeks. The mosquito readily adopted the casks used for shipboard storage of water as breeding sites. The water probably contained enough organic material to support several generations of mosquito per voyage, and the slaves were an abundant source of blood. With the slaves and the mosquito came the deadly yellow fever virus (YFV). It was not uncommon for ships with dead or dying persons to arrive in port, hence the yellow flag of quarantine. From the 16th Century onwards, epidemics

of yellow fever occurred in all countries involved in the West Africa slave trade, and were a major cause of mortality in North America as far north as Boston. In the great epidemic of 1898-1899, for example, the city of Memphis, Tennessee, was virtually depopulated and the virus spread over much of the country, with an estimated 100,000 cases and 10% mortality. In Europe, outbreaks occurred in many port cities as far north as Brest, Cardiff and Dublin.

Yellow fever is a zoonotic disease of primates transmitted in forested areas between monkeys, primarily by day-active mosquitoes of the genus *Aedes* (sub-genus *Stegomyia*) that feed exclusively on primates. Humans who enter the forest, or live close to forested areas, are infected by the bites of infected mosquitoes. Outside the forest, closely related species can continue transmission given the presence of humans or other primates. Of these, *Ae. aegypti* is remarkable because it has adopted the human domestic environment to great advantage. It remains day-active with a preference for heavy shade. It freely enters homes and other buildings, and spends much of its time skulking in dark places – often hidden among clothing – which provide a stable microclimate with few predators. Its host is superabundant and lives under the same roof, an arrangement that minimises the hazards of questing for a blood meal. It oviposits freely in man-made articles that contain water, from discarded tyres and buckets to the saucers under flowerpots and water-storage barrels. In urban areas, humans are literally the perfect host: they provide safe shelter, plentiful food and abundant sites for procreation. Indeed, in most of the crowded cities of the tropics, homes are so close together and breeding sites so abundant that urbanisations can be regarded as a single unit, a factory for mosquitoes.

The implication of *Ae. aegypti* as a vector of yellow fever by Carlos Finlay in Havana, Cuba, and experimental confirmation by Walter Reed, led to major sanitation campaigns and an end to major urban transmission in most of the Americas. In the 1920s, however, it became clear that the virus was established in enzootic transmission in the forests of Mexico and Central and South America, transmitted by New World mosquitoes. Epizootic waves of transmission continue to occur in the South American rainforest, and small numbers of human cases still occur every year. In the mid-1950s, the Pan American Health Organization (PAHO) initiated a hemispheric *Ae. aegypti* eradication campaign with the express purpose of eliminating the risk of urban yellow fever transmission. In less than ten years, 22 countries were declared free of the species, a stupendous achievement.

Unfortunately, for a variety of reasons (35) the programme was abandoned, and the species has regained and extended its former territory and is ubiquitous from Mexico to

northern Argentina. Until recently it was also common in the United States of America (USA), but it has been displaced by *Ae. albopictus* in many regions. Large-scale endemic transmission of dengue has followed this re-infestation; all four serotypes (see next section) circulate in much of the continent, often with massive outbreaks, particularly in urban areas. Given that YFV shares the same vector and transmission dynamics, there is every reason to believe that the introduction of YFV to such areas could initiate a similar epidemic, with potentially catastrophic consequences.

In summary, human activities and a man-made urban ecology have enabled the mosquito and the virus to spread far beyond Africa (though to date it has never been transmitted in Asia). For reasons that are not clear – but possibly due to anti-malaria campaigns – *Ae. aegypti* has disappeared from Europe, but its current distribution in the USA, in 11 states from Texas to South Carolina, confirms that there is no climatic reason why it could not return. A safe and effective vaccine is available, but is little used except in Brazil and by travellers. In the event of an outbreak, mass vaccination would be required. The problem would be availability: given the mobility of people and the risks of worldwide dissemination, current stocks would be inadequate to answer demand.

Dengue

Dengue is a virus closely related to yellow fever (both are in the Japanese encephalitis sub-group of the family *Flaviviridae*), and also originated in forested areas, transmitted between monkeys. The first major epidemic of dengue was recorded in Philadelphia in 1780, and was concurrent with documented epidemics in Indonesia, India, Persia, Arabia, Egypt and Spain. Epidemics were common in North America and in Europe until the mid-20th Century. The greatest of these occurred in Greece in 1927-1928, with an estimated 1 million cases and 1,000 deaths (13).

Dengue is now the most important mosquito-borne viral disease affecting humans; its global distribution is comparable to that of malaria, and an estimated 2.5 billion people live in areas at risk for epidemic transmission. About 5% of clinical cases require hospitalisation (when available) and 1% to 5% of such cases are fatal. Unfortunately, sustained prevention of dengue transmission by mosquito control has never been achieved, except during the *Ae. aegypti* eradication campaign already mentioned.

Unlike yellow fever, dengue exists in four distinct serotypes; in theory, a person can suffer four infections before becoming immune to the disease. Serosurveys have revealed that up to 80% of children in cities such as

Bangkok and Kuala Lumpur have been infected by more than one serotype by the age of fifteen. Epidemics of different serotypes are often asynchronous, their timing dominated by local history of transmission – the ‘herd immunity’ – rather than any obvious climatic factor. At present, no vaccines are available.

Outbreaks of dengue in the USA continued until after World War II. During the post-war malaria eradication campaign, screening of doors and windows of houses became obligatory in most states. This may have contributed to the decline of the disease. The advent of cheap air conditioning was undoubtedly another. In 1999, during an outbreak on the USA/Mexico border, populations of *Ae. aegypti* were higher on the Texas side (probably due to limited mosquito control), but the incidence of cases was sixteen times higher on the Mexican side, where relatively few homes and buildings were air-conditioned (36). As with malaria, economics, environment and human behaviour, rather than climate, are often the dominant factors in dengue transmission.

Chikungunya

Chikungunya is a third primatophilic virus (family *Togaviridae*) that is enzootic in African (and perhaps Asian) forests and transmitted by primatophilic mosquitoes. Although not generally life threatening, symptoms include painful arthralgias that can persist for months and even years. The disease received relatively little attention until 2005, when it appeared on a number of Indian Ocean islands, notably Reunion, Mauritius and the Seychelles (38). Transmission was part of a pandemic that spread through southern Asia and into Indonesia and the Philippines and is continuing at the time of writing (January 2008). There have been an estimated 1.2 million cases in India alone, though apart from the highly publicised outbreaks in the Indian Ocean (major tourist destinations) there has been little attention to this in the world press.

The chikungunya outbreak highlighted a second forest vector species that has adapted to the urban environment, *Ae. albopictus*. Until the outbreaks on Reunion and Mauritius, this species had been regarded as a ‘secondary’ vector, less efficient than *Ae. aegypti* in transmission because it is not specifically primatophilic (34). *Ae. aegypti* is virtually absent from both islands, so its role is being re-examined.

The saga of *Ae. albopictus* over the past forty years is analogous to that of *Ae. aegypti* in the days of the slave trade, but in a modern scenario. In 1983, a single specimen appeared in Memphis, Tennessee, the first such capture in the New World (33). In place of water casks in sailing ships, it appeared that containerised shipping was

to blame. In the past 50 years, containerisation has revolutionised the transport industry, and the speed at which goods packed in containers are transported worldwide, by sea, rail and road, adds a new dimension to the mobility of vectors and other organisms. Moreover, this emphasis on speed means that dockside inspections of cargo are next to impracticable.

In 1985, the mosquito appeared as a major pest species in Houston, Texas. Discarded tyres, common on wasteland throughout the county, appeared to be the principal breeding site. A chance observation – two people collecting such tyres – revealed an international trade in used tyres that involves nearly every country in the world (37). Japan was (and remains) the principal exporter, with more than a million tyres to 149 countries per year, but the USA and Europe are also heavily involved (30). A subsequent survey revealed that all states bordering the Gulf of Mexico were infested with what is now known as the ‘Asian Tiger mosquito’. At the port of Seattle, five species of Japanese mosquito were found in shipping containers packed with 20,000 tyres shipped from Japan. A laboratory study demonstrated that the day-length period required to trigger the onset of winter diapause in the Texas mosquitoes was identical to that in Japan (15).

In retrospect, we know that Albania had been infested from the early 1970s (1), and the species was established in many regions of Brazil. It is now present in nearly all countries of the Americas, in at least 12 countries in Europe, in Nigeria, Gabon and the Cameroons, and in the Middle East. In the USA, it is present as far north as Nebraska and Illinois, where winter temperatures below -20°C are normal. There is little doubt that it will extend its range to most, if not all countries in Europe. New infestations, attributed to importation of ‘Lucky Bamboo’ plants from Asia, have already been identified in the Netherlands and Belgium.

The used-tyre trade is a direct result of containerisation; shipments of loose tyres would be difficult to handle by older methods of unloading cargoes at the wharf side. The epidemics of chikungunya on Indian Ocean islands are a consequence of a new human behaviour: flying. Infected persons can travel virtually anywhere in the world within 36 h. A strain of dengue virus circulating in an epidemic in Sri Lanka appeared in the same year in Puerto Rico, another circulating in an epidemic in Tahiti appeared in the Hawaiian Islands. We must now regard Airbus and Boeing as effective vectors!

In the context of the preceding paragraphs, it is regrettable that the appearance of an exotic vector or disease is almost invariably attributed to climate change. For example, Italy has been plagued by *Ae. albopictus* since the early 1990s (7), apparently introduced in shipments of used tyres from Atlanta, Georgia (7). The aggressive bites of *la zanzare tigre*

are a painful nuisance in Rome and many other cities, but given that the species thrives in Beijing and Chicago, it is no surprise that it can survive in the Mediterranean climate.

In 2007, a traveller from India developed a fever shortly after arriving in a small town in northern Italy. His illness triggered a small outbreak of chikungunya, transmitted by *Ae. albopictus* (2). The town is in the delta region of the river Po. The area was once notoriously malarious, but the disease disappeared when the marshes were drained at the beginning of the 20th Century (4). Thus, human activities that had altered the local ecology and eliminated malaria provided a new environment (human settlement) suitable for the establishment of an exotic species of mosquito, well-adapted to freezing winters, that had been carried in containerised cargo across the Pacific Ocean and subsequently the Atlantic Ocean by modern transportation and was followed by an exotic virus that arrived in a passenger who had been infected on yet another continent and had been transported by jet aircraft.

Given this remarkable sequence of events, it is regrettable that shortly before an international conference on climate change, a number of authoritative statements were made that implied that both the presence of the mosquito, and the occurrence of the outbreak may have been due to climate change. If the virus is present in the eggs of infected mosquito, survives the 2007-2008 winter (a mechanism known as vertical transmission), and reappears in the spring, such statements will probably be repeated.

West Nile virus

Rapid transportation by aircraft is not limited to people. West Nile virus (WNV) is yet another flavivirus, but one which is transmitted between birds, mainly by mosquitoes of the genus *Culex*. It is native to the Old World and, prior to the late 1990s, was already the world's most widely distributed arbovirus, extending from Europe to Australia. In 1999, however, a topotype circulating in Tunisia and the Middle East appeared in the Bronx, New York, presumably imported in a live bird or birds (17). The subsequent spread of the virus throughout the USA was dramatic: within four years it was present in all states and in nearly every county in all states east of the Rocky Mountains. Today it is transmitted every year, from up to seven provinces in Canada to Venezuela, and possibly further south. In temperate regions, incidence does not appear to follow a latitudinal trend, so climate is unlikely to be a dominant factor in transmission.

West Nile virus is typical of the many arboviral zoonoses that are characterised by long periods of invisibility, when little or no evidence of their existence can be detected. At erratic intervals, sometimes separated by several decades,

there is a sudden recrudescence, often developing into an explosive epidemic. Retrospective studies of such epidemics frequently suggest, by association, weather-related factors that could have been responsible for triggering this recrudescence and these associations offer fertile ground for speculation. Nevertheless, the timing of recrudescence remains enigmatic and notoriously unpredictable (29).

Until the New World panzootic, WNV received little attention. It can cause encephalitis in horses, and equine cases, although rare, are often the first indication of local transmission. Human clinical cases are even rarer, but small clusters have been identified at erratic intervals in several European countries (26). Two sizeable epidemics, however, have occurred in urban areas in Eastern Europe:

- Bucharest, Romania, in 1996 (393 confirmed cases, 39 deaths)
- Volgograd, Russia, 1999 and 2005 (234 confirmed cases, 77 deaths)

Both were associated with poorly maintained plumbing in Soviet-style apartment blocks; cellars flooded with sewage-containing water were a virtual factory for *Culex pipiens*, an effective vector (39). Outside Europe, Israel (43) has had two comparable epidemics, in 1956-1957 and 2000 (total: 836 confirmed cases, 37 deaths), plus 261 cases and five deaths in the past seven years. All three sites are on major migratory routes of birds that overwinter in Africa, but by far the largest outbreak on record anywhere in the world was in South Africa in 1974, with an estimated 30,000 suspected cases. Algeria, Tunisia, Sudan and Morocco have had smaller outbreaks.

Despite this widespread activity, a mere 188 fatal cases have been confirmed in humans in the Old World over the past 60 years. Of course, the efficacy of surveillance varies greatly between countries, and we have little information for many countries, including most of Asia, but it is safe to say that despite the ubiquity of the virus, human cases of WNV in the Old World are very rare.

In the New World, the situation is entirely different (18). The virus is lethal to native species of wild birds and has been isolated from dead specimens of more than 250 species, as well as native mammals and even alligators. From 1999 to 2007, 32,018 human cases were confirmed in North America (excluding Mexico), 14% (4,533) of which were in Canada. The death toll for the two countries over the same period was 1,166 (0.04%). There can be little doubt that these figures reflect a much higher prevalence and incidence of zoonotic infections than in the Old World, although funding for WNV surveillance and control dwarfs that in the Old World, probably exceeding US\$ 500 million in the past nine years.

The devastation of WNV as an enzootic pathogen in the New World is analogous to that of YFV in the American rainforest. In Africa, yellow fever circulates in its sylvatic hosts without apparent clinical symptoms. In the New World, it is lethal: local people recognise that when the jungle goes silent – the Howler monkeys are dying – yellow fever is circulating. Thus, it is not necessary for a virus to be unusually virulent for it to cause havoc; in both cases, a virus that co-exists with its primate hosts in its original habitat is highly pathogenic for naïve populations in areas where it is exotic. We have no knowledge of when YFV became enzootic in the Americas; it may have happened as early as the 17th Century. Whatever the date, YFV is still pathogenic for New World monkeys, so it is likely that WNV will continue its catastrophic ecologic impact for many years to come.

West Nile virus has a closely related counterpart in the New World: Saint Louis encephalitis virus (SLEV). This virus is similar to WNV in the Old World in several ways:

- SLEV is in the Japanese encephalitis group of the *Flaviviridae* (as are dengue and yellow fever)
- transmission is between birds by ornithophilic mosquitoes, mainly *Culex*
- infection of New World species of birds is ‘silent’, i.e. the virus is not seriously pathogenic
- viraemia in humans and horses is low, so they are considered ‘dead-end hosts’
- epizootics are generally signalled by small clusters of equine and human encephalitis
- larger urban epidemics, as in Saint Louis, Missouri, in 1932-1933, are associated with sewage-polluted ditches or other collections of water with high organic content that produce large numbers of *Culex* mosquitoes
- SLEV is disseminated by migratory birds
- the range of SLEV stretches from Canada to Argentina.

Studies of Saint Louis encephalitis (SLE) in North America far outstrip efforts to understand the epidemiology of WNV in Europe, and are an acceptable model for speculations on factors affecting transmission of both viruses.

Many attempts have been made to associate the erratic appearance of SLE with specific weather conditions. In a review, Monath concluded that warm winters, late wet springs, and hot drought summers were associated with epizootic activities of SLE (24). He suggested that survival of *Culex* species was higher in warmer winters. However, no difference in the mortality of overwintering *Culex pipiens* was observed in Memphis, Tennessee, in the winters of 1981-1982 and 1982-1983, although the first

was colder than average, with minimum temperatures as low as -18°C and the second was the fourth warmest on record (Reiter, unpublished). It has been suggested that a cool April delays the nesting activity of birds, thereby inducing synchrony between high mosquito populations and the availability of non-immune nestlings, yet low temperatures will also delay the multiplication of vectors, so a normal or warm April followed by a warm May would seem more advantageous to continued virus amplification. The author has put forward an alternate suggestion (29). He observed that *Culex restuans*, a species that is dominant in the cooler weather of springtime but is dormant during the summer, is reactivated by short periods of cold weather during the hotter months. He hypothesised that such anomalies could enable the spring species to relay virus via avian hosts to *Culex pipiens*, a species that peaks in July and August. This held true for many, but not all years of high transmission, and there were a number of years when transmission was not evident despite these weather anomalies (29). Thus, the epidemiology of these viruses is far from clear. Moreover, there has been little evidence of SLE transmission since the mid-1970s, despite warmer winters, record hot dry summers and an unprecedented effort at surveillance for WNV, which uses methods that are common to both viruses. For example, 3,576 human cases of WNV, but only seven cases of SLE, were confirmed in the USA in 2007.

In Europe, it has been suggested that WNV outbreaks are associated with hot dry summers, but the relationship is tenuous at best. For example, during the first three years of a current study of WNV – part of a European Commission project ‘Emerging Diseases in a Changing European Environment’ (codenamed EDEN: http://www.eden-fp6project.net/diseases/west_nile_virus) – there was record rainfall in Romania in the spring and summer of 2005 and 2006 followed by record heat and drought in 2007. In the same years, southern Spain had two years of severe drought followed by a wetter, cooler summer, yet neither region had any remarkable WNV activity. Indeed, fewer than ten human cases of WNV infection were confirmed for the whole continent during this period. Clearly, climate is not the determinant factor for transmission.

The West Nile epizootic in the New World prompted new interest in this previously obscure virus in Europe. Sequencing data show a wide range of topotypes that appear both north and south of the Sahara. Thus, we can regard WNV and SLEV as migratory viruses transported by birds. This may explain why the virus has no specificity for vector or host: in its movements between distant habitats it inevitably encounters different species of vector and host.

Sequencing of WNV reveals two lineages, but whereas Lineage I is ubiquitous in Africa and Europe, Lineage II has rarely appeared north of the Mediterranean (Fig. 2). The same is true for a New World virus, Eastern equine

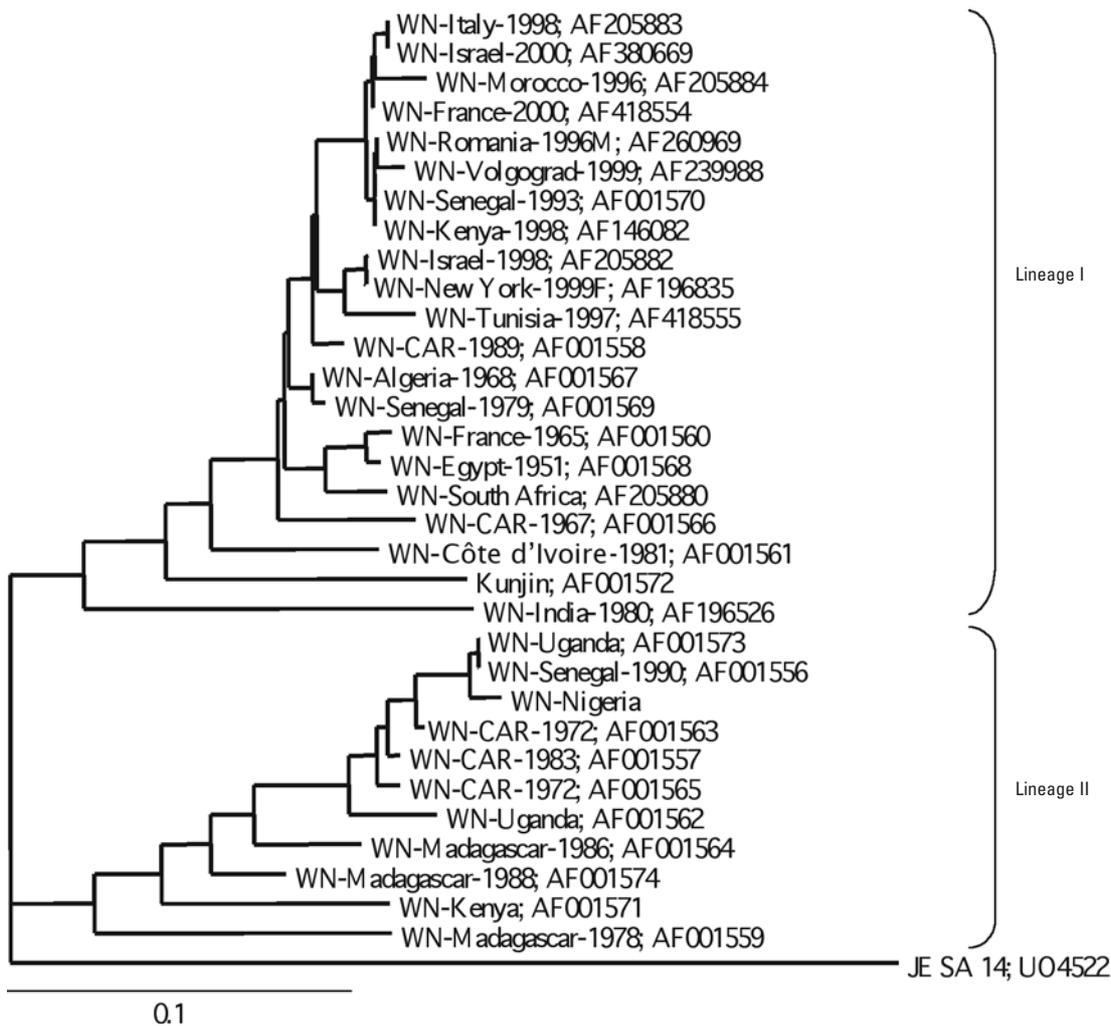


Fig. 2

Phylogenetic tree based on nucleic sequence data of West Nile virus E-protein gene fragment of 254bp

Genebank accession numbers for the sequences included in the tree are indicated (27). The tree indicates evidence of widespread dispersal of virus in migratory birds. Note for example, the close similarity between isolates from Senegal, Kenya, Romania and the Russian Federation

encephalitis, a mosquito-borne *Alphavirus* of birds that occasionally affects humans and horses. The lineage that is enzootic in North America is quite distinct from the one in South America. Both lineages infect resident and migratory birds, but evidently critical elements in their intercontinental movement are missing.

West Nile virus occasionally affects other domesticated animals. For example, high mortality in domestic geese (associated with significant numbers of human cases) was observed in Israel (3) and in some migratory birds, but such events are rare. Recent studies (5) revealed high seroprevalence (78%) in horses in Senegal. Interestingly, unlike in Europe, equine infections in that country appear to be asymptomatic, perhaps an indicator of prolonged and consistent exposure to the virus. The same appears to be true for SLE infections of horses in South America.

In conclusion, despite attempts to identify climate factors as determinants of the irregular appearance of WNV and SLEV, the issue remains enigmatic. The high seroprevalence of WNV in horses in Senegal may mean that factors, including climate, which influence transmission south of the Sahara are the principal determinants of the appearance of the virus in North Africa and Europe. In other words, transmission in Europe and North America may be the 'tip of the iceberg' of transmission in the tropics. Whatever the explanation, it is illogical to view the panzootic of WNV in the New World as a portent of future WNV transmission in the Old World; the two are entirely different situations. On the other hand, it is probably valid to fear that the accidental introduction of SLEV into Europe could have a catastrophic impact on wildlife in the Old World. Strict quarantine of birds imported from the Americas, with effective mosquito-

screening of cages should be considered as a precaution. Apart from this, as with most zoonoses, there is little that can be done to protect the human population against infection, but effective sewage disposal and the elimination of standing, polluted water may limit risk by reducing populations of *Culex* mosquitoes.

Japanese encephalitis

Japanese encephalitis (JE) is yet another flavivirus transmitted between birds by *Culex* mosquitoes, but unlike WNV and SLEV, major epidemics involving tens of thousands of cases have occurred from India to north-eastern China, and continue to be a major public health problem in many regions despite the availability of a cheap effective vaccine. As with WNV and SLEV, avian transmission is relatively silent, but unlike these viruses, JE produces high titres in mammals, notably the domestic pig. For this reason, pigs serve as amplifying hosts, greatly augmenting the infection rate of local mosquitoes, including species that readily feed on humans. In many Asian countries, people and domestic pigs live in close proximity, so the incidence of human infections is far higher than if transmission were directly from birds. This is particularly true in rice-growing areas, where an abundant species, *Culex tritaeniorhynchus*, feeds readily on pigs and humans. Thus, once again, human ecology and human behaviour, not climate, are the key factors in transmission.

Rift Valley fever

Rift Valley fever is a zoonosis that affects livestock, principally sheep and goats. During periods of drought, the virus survives in the eggs of certain species of *Aedes* that hatch when rainfall returns. It is transmitted to humans by mosquito bite, but more often by contact with the body fluids of dead animals. The completion of a trans-Saharan road will heighten the risk of introduction of this virus north of the Sahara. Major trade in animals already

exists between Africa and the Arabian Peninsula; an estimated seven million animals are exported to Saudi Arabia during the pilgrimage seasons every year. If the virus were introduced into Europe, native European mosquitoes are probably competent for transmission. Rift Valley fever is enzootic in many parts of Africa, including the highlands of Kenya, so there is little reason to believe that lower temperatures in northern Europe would limit transmission. The virus is dealt with in more detail in another article in this *Review* (22).

Final comment

The ecology and natural history of disease transmission, particularly transmission by arthropods, involves the interplay of a multitude of interacting factors that defy simplistic analysis. The rapid increase in the incidence and worldwide dispersal of human and animal diseases is a major cause for concern – and will continue to spring surprises – but obsessive emphasis on the role of climate is unwarranted, and only serves to misdirect efforts to tackle the problem. Priority should be given to effective quarantine, surveillance, well-managed contingency plans, and improvements in our understanding of the dynamics of transmission.

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Le changement climatique et les maladies transmises par les moustiques : ne pas mettre la charrue devant les bœufs

P. Reiter

Résumé

Les spéculations sur les impacts potentiels du changement climatique sur la santé animale mettent souvent l'accent sur les maladies transmises par les moustiques, en ignorant complètement la complexité des très nombreux facteurs en interaction qui exercent une influence sur la dynamique de la transmission de ces maladies. L'examen holistique de cette complexité (prenant en compte l'écologie et le comportement de l'hôte ainsi que ceux du vecteur) est le seul point de départ acceptable pour évaluer correctement le rôle du climat dans la prévalence et l'incidence de ces maladies.

Mots-clés

Arbovirus – Changement climatique – Chikungunya – Dengue – Encéphalite St Louis – Fièvre de West Nile – Fièvre jaune – Maladie émergente – Moustique.



El cambio climático y las enfermedades transmitidas por mosquitos (o por qué no hay que empezar la casa por el tejado...)

P. Reiter

Resumen

Las especulaciones sobre los posibles efectos del cambio climático en la salud humana suelen girar en torno a las enfermedades transmitidas por mosquitos, pero a menudo dejan de lado la compleja interrelación de la miríada de factores que en general dominan la dinámica de transmisión de dichas enfermedades. El único punto de partida válido para determinar la influencia del clima en la prevalencia e incidencia de tales patologías estriba en adoptar una visión holística de esta compleja cuestión, y en especial de la ecología y el comportamiento tanto de los hospedadores como de los vectores.

Palabras clave

Arbovirus – Cambio climático – Chikungunya – Dengue – Encefalitis de Saint Louis – Enfermedad emergente – Fiebre amarilla – Mosquito – Virus West Nile.



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