CLINICAL MICROBIOLOGY REVIEWS, Jan. 2004, p. 136–173 Vol. 17, No. 1
0893-8512/04/$08.00+0 DOI: 10.1128/CMR.17.1.136–173.2004

Global Change and Human Vulnerability to Vector-Borne Diseases

Robert W. Sutherst*

CSIRO Entomology, Indooroopilly, Queensland, Australia 4068

* Mailing address: CSIRO Entomology, Long Pocket Laboratories, 120 Meiers Rd, Indooroopilly, Queensland, Australia 4068. Phone: (617) 3214 2800. Fax: (617) 3214 2881. E-mail: Bob.Sutherst@csiro.au.

INTRODUCTION

Global change refers to the complex of environmental changes that is occurring around the world as a result of human activities. Some scientists refer to it as a huge human experiment on the Earth, for which we have little idea of the ultimate outcome, limited ways of finding out a priori, and perhaps no way of reversing. Global change is occurring across a wide range of fields, and those changes affect almost every aspect of human societies.

There have been a number of recent reviews covering aspects of global change and human health, including infectious diseases (53, 61, 117, 126, 134, 205, 206, 222, 223, 246, 249). Several reviews have specifically targeted vector-borne diseases (121, 125, 249, 270, 303, 304, 307, 318). There have not yet been thorough quantitative studies addressing the many processes at work (53, 210, 211, 248, 304, 309, 310). In part this is because of the complexity of the many indirect and feedback mechanisms that bear on all aspects of global change. Any consideration of one particular cause of change cannot be made in isolation because of the many interactions between the different drivers of change. As a result, appeals have been made to take a holistic approach to risk assessment and management of vector-borne diseases (117, 121, 208, 220, 268, 307, 347). Unfortunately, the state of current analytical skills and data and the limited resources of the scientific community have resulted in consideration of isolated subsets of those changes in any quantitative risk assessment.

This review focuses on developing a holistic approach to the assessment of vulnerability of societies to vector-borne diseases. The aim is to assess the risks of potential changes in the status of vector-borne diseases in a changing world and to consider approaches to effective adaptation to those changes. The review presents a framework for an integrated assessment of the impacts of different global change drivers and their interactions on vector-borne diseases. The framework enables potentially important secondary interactions or mechanisms and important research gaps to be identified and provides a means of integrating targeted research from a variety of disciplines into an enhanced understanding of the whole system.

The ecology and epidemiology of vector-borne diseases can be described using the "disease triangle" of host-pathogen-environment originally developed by plant pathologists. The disease triangle concept was extended (305–307) to emphasize the role of management in adapting to risks from invasive species and animal parasites. The risk assessment community's concept of vulnerability, as used by the Intergovernmental Panel on Climate Change (IPCC) (244), and the quarantine community's concept of pest risk analysis (146) were included. Here this combined approach is used to structure review material on vector-borne diseases of humans (Fig. 1).

The scheme provides a framework to guide the evaluation of risks and opportunities arising from global change effects on vector-borne diseases at a given location. It summarizes the components of the human disease complex that need to be addressed in any risk assessment. Hosts include both primary and secondary vertebrate hosts (including humans), and vectors include insects, ticks, and snails. The pathogens considered are restricted to vector-borne diseases that affect humans, including zoonoses. A broad view is taken of the environment as it affects vector-borne diseases because socioeconomic changes occurring around the world have major significance for future trends in disease patterns.

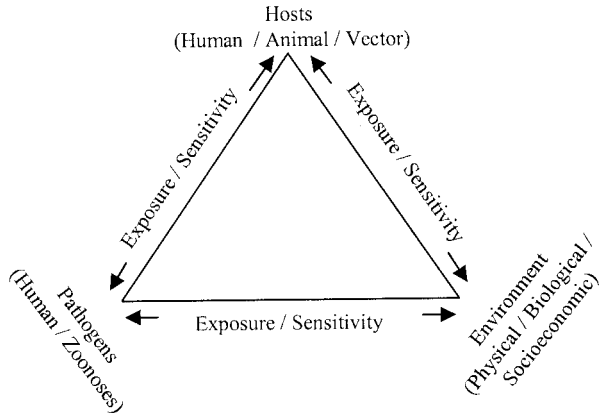

FIG. 1. A host-pathogen-vector-environment framework for the assessment of risks to humans from vector-borne diseases under global change.

SCENARIOS OF GLOBAL CHANGE

There are a number of drivers of global change that are changing the physical and social environment on Earth to such an extent that they have the potential to influence the status of many vector-borne diseases (Fig. 2). Global change drivers differ in that some, such as increases in the concentration of atmospheric carbon dioxide (CO_2) or climate change, have global origins with global impacts while others, like land use or irrigation, have local origins but are occurring on a global scale. It is important to emphasize that there is considerable uncertainty about the extent to which each of the changes will occur in the future. This is because the changes depend on human behavior and economic growth, the ability of the Earth's natural systems to act as a buffer against those changes, and the degree of skill that has been achieved in the science involved in estimating the environmental impacts of those changes.

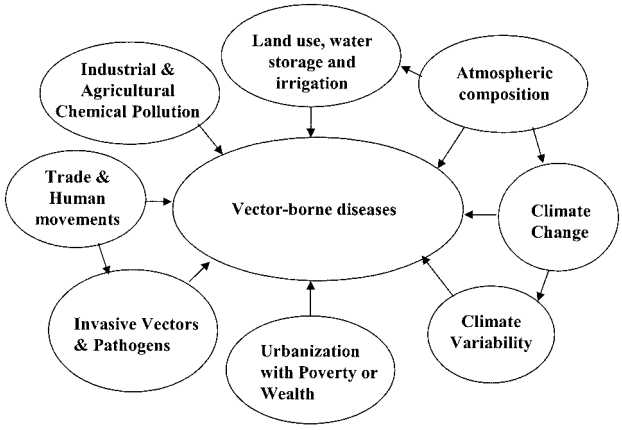

FIG. 2. Drivers of global change considered in relation to potential changes in the status of vector-borne diseases.

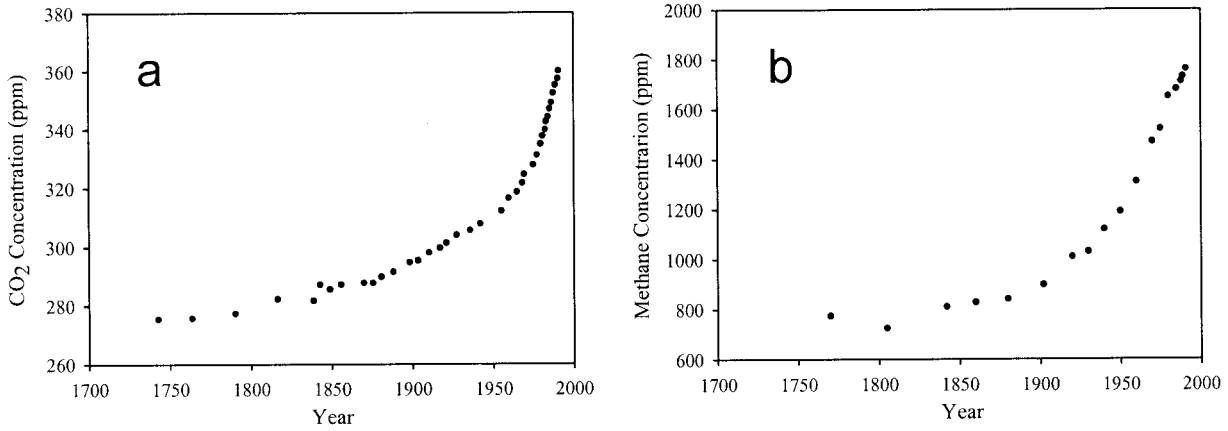

FIG. 3. Changes in the concentration of the key greenhouse gases carbon dioxide (a) and methane (b) since preindustrial times. Reprinted from http://www.ipcc.ch/press/sp-cop6/sld5.jpg with permission from Intergovernmental Panel on Climate Change (data archived at the Hadley Centre for Climate Prediction and Research).

Atmospheric Composition

The Earth's surface is kept warm by a blanket of greenhouse gases, including water vapor, CO_2 (261), methane, nitrous oxide, and some industrial gases like chlorofluorocarbons. Each gas has different warming properties depending on its structure and persistence in the atmosphere. The composition of the atmosphere has been changing over the past century, with the concentrations of these gases, except perhaps water vapor, rising as a result of the burgeoning anthropogenic activities (144). In particular, burning of fossil fuels for power and transport is transferring millions of tons of buried fossil fuels into the atmosphere each year in the form of CO_2. Livestock, rice paddies, and leakage from coal beds are also increasing the concentration of methane. There is less uncertainty about the extent of the increase in the concentrations of these gases than there is about the consequential changes in the climate. Nevertheless, changes in the concentration of CO_2 are subject to widely different estimates that depend on assumptions about future patterns of growth in the consumption of fossil fuels. Other anthropogenic changes such as urbanization, water supply and distribution, forest clearing, agriculture, and trade issues are more predictable.

This giant undesigned and untestable human experiment with the Earth's climate and atmosphere (it is the only one that we have) has already increased the atmospheric concentration of CO_2 by almost one-third (Fig. 3a) and doubled the concentration of methane in the atmosphere (Fig. 3b). None of these changes in atmospheric composition is known to affect vector-borne diseases directly. However, the effects of higher concentrations of CO_2 on plants are to reduce their water loss through transpiration and to act as a fertilizer. The result is that plants produce more foliage with the same amount of water (261), provided that they do not exhaust the supply of other nutrients. Two consequences of this phenomenon that are relevant to the current consideration of the effects on vector-borne diseases are that the increased density of plant foliage will provide more favorable microclimates for insect vectors and that plant growth seasons will be extended in some situations, effectively increasing the duration of favorable microclimates each year. A further consequence in some habitats may be a larger residual amount of water being left in the soil after maturation of a crop. This could affect water tables and the speed with which soils saturate and produce surface water reservoirs suitable for breeding of mosquitoes. It follows that the increased water use efficiency of plants at high CO_2 concentrations may result in an expansion of the ranges of woodlands into lower rainfall areas with adequate soil nutrients, leading to spatial changes in the ranges of vectors in response to habitat changes (95).

Climate Change

The issue of human-induced climate change is a contentious one because it is difficult to detect a slight trend in average temperatures when it is masked by a large amount of annual variability. However, in 1996 the IPCC, an international panel of scientists commissioned to advise governments on progress in the science that underpins the understanding of climate change, stated for the first time, that "the balance of scientific evidence suggests that human activities during the last century have begun to have a discernible effect on the world's climate, causing it to warm" (140). Projected changes in the average climate depend strongly on assumptions about the relationship between the global temperature and greenhouse gases produced by human activities (144). A statistical analysis to separate solar and anthropogenic influences implied that 60% of the warming in the last 140 years was due to human activity (27). A similar analysis showed that in recent decades, the temperatures have broken out above the band of variation that has been observed over the past 1,000 years and the rate of increase is accelerating (71). This image has been referred to within the global-change community as "the image of the millennium" and provides a sobering summary of the last 200 years of human impacts on Earth. Unfortunately, one consequence of this analysis is that future rates of anthropogenic warming are expected to be greater than previously estimated because earlier analyses overestimated historical contributions from anthropogenic activity. This contributed to an update of the future scenarios for climate change (144).

These projected changes rely on extrapolation of expected trends and do not consider possible triggers that may be set off

as the Earth's atmosphere warms. One phenomenon that could have overwhelming effects is a failure of the circulation of warm water from the Gulf Stream into the North Atlantic Current, which forms part of a global salt conveyer belt. The current is driven by cold, saline water sinking in giant underwater waterfalls off Labrador and Greenland, which flush the cold water back into the warm Atlantic. Global warming could cause a failure in the flushing mechanism by diluting the saline water with bursting of ice dams from melting glaciers, by increasing rainfall in the region, or by reducing the temperature gradients in the sea. In the past, this has triggered very large (up to 10°C) and very rapid (a decade or century) "flips" in climate every few thousand years, with equally rapid reversals or "flops," leading Calvin (52) to call them climate "flip-flops." The effect is to put the world into a cold-dry climate, with Europe's climate equating to present-day Siberia, with devastating consequences in terms of food supplies for the world as a whole. This would reduce risks of almost all vector-borne diseases, except perhaps flea-borne diseases, among a starving population. An equally rapid warming event would have catastrophic implications for vector-borne diseases, with rapid geographical expansion of tropical ranges affecting nonimmune populations. Since any sudden cooling will greatly reduce the risks of vector-borne diseases and a subsequent warming would be well beyond the time horizon that is relevant to the present topic, these flip-flops are noted for their wider risks but are not considered in this review.

Projected changes in rainfall are even more uncertain than those for temperature, with large differences in the climate projections from different global climate models (GCMs). The consensus is that most tropical areas, particularly over oceans, will receive more rainfall, with decreases in most of the subtropics and relatively smaller increases in high latitudes (144). The uncertainty about rainfall is increased by the potential for geographical and seasonal shifts in rainfall patterns, so that local outcomes are difficult to foresee. Readers are cautioned to interpret the following projections of changes in the status of vector-borne diseases with climate change with care. They are indicative only and are intended to alert the community to some of the steps that can be taken to insure against any deterioration in public health caused by vector-borne diseases.

There have been numerous reports of physical and biological changes in the environment that are consistent with current warming of the Earth's surface. These include an increase in the altitude of the freezing point in the tropics by 110 m (83) and the melting of tropical glaciers around the world (321). A wide range of biological effects of recent climate change has been noted (142, 219, 243, 282), including population and life history changes, shifts in geographical ranges, changes in species composition in communities, and changes in the structure and functioning of ecosystems. In contrast to the tropical effects noted above, increases in the altitudinal range of five species of trees by 120 to 375 m, together with an increase in the tree limit by 100 to 150 m, have been noted at high latitudes in the Swedish Scandes (170). Such widespread biological changes were noted by Epstein (89), who cited them in support of the notion that recent climate change could have contributed to some current changes in patterns of vector-borne diseases. The difficulty faced by researchers is how to separate such effects from the many other simultaneous influences that are usually involved.

Climate variability and extremes. While the primary effect of global warming will be to increase the average temperature of the Earth, the features of climate change that deserve most attention in the context of vector-borne diseases are possible changes in the frequency and severity of extreme weather events and in climatic variability. Even if the variability of the climate relative to the average remains the same, there will be disproportionate changes in the frequency of extreme events, such as fewer frosts and more floods (346), that can have large effects on disease vectors. Of further concern is the fact that the frequency of two successive extreme events is even more sensitive to small changes in the mean. The increasing temperatures will also intensify the hydrological (rainfall and evaporation) cycle (251), leading to an increased frequency and intensity of extreme weather events such as storms, floods, and droughts. Empirical evidence for such a trend is evident in a pattern of steadily increasing proportions of higher rainfall events in the United States (144).

The assumption that the variability of the climate will not change does not appear to hold (154), and it is expected that more cloud cover will increase minimum temperatures and lower the rate of increase of maximum temperatures. The result is likely to be fewer frosts and more moderate increases in the frequency of suboptimal maximum temperatures.

Analogues of climate change. Since the effects of climate change are difficult to study, analogues have been sought to explore the likely consequences of increases in temperature or changes in rainfall (112). They have included historical climates that show insect distributions tracking climate change (63) and different geographical locations, with the expected higher temperatures, for vectors (264). The most popular analogue is the El Niño phase of the El Niño southern oscillation (ENSO) cycle to simulate the effect of global warming. In the absence of the opportunity to observe the effect of climate change over a short period, the temporary, regional warming events associated with the ENSO cycle form an attractive analogue for climate change (37, 127). It is acknowledged that global warming is likely to lead to different combinations of changes in temperature and moisture compared with the ENSO cycle. Nevertheless, some interesting correlations have been made on the incidence of vector-borne diseases in relation to the ENSO cycle.

The ENSO has effects that are felt around the globe (112). El Niño is often associated with heat waves and drought in southern Africa and Southeast Asia including Australia, while it brings floods to the west coast of South America and to central Africa. The opposite phase, La Niña, reverses these patterns. However, enthusiasm for the use of the ENSO may have arisen during a period when the correlation of the index with summer rainfall in northeastern Australia (for example) was particularly high (Fig. 4) (51). The reliability of the ENSO as a surrogate for climate change or as a predictive tool must be questioned in the light of the large, decade-long fluctuations in the relationship. Since the ENSO cycle plays such a dominant role in causing seasonal changes in climate, there is concern that any interaction between anthropogenic climate change and the mechanisms driving the ENSO could have unpredictable results. Unfortunately, there is already a sugges-

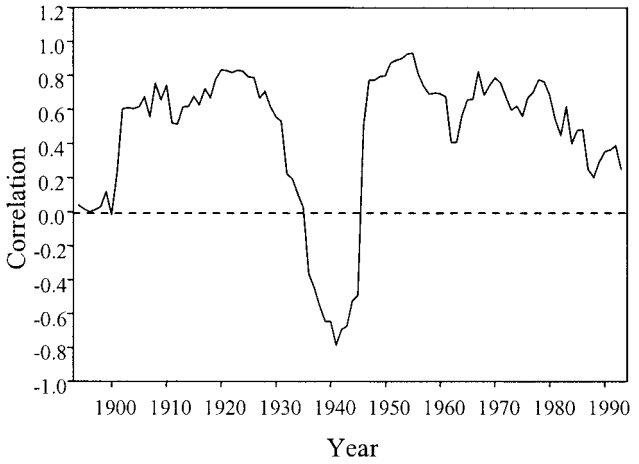

FIG. 4. Long-term variation in the relationship between the ENSO index and summer rainfall in north-eastern Australia. Modified from reference 51 with permission.

tion that the severity of the ENSO cycle may be increasing, with the 1997 to 1998 event being the strongest on record (75), and it occurred simultaneously with an accelerated period of global warming since the 1970s (144).

Urbanization

The human population has increased from approximately 1 billion at the turn of the 20th century to 6 billion by the end of the century, and it is projected to grow to around 10 billion by 2050 (323). The world's urban populations increased from 1.7 billion (39%) in 1980 to 2.7 billion (46%) in 1997 (12) and are expected to reach 5 billion (60%) by 2030 (14). Over the next 25 years, urban populations in Africa are expected to more than double, those in Asia will almost double, and those in Latin America and the Caribbean are expected to increase by almost 50% (351). The density of humans will increase disproportionately because a higher proportion of those people will live in cities compared with today (10).

Drainage and water supplies are critical factors that determine the extent to which many diseases are either contained or propagate in urban communities. Poverty associated with rapid population growth leads to concentrations of people without the necessary infrastructure for the safe storage and distribution of water and drainage of wastewater. Used containers and tires provide breeding sites for mosquito vectors. In addition, the deteriorating public health infrastructure in many countries exacerbates the health problems (121). Each of these negative societal trends is expected to continue, and water-related issues in particular are expected to increase in importance in the developing world over the next few decades (352). On the other hand, in wealthy communities there is encroachment of residential or recreational populations into forested areas where natural hosts and vectors of vector-borne diseases exist.

Land Use, Land Cover, and Biodiversity

The burgeoning world population (326) is driving an intensification of agriculture and its spread into new areas where forests now exist. With such development comes the need for deforestation and for the storage, supply, and distribution of water for human consumption and for irrigation. World rates of deforestation in 1990 to 1995 averaged 101,724/km^2, or 0.3% per annum (12). Future projections of agricultural expansion indicate that there will be more dependence on intensive agriculture and use of irrigation where water supplies permit, with the associated habitat modification, water storage, and sanitation issues (94, 96, 118, 119, 139, 173, 323). Each of these developments affects the opportunities available for breeding by vectors of diseases.

Future land cover change will occur mostly in the tropics and subtropics. It is likely to result in increases in surface temperatures of up to 2°C, with drier conditions where the land cover is reduced. In contrast to the reduced diurnal temperature range expected with greenhouse warming, future land cover change in the tropics may increase the temperature range by decreasing evaporative cooling during the day. The sensitivity of surface temperatures to future anthropogenic land cover change in the tropics is up to 1.5°C warmer than the range induced by decadal-scale interannual variability in vegetation density (80).

With changes in land use comes fragmentation of habitats, loss of biodiversity and alteration of existing vector-host-parasite relationships. The rate of species loss is now higher than at any time since the period when the dinosaurs went extinct (175). Fragmentation of habitats isolates populations with low mobility but still provides access to mobile species, thus altering the species balance in undisturbed areas. This can lead to changes in the physical environment for vectors and hence affect patterns of disease.

Industrial and Agricultural Pollution with Hormone-Disrupting Chemicals

The burgeoning industrial and agricultural chemical industries are producing thousands of new products each year. Very few are assessed for health risks, and many are being found to either mimic or disrupt the activity of hormones, especially estrogen and thyroid hormones, in humans and animals (60). Such endocrine-disrupting chemicals (EDCs) include alkyl phenols, dioxins, organochlorine pesticides, phthalates, polychlorinated biphenyls, polybrominated diphenyl ethers, and synthetic pyrethroids (167). They are found in plastics, herbicides, and pesticides that are distributed widely around the world. Apart from the potentially devastating effects on human sexual development and neurological function, there is evidence that many such chemicals also degrade immunological function (22, 69). From the perspective of risk assessments and prevention, an even greater concern is that such effects are sometimes associated only with mixtures with each other or with nitrate fertilizers in groundwater at concentrations found in groundwater across the United States (255). The side effects of these chemicals could reduce options for human adaptation to vector-borne diseases either by degrading immune responses or by withdrawal of vector control products from the market.

Trade and Travel

Increasing affluence in the developed world, combined with more economical mass transport and liberalization of international trade, is accelerating the increase in the numbers of

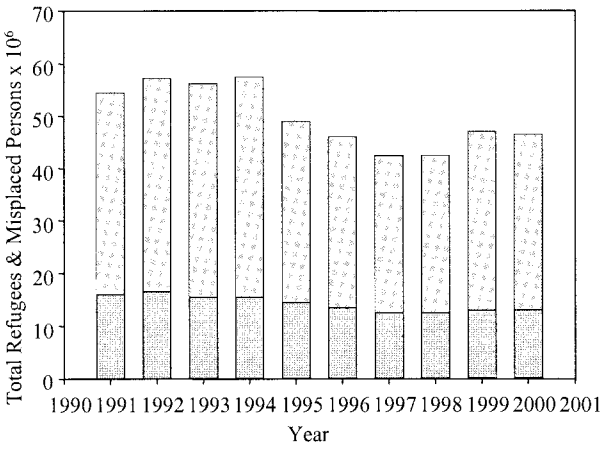

FIG. 5. Numbers of refugees (light shading) and internally displaced people (darker shading) in the world in 2000. Reprinted from reference 13 with permission.

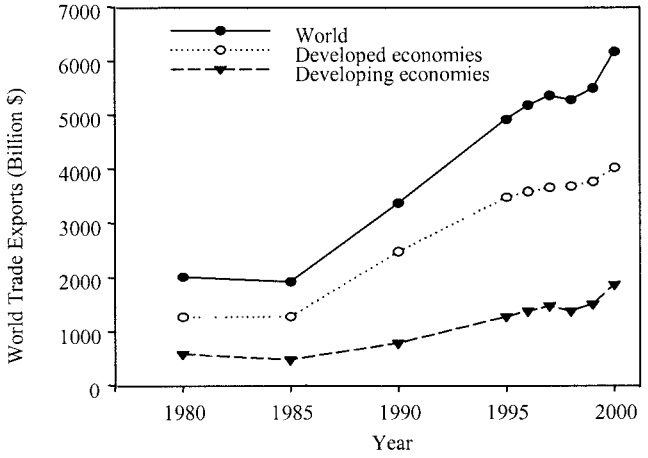

FIG. 6. Volume of international trade between 1980 and 2000. Reprinted from http://www.wto.org/english/res_e/statis_e/webpub_e.xls with permission from the World Trade Organization.

people and the quantity of materials that are being transported around the world. Humans travel on scales from local to global. One million people are reported to travel internationally each day, and one million people travel from developed to developing countries (and vice versa) each week (106). A more recent report quoted a figure of 700 million tourist arrivals per year (115).

There were more than 14.5 million refugees worldwide at the end of 2000, 1 million more than 2 years previously (Fig. 5). From the perspective of vector-borne diseases, the most significant problems are likely to occur in Africa, with more than 3.3 million refugees, South and Central Asia, with 2.6 million, East Asia and the Pacific, with 0.8 million, and the Americas, with 0.6 million (13). In addition, a similar number of people were internally displaced within countries, usually from rural areas into cities.

Each of these types of movements has the potential to spread disease pathogens and their vectors over long distances.

International trade in merchandise has increased three- to fourfold over the period from 1980 to 2000, with most of the increase occurring in Asia, where there was a fivefold increase in the value of exports (World Trade Organization, http://www.wto.org/english/res_e/statis_e/webpub_e.xls) (Fig. 6). Inevitably, this must lead to an increase in the incidence of vectors being transported to other countries.

In this review, the risks and opportunities arising from each of these drivers of global change in relation to the vector-borne diseases are discussed, both in isolation and in combination when appropriate. The potential environmental effects of each global change driver and their additive or interactive combinations that could affect vector-borne diseases are summarized in Table 1. The effects are proximal causes of changes in transmission rates of vector-borne diseases. As can be seen in the second column of Table 1, combinations of global change drivers tend to increase the suitability of the environment compared with the effects of each driver separately. These include combinations of climate change, increased trade and travel, increased urbanization in poor countries, and intensification of agriculture with irrigation, deforestation, and loss of biodiversity. Few interactions reduce the risks, but any that do are likely to be related to the availability of surface water for breeding of mosquitoes under any regional drying due to changed rainfall patterns and the intensification of the hydrological cycle.

Before impacts can be reviewed, it is necessary to establish a framework for assessing the risks.

FRAMEWORK FOR ASSESSMENT OF IMPACTS TO VECTOR-BORNE DISEASES UNDER GLOBAL CHANGE

The global scientific community is faced with the huge task of assessing the likely future impacts of global change drivers on vector-borne diseases, in addition to all of the other current influences on human health, agriculture, and natural ecosystems. The numerous species and stakeholders, combined with the great variation in quality of information and data, make the task quite daunting and demand generic approaches with a hierarchy of analytical tools (315).

To develop a holistic approach to risk assessment of vector-borne diseases under global change, we need to combine the approaches developed by the different research and policy communities into a comprehensive risk assessment framework. In this review, each of these approaches is called upon to address particular issues.

The concept of vulnerability is useful for assessing risks to human societies from vector-borne diseases. It is used in the scientific and policy communities investigating the likely threats from climate change (140, 144). Vulnerability is a measure of the potential impacts of a given change, taking into account the adaptive capacity that is available to the affected system or community to respond to that change. In other words, it describes the sensitivity of the particular system of interest to vector-borne diseases, taking its adaptive capacity into account (348). The term avoids the misleading practice of considering risks in the absence of a societal response, which can give an exaggerated picture of the perceived risks. In the present context, impacts are a combination of a change in exposure of humans to pathogens with environmental change and the sensitivity of the population to that change. Adaptive capacity consists of the adaptation technologies and cultural

TABLE 1. Environmental effects of global change drivers pertinent to vector-borne diseases, and their potential biological effects

Global change driver	Potential effects on vector, pathogen, and host environments	Potential effects on vectors, pathogens, and hosts
Higher CO_2 concn	Increased ambient temperature and plant biomass; range expansion of woody vegetation; longer plant growth season with humid microclimates	Increased vector longevity for the same rainfall and temperature through more humide microclimates, with possible range expansion of humid-zone vectors
Temperature increase (regional/temporal variation)	Expansion of warm climatic zones, with longer growth seasons, less extreme low temperatures, and more frequent extreme high temperatures	Faster vector and pathogen development, with more generations per year; shorter life spans of vectors at high temperatures, reduced low-temperature mortality of vectors, and range expansion of warm-climate vectors and pathogens
Rainfall	Too uncertain and regionally variable to estimate, but increased frequency of extreme rainfall events	Altered patterns of breeding of mosquitoes, with more flushing of mosquito breeding with increased flooding
Urbanization	Increased density of human hosts, with poorer sanitation and water supply in developing countries Increased outer urban development in or near forests in developed countries	Higher rate of disease transmission at same vector density; more vector-breeding sites Increased contact between humans and vectors in periurban forested areas
Deforestation	Increased human entry into forests and increased surface water from soils exposed by logging or new agriculture	More vector-breeding sites and more contact between humans and vectors
Irrigation and water storage	Increased surface water, prevention of seasonal flooding	More vector-breeding sites; reduced flushing of snails and mosquitoes
Intensification of agriculture	Increased disturbance of land and vegetation and increased surface water; reduced biodiversity	More diversity of vector breeding sites, with reduced predation of vectors
Chemical pollution	Fertilizer, pesticide, herbicide and industrial toxins and endocrine-disrupting chemicals	Impaired human immune systems
Increased trade	Increased volume of shipped goods	Increased transport of vectors, leading to "homogenization" of vectors in receptive areas
Increased travel	Increased movement of people between North and South and East and West	Increased transfer of pathogens between regions of endemicity and disease-free regions, and increased exposure of visitors to regions of endemicity

tools and the public health infrastructure and resources that are available to implement appropriate management responses. Inclusion of a given society's capacity to implement appropriate adaptive measures discriminates between groups with disparate cultural, economic, or environmental resources that are needed to implement those measures. It helps to highlight those communities, mostly in the developing world, that are not equipped to manage the changes. The relationships of impacts, adaptation and vulnerability are shown below:

$$\text{Vulnerability} = \text{impacts} \times (1 - \text{adaptive capacity})$$

$$\text{Impacts} = \text{exposure} \times \text{sensitivity}$$

$$\text{Adaptive capacity} = (\text{adaptation products and practices}) \times \text{resources}$$

Exposure

A change in the geographical distribution of a vector-borne disease has a quantal effect on the exposure of naive hosts to that disease. Such a change can come about from the movement of either a vector or pathogen to a new environment through trade, human movement, or natural means. Alternatively, it can result from climate change allowing a vector or pathogen to shift its geographical range into environments that become more suitable.

At the global level, assessment of the risks associated with different sources, pathways, and destinations of vectors and pathogens can be assessed by following the quarantine procedures that operate under international "pest risk analysis" agreements for plant health (146). Linking of global change risk assessment approaches with those used by the quarantine community has been proposed (18, 305). The procedure at-

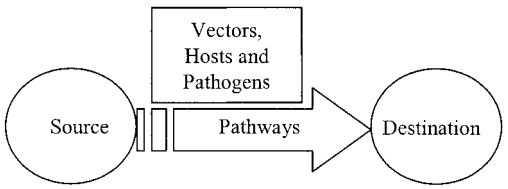

FIG. 7. The plant and animal protection concept of sources, pathways, and destinations of exotic species translocations.

tempts to identify and manage risks by targeting weaknesses at the source of an infection, along the transport pathway and at the destination (Fig. 7). We will see below, when considering adaptation options, that it is more difficult to manage risks when humans are the host of a vector-borne disease than when plants or animals are involved.

In the case of introduction of an exotic vector or pathogen from another continent or its spread to an area from an adjoining zone of endemicity, it is necessary to establish whether the pathogen or vector is able to persist in that new environment. The local habitat forms the template on which ecological processes operate (298). In a risk assessment, the first feature of the habitat that is usually considered is climate, partly for pragmatic reasons—meteorological data are more readily available than other types of data—but other features need to be included systematically. In the context of detection of risks of new exposure, the question is whether the species will be able to persist. This requires analytical tools with which to estimate the response of the species to the new environmental conditions. These are discussed below as part of a review of impact assessment tools. The next question relates to the sensitivity of the local population to the disease and that requires measures of the abundance of the vector and pathogen in the habitat on one hand and the immune status of the host population on the other.

Sensitivity

Sensitivity is the degree to which a system responds to an external perturbation, such as a change of temperature (144). It is essential to define clearly which attribute of a system is being used as the measure of sensitivity because different parts of any system can respond by different amounts. For example, for vector-borne diseases, the potential transmission rate may be very sensitive to a temperature change but the incidence of clinical disease may not alter if the host population is already immune. In this review, when referring to sensitivity of vector-borne diseases, we are referring to potential transmission rates. Host immunity is treated as an adaptation to infection.

Before proceeding further, it is also necessary to appreciate the nonlinear nature of many biological responses to changes in the environment. These arise from a number of features of biological systems, including thresholds such as developmental or behavioral temperature thresholds, discontinuities at the edges of the ranges of species, nonlinear responses to temperature and moisture, multiplicative effects of population growth in vectors with multiple generations each year, negative feedback associated with competition or predation as population densities increase, interactions between variables resulting in

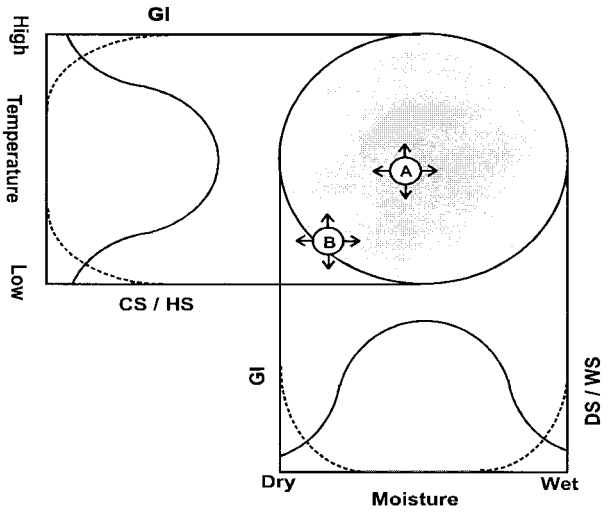

FIG. 8. A conceptual model of the geographical distribution of a species related to its climatic envelope. A population (A) near the center of the climatic envelope will be subjected to variations in temperature and moisture in a more favorable range of values than will a population (B) at the edge of the envelope. GI is the CLIMEX model growth index, and CS, HS, DS, and WS are the cold, hot, dry, and wet stress indices, respectively. Reprinted from reference 305 with permission.

nonadditive effects, and the disproportionate effects of changes in the frequency of extreme events with small changes in the value of the mean. Awareness of such nonlinear effects helps to prevent surprises and so leads to more sustainable adaptation to global change. One consequence of these behaviors is the need to augment empirical and descriptive approaches, such as statistical models, with mechanistic computer simulation models (307).

The sensitivity of a human population to a given disease under global change depends on the combined responses of the pathogen, vector, and host populations. This combination has the potential to generate significant complexity. The geographical location is also a key determinant of the sensitivity of a species to environmental change. A change in the suitability of the environment within the current geographical distribution of the disease will alter the development, survival, and reproductive rates of vectors and pathogens and so affect the intensity of disease transmission and resultant exposure of the population to the disease. The extent to which the exposure changes, following a new introduction of a vector or pathogen or a change in the density of an endemic vector with climate change, depends on the position of the particular habitat relative to the potential geographical distribution of the vector or pathogen in relation to climate (Fig. 8).

Computer models help to identify places where changes in the values of climatic variables are in the sensitive range of a pathogen or vector (307). This is illustrated schematically by a "climatic envelope" in Fig. 8, which shows why populations at different locations within the geographical distribution of a species respond differently to a given change in the value of a climatic variable. Populations within the core of the distribution, A, in Fig. 8, defined as the zone with minimal stresses on the species (314), are relatively insensitive to a given change in temperature or moisture because the change occurs in a part of the response curve that is relatively flat. In contrast, popula-

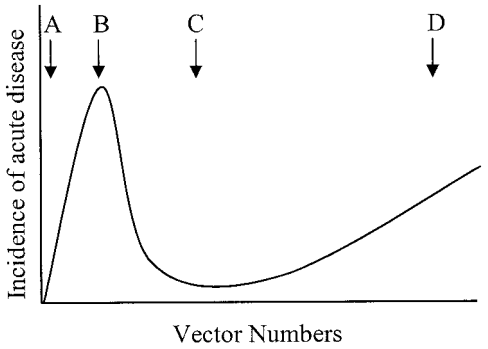

FIG. 9. Conceptual model of the relationship between the incidence of human disease and disease transmission rates as determined by vector densities. A, establishment/extinction/eradication zone; B, epidemic/acute-disease zone; C, endemic stability/chronic-disease zone; D, overload/acute-disease zone.

tions in marginal parts of the distribution, B, occur where response curves are likely to be steeper and thresholds exist for some physiological processes and so are more responsive to an equal degree of change. Additionally, at or near the edges of the distribution, there is great potential for high variability in the occurrence of limiting conditions because a given change in conditions can flip a population between persistence and extinction very readily. Thus, it is evident that the underlying pressures driving the transmission dynamics of vector-borne diseases will vary more around the edges of the area of endemicity in response to climatic variability (9, 67).

Recognition of variation in the susceptibility of humans to vector-borne diseases, based either on genetic (e.g., sickle cells and malaria) or acquired immunity developed in response to exposure, is needed. The concept of herd immunity leading to endemic stability of a disease is crucial to understanding the dynamics of diseases, the likely susceptibility of populations to such diseases, and the likely consequences of interventions to reduce transmission rates (296). Since the nature of clinical symptoms differs with different transmission rates, it is essential to understand the relationships between pathogen infection, morbidity, and disease outcomes in order to plan interventions that avoid undesirable consequences. These relationships vary greatly with different pathogens, and so a case-by-case approach is necessary.

The sensitivity of a human population to a change in exposure depends on the immune status of the population. Diseases affect human health most severely when there is initial contact resulting from humans entering new habitats, from a spread of disease organisms and their vectors, or from temporary surges in transmission rates during abnormal seasonal conditions, for example. In such cases, naive, nonimmune populations are especially susceptible to epidemics of acute disease.

The rate of disease transmission leads to different disease patterns, such as that for pathogens to which humans can acquire immunity, like malaria (Fig. 9). On a spatial scale, the graph represents a cross-section of Fig. 8. At high transmission rates, a condition known as endemic stability is created, whereby most hosts are immune, creating herd immunity (C). Around the edges of the area of endemicity there are areas with intermittent epidemics of disease (B), which are referred to as endemically unstable areas. These frequently cause the greatest concern because they involve nonimmune hosts that are particularly susceptible to infection in a high-risk environment. The disease is absent from areas (A) that do not provide suitable environmental or socioeconomic conditions for transmission. These areas may be too cold or too dry for the pathogen or vector to develop and survive during the unfavorable season, or they may have human living conditions, such as insect screens or air conditioning, that prevent contact with the vectors. In areas with very high transmission rates, the hosts may succumb to acute forms of the disease if their health is in any way impeded, creating an "overload" condition (D). In the case of dengue, subsequent infection with a different serotype greatly increases this latter risk by causing additional clinical effects with hemorrhagic symptoms (153).

Once we have defined the extent to which a population is likely to be exposed to a vector-borne disease under global change and have also assessed its sensitivity, we are able to derive a measure of the likely impact on the population, in the absence of any intervention to manage that risk as part of an adaptation strategy. This provides us with a baseline measure of risk against which we can estimate the benefits of different options to adapt to the risks.

Impacts

Two approaches have been recommended for analyses of likely impacts of climate change used by the IPCC (244). These are referred to as the top-down and bottom-up approaches. Many authors have used climate change scenarios generated by GCMs as a means of investigating likely impacts of vector-borne diseases (147, 208, 209, 212, 280). The alternative approach relies on sensitivity analyses of a range of climatic variables, and was preferred by Sutherst (304, 307) on the grounds that the climate change scenarios are too immature and changeable to be of lasting value. The use of sensitivity analyses covering the broadest range identified by the global climate modelers avoids the problem of rapid dating that occurs with scenarios. On the other hand, when calculating the net present value of future costs, it is necessary to attach a date to the sensitivity analyses so that discounting can be applied. The two approaches have been combined into a risk management approach (151).

Climate change and trade and transport in particular have the potential to affect the geographical distribution of vectors. While climate change alters the immediate environment of a vector, translocation to a new region presents similar and probably greater changes for vectors. Such changes need to be studied by using geographical-scale approaches. Sutherst (305) presented a conceptual framework for studying the effects of climate on the distribution and abundance of species and how they are affected by climate. As shown in Fig. 8, populations respond differently to a given change in a climatic variable depending on where they are situated in relation to their climatic envelope.

Integrated assessment frameworks to bring some of these elements together are under development (53, 205, 248) but do not yet incorporate local environmental circumstances (220). A framework for analyzing impacts on parasites has been described (307) based on theoretical ecology and the framework outlined above. The adoption of political ecology as a frame-

work for analysis of emerging infectious diseases has also been advocated (217). The discipline incorporates social, economic, environmental, and biological components to present a holistic approach. Each of these approaches needs a set of analytical tools.

Tools for risk assessment under global change have been reviewed elsewhere (220, 312). A wide range of approaches have been applied to the assessment of risks for humans to vector-borne diseases under global change. They have ranged from the use of historical analogues (121, 267, 269, 270), and geographical analogues (264) to a variety of statistical (193, 194, 280) and modeling (189, 205, 210, 212, 248, 304, 307, 312, 315) tool and models combined with fuzzy logic or rules (68). Historical events are helpful in providing pointers to potential causes of changes in status of diseases (269) but usually suffer from a lack of firm data, sometimes leading to uncertainty in interpretation.

Each technique has limitations, but the most important considerations are the need to apply basic scientific principles (55, 304, 311). Using independent data to test the resultant models, complying with the limitations of chosen analytical or descriptive tools and data sets, and avoiding parameterization of models based on data sets with very narrow ranges of variation can achieve compliance. Often, apparently accurate statistical models fail to demonstrate predictive ability when tested against independent data rather than data derived by dividing a set of data and using one set for fitting and the other for testing the models (262, 278, 279). In addition, popular statistical models, like logistic regression and discriminant functions, rely on pattern matching with meteorological data and so cannot cope with novel climates or with extrapolation to other locations with different patterns of temperature and rainfall, even though they may describe the current range of a species quite accurately. Hence, such descriptive techniques are suited only to answering questions that involve small incremental changes in conditions within the existing ranges.

The ranges and relative abundance of two important African malaria vectors, *Anopheles gambiae* sensu stricto and *A. arabiensis,* have been related to temperature and a ratio of potential evaporation to rainfall as a measure of moisture availability (193). The population at risk from lymphatic filariasis in Africa was also related to these climatic variables (194). Using a combined model and rule-based approach, thresholds for temperature and rainfall have been inferred by using observations from areas of Africa with different malaria transmission patterns (68). The CLIMEX model (304, 311, 313) incorporates a hydrological model to describe the availability of moisture and so accounts for the effects of changes in temperature, rainfall, and evaporation when assessing risks from climate change. It automatically takes any temperature-moisture interactions into account when provided with appropriate meteorological data that include relative humidity or equivalent readings. CLIMEX has been used widely for risk assessments under climate change (303, 304, 307). The malaria transmission factors, biting and entomological inoculation rates, were predicted in Kenya using a soil moisture model (250). The model substantially improved the prediction of biting rates compared to rainfall, explaining up to 45% of *A. gambiae* biting variability and 32% of the variability of *A. funestus* when given different time lags.

Each species of vector has characteristic climatic requirements (194, 304) and vector competence for a given biotype of parasite (344) (29). This flags the need to keep each element of the disease triangle (Fig. 1) in mind because the climatic requirements of each vector-pathogen combination needs be taken into account in order to develop a realistic measure of risk (48, 304). Incorporation of species-specific vectorial capacity into global risk assessments has started (208). Integrated assessment frameworks are being developed to bring some of these elements together, with applications to malaria, dengue, and schistosomiasis (53, 205, 220, 248, 315). The use of spatial tools, such as geographical information systems and landscape ecology, in studies of vector management and global change effects on vector-borne diseases has been advocated (43, 97, 159).

Benchmarks for Measuring Impacts

To detect impacts of global change, we need monitoring data for a number of environmental and disease related variables covering long time series. While historical records of disease incidence provide a valuable basis for detecting a change in transmission patterns, we also need to monitor concurrent environmental and social conditions. This provides benchmarks against which to measure the likely impacts of changes in any given variable.

Temperature is one such variable that varies systematically with latitude and altitude. The effect of altitude on temperatures is approximately equivalent to 5.7°C/km of elevation. The expected altitudinal range shift with increasing temperatures can be calculated using the formula (183)

$$T = T_c - 0.006\mathrm{h}$$

where T is the screen temperature at height h (meters) and T_c is the equivalent at sea level. Thus, ignoring regional variations in sensitivity to global warming, for each 1°C increase in the global temperature there will be a potential increase of ~170 m in the elevation of a given transmission rate of vector-borne diseases. Warming over the past century has been ~0.6°C (144). Thus, reported changes must be within the range of 100 m to have credibility. For example, one credible report is of an increase in height of the freezing point in the tropics of ~110 m (83).

Similarly, expected latitudinal shifts in species ranges with global warming can be expected to be broadly consistent with effects of latitude on temperatures. The approximate formula (183)

$$T_c = [27 - 0.008A^2]$$

where T_c is the long-term sea level temperature at latitude A, describes the difference in temperature between that latitude and the equatorial temperature. Thus, on average, there is an approximate difference in temperature of 0.6°C per degree of latitude. Hence, range shifts of about 1.7° of latitude or 200 km can be expected for each 1°C increase in global temperatures. Again, a rise of 0.6°C in the last century can be expected to have been accompanied by range shifts of ~118 km. These figures provide a benchmark against which to relate reported changes in the distribution of vector-borne diseases with re-

spect to global warming, but they need to be related to local modifying factors that create different microclimates and so change the actual area at risk.

Similar benchmarks need to be provided for all other environmental and social variables, with rigorous interpretation of historical events that have often been poorly documented or misinterpreted.

Climate change has the potential to change the intensity of transmission of vector-borne diseases in addition to altering the exposure to the diseases by shifting the geographical distributions, as shown above. The extent to which the disease is sensitive to changes in transmission rates depends on a number of variables, including the responses of vector and pathogen to changes in the particular range of temperature or moisture concerned, and the immune status of the host population. Ideally, it would be useful to have a readily measurable benchmark against which to assess reported claims of involvement by climate in observed changes in the status of established vector-borne diseases. Unfortunately, the species-specific nature of the transmission dynamics of each pathogen renders that more difficult than the task of benchmarking changes in geographical distributions. However, it is still possible to match geographical locations with similar intensity of transmission by using models such as CLIMEX. Alternatively, mathematical models of the biological processes in the transmission cycle (also called mechanistic models) can be used to infer the sensitivity of the transmission rates of vector-borne diseases to changes in climate (189, 210, 212, 307). The major advantage of dynamic models over nonmathematical approaches or statistical models is that they are able to detect surprises or so-called emergent properties of systems that arise from discontinuities, such as thresholds or nonlinearities in biological processes.

IMPACTS

The effects of individual global change drivers on the biology of vectors and disease pathogens are summarized in Table 1. The combined effects of simultaneous changes in some of the drivers are examined below. Information comes from IPCC (144) and the general literature on the biology of vectors. In general, the projected changes are negative for human societies, since they tend to favour increases in transmission of vector-borne diseases. Such generalizations need to be treated cautiously because the outcomes are very location specific. The main reason for the trend with climate is that most of the endemic vector-borne diseases are tropical and so global warming and intensification of water storage and irrigation will naturally create a tendency to expand the range into temperate zones and increase the rate of reproduction of vectors in cooler parts of the range. Some complementary reductions in ranges and reproductive rates can be expected in the hottest parts of the current ranges. These tendencies will be exacerbated in some cases by increased rates of dispersal of the pathogens and vectors in human-mediated transport, and opportunities for intensification of transmission will increase as human population densities increase. On the other hand, many adaptive responses are possible, and if there is an improvement in public health facilities, they are likely to counter most of the changes favoring vectors and pathogens.

Climatic and nonclimatic global change drivers, such as human movements, land use and irrigation, and drug or pesticide resistance, can have large effects on disease transmission. Since some environmental changes are global but vary on a regional scale, the degree of exposure of each human-vector-pathogen system will vary with both the driver involved and the geographical location. The risks associated with each type of change need to be addressed on a disease-by-disease and location-by-location basis. An assessment of relative risks associated with each disease and global change driver is needed to prioritize the allocation of resources to adaptive measures. Such a rating system does not exist at present, and its production will require inputs from panels of experts. While most projected environmental changes appear to favor water-breeding vectors, temperature effects on other types of vectors are likely to be local and less severe.

While humans have different exposures to vector-borne diseases under each global change driver, the disease systems also vary in their sensitivity. The extent to which the incidence of a disease is sensitive to a nominated change at a particular geographical location depends on the interaction of the disease organism, its vector, its host population, and the environment (Fig. 1). The global change drivers are likely to have their greatest effect by influencing the numbers and seasonal patterns of activity of the vectors or by moving or accelerating the development of the pathogens. The degree of contact between hosts, vectors, and pathogens and the immune status of the host population will also be sensitive to change.

In most historical instances, the resurgence of diseases can be related to local ecological changes that favored increased vector densities or host-vector contacts, reintroductions of pathogens, or breakdown of vector control measures (121, 270). Development projects such as irrigation and water storage, urbanization, and deforestation have resulted in changes in communities of vectors, with increased population densities of certain species that led to the outbreaks of vector-borne diseases. Increased travel and transport have introduced infectious agents and vectors into new areas. The advent of global-scale environmental changes in recent decades has been an additional risk. The next sections review the evidence for the effect of environmental change on the key vector-borne diseases with likely future global change scenarios.

Atmospheric Composition

An indirect effect of increasing concentrations of CO_2 in the atmosphere is that the water use efficiency of plants is increased. Under good climatic and nutritional conditions, this will result in larger plants that provide more humid shelter for insect vectors and for plant pathogens. However, since plant growth under field conditions is often limited by factors other than water, such as nutrients, there is likely to be a generally higher water table and soil moisture content than occurs at present, unless global warming results in reduced rainfall or substantially increased evaporation (261). Such conditions are conducive to an increase in the frequency of pools of open water that provide suitable habitat for mosquito breeding. This would have consequences for both freshwater- and fouled-water-breeding mosquitoes and the diseases that they transmit.

Climate Change

Climate change has the potential to alter the average exposure of human populations to vector-borne diseases by changing the geographical distribution of conditions that are suitable for the vectors and disease pathogens. An increase in global temperatures will result in an expansion of warm temperature regimens into higher altitudes and latitudes. Any associated changes in rainfall in tropical and subtropical zones will also render habitats more or less suitable for vectors. In addition, the implications of the asymmetrical increases of temperature with global warming (154) for the epidemiology of vector-borne diseases need to be clarified. Greater effects can be expected from the extended relaxation of limiting effects of low temperatures on vector survival, behavior, and disease transmission in cold-limited climates than from smaller and less frequent increases in extreme maximum temperatures. These changes would make temperate environments more receptive to many tropical vector-borne diseases while having less negative effects on tropical environments.

Extreme climatic events have major effects on the transmission rates of vector-borne diseases. In the light of expectations that climate change will increase the frequency of such events disproportionably, such extreme events may emerge as a more important feature of climate change than are changes in average climatic conditions. They are therefore considered in more detail below.

There have been a large number of studies and reviews of the sensitivity of vector-borne diseases to climate change (37, 40, 49, 50, 61, 62, 82, 84, 88–90, 110, 121, 123, 125, 126, 134, 164–166, 169, 186–189, 191, 192, 206, 209, 215, 220–223, 225, 228, 230, 245, 246, 249, 264, 266, 267, 269, 270, 295, 303, 307, 309, 310, 335, 350). The results have led to quite different perceptions of the role of climatic change and other factors in historical patterns of disease incidence.

The coherent pattern of the retreat of tropical glaciers, an upward shift in the freezing isotherm in the tropics, increases or decreases in the geographical ranges of temperate or Arctic species, respectively, at higher latitudes, earlier spring migration and breeding by birds, and earlier seasonal activity of insects have been cited as examples of impacts of gradual global warming (90, 125, 126, 243, 282). The observations were claimed to be consistent with increasing global temperatures and with model predictions. Taken together, these phenomena provide strong evidence that climatic changes in recent decades are already affecting up to 50% of the species examined in a survey of the literature (243, 282). There is no reason to believe that vector-borne diseases are exceptions to this experience of small and gradual changes in seasonal activity and expansion of ranges to higher altitudes and latitudes. The issue for workers in the field is to establish adequate baseline data on seasonal transmission patterns, prevalence of disease and geographical distributions, benchmarks to monitor and assess the consistency of changes with known physiological processes, and sufficiently accurate monitoring data in strategic locations to be able to detect the changes as they occur around species range boundaries initially. Only then will the medical community be able to separate the subtle effects of climate change on vector-borne diseases from the more obvious effects of other factors.

A number of authors have raised the possibility that global warming may have played some part in the recent range expansions and outbreaks of vector-borne diseases (37, 40, 89, 90, 125, 163, 186, 188, 197). Two types of climatic effects could theoretically have been involved. First, changes like the ones observed for other species of plants and animals referred to above will gradually increase the transmission rates in cooler climates and so extend transmission into previously disease-free areas while slowing transmission in areas that become too hot. In some cases, realization of this expectation with vector-borne diseases will be different for other species because often the vectors are already there but the pathogens have been eliminated. Second, changes in the intensity of extreme climatic events will alter the patterns of epidemics. Any change in the intensity and frequency of extreme climatic events may take decades to detect against a background of insufficiently long historical records and high climatic variability with ENSO-like events, and it is probably too early to invoke this effect in any historical events.

Other authors (34, 121, 136, 266, 270, 294), citing historical outbreaks and identifying the largest current signals in a set of data, concluded that other factors were more important than climate and questioned the veracity of claims (90, 197, 206, 223) that anthropogenic climate change could have contributed to the epidemics. For example, it has been suggested (34) that replacement of forest by agriculture provided new habitats for breeding of mosquitoes at Usambara in Tanzania, rather than local temperatures rising as a result of land clearing, as was previously suggested (214). The role of climate change in an outbreak of malaria in Rwanda (197) was questioned because it coincided with a change in detection methods that was more likely to explain the jump in reported incidence of infections (270). Opposing interpretations of historical temperature data in East Africa, based on interpolated meteorological data (235), led to different interpretations of the role of global warming in the observed increase in incidence of malaria in recent decades (136, 247; J. A. Patz, M. Hulme, C. Rosenzweig, T. D. Mitchell, R. A. Goldberg, A. K. Githeko, S. Lele, A. J. McMichael, and D. Le Sueur, Letter, Nature **420:**627–628, 2002). A negligible role was seen for global warming in the resurgence of vector-borne disease in Latin America, Africa, and Asia in the past two decades (121, 266, 270, 294). It was claimed to be inappropriate to use climate-based models to predict future prevalence because climate plays a small role in disease outbreaks (270). That view does not take sufficient account of the role of climate in determining the underlying seasonal phenology or geographical distributions of vectors and pathogens. Neither does it recognize the contribution of climate-based modeling in allowing researchers to extrapolate results from one geographical location to another. What has been missing from the global change studies is adequate inclusion of nonclimatic variables in the analyses, which reflects the difficulty in building and maintaining global databases of local environmental changes.

In a more pragmatic view, global warming was considered to be unlikely to cause major epidemics of tropical mosquito-borne disease in the United States (121) and Australia (48) as long as the public health infrastructure and living conditions remain the same. It is not surprising that the role of climate change in historical events has been contentious because the

extent of the changes is only just beginning to be large enough to be distinguished from natural variability and the events were not sufficiently well documented to ensure that all variables could be accounted for. Despite the differences in emphasis and focus on historical or future events, all authors agree that there are multifactorial causes of change in the incidence of vector-borne diseases. Land use events will be more important in the short term, but climate change has the potential to be important in the longer term.

Climate change will affect both the invertebrate vectors and the development of pathogens in those vectors. Basic biological considerations indicate that with global warming, the duration of the growth season will increase, allowing more generations of vectors each year in cooler areas. Development is prevented at low temperatures, but as temperatures rise, a race develops between parasite development and accelerated mortality of the vector. The winters will be shorter and less severe and so will reduce the mortality rates of species of vectors that are currently limited by low temperatures. Other temperate species of vectors are insensitive to winter conditions in some environments (270). In some environments, temperatures will rise to levels where the mortality rates of the vectors are so high that they die before being able to transmit a pathogen. Changes in future moisture regimens are much more uncertain.

Malaria. (i) Exposure and sensitivity. Most of the analyses of the impacts of climate change on vector-borne diseases have been aimed at malaria, consistent with the dominant global impact of that disease. The initial emphasis has been focused on the direct effects of changes in temperature on development of the parasites and longevity of the adult mosquitoes. This reflects the ease of investigating temperature effects rather than their relative importance compared with other drivers of change. Small increases at low temperatures were shown to increase the risk of transmission disproportionately, and it was concluded that vulnerable communities in malaria-free areas or those with unstable malaria are likely to be at increased risk of future outbreaks (189). An increase of 12 to 27% in the epidemic potential of malaria transmission compared with current areas of endemicity has been projected as an indication of the sensitivity of malaria to climate change (209).

Modeling studies indicate that higher temperatures will lead to an increase in the population that is exposed to malaria as a result of an expansion of the geographical distributions of vector-borne diseases into higher altitudes and latitudes (49, 50, 189, 192, 211–213, 248). A mathematical model, designed to identify malaria epidemic-prone regions, was used to explore possible changes in epidemiology with projected global climate change in the African highlands (192). It was assumed that free water for breeding sites would be available when higher temperatures occur because water is not currently limiting. Most malaria epidemics in the endemically unstable highlands are due to *Plasmodium falciparum,* the cause of the most severe form of clinical malaria. A plea was made to accord these areas special status and recognize them as having a high risk under climate change.

Europe has experienced significant warming in recent decades, and there is evidence of climatic effects in the northern spread of tick vectors in Sweden (165). Nevertheless, the current geographical range of malaria in Europe is much smaller than its potential range as shown from historical records (148, 149, 191, 269, 303). In many regions the vectors are present but malaria transmission does not occur because the pathogens have been eliminated. An increase in average temperature has the largest effect on epidemic potential where parasite development is limited by low temperatures in temperate areas, consistent with the conceptual models in Fig. 8 and 9. Infected mosquitoes introduced through airports are also likely to survive longer in the future if there is increased rainfall and will therefore enhance the problem known as airport malaria (295).

A claim that Australia was highly vulnerable to malaria under climate change (233) has been refuted (48, 332). The suitable area is determined mostly by the climatic requirements of the only highly competent vector, *A. farauti,* rather than the temperatures required for the development of malaria parasites (48, 304). The CLIMEX model was used to determine the area at risk of malaria after an increase in temperature, so any reduction in soil moisture due to increased evaporation at the higher temperatures was factored into the calculation. An increase of 1.5°C was expected to allow *A. farauti* to colonize Gladstone, a town on the east coast of Australia 800 km further south of its current range limit, with islands even further south being potential habitats. The results exceed the benchmark for the effects of such a temperature rise and illustrate the need to consider localized effects of topography on likely range expansions. Whether this potential is realized will depend on many other variables, particularly the state of the public health system. More recently, the mosquito has been detected at Mackay, 2° south of the previous southernmost record near Townsville (328). The finding confirmed earlier unpublished records and is not thought to relate to any change in temperatures.

Both the direct and indirect effects of increased temperature on anopheline mosquitoes, malaria parasites, and their hosts have been examined (295). It was concluded that the most likely effects of climate change would be on the availability of surface water for larval habitats. It may also be assumed that any increase in the density of foliage of plants growing in an enriched CO_2 atmosphere will provide more favorable shelter for adults of some species of mosquitoes, extending their longevity. If the residual soil moisture also increases as the water use efficiency of plants increases, there may also be an increase in the amount of surface water during the season and the expanded range of sheltered habitats referred to above. These scenarios are still highly speculative.

A descriptive, statistical model was used to challenge claims that the global distribution of *P. falciparum* malaria is likely to increase significantly under climate change (280). Several comments about this analysis are necessary. First, it was claimed that little change is likely in the area at risk because those areas, which become more receptive with higher temperatures, will suffer increased moisture deficits. This point had been noted previously (148), but as we saw above, moisture-related climate change scenarios are still too uncertain to be useful. The complicated relationship between the incidence of malaria and floods and droughts makes the task even more difficult. Second, the current distribution of "malaria," used to define the current global area at risk, was not very specific and the analysis did not take into account the different climatic needs

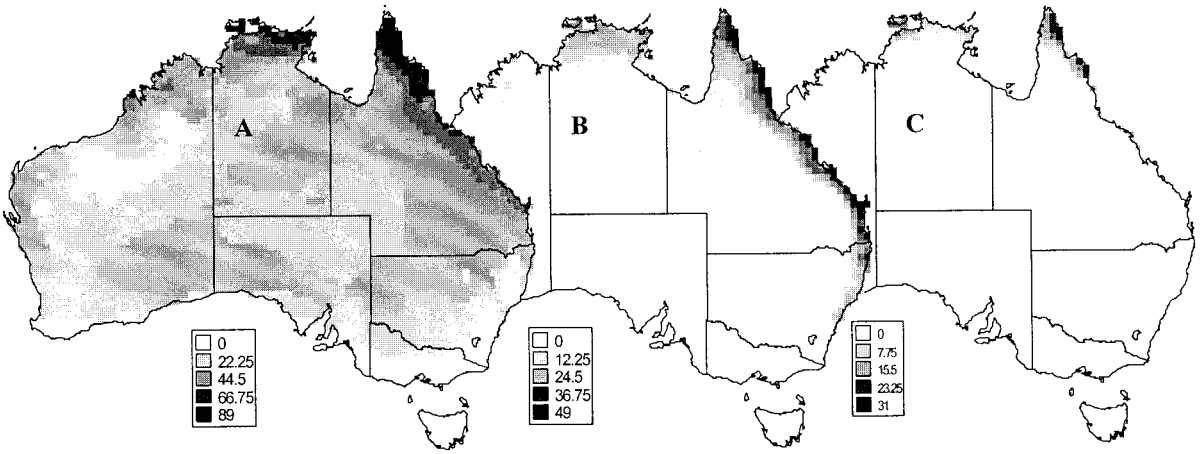

FIG. 10. (A) Comparison of the estimates of areas at risk from *P. falciparum* malaria in Australia, based on the pathogen only, related to temperature for development. (B) As for panel A but including moisture limitation for mosquito breeding. (C) As for panel A but including the restriction imposed by the distribution of the only highly competent malaria vector, *Anopheles farauti,* as limited by climate. Modified from reference 304 with permission.

and vector competence of the 50 or more species of mosquitoes, of which about half are considered to be primary vectors (344). This is critical, as is evident in Australia, where the area at risk has been shown previously to differ vastly when estimated using the responses of the only highly competent vector, *A. farauti,* or of the *P. falciparum* pathogen (Fig. 10) (48). The global area currently at risk of malaria transmission greatly exceeds the area of endemicity because the pathogens have been eliminated from large parts of the world but the vectors remain and pose a threat if reinfected (148). Third, the assumption that adaptation measures in developed countries would prevent the spread of malaria is vulnerable to social unrest and economic decline, such as have occurred in Eastern Europe and central Asia. Finally, statistical models are inappropriate tools for extrapolating geographical distributions because they rely on pattern matching of meteorological data and so cannot cope with novel climates that arise with climate change (168, 304). A credible global risk assessment of malaria must consist of an aggregation of regional assessments, taking into account their local differences in vectors, pathogens, and current disease status, and must be developed using dynamic simulation models rather than statistical models.

The complexity of assessments of risks from vector-borne diseases, in different geographical ranges and different habitats, is further illustrated by some elegant work on nonvector mosquitoes. The temperature regimen interacts with the annual cycle of day length at 50°N latitude in North America, affecting not only the seasonal phenology of the mosquito species (*Wyeomyia smithii*) but also its genetic composition. The critical photoperiod that triggers diapause decreased by over 30 min between 1972 and 1998 with increasing temperature (42). This resulted in the mosquitoes remaining active for an extra 9 days in the warmer climate. Hence, some species are able to adapt very rapidly to changes in their environment and the outcome in any particular ecosystem will depend on the relative ability of each species to track the multiplicity of changes in any environment. The example emphasizes a dimension of species adaptation to change that has been given insufficient attention in global change research, namely, polygenic inheritance of adaptive characters. There is often a large amount of genetic variation present in populations that allows them to adapt rapidly to year-to-year variation in seasonal conditions (317) and hence to climate change.

(ii) Extreme climatic events and malaria transmission. Since most climate-related vector-borne disease events occur when there is a marked deviation from average climatic conditions, it is important to determine the impact of the predicted increase in extreme climatic conditions on the incidence of these diseases. If the climate change scenarios are correct and there is a trend toward more extreme climatic events, there is a need to apply a different form of analysis in order to define the changes in the frequency and intensity of such events. Ecologists have identified appropriate statistical tools (101), but these tools have not yet been applied to vector-borne diseases. In the meantime, it is possible only to access qualitative analyses of such events.

Referring again to Fig. 8, it is evident from theory that changes in temperature or moisture will trigger the greatest responses from vector-borne diseases in geographical regions where transmission is most sensitive to change around the edges of geographical distributions. Here we examine some examples of epidemics or lulls in transmission arising from extreme climatic events, which are summarized in Table 2. They range from droughts that dry out rivers into ponds, which provide favorable breeding sites for mosquitoes (38, 41, 200, 256), to floods that either cause malaria epidemics in arid areas (195) or, conversely, wash away vector populations in humid environments, temporarily suppressing breeding in some habitats while increasing it in others (25, 190). Temporary periods of high temperature can overcome the cold limitation of parasite development in vectors at high altitudes in the tropics (105).

It is instructive to compare these observations with the major outbreak of the tick (*Boophilus microplus*) vector of a malaria-like parasite, *Babesia,* of cattle, at Mt. Tamborine in Australia during a warm El Niño year (Fig. 11) (302). Animal

TABLE 2. Examples of the effects of extreme climatic events on the incidence of malaria[a]

Avg rainfall	Event
Low	Epidemic — El Niño high temperatures and rainfall in cool-dry, high-altitude areas of Pakistan (37)
	Epidemic — high rainfall: arid or semiarid areas of Kenya (6), Gujarat (3), Punjab (41)
	Epidemic — high temperatures and rainfall: tropical highlands with little moisture deficit (Kenya [234], and Uganda highlands [184])
	Epidemic — high rainfall with La Niña 1988: extended area of endemicity on northeastern coast of Venezuela (23)
	Lapse in transmission — flooding: hot-wet areas with flooding that washes away breeding sites (Usambara [190], South Africa and Mozambique 2000 [25])
High	Epidemic — drought: humid areas with ponding of rivers (Sri Lanka [41], Colombia [39, 256], drought in Venezuela [36])

[a] Note that in each case other factors may be involved.

examples are often useful to illustrate some features of human vector-borne diseases epidemiology because the data are more detailed and may be less severely affected by interventions to curtail transmission. With an average warm season maximum temperature that was 1.6°C above the long-term average at this temperature-limited location, four times as many ticks were produced and the highest daily infestation increased from ~200 to over 1,400 per animal. The increase was caused by the compound growth of three generations, magnified by the accelerated development rate of eggs that enabled many more to hatch before the onset of winter. Such changes are likely to be experienced in areas where vectors have several generations each year and there is weak density-related mortality. This illustrates the important point that there is the potential for disproportionately large increases in the rates of disease transmission with small increases in temperature in cool-limited habitats (189). It gives some credence to claims that higher temperatures may have contributed to some recent epidemics of malaria (37, 38, 41, 128), but that does not imply that these effects are related to climate change. The above results illustrate how extremes of high temperatures and both high and low rainfall have the potential to have profound effects on the incidence of malaria (163). Whether or not higher temperatures per se have been responsible for some of the historical outbreaks referred to earlier is uncertain, given the concurrency of other events and unquantified data for all significant variables involved.

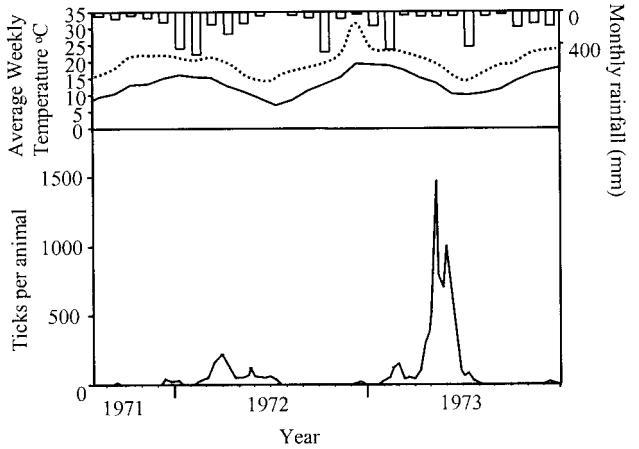

FIG. 11. Numbers of the tick vector (*Boophilus microplus*) of the bovine malaria-like parasites *Babesia* spp., at Mt Tamborine, Australia, over 2 years with different temperatures in 1971 to 1973. Modified from reference 302 with permission.

The challenge for scientists is to translate climate change scenarios, with their higher average temperatures and intensification of the hydrological cycle, into meaningful measures of malaria transmission. It is not yet clear what effect the projected increase in intensity of rainfall and evaporation, combined with fewer but heavier rainfall events, will have on mosquito breeding sites, but the above incidents suggest that there will be more variability in transmission rates. Hydrological studies are needed to determine the probabilities of changes in the habitats of mosquitoes that will affect their breeding opportunities. Working with soil moisture instead of rainfall and evaporation is essential to achieve more accurate results.

Vector-borne diseases other than malaria. (i) Exposure and sensitivity. Few climate change risk assessments have been reported for diseases other than malaria. A summary of those studies is given below.

The complex, mediating effect of climate on the transmission of vector-borne diseases is well illustrated by the work on *Culex tarsalis* Coquillett, the primary vector of St. Louis encephalitis (SLE) and Western equine encephalomyelitis (WEE) in the western United States (264). The survival of mosquito larvae in aquatic environments is severely reduced at higher temperatures, and the survival rate of the adults also declines. Hence, the viruses are involved in a race to complete their development in the adult mosquito before it dies. At 32°C the mosquito is able to restrict the development of WEE virus but not that of SLE virus. High summer temperatures in southern California are therefore likely to break the transmission of WEE. In cooler areas, the higher summer temperatures would curtail the survival of adults of *C. tarsalis* and overwintering survival could alter because they go into diapause. Thus, increases in temperature, of the order projected under climate change, have the potential to extend the northern range of both viruses and to reduce the southern range of WEE virus. On the other hand, some temperate species of mosquitoes, such as *C. pipiens,* are insensitive to variation in the winter conditions that occur in the southern United States (265).

Schistosomiasis is a snail-borne disease that is increasing in incidence as a result of the provision of water storage facilities. The transmission potential of *Schistosoma* spp. is sensitive to climate change around the edges of current areas of endemicity (209). These authors expected the epidemic potential of schistosomiasis to decrease by 11 to 17% with global warming due to higher mortality rates of miracidia, cercariae, and the

TABLE 3. Examples of effects of extreme climatic events on the incidence of vector-borne diseases other than malaria

Avg rainfall	Event
Low	Epidemic: Rift Valley fever affecting humans in arid northeastern Kenya after heavy rain (195)
	Epidemic: dengue fever with heavy rainfall in Malaysia (99) and the South Pacific, but introduction of virus is more important (129)
	Epidemic: Ross River virus outbreaks after summer floods if nonimmune native hosts are available (200)
	Epidemic: Murray Valley encephalitis in heavy-rainfall year in northern Australia (237)
	Epidemic: ponding of rivers during drought causing SLE and Japanese encephalitis in Papua New Guinea (200)
High	Epidemic: dengue in the Western Pacific in early 1998 during the latter part of an El Niño cycle (11), with higher than average sea surface temperatures in the central Pacific (http://iri.columbia.edu/climate/ENSO/background/monitoring.html) virus introductions also important.

[a] Note that in each case other factors such as fluctuating host immunity may be involved.

snail vectors. Health impacts of climate change were expected to be most pronounced in populations living in less economically developed, temperate areas in which endemicity is currently low or absent.

Dengue fever epidemics occur around the tropics, but, perhaps because they are usually urban events driven largely by the availability of the virus and man-made waste acting as water containers for breeding by the vector *Aedes aegypti,* there appears to be a smaller climatic influence on the disease than occurs with other arboviruses. Higher temperatures can accelerate the transmission of diseases such as dengue even during low rainfall periods because artificial water storage containers are favored breeding sites for *A. aegypti* in particular. The results of modeling indicate that global warming can be expected to increase the latitudinal and altitudinal range of dengue and extend the duration of the transmission season in temperate locations as well (81, 98, 147, 209). An increase in temperature-related transmission intensity can also be expected to increase the number of secondary infections of young people who are the most susceptible to dengue hemorrhagic fever and shock syndrome (147). Further insight into the likely effects of global warming on dengue transmission is provided by experience with periods of extreme temperatures associated with the ENSO cycle, as discussed below.

Visceral and cutaneous forms of leishmaniasis are transmitted by a group of biting flies known as sand flies, the main genus of which is *Phlebotomus.* The reservoir hosts are rodents and dogs, and the disease is usually associated with rural environments, where the sand flies breed and shelter in rodent burrows. The disease occurs widely in the tropics, in semi-arid regions in particular. Two studies have indicated potential changes in the geographical distribution of the vectors. Modeling studies in southwest Asia have indicated potential range expansion of *Phlebotomus papatasi* with global warming (70). In Italy, visceral leishmaniasis caused by *Leishmania infantum* is prevalent in the milder parts, where it is transmitted by *P. perniciosus.* Low temperature appears to be one of the main factors preventing its spread into northern Europe (169). *P. perfiliewi,* suspected of transmitting cutaneous leishmanisais, is found in regions with more extreme high and low temperatures. Increases in temperature are likely to accelerate the development of the leishmania organisms but inhibit *P. perniciosus;* therefore, the outcomes are not clear. Little change is expected with the cutaneous form.

There have been studies of the effect of climate change on tsetse flies, including *Glossina morsitans,* a vector of human trypanosomiasis, in Africa (278). Unfortunately, the analyses involved descriptive, statistical models, fitted to very geographically limited data sets, and so they do not have predictive value (304). Given the extent of interactions between species of *Glossina* and the replacement of displaced species by others, a meaningful assessment of the likely changes in the distribution and abundance of tsetse flies and the incidence of trypanosomiasis needs to take them into account (116), in addition to the likely direct effects of such climatic changes on the *Glossina* flies and their habitats.

Chagas' disease, caused by *Trypanosoma cruzi,* is transmitted by the triatomid bug, *Triatoma infestans,* in rural areas with poor housing in South America. Analogue and simulation models were used to indicate that the population growth of the vector in Argentina would be slowed with global warming and so the risks from that disease would be reduced (49).

A marked northward spread of *Ixodes ricinus* has been observed over the past two decades in Sweden (186, 188). The increased range of about 100 km and higher incidence of tick-borne encephalitis transmitted by *I. ricinus* between the early 1980s and mid-1990s were closely related to warmer summers and winters in the 1990s compared with the previous three decades (188). There were consistent direct and indirect relationships between climate and disease incidence, and a model was developed to predict changes in disease incidence based on bioclimatic thresholds. The extent of the biological changes is also consistent with our benchmark (see above) for responses to increases in temperature in the past century.

In Australia there are a number of mosquito-borne viruses that currently cause diseases of various severity in the human population (286). An attempt to evaluate the risks of these diseases under climate change was made difficult by the great uncertainties about the future direction of the change in rainfall. Some GCMs were indicating increases, while others gave opposite results, and the directions also changed in summer and winter. There is also insufficient understanding of the biology of the many vectors involved and the roles of their habitats and alternate hosts (286).

(ii) Extreme climatic events and vector-borne diseases other than malaria. Much less work has been done on relating the incidence of vector-borne diseases other than malaria to extreme climatic events. Some such events are summarized in Table 3. They show that extremes of both high and low rainfall are correlated with the incidence of mosquito-borne diseases in different environments. Causation has not been proven.

The relative insensitivity of dengue fever transmission to climate suggests that the incidence will vary little with climatic variability. In practice, there is sparse information in the field, although the dengue outbreaks in the Western Pacific in 1998 (11) occurred when the negative, El Niño phase of the ENSO was in place, with high temperatures in the area (http://iridl.ldeo.columbia.edu). A study in the South Pacific found a variable correlation between dengue and the ENSO. However, the population density and amount of travel between islands, transferring the virus from place to place, appeared to have a large effect (128), consistent with other observations on the dominant roles of socioeconomic and political factors in dengue transmission (81).

Murray Valley encephalitis is an arbovirus disease that is endemic in the tropics in Australia, with reservoirs of infection in water birds. Infrequent, severe epidemics of Murray Valley encephalitis occur in temperate southeastern Australia after heavy rainfall and flooding, and the ENSO has been proposed as a predictive tool (237).

Ross River virus, which causes epidemic polyarthritis, is transmitted by a large number of species of mosquito, and its life cycle can involve different species of intermediate hosts, including kangaroos. The disease is distributed throughout Australia and Papua New Guinea. Heavy rain or flooding, which leads to increased breeding of mosquitoes, can cause outbreaks of the disease (200) provided that other conditions are suitable. These include the availability of a reservoir of uninfected, vertebrate hosts and suitable seasonal temperatures.

Urbanization

The higher human population densities and lack of the necessary urban infrastructure in tropical regions in particular have profound effects on the transmission potential of diseases (123, 221). Dense urban development with poor infrastructure is widespread in the developing world and leads to increases in the incidence of human diseases that need large human populations to persist and wastewater for the vectors to breed (123). The deteriorating public health infrastructure in many countries exacerbates the problem. Vectors of dengue fever and yellow fever are able to exploit artificial sources of water such as water storage pots, tires, or old containers in garbage. Polluted wastewater also provides a suitable breeding environment for *Culex* mosquitoes that transmit lymphatic filariasis (199) and arboviruses such as SLE virus in the United States and Rift Valley fever virus in Africa (292). Meanwhile, rural-urban migration is credited with leading to a new pattern of infection referred to as urban schistosomiasis (329). On the other hand, the reduction in the incidence of Chagas' disease with urbanization has been alluded to above in relation to climate change.

Land Use, Land Cover, and Biodiversity

The effects of environmental change on emerging parasitic diseases have been reviewed recently (249). Examples were cited of upsurges in malaria with deforestation in Africa, Asia, and Latin America, where the diversity of vector species ensures that there is continuing transmission, because habitat changes favor different species of mosquitoes. The types of vegetation and ground cover determine the vector species that occurs following deforestation, with natural and human-built water storage facilities playing a major role. Agriculture has pervasive local effects on vector-borne diseases by affecting the availability of breeding sites for different species of vectors (229). A number of land use issues that affect the incidence of vector-borne diseases have been identified, including deforestation, land cultivation, and various water storage, distribution, and irrigation structures and practices (64, 105, 229, 231, 303). They can be expected to continue to affect the future patterns of those diseases as the land use changes accelerate. For example, clearing of cattail marshes in Africa for cultivation removes breeding sites for *Anopheles funestrus,* but cultivation of papyrus swamps and deforestation provide open, sunlit water that is suitable for breeding by *A. gambiensis* (231). Cultivation of irrigated rice can either increase the incidence of malaria greatly or have no effect when the vector is *A. funestrus* in mainland Africa (66, 174). Similar differences in the responses of different species of mosquito to irrigation were observed with malaria vectors in Sri Lanka (7). Forecasting the consequences of changes in environmental management requires the involvement of multidisciplinary teams in the planning and implementation of the projects (230).

Deforestation combined with industrial, residential, and agricultural development in the Amazon has had widespread effects on the species of anopheline mosquitoes present and on the rates of transmission of malaria (316). The most significant effects were altered breeding grounds and shelter for the mosquitoes, which changed the intensity of contact with humans. Notable was the great diversity of effects in different regions; however, changes that favoured *Anopheles darlingi,* the most efficient malaria vector, were the most important.

The implications of a number of environmental changes associated with rural development have been investigated. Forest penetration has involved humans in viral and leishmanial zoonoses and has introduced *Onchocerca volvulus* into Central and South American forests. Clearing of forests for agricultural developments such as rubber plantations in Malaysia has resulted in increases in malaria, and there has been a spread of the snail vectors of schistosomiasis into forests. In Indonesia the incidence of lymphatic filariasis was reduced by forest clearing and development, which exposed the mosquito breeding sites to sunlight (182). Similarly, clearing is used to control malaria in Asia by reducing the breeding of *Anopheles balabacensis* (229). However, deforestation can increase the breeding of sun-loving *Anopheles* vectors of malaria in Africa, as mentioned above (229).

An "edge effect" changed the patterns of transmission of trypanosomiasis and loiasis in West Africa. Occupation of land, with the resultant change in vegetation cover, affected the transmission dynamics of triatomine vectors of *T. cruzi,* phlebotomine transmission of leishmaniasis, and tsetse fly transmission of *T. rhodesiense* (64). Each of these effects are destined to continue as deforestation continues apace around the tropics.

Water storage reservoirs, from jars to dams, and irrigation practices provide breeding sites for mosquito vectors of several viral and protozoan diseases including malaria, while large, still water bodies are particularly well suited to the breeding of snail vectors of schistosomiasis. There has been a changing

incidence and geographical distribution of schistosomiasis, partly due to human migration, new irrigation and water impoundments, particularly in Africa, and successful eradication in some countries (30, 56). Ecological changes resulting from the building of the Aswan Dam in Egypt have resulted in a shift from predominantly *S. haematobium* to *S. mansoni.* There was a massive outbreak of *S. mansoni* in northern Senegal, due to intense transmission, after the construction of the Diama dam on the Senegal river and the Manantali dam on the Bafing river, Mali (297). The Three Gorges Dam in southern China is expected to increase the transmission of *S. mansoni* over a vast area by preventing annual flushing of the snail vectors (180).

Some of the effects of various water-related activities on vector-borne diseases have been summarized (229). They include reduction in the incidence of dracunculiasis by controlling the *Cyclops* intermediate hosts in drinking water; artificial lakes that drown the breeding habitats of *Simulium* spp. (vectors of onchocerciasis) while creating new habitat for *Anopheles* vectors of malaria and filariasis and snail hosts (*Biomphalaria* and *Bulinus* spp.) of schistosomiasis; dam spillways providing larval habitats for *Simulium* spp., resulting in artificial foci of onchocerciasis in West Africa; heavily vegetated irrigation canals that provide habitats for *Anopheles* spp. and snails; and irrigated rice fields that provide habitats for *Anopheles* and *Culex* spp., including *C. tritaeniorhynchus,* an important vector of Japanese encephalitis virus.

A complex relationship exists between irrigation and malaria incidence in Africa (143). In environments with small populations of mosquitoes, increased numbers of vectors following the introduction of irrigation can increase the incidence of malaria in areas of unstable transmission, such as the African highlands and on the fringes of deserts. However, irrigation has little impact on malaria transmission for most of sub-Saharan Africa, where it is stable. The lower incidence of malaria in some communities with irrigation than in surrounding areas was explained by a combination of changes in the species composition of the mosquitoes and better protective measures made possible by increased wealth of the community.

Irrigation in two large-scale agricultural areas of western Kenya facilitated the transmission of malaria throughout the year by providing habitats for the two main vectors (111). At Ahero, *Anopheles arabiensis* was most abundant when the rice crop was immature, followed by *A. funestus* when the crop was mature. At Miwani, populations of *A. gambiae* peaked during the long rains whereas the proportion of *A. arabiensis* was greatest during the dry season.

Malaria incidence increased in the Usambara Mountains in Tanzania, following forest clearing to make way for tea plantations and later for agriculture (34, 214). Immigration of malaria-infected laborers from the surrounding lowlands spread the disease in the highlands. Interpretation of these historical changes in the incidence of malaria around Amani has been the subject of continuing debate, and the data have been extensively quoted as an example of the effects of higher local temperatures, resulting from land clearing, on the transmission of malaria. Reiter (270) favored an explanation based on the social changes associated with immigration of infected workers. Reports of the history of malaria in the area have recently been reinterpreted (34). The earlier increases in incidence were explained by intensive agriculture providing more breeding sites for the mosquito vectors that were previously uncommon in this highland habitat. A recent resurgence of malaria in the area was attributed to widespread development of resistance of the parasites to chloroquine. The same explanation was provided by Shanks et al. (294) for the dramatic increases in malaria cases since 1965 at tea plantations in the western highlands of Kenya.

The effect of land use change on malaria transmission was investigated at Kabale in the southwestern highlands of Uganda from December 1997 to July 1998 (185). Mosquito density, biting rates, sporozoite rates, and entomological inoculation rates were compared between eight villages near natural papyrus swamps and eight villages near swamps that had been drained and cultivated. Associated microclimatic conditions were also compared. There was a nonsignificant tendency for all malaria indices to be higher near the cultivated swamps. The numbers of *A. gambiae* sensu lato were associated with higher temperatures near the cultivated swamps, which resulted from the change in land cover.

The increasing incidence of malaria in Africa has been attributed to the growing reliance on corn as a staple food crop (356). In the absence of corn pollen, the silt-laden puddles of water, in which the *A. arabiensis* mosquitoes breed, are very low in nutrients. Corn pollen provides a rich and widespread source of nutrients for mosquito larvae. This could contribute significantly to increasing vector population growth during the flowering season of the crop, which corresponds to the increase in the numbers of mosquitoes in Ethiopia. It was suggested that the force of transmission of malaria in sub-Saharan Africa might be reduced if maize plantings were removed from the immediate vicinity of homes, as apparently was required in Rhodesia some decades ago.

Lyme disease in the northeastern United States and tick-borne encephalitis in Europe are increasing problems as human settlements encroach on forested areas (123). Emergence of Lyme disease, caused by the spirochete *Borrelia burgdorferi*, has been attributed partly to reforestation of outer suburban and agricultural areas in the northeastern United States (21). There were concurrent moves to conserve native fauna, particularly the white-tailed deer, *Odocoileus virginianus,* which are suitable hosts for adults of the tick vector, *Ixodes dammini* (21). White-footed mice, *Peromyscus leucopus,* provide suitable hosts for burgeoning populations of the tick larvae (100), which are efficient vectors of *B. burgdorferi* (172). However, habitat fragmentation also reduces biodiversity and so leads to a preponderance of these mice. The disease "dilution effect," from the tick larvae feeding on less competent hosts, is lost, with the result that a large proportion of the larval population become infected (240). Infected nymphs then pose the major threat to humans. The ticks have recently been found to transmit other bacteria that may cause similar symptoms, such as *Babesia microti* and unnamed *Borrelia, Ehrlichia,* and *Bartonella* species (91, 337).

As just observed, natural biodiversity of hosts can reduce the transmission of vector-borne diseases, and there is also substantial information indicating the importance of natural enemies in controlling vectors of disease (57). This topic has been studied widely, and biological agents have been exploited for biological control (176, 285). Most of the effort has been directed against aquatic Diptera. The natural-enemy component

TABLE 4. Examples of vectors and vector-borne diseases that have been spread around the world naturally or aided by human activity

Invader species	Destination	Source	Pathway
Vectors			
Aedes albopictus	Americas, Pacific	Japan	Second-hand tires
Ochlerotatus japonicus	North America	Japan	Shipping likely
C. pipiens (pesticide resistant)	Global	Asia	Multiple
Ochlerotatus camptorhynchus	New Zealand	Australia	Unknown
Pathogens			
West Nile virus	United States	Middle East	Unknown
Dengue virus (122, 124)	Americas, Pacific and most tropical countries, Australia	Asian source increased greatly with population increase, urbanization, and decline of vector control and public health infrastructure.	Human air travel
Japanese encephalitis virus	Southeast Asia, Australia	Far East and Southeast Asia	Migratory birds and dispersal of vectors
Plasmodium spp. (including drug resistant strains) (44, 47, 203, 207, 214, 259)	Widespread	Southeast Asia and western Pacific	Humans
Rift valley fever virus	Egypt	Sudan	Trade in livestock (87)
Ross River virus	Fiji and Pacific Islands (114), New Zealand (121, 202)	Australia	Humans

was shown to be responsible for significant population reduction and to be indispensable to integrated control approaches. Outbreaks of malaria in Venezuela 1 year after ENSO-related droughts may have been caused by the death of the natural enemies of the mosquito vectors during the droughts (36).

This sampling of the large literature on the effects of land use on vector-borne diseases gives an indication of the diversity of changes and of the wide range of effects that they have on a number of vector-borne diseases. It also illustrates the difficulty facing researchers in trying to extract generalizations from such disparate observations and to create global databases in order to predict future global trends and impacts.

Endocrine Hormone Disruptors

It would be remise not to at least mention the risk that is posed to human health in general, and threats from vector-borne diseases in particular, by the global contamination of even the most remote habitats with EDCs. Of particular concern in the present context is the listing of synthetic pyrethroids as active EDCs (113) because they are being used so widely in agriculture and in impregnated bednets to prevent malaria. At present there have been no records of reduced immunity involving vector-borne diseases (22, 76), but observations of the impairment of the immune system by currently recorded groundwater concentrations of mixtures of agricultural chemicals across the United States is a warning sign (255). Health and safety issues receive less attention in developing countries, and such pollution with industrial and agricultural chemicals is widespread. The traditional reliance on natural immunity to diseases such as malaria and schistosomiasis in the developing world may be under threat. The paramount importance of herd immunity to malaria, in particular, in protecting populations from acute disease makes any such decline of immunity dangerous.

Trade and Travel

There are a number of different dimensions to the movement of people and materials around the world that affect the distribution and incidence of vector-borne diseases. People can either act as carriers of pathogens into new environments or accidentally translocate vectors in transport vehicles. People can also become victims of vector-borne diseases when they travel to new countries where they are exposed to diseases for the first time. Such people are usually naive to the disease, and thus morbidity and mortality rates are relatively high. Some examples of past incidents are listed as an indication of the potential for future spread of vector-borne diseases as trade and travel increase with globalization of trade and increasing wealth.

Movements of people, materials, or vehicles have been responsible for short- and long-distance transfer of several disease vectors (109) (Table 4). *Aedes albopictus,* a vector of dengue, was transported from Japan into the Americas and Europe (135, 161, 287), *Ochlerotatus japonicus,* a vector of arbovirus, was carried from Japan into the United States (253), and *Ochlerotatus camptorhynchus,* a known vector of Ross River virus, was moved from Australia into New Zealand (156). The worldwide migration of insecticide resistance genotypes of mosquitoes is an excellent example of the extent to which vectors have been spread around the world (263).

The global spread of vector-borne diseases is being driven not only by human activities but also by natural forces. Vector-borne diseases have been spreading for centuries, and the shifts in their geographical distributions are an integral part of the epidemiology of the diseases. Human sleeping sickness, caused by *Trypanosoma brucei gambiense* and *T. brucei rhodesiense,* entered Kenya in about 1901 and the 1950s, respectively. The former disease was eradicated by attacking *Glossina fuscipes* with DDT, but the latter disease still persists in the Lambwe Valley in Western Kenya (338). Japanese encephalitis

TABLE 5. Types of movements associated with malaria problems in different regions of the world[a]

Type of movement	Region		
	Americas	Africa	Asia
New settlements for agriculture or mining	Central America, Amazon		Southeast Asia and western Pacific
Populations displaced by war, civil unrest; refugee migrations		Central Africa	Middle East, Central Asia
Resettlements		Ethiopia, East African highlands, Madagascar	
Population movements in response to exceptional rain		Dry savanna, desert fringes, southern Africa	Indian subcontinent

[a] Data from reference 259.

virus and related mosquito-borne viruses have caused outbreaks in Malaysia and India, but the source of the virus is unknown (86, 320, 333). The virus also spread into north Queensland, Australia, in 1995, apparently either by natural wind-borne transfer of infected mosquitoes, perhaps *Culex annulirostris,* from Papua New Guinea (273) or in migrating birds (132).

Increasing travel opportunities, population pressures in rural areas, and natural disasters and civil unrest are increasing the numbers of people traveling and being exposed to vector-borne diseases (65, 293). Each year, 20 million people visit malarious areas, and there are 10,000 cases of imported malaria in the European Community alone, most of which are caused by the more virulent *P. falciparum* (115). The types of human movements that influenced the incidence of malaria in different regions are summarized in Table 5. They show the variety and geographical range of such movements. Travelers have carried pathogens into other countries (258), including malaria into several countries (44, 47, 203, 207, 214, 259) and dengue viruses of all four serotypes into many countries but particularly the western Pacific, South Asia, and South America (124), and Ross River virus into Fiji and other islands in the Pacific (114, 284) and into New Zealand (121, 202).

Genetic variation in both disease competence in vectors and virulence of pathogens adds another dimension to the observed spread of vector-borne diseases around the world. In particular, dengue virus and its vector, *Aedes aegypti,* exhibit major variation in virulence and competence, respectively, in different geographical strains (301). Two molecular groups of the mosquito, with different geographical origins, varied in susceptibility to the dengue virus. A domestic form, *A. aedes aegypti,* from Southeast Asia, the South Pacific islands, and South America, had high dengue virus infection rates compared with a sylvan form, *A. aedes formosus,* from West Africa and some Indian Ocean islands. This is resulting in an expansion of the geographical range and changes in the epidemiology of the disease (93).

The potential impact of the spread of vectors and pathogens around the world greatly exceeds that of potential range expansions under climate change. While the latter are incremental increases, the former can change the risk level of a whole continent (304) by introducing a competent vector for the first time. Similarly, the above example of dengue fever illustrates how the introduction of a pathogen into new areas where competent vectors already exist has caused massive disease epidemics.

Interactive Effects of Global Change Drivers

While each of the drivers of global change will have effects on the transmission of vector-borne diseases, the combined effects have the potential in some cases to multiply the risks. The portion of the world that is becoming climatically suitable for tropical vectors with global warming is increasing. Possible higher tropical rainfall combined with higher CO_2 concentrations may offset greater evaporation at higher temperatures, so that both factors will tend to increase the amount of surface water available for breeding by mosquitoes in the expanded area that is made suitable for breeding by the increase in temperatures. Higher temperatures will not only increase evaporation but also accelerate development of pathogens and reduce the longevity of vectors. These counteracting climatic changes will have a significant effect on the demand for irrigation, which itself will be driven by the need to intensify agriculture to feed the burgeoning human population in the developing world. While increased urbanization will raise the density of human populations, global population growth will also increase the total numbers of people at risk. Globalization of trade and movement of goods and people are accelerating, and the intensity of contacts between humans is increasing in the emerging megacities with inadequate water supply, sanitation, and public health infrastructures.

These combined forces suggest a tendency toward increased risks of spread and transmission of vector-borne diseases. The greatest risks from global change appear to be associated with mosquito-borne diseases, particularly malaria and dengue fever. The greatest potential impacts probably lie in the interactions between invasions of vectors or pathogens from tropical and subtropical regions into an expanded receptive zone and increasing urbanization and poverty in developing countries. This latter effect is illustrated by the spread of dengue into the Americas since 1980 (121). On the other hand, as discussed below, social changes and adaptive management have the potential to counter many of these negative influences, provided that resources are redirected into public health.

Summary of Potential Impacts on Key Vector-Borne Diseases

Perceptions of the risks of the different global change drivers affecting vector-borne diseases vary according to the method

used for assessment of those risks. Biologists often adopt a reductionist approach and try to isolate each variable and define its influence on the system concerned, even if the effect is small. Economists assess the relative importance of each of the variables and are not concerned with small or future effects (243). Biologists are concerned with small effects that may become larger in the future. They are also concerned with nonlinear and often disproportionate responses to small changes in (say) temperature around threshold developmental temperatures, for example (307). This dichotomy of views is also evident in the community investigating global change and risks of vector-borne diseases. Theoreticians and modelers have tended to emphasize the effects of climate change because it is part of a large global activity, it is tractable, and it can be supported by sound physiological data from the laboratory. Systems scientists and ecologists are anxious to take holistic approaches to global change issues, as evidenced by the The Amsterdam Declaration on Global Change (http://www.sciconf.igbp.kva.se/Amsterdam_Declaration.html), but are frustrated by a lack of tools to integrate physical and social systems, data on local effects, and social structures that facilitate that type of research. Public health practitioners, on the other hand, have been more concerned with weighing the risks from each source under current conditions. While all agree that there are many factors affecting the status of each disease, it is difficult to generalize across regions, as we saw in Fig. 8, and the more subtle effects of small changes in climate, for example, are difficult to isolate and quantify. However, that does not mean that climate change will not be a major concern in the future, since numerous modeling studies forecast significant changes in phenology and vector numbers with increasing temperatures in cooler environments. Practitioners also argue that the vectors are usually already present in areas adjacent to current zones of endemicity but the pathogens are not, suggesting that more emphasis needs to be placed on analysis of the pathogen part of the triangle in Fig. 1. Practitioners may also be dismissive of modeling because they do not appreciate the significance of nonlinearity of responses such as that shown in the field observations in Fig. 11. We need to remember that the ecology of vector-borne diseases is highly complex and defies simplistic analyses (270).

It is evident that changes in human population growth, modification of the environment for agriculture, and trade and travel are important current influences on vector-borne diseases. The development of resistance in both vectors and pathogens and the deterioration of public health infrastructure and sanitation are major contributing factors to a deteriorating global problem of dengue and malaria in particular. In future, accumulating residues of EDCs may also emerge as a major issue in the maintenance of human immunity to vector-borne diseases. These latter factors represent failures of management rather than direct increases in risks from environmental changes. They portend problems with future efforts at adaptation. It is sobering to find that more people are dying from malaria today than 30 years ago (254). Future risks may arise from much more subtle effects from uncertain directions such as anthropogenic climate change and variability, and EDCs, but only time and more research will clarify those risks.

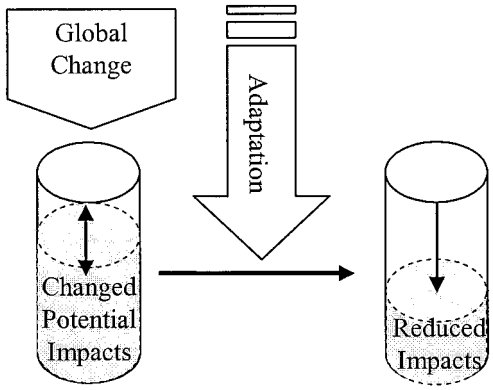

FIG. 12. "Adaptation" reduces potential impacts by applying technology.

FRAMEWORK FOR DESIGNING ADAPTATION OPTIONS UNDER GLOBAL CHANGE

Adaptation is the process by which the potential impacts are reduced by applying a range of management options (Fig. 12). To ameliorate the impacts of vector-borne diseases on human health under global change, societies will need to implement adaptive strategies. General guidelines for the design of adaptation to climate change have been developed within the IPCC (244) and are equally applicable to other global change drivers. Responses to climate change can be either autonomous (automatic as part of daily business) or planned (when the adaptation strategies require deliberate policy decisions) (144). Adaptive responses have also been classified as being behavioral, engineering, or administrative/legislative (245). Here a specific approach is presented for adaptation to changes in vector-borne diseases under global change. Sustainable management of vector-borne diseases depends on a holistic approach, incorporating measures that address vectors, pathogens, hosts, and their interactions with each other and the environment. This means putting management at the center of the host-vector-disease triangle (Fig. 13).

Without foresight in relation to new technologies, an assessment of the options that are currently available for future

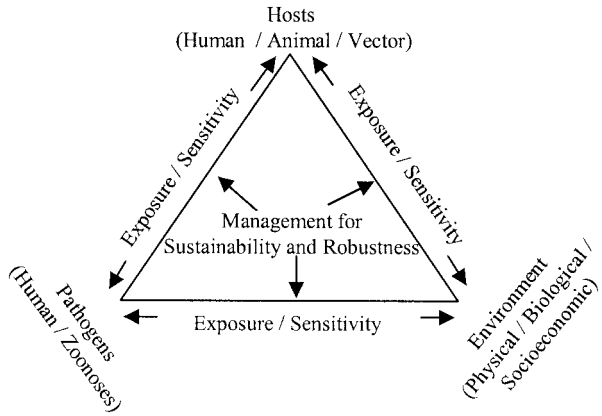

FIG. 13. The host-pathogen-vector-environment triangle including management interventions to minimize the vulnerability of humans to vector-borne diseases under global change.

adaptation to global change will need first to identify the current and past practices that have been found to be effective in managing the risks from vector-borne diseases. We can then explore their potential for use as tools with which to facilitate the adaptation of human societies to the changing risks from vector-borne diseases under global change. Specific future technologies are impossible to anticipate due to the aggregate creativity of the many human minds available to generate new ideas.

Successful control of vector-borne diseases depends on three capacities: effective surveillance to provide feedback on progress (assuming that benchmarks have been established), community ownership of the new measures, and a viable public health infrastructure to deliver the services (181). Recognition of the problem requires some measures of change to be fed back to the community to raise awareness of the issue. These are provided by indicators, suitably chosen to maximize the visibility of the changes taking place (17). Suitable indicators also provide feedback to the community on the progress associated with adoption of the new approaches to manage the necessary changes. Without this feedback, recognition of the problem and adoption of new approaches are likely to be too slow to avoid some disasters. Thus, while monitoring or surveillance activities are considered by many scientists to lack challenge, they provide the key to motivation for change (17).

Implementation of adaptive measures is likely to be successful only if effective service delivery systems (123) are integrated with existing management practices (144). Early intersectorial involvement is essential in planning for rural development based on epidemiological guidelines (64).

Adaptation depends on adoption of innovative approaches or products to prevent or control vector-borne diseases in a changing environment. This, in turn, needs promotion of new approaches, critiques of current practices, and facilitation of change, which always has a cost that needs to be outweighed by the benefits provided by the new technology (17). The attributes of management tools that make them more likely to be available for adaptation to global change in the decades ahead are important in identifying future options. Each adaptation option needs to be evaluated against specific objectives by using criteria such as effectiveness and constraints (244) or sustainability and robustness (309). A multidisciplinary group of scientists involved with global change developed a set of criteria with which to evaluate adaptation options (309, 310). The criteria addressed the issue of sustainability and robustness of current management options. The robustness of each option needs to be determined in order to ensure that the technique or product is able to perform under variable conditions. Each approach is also evaluated in terms of its sensitivity to changes in the timing, intensity, and spatial movement of the target species under global change. Their sustainability is based on their likely susceptibility to a number of risks such as the development of resistance, economic viability, and changes in both societal values and environmental awareness. In summary, their performance needs to meet standards set by using the accounting concept of the "triple bottom line" (http://www.sustainability.com/philosophy/triple-bottom/tbl-intro.asp). Some of the key principles of sustainability are to think long-term, to understand the system, to recognize natural limits to human population growth, to protect nature and the services that it provides such as natural enemies of disease vectors, to transform the way we do business by guiding development without growth in the use of resources, to be fair to each other, to nature, and to future generations and, in so doing, reduce risks to all, and, finally, to embrace creativity in order to develop novel ways of adapting to change (17).

Social values change over time and vary in different communities and so may determine the acceptability of a given adaptation option. For example, attitudes to safety and effects on the environment have changed greatly over the past few decades. The key to successful adaptation is considered to be the provision of information to managers in order to allow them to fine-tune control practices to track environmental changes. This would be based on a menu of available procedures and products, together with analytical tools to assess their potential impacts and likely benefits. Such a hypothetical decision support system (DSS) (Fig. 14) could then be coupled directly to the Internet to ensure efficient delivery of relevant and timely information to stakeholders. The DSS consists of computer simulation models of each of the target and nontarget components of the environment that are affected in either a beneficial or adverse way by a proposed product or practice. Sustainable strategies must minimize adverse effects of chemical residues on human health and the environment. Thus, an environmental lifecycle assessment, in which the effects of a product or practice are defined from cradle to grave, forms one pillar of any information system that is used to guide the sustainable management of vector-borne diseases. Such an analysis of the product would cover the period from invention to disposal, including effects on all target and nontarget species (157). As discussed above, particular concern currently exists about the many industrial and agricultural EDCs. Sustainable management of both vectors and pathogens also demands additional measures to delay the selection of resistance genes that shorten the useful life of so many pesticides and drugs.

Historical patterns of vector ecology and disease transmission have traditionally been used as a basis for the design of management strategies in public health and in agriculture. That has been possible only because environmental conditions, such as the climate, were relatively constant from year to year. With climate change, this no longer applies because there is a trend of change over time. In future, adaptation is going to have to rely on interpretative and predictive tools that can track and anticipate the future conditions and allow the user to tune the adaptation strategy accordingly. These tools will be mechanistic computer simulation models that can both predict and explain the biological responses of vectors, pathogens, and humans to the specific environmental change (305, 315).

Designers of management strategies for vector-borne diseases must also consider the broader implications for communities of any intervention in terms of herd immunity (296). In the case of malaria, there is the potential to alter clinical patterns in areas of endemic infection by creating populations that are nonimmune to a disease when decreased transmission reduces immunity of both the existing population and future children (227). In the event that there is a lapse in the effectiveness of the disease control program, these nonimmune hosts are likely to be at high risk of severe infections associated with resurgent disease transmission in areas where infection is normally endemic (Fig. 9). This raises some very difficult eth-

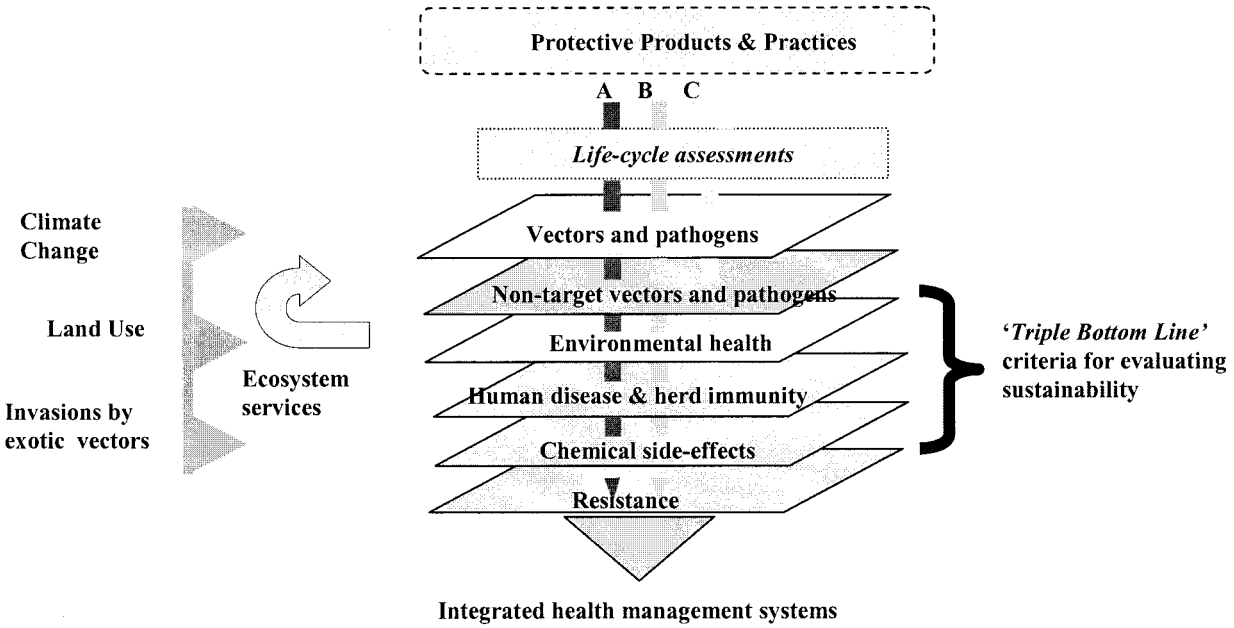

FIG. 14. Decision support system to guide the design or sustainable and robust management strategies for adaptation to changes in the status of vector-borne diseases with global change.

ical questions. Who should receive treatment? What is the balance of benefits and risk from immunity and debilitating effects of chronic infection? Who should be responsible for any ensuing increases in the risks of more severe clinical disease in the community? What constitutes a safe approach when some members of a community may benefit at the expense of others?

The risk of severe clinical symptoms with successive infections with viruses like dengue fever virus are important. Prior infection with one serotype predisposes the patient to the dangerous dengue hemorrhagic fever when subsequently infected with another virulent serotype (153). This creates the opposite effect to immunity and emphasizes the need to take a preventative approach. The need to consider whole systems when planning interventions is illustrated further by the increased production of adults of *Aedes aegypti* after removal of a proportion of larvae from rearing containers with limited food supplies (2). Crowding of larvae reduced the overall production of these mosquitoes.

It is necessary to identify causes of any changes in effectiveness of a given strategy over time because they could be incorrectly attributed to one of several possible causes such as selection of resistance genes, operator error, changes in observational procedures, or changing seasonal phenology due to climate variability or long-term climate change (121, 270, 307). The proposed DSS would have to include computer models of the biological, physical, and sociological processes involved in determining the transmission rates of pathogens for each disease. There have not yet been many studies to design options for adaptation to changes in the risks from vector-borne diseases (224, 307). Some models have been designed to guide the interpretation and on-site management of vector-borne diseases affecting humans (81, 97, 98).

The skill of climatic forecasting is increasing and promising some opportunities to provide advance warning of some high-risk situations associated with the ENSO cycle, for example (127, 201, 237, 238). However, the ENSO is thought to be a chaotic system that is difficult to predict, and its effects on rainfall can be very variable over short distances (306). In addition, as discussed above, the correlation between the ENSO and climatic variables has varied greatly over time (Fig. 4) (5, 51), making it less reliable than some recent experiences would suggest. Therefore, the ENSO is likely to provide information of limited reliability to add to that available from existing tools, such as systematic monitoring and modeling based on direct relationships between biological and climatic variables, that are available to entomologists at present (306). The most useful ENSO-type information would be that which is relevant to forward planning in order to ensure adequate supplies of drugs or pesticides to meet any increase in vector populations (306).

Additional or alternative means of forewarning of impending increases in disease transmission are provided by surveillance systems as an integral part of a public health infrastructure (286). For example, monitoring of *Anopheles gambiae* mosquitoes in houses was suggested as a means of warning of impending malaria epidemic conditions (185). Such monitoring will automatically take into account any changes in the phenology of the vector and so will be a highly efficient component of an adaptation strategy for climate change. The use of geographical information systems to enhance the spatial and temporal resolution of surveillance data provides further opportunities for efficiencies (35, 97). Of course, explanations for changing patterns will still be needed to interpret the causes of these changes and avoid inappropriate responses (307).

Vector-borne diseases will continue to be a problem because of the adaptability of pathogens and vectors to drugs and pesticides, respectively, and the difficulties of managing vector control programs through decentralized health systems when

external activities can increase vector numbers and hence the rate of disease transmission (228). It is essential to understand the factors that increase the transmission of disease in order to prevent outbreaks of diseases, as well as to provide a basis for their effective control (117). However, a more pessimistic view is that the current world circumstances juxtapose people, parasites, plants, animals, and chemicals in a way that precludes timely adaptation (347). The combination of increasing human movements and major changes in the physical environment is responsible for the unexpected spread of diseases via many different pathways. Vector-borne diseases are emerging or resurging as a result of changes in a number of different fields, but particularly as a result of the failure of preventive strategies and their replacement by emergency responses to disease outbreaks (123). Diseases have resurged as a consequence of insecticide and drug resistance, demographic and societal changes, and genetic changes in pathogens. Such forces of change are integral components of the pattern of global change taking place around the world.

The likely sustainability of the currently available approaches can be evaluated using a range of scenarios for the future. Formal means of generating and evaluating future scenarios are also needed (290). Sensitivity analysis is a more practical planning and design approach for the design of adaptation strategies than is the use of climate change scenarios because solutions require the design of strategies that are insensitive to climatic perturbations rather than being optimal for a particular amount of change that is specified in a given scenario (304).

A comprehensive review of experiences with the available methods of control of vector-borne disease is beyond the scope of this paper, but some indication of the current status of the field is necessary to provide a platform on which to develop a sound approach to adaptation to environmental change.

ADAPTATION OPTIONS

Legislative

Many deliberate policy changes could be implemented to enable us to adapt to the impacts of vector-borne diseases under global change. They involve legislation or administrative actions to respond to changes in distributions of vectors, diseases, and human hosts. The measures include changes of monitoring, case detection, diagnosis and reporting, public information and education, knowledge capture and management using information technologies such as remote sensing and mapping with geographical information systems (138, 239), climate forecasting, computer modeling, quarantine surveillance, early-warning systems, and mass vaccination programs. Most of these activities are integral components of any effective preventative health system and so ought to be implemented to meet current needs. While eradication is an idealistic goal, it is usually either unattainable or unsustainable, judging from past efforts with malaria in particular (349).

The failure of some vector or disease eradication programs has been attributed to a lack of funds (242). Efforts to eradicate malaria with insecticides failed in many regions due to the withdrawal of DDT, the development of resistance to the pesticides, or the reintroduction of the mosquitoes from other areas (349). Partial success was achieved with eradication of the main vector of dengue fever virus, *Aedes aegypti,* with successes in southern, temperate zones of Australia but failure in the Americas after initial success in Central America and Brazil (121).

There have, however, been some impressive results from concerted and coordinated efforts to minimize the transmission of vector-borne diseases over large areas. These have relied on suppression of the vector populations or saturation treatment of the pathogens. Eradication of malaria was successful in most of Europe by using DDT, removing breeding sites by draining swamps, and encouraging the keeping of cattle in proximity to homesteads in order to provide an alternative host for the mosquitoes of the malaria pathogens (191, 269, 358). However, in Ethiopia there was an increased incidence of malaria in children sharing the same house with cattle, therefore, there needs to be some distance between the livestock and human housing (108). In South America, eradication of the *Anopheles gambiae* mosquito from northeast Brazil in the 1930s was a significant watershed in the history of malaria control (241). More recently the global Roll Back Malaria campaign, being conducted by agencies of the United Nations during the decade from 2001 to 2010, has launched a concerted effort to halve the incidence of malaria around the world by using a combination of vector control and early treatment of infections in vulnerable populations (271).

Pesticide-based vector control programmes greatly reduced the incidence of onchocerciasis (or river blindness) in West Africa and Chagas' disease in South America (228) by reducing populations of the *Simulium* and *Triatoma* vectors, respectively. In West Africa, eradication of onchocerciasis by aerial spraying of the breeding sites of *Simulium* in fast-flowing rivers was successful in several countries. Further attempts, involving mass treatments of several million people with ivermectin, were initially hindered by a lack of coordination until the advent of the African Programme for Onchocerciasis Control in 1995 (92). Widespread treatment of the human population with ivermectin also reversed anterior-chamber lesions, but there were some adverse reactions to ivermectin treatment when people were heavily coinfected with *Loa loa* (102). There is optimism that similar approaches can be applied to eradicate lymphatic filariasis in India by using diethylcarbamazine and ivermectin (10).

Long-term success in eradication of the reduvid bug, *Triatoma infestans,* has been achieved in the State of Sao Paulo, Brazil (275). Control of Chagas' disease, caused by *Trypanosoma cruzi,* was achieved by suppressing the vectors with insecticides and providing improved housing. In contrast, eradication of domestic *T. infestans* failed in an area of Santiago del Estero in Argentina (289). It is hoped that Chagas' disease can be controlled by using a combination of insecticides and control of blood banks in South America (10).

In Africa, eradication of the tsetse fly (*Glossina* spp.) vectors of human and animal trypanosomiasis has met with mixed success because the fly tends to reinvade areas that have been cleared unless development follows and permanent vegetation-free buffer zones are maintained (133, 338). Stronger links between tsetse control policy and rural development, with intersectorial participation, are essential (64). This means that eradication of vectors such as the tsetse fly must be a slow and

TABLE 6. Sustainability (socially, economically and environmentally) and robustness under global change (resilience to changed environment, timing, spatial movements, habitat change) of some available methods of vector and disease prevention and control[a]

Product or practice	Disadvantages	Advantages	Sustainability	Robustness
Engineering				
Biological vector control with parasites, predators, pathogens	High exploration and testing costs, risk of nontarget impacts, effectiveness varies from nil to total suppression, usually needs regular "inundative" releases	'Free' vector suppression once established, minimal side effects if highly specific, minimal maintenance	++++	+++
Drugs	Adverse side effects, drug resistance, high recurrent costs	Prophylactic or therapeutic; rapid response	++	++++
Pesticides	Pesticide resistance, nontarget impacts, high recurrent costs	Rapid response, high effectiveness	++	++
Vaccines	Ineffective against key protozoa and viruses, short protection from molecular vaccines, time lag in responses	Simple implementation, safe technology, lifetime protection in some cases	++++	++++
Management of environment or housing	Reduction of vector breeding or exposure to vectors, competing interests, Manipulation is temporary, high cost and demands on management	Modification has long-term effectiveness, low maintenance costs	+++	++++
Integration of vector and disease management	Complex to implement, adoption is low	Many of the above	+++	+++
Administrative				
Quarantine, surveillance, education	Large infrastructure needed, high maintenance costs, low reliability	Benefits large areas and populations	++	++
Behavioral				
Avoidance of exposure use of repellents	Adoption is low, complex to manage, variable effectiveness	Long-term effect, moderately high efficacy	+++	+++

[a] Ratings scaled from a base of 0 to a maximum of ++++.

cautious process (24). Failures to eradicate *Glossina pallidipes* from parts of Africa, including the Lambwe Valley in Kenya, has led to persistent outbreaks of human trypanosomiasis. In Uganda, a resurgence of human sleeping sickness was associated with encroachment of the dense, exotic shrub *Lantana camara.* The epidemic was stopped by the use of insecticide-impregnated tsetse traps. Social resistance to the clearing of bush in valleys and later civil war has led to a catastrophic increase in the incidence of epidemics of sleeping sickness caused by *Trypanosoma rhodesiense* in Zaire and Central Africa, as public health programmes have failed (228, 260). Environmental concerns related to land degradation and loss of wildlife following successful eradication of the tsetse fly in regions of Africa reduce the attractiveness of eradication of the fly from unfarmed land (133). Where human trypanosomiasis is concerned, the case is much more compelling. Recent attempts have been made to promote area-wide eradication of tsetse flies in Africa following success on a small island in Zanzibar (158). These initiatives have been questioned on historical, ecological, logistical, and financial grounds (281).

Engineering and Behavioral

The usual engineering or behavioral response by affected individuals to vector-borne disease is to change their behavior at crucial times or to use one or more of a wide range of options to control either the vector or the pathogen or both. Some personal behavioral responses include avoidance of exposure to vectors by staying indoors at dawn and dusk and wearing protective clothing. Routine responses by communities, as part of everyday operations in response to a perceived increase in climatic variability, could include tuning tactics in a surveillance program to detect earlier infections that may initiate outbreaks. Engineering options for vector control include habitat modification, insect screens, bednets, biological control, pesticides, repellents, and more effective integration of these approaches. Targeting of pathogens with drugs or vaccines also provides options to reduce transmission and to reduce symptoms. To identify the tools that have the greatest potential for use to address global change, it is necessary to evaluate their future sustainability and robustness under a wide range of conditions (309). Some of the options that are currently available are rated for these attributes in Table 6. Preventative measures based on environmental management rate highly in terms of their robustness, but their potential sustainability is limited by their demands on management. To date, no approach has been successful without social stability and maintenance of an effective public health system.

Management of vector-borne diseases by vector control. A range of chemical, biological, trapping, and environmental management techniques are available for the control of disease vectors (64, 329, 334). The incidence of Japanese encephalitis in East Asia has been greatly reduced by a combination of mass vaccination of children, improved living conditions, reduced use of water with new rice cultivars, and rehousing and relocation of piggeries to prevent mosquito feeding and reduce

contact with human populations (141, 152, 355). Improvement of housing, water supplies, and sanitation and the return of livestock to provide alternative hosts for anopheline mosquitoes are also valuable. Entomopathogens have proved to be effective against mosquito larvae when used as biopesticides (171), but they have not shown adequate recycling capacity or ability to provide toxin-bearing spores on the water surface, and so they have limited capability as biocontrol agents (79). The use of biological pesticides (biopesticides) in the form of *Bacillus thuringiensis* and *B. sphaericus* reduced the incidence of malaria in Managua, Nicaragua, by 90% from 1996 to 2000 (15) and by similar amounts in Hubei Province in China (357) and Maroua in Cameroon (20). Several of the above authors emphasized the need for a good knowledge of the location and dynamics of breeding sites, the biology of the mosquitoes, and improved formulations of *Bacillus* spp.

Biological control has the potential in some cases to provide long-term, low-cost control of vector populations that are sustainable under a range of circumstances. Natural solutions for vector-borne diseases are preferable to the use of artificial chemicals, which are prone to failure due to the development of resistance, are costly and demanding on management, and often have deleterious side effects on humans and on the environment (196, 330). Biological control of mosquito populations by using natural enemies is a well-established practice and is based mostly on predatory fish (254, 334). Success has been achieved against *Aedes aegypti,* a vector of dengue fever, in specific situations like Australian wells and gold mines by using inundative releases of the copepod *Mesocyclops aspericornis* (285). However, biological control does have risks to the local fauna if it is not carefully evaluated before being implemented. The mosquito fish, *Gambusia affinis,* selectively removed the early instars of predacious insects (including *Notonecta unifasciata, Buenoa* sp., *Belostoma flumineum,* Odonata, dytiscids, and *Tropisternus lateralis*) in rice fields in California (28). This increased mosquito survival, but simultaneous removal of zooplankton by *Gambusia* reduced mosquito survival. In addition, introduced *Gambusia* strains have caused irreversible impacts, reducing the native fish fauna (16, 232). Thus, there is scope for considerable improvement in the practice of biological control of disease vectors and in the range of situations in which it can be applied.

Preventative measures are preferable and include the design of water reservoirs to avoid areas of shallow water that are suitable for breeding of mosquitoes (150). Sound design and maintenance of dam spillways and irrigation canals can reduce the incidence of vector-borne diseases (229). Alternating wet-dry irrigation of rice is credited with reducing the incidence of both malaria and Japanese encephalitis in areas where the vector mosquitoes breed in rice fields (329).

Since no treatment of or vaccination for dengue is available, mosquito control is the only way to reduce the incidence of dengue around the world (276). Environmental management to remove breeding sites is very efficient and is a core strategy when dealing with container-breeding mosquitoes like *A. aegypti.* Other mechanical methods can also be very effective in controlling mosquito breeding in specific situations (216). A reduction of 99.7% was achieved in the number of infective bites by *Culex quinquefasciatus* carrying larvae of *Wuchereria bancrofti,* by covering the surface of wet pit latrines in the town of Makunduchi, Zanzibar, with expanded polystyrene beads and mass treatment of the population with diethylcarbamazine to reduce the incidence of microfilariae.

There are good historical examples of successful use of environmental management to control malaria for prolonged periods in selected areas (327). A package of control measures was used, consisting of vegetation clearance, modification of river boundaries, drainage of swamps, application of oil to open water bodies, and house screening. This was combined with the use of quinine and mosquito nets on part of the population to reduce malaria incidence in Zambian copper mines by 70 to 95% for a period of 20 years. The use of insecticide-impregnated bednets for control of malaria is recognized as a potential means of reducing morbidity and mortality in children (228, 254) and is a cornerstone of the global Roll Back Malaria campaign. The bednets have produced dramatic reductions in the number of cases of malaria in regions such as southern China (354) and in child mortality in trials in sub-Saharan Africa (160), and their use is being extended widely. However, there is evidence that the nets are much less effective during general use by communities compared with during trials. Suboptimal community use of bednets and resistance to insecticides may reduce the sustainability of bednets, although they have been shown to continue to reduce malaria even when resistance has developed in populations of *A. gambiae* senau stricto (78). An emerging concern referred to above is that some synthetic pyrethroids, such as permethrin and cypermethrin, may act as EDCs (164) and threaten the sustainability of this approach.

Recommended future directions in vector control include environmentally safe insecticides, new approaches to vector control, and training programs for health care workers (123).

Management of vector-borne diseases by targeting the pathogens. The second approach to the control of vector-borne diseases is to prevent or treat infections of the pathogens by using drugs or vaccines.

(i) Chemotherapy. Together with vector control, chemotherapy has provided the foundation for the control of vector-borne diseases for decades. Chemotherapy is a vast topic, and it is appropriate here only to note that there have been some major contributions from the use of drugs, as described above, as part of combined drug and vector control programmes but that there are limits to the sustainability of such drugs. The two main constraints are that most people in the developing world cannot afford the cost of modern drugs and that pathogens have a propensity to develop resistance to most drugs that have been used on a wide scale. Malaria, in particular, has become resistant to every drug that is currently available in Asia (254). Therefore, there are questions about the future role of chemotherapy in the control of vector-borne diseases. In the case of malaria, concerns about the maintenance of the efficacy of old and new antimarlarial drugs dominate current thinking (254).

(ii) Vaccines. Vaccines are the preventative panacea that medical practitioners dream about. There has been apparent success with a Japanese encephalitis vaccine in east Asia (329), as described above in relation to vector control. Mass vaccination of children provided the basis for the integrated program.

Unfortunately, to date vaccines have not shown promise against protozoan pathogens like *Plasmodium* or *Trypano-*

soma, metazoan parasites like *Schistosoma,* or viruses like dengue fever virus, for a variety of reasons. Protozoa have proved particularly difficult to control with vaccines because of their capacity to vary their antigens and so avoid recognition by the immune system of the host. Despite this, there was optimism about the prospects for an effective vaccine against malaria, mixed with recognition of the significant constraints that remain due to the antigenic polymorphism exhibited by wild parasite strains and the genetic restriction of immune responses (300). Priorities for research include the need to understand the mechanism of immunity to malaria, the search for antimalarial vaccines, and the potential completion and delivery of benefits from the malaria genome project (254). While naturally acquired immunity can protect against acute malaria infections, practical vaccines are many years away and so is the necessary infrastructure to deliver the vaccines in Africa (272). Loss of natural immunity following radical drug cures highlights the conundrum faced by health care workers in that prevention or drug-based cures of natural infections can leave populations without the natural immunity that currently protects them from acute infection (299).

No vaccine is available for leishmaniasis, and a major vaccine development program, aimed initially at cutaneous leishmaniasis and employing a range of molecular tools, is under way (131). International efforts to create a schistosomiasis vaccine have offered little hope of early success (31). The feasibility of producing an effective vaccine against a parasite that is so well adapted to its host that it can survive in host tissue for decades has been challenged, and the need for a vaccine has been questioned when chemotherapy is very effective and the primary needs are to provide safe water, sanitation, education, and access to good public health facilities (120). Vaccination against the bacterium *Borrelia burgdorferi*, a causative agent of Lyme disease, is controversial, with claims of adverse reactions and reactivation of past infections (336). Dengue virus has several different serotypes that do not respond to the same vaccine. Indeed, prior infection with one strain predisposes the patient to dengue hemorrhagic fever and a vaccine developed against any single strain has the risk of enhancing virus replication (153). The burgeoning molecular biology industry may yet create a raft of novel tools and techniques to protect against such parasites (254), but the short protective periods of tested recombinant vaccines is an obstacle to their effectiveness in creating stable epidemiological situations.

As the examples above have shown, success depends on integration of different approaches aimed at both the pathogen and the vector. This lesson needs to be learned by every new generation of researchers and policy makers to avoid the temptation to seek simple solutions based on magic bullets.

Adaptation of Control Measures for Vector-Borne Diseases in Response to Global Change

Responses to changes in the timing and intensity of disease transmission under global change need to be designed a priori to enable them to be proactive rather than reactive, as illustrated by the preventative vaccination against rabies in North America (274, 283). This calls for a thorough understanding of the biogeography and epidemiology of each disease in the local area at risk. High-risk areas and communities need to be identified in order to focus efforts toward adaptation of the existing disease management programs. Some indication of the needs for modification of current management tools, in order to accommodate global change, are summarized in Table 7. All techniques and approaches need to be tuned to make them more flexible and adaptable to a changing environment, as shown by the low success rate with their current application around the world. This demands a more knowledge-based, rather than product-based, approach.

Adaptation to climate change requires a combination of monitoring, interpretation of field observations based on an understanding of the system involved, and adjustment of existing management actions to accommodate the changes in geographical distribution, seasonal numbers, and timing of vectors (307). As discussed above, it is critical that the cause of changed transmission rates is determined to avoid inappropriate responses based on assumptions about the cause of failure (307). Provision of protection for the most sensitive human populations, without acquired immunity to the pathogen concerned, will be a priority. These people will be found in the vicinity of the altitudinal and horizontal boundaries of the geographical distribution of the species when the variation in climate leads to exceptional divergence from average conditions. They are likely to be found among the most underprivileged communities.

In the case of local environmental changes brought about by local disturbances such as introduction of dams and irrigation or deforestation, there are less likely to be qualitatively different risks, and so implementation of current management practices will be appropriate.

Adaptation to invasions by exotic vectors and pathogens. A holistic approach will address the risks from exotic invasions by managing the sources, pathways, and destinations of exotic vectors and vector-borne diseases (Fig. 15). As in the case of transported plant and animal material, there are potential opportunities to apply rigorous risk management procedures to minimize the risk of entry of exotic species into new environments. Risks at each step can be managed by taking appropriate steps to reduce the chances of a vector passing through barriers to new locations. This requires steps to be taken to reduce the chances of an infection at the source from entering international transport, to reduce its chances of survival in transit, and then to prevent its entry into and establishment at the destination. Failing these measures, there are sometimes options to contain or eradicate the infection if it is detected very quickly. Otherwise, it is usually only possible to alleviate the effects if the vector or pathogen becomes established widely before blocking measures can be put in place. Such measures must be compatible with the current laws of the World Trade Organization. This means that they must be based on justifiable cost-benefit analyses, with the application of the concept of "acceptable" rather than "minimal" risk to the decision about whether to allow the entry of a product (146).

There are no technical reasons why such criteria cannot be applied to vectors of human vector-borne diseases. On the other hand, there are large social deterrents to applying them to humans themselves to avoid transporting the pathogens as they travel. This distinguishes human vector-borne diseases from diseases of plants and other animals and means that the

FIG. 15. The plant and animal protection concept of sources, pathways, and destinations with adaptation measures to manage the changes arising from global change drivers.

risks of expansion of the geographical distributions of human vector-borne diseases exceed those of the diseases of plants and animals. Therefore, it is more difficult to manage the risks when humans are the host of a vector-borne disease. If the health of humans, agricultural systems, and natural ecosystems are going to be maintained, it will be incumbent on the World Trade Organization to reconsider the weighting given to economic, public health, and environmental considerations to minimize the risks whenever possible.

Management of vector-borne diseases at the source of infection requires measures to be taken to remove the pathogen and/or vector from the environment, as discussed above. This has been achieved successfully in many countries in relation to malaria and human yellow fever, but there has been less success with dengue virus (123). Measures included vaccination of humans for yellow fever and control of pathogens with drugs, combined with vector management, for malaria or vector management alone for dengue fever.

Identification and management of pathways of infection have been less successful, judging by the continuing arrival of exotic vectors into new countries. This is illustrated by the numerous reports cited above of historical spread of vector-borne diseases around the world. Regulatory responses have included the treatment of waste tires with chemicals or biological control agents and increased surveillance at ports of entry.

Surveillance has been increased to reduce the risk of establishment of exotic species, but results with vectors of human diseases and the disease organisms themselves continue to show how difficult it is to achieve total exclusion (8, 121, 135). Quarantine services in recipient countries (destinations) focus their effort on inspections on arrival and on surveillance and responses to infections when the barrier fails. The examples cited in relation to the management of pathways illustrate the failure of the management of both sources and destinations to prevent the dispersal of exotic diseases and their vectors. The hope must be that dispersal rates are reduced enough to delay the spread of these diseases by useful amounts.

Threats to Sustainability of Adaptation Options

Resistance. Drugs and pesticides are used widely to reduce the transmission of diseases, and there has been a long history of the development of resistant strains. Changes in the genetic susceptibility of vector-borne diseases and of their vectors have the potential for profound effects on the ability of public health systems to adapt to the impacts of some diseases under global change.

TABLE 7. Indicative changes needed to some vector and pathogen control methods in order to address changed risks from environmental change and international trade and travel

Global change	Changes in vector and pathogen control methods[a]							
	Pesticides	Biological control	Environmental management	Traps/Bednets	Quarantine	Public health infrastructure	Drugs	Vaccines
Environmental change	++ (different seasonal vector populations, resistance)	++ (variation in effectiveness around edges of distribution)	+ (integrated management of breeding sites)	+ (change pesticides if involved)	+ (low efficiency)	++ (preventative measures, delivery systems)	++ (resistance)	++ (efficacy, antigenic variation)
Trade and transport	+ (exotic-vector ecology and resistance)	++ (import new agents for exotic species)	+ (different exotic-vector ecology)	+ (exotic species with new behaviour)	++ (capacity to monitor the volume of migration and traded goods)	++ (incursion prevention and response capability)	++ (new resistance profile)	++ (strain variation)

[a] 0, business as usual; +, minor tuning; ++, significant alteration. Issues related to changing needs are in parentheses.

Drug resistance has been an ongoing problem for decades and has formed the subject of many reviews (10, 33, 59, 73, 162, 198, 226, 236, 322, 339–343, 345). Resistance genes continue to be selected in malaria organisms (34, 203), causing resurgences in disease incidence. The international spread of multiple drug-resistant malaria organisms in Southeast Asia has been attributed largely to movements of civilians during civil disturbances (293).

Similarly, insecticide resistance in mosquitoes continues to threaten efforts to prevent transmission (19, 46, 72, 171, 349). Insecticide-impregnated bednets, traps, and lethal targets are effective, but the early detection of resistance to pyrethroids in bednets emphasizes the low sustainability of any approaches that depend solely on pesticides (64). Resistance in mosquitoes appears to have arisen from both agricultural (4, 74, 242) and urban (4, 331) exposure. Resistance has been reported to permethrin and deltramethrin in *Anophales gambiae* in West Africa (54). As in the case of drug resistance, such pesticide resistance genes are being dispersed widely around the world (177, 263).

Unexpected side effects can arise from the selection of resistance genes. It has been reported (218) that insecticide resistance inhibited the vectorial capacity of mosquitoes that transmit *Wuchereria bancrofti.* Prasittisuk and Curtis (257), on the other hand, found in an experimental system that selection for resistance to DDT in *A. gambiae* had no effect on the susceptibility of the mosquito to a *Plasmodium* sp. in rodents.

Strategies for managing the selection of pesticide resistance in disease vectors have been derived mainly from those designed by entomologists working on agricultural or veterinary problems. Sutherst and Comins (308) first coined the terms "saturation" and "moderation" to describe two opposite strategies. The former attempts to minimize the size of the vector or pathogen population and hence the probability of generating resistance genes. The latter attempts to minimize the selection pressure applied by any single produce or practice by adopting an integrated approach, referred to as integrated pest management. These approaches built on the pioneering work of Georghiou and Taylor in the 1970s, which was summarized by Georghiou (107), who also expanded the saturation/moderation options to include management by multiple attack. This applies to the use of chemical rotations or mixtures, which can be applied to give either moderation or saturation depending on the concentration and intensity of use.

The balance of opinion is that resistance needs to be managed by avoiding a magic-bullet (saturation) approach that intensifies selection and adopting multipronged measures (moderation) that reduce the need for the use of any one chemical (32, 198, 226, 252, 288, 319, 341).

Human safety and nontarget effects of vector control. The widespread use of pesticides in vector control has inevitably had its effects on both the local human population and local fauna. The early effects of DDT on bird life are well known, but the replacement chemicals were also not without their risks (204). For example, efforts to control dengue fever by controlling the vector, *Aedes aegypti*, with organophosphorus insecticide led to three poisonings and reduced cholinesterase levels in 53 out of 2,391 people sampled from the local population in southern Brazil (291).

Pesticides applied on soil at recommended levels rarely had a detrimental effect on microbial populations in temperate wetland rice fields. They did affect invertebrate populations, inducing the blooming of individual species of floodwater zooplankton and reducing populations of aquatic oligochaetes in soil. The observations raise concerns about the long-term effects of pesticides on microorganisms, invertebrates that are important to soil fertility, natural enemies of rice pests and mosquitoes, and biodegradation of pesticides (277).

The nontarget effects of biological control agents for mosquitoes have been noted above. Chemical control of *Simulium, Glossina,* and *Anopheles,* the vectors of onchocerciasis, trypanosomiasis, and malaria, respectively, and of the snail intermediate hosts (*Bulinus* and *Biomphalaria*) of *Schistosoma* can have effects on the fauna of aquatic environments. For example, chemicals used in the control of *Simulium* had several environmental impacts on nontarget invertebrates and fish when used in the Onchocerciasis Control Programme of West Africa (178). The nontarget effects of area-wide spraying with chemical pesticides for the control of tsetse flies in Africa have been reduced in recent times, with more selective use of insecticide-treated cloth targets and selective spraying of resting sites with low-drift sprays (85).

Community health and public health infrastructure. The capability of a society to adapt to global change depends not only on the technical options that are available but also on the human resources that the society can bring to bear to address the issue. Prevention of outbreaks of many vector-borne diseases requires an operational public health system. These resources depend on the economic and public health of the society, so that developing countries have far fewer options available to them than do developed countries. On top of this handicap, several developing countries, particularly in Africa and Asia, are experiencing an erosion of their economic capacity due to the epidemic of AIDS (26), with serious implications for their capacity to manage both human health and agriculture as a result of the loss of able-bodied workers (130, 325). Human trypanosomiasis, caused by *T. brucei gambiense* or *T. brucei rhodesiense,* is increasing in East Africa, where containment measures for tsetse fly vectors (*Glossina fuscipes*) have declined in effectiveness with political unrest and demands placed on the health budgets by AIDS (1). Such a human immunodeficiency virus-induced shortage of labor and capital poses risks for efforts to maintain public health under global change and particularly the containment of trypanosomiasis, for which vegetation must be cleared regularly to remove shelter for tsetse flies (303, 307).

Social disturbances such as wars and civil unrest cause public health services to fail, with resultant outbreaks and spread of infectious and vector-borne diseases, particularly malaria (45, 58, 293, 324). During the war in Nicaragua from 1983 to 1987, population movements and resettlement into rural areas, where preventive care was not available, caused epidemics of malaria and other diseases. The incidence of malaria increased in the war zone in Nicaragua, while there was a large decrease in incidence in the non-war zone (103, 104).

By now it should be evident that risk assessments without consideration of adaptation options give an incomplete picture of the risks from global change. Adaptation is an ongoing process in human societies, and continuing effort needs to be

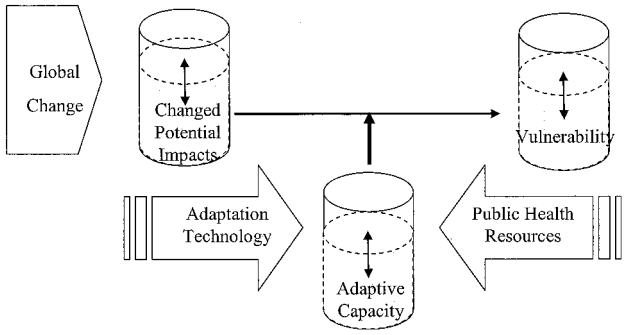

FIG. 16. "Vulnerability" is determined by the extent of change in potential impacts and the adaptive capacity of the affected community.

focused on updating management practices to respond to the changing environment. The next section discusses how a measure of risk from impacts can be combined with fine-tuning of adaptive management measures to develop measures of societal vulnerability to each driver of global change.

Adaptive capacity of different social groups. This review of the adaptation options available to manage vector-borne diseases under global change highlights the many technologies available. In order to exploit them, societies need to have the cultural, economic, and environmental resources to implement the necessary programs. The combination of technologies and resources defines a community's adaptive capacity to respond to vector-borne diseases under global change. We have seen how successful control of vector-borne diseases depends on effective surveillance, community ownership, and a viable public infrastructure (181). Adaptive capacity is clearly related to economic and social development and stability. As such, we can readily determine the capacities of different nations and community groups to adapt to the changes in vector-borne diseases under global change. Documentation of those communities is beyond the scope of this review.

FRAMEWORK FOR ASSESSMENT OF VULNERABILITY

Now that we have identified the key potential impacts of vector-borne diseases under global change and are able to evaluate adaptation options, the next step is to obtain measures of vulnerability of targeted communities. This is done by combining impacts and adaptation options with the adaptive capacity of the affected communities into measures of social vulnerability (Fig. 16).

Examples of some likely increases in vulnerability of different communities to vector-borne diseases under different global changes are given in Table 8. There is very large potential for the vulnerability of urban populations in developing countries to dengue fever and dengue hemorrhagic fever to increase as increasing population densities in megacities outstrip the capacity of the authorities to build appropriate public health infrastructure. In the case of malaria, drug and insecticide resistance, increased irrigation in agriculture, and global warming each have the potential to increase the vulnerability of communities in developing countries. Accelerating travel between developed and developing countries will increase the incidence of airport malaria, but existing public health services should be able to contain its spread and prevent local transmission. Lyme disease also has the potential to increase in affluent developed countries as populations seek more leisure in forested areas where animal conservation is increasing. Adaptive behaviors and use of repellents provide simple solutions to that problem if transmission rates are reduced by maintaining biodiversity.

The key measures that are needed to reduce the vulnerability of different communities around the world, by managing the impacts of each global change driver are as follows. (i) Raise standards of living in developing countries to protect their inhabitants and to indirectly reduce the risks to inhabitants of developed countries. (ii) Reinstate a preventative approach to public health as the foundation of control of vector-borne diseases. This will include ongoing monitoring as well as management of vector breeding sites, avoidance of contact with

TABLE 8. Potential for change in the vulnerability of human societies in some representative situations of key vector-borne diseases[a]

Vector-borne disease	Potential for:			
	Change in exposure	Change in sensitivity	Adaptation	Change in vulnerability
Malaria				
Tropical lowlands	++ (resistance, movement)	++ (resistance, irrigation)	+	+++
Tropical highlands	++ (resistance, movement, climate change)	+++ (resistance, climate change, agriculture)	+	++++
Temperate developed	+ (climate change, movement)	+ (climate change)	+++	+
	+ (climate change)		+	++
Temperate developing		++ (climate change)		
Dengue fever				
Urban developed	+ (movement)	+ (waste)	+++	+
Urban developing	+++ (water services)	+++ (water services, waste)	+	+++++
Rural	+	+ (waste)	+	+
Lyme disease				
Urban wealthy	++ (reforestation, behavior)	++ (behavior)	+	+++

[a] Plus signs indicate potential changes; the extent of potential change is indicated by the numbers of plus signs.

TABLE 9. What we know, what we can expect, what we do from here, and how successful our efforts might be

Global change	What we know	What we can expect	What we do from here	How successful our efforts might be
Climate and atmospheric greenhouse gases	The rates of increase of concentrations of greenhouse gases are accelerating.	Double to treble the concentration of CO_2 by the end of the century.	Stop transferring coal, oil, and gas from the ground into the air by burning fossil fuels.	The global consumption juggernaut is almost unstoppable, but moves toward sustainability are being made.
Climate change	Global average temperatures have increased by over 0.5°C over the past half-century, but warming is not evenly spread.	Further increases in temperature of 1–6°C (144) during the next century, with changed geographical ranges, seasonal patterns, and intensity of transmission of vector-borne diseases.	As above. Develop and implement adaptation measures, including better monitoring, predictive systems, and preventative measures, to anticipate changes. Most emphasis in developing countries.	As above. Adaptations are feasible given awareness, resources, political will, social stability, and development.
	The frequency of extreme hot days has increased, and that of cold nights has decreased	Trend to continue, with altered vector breeding and disease transmission rates.	Develop and implement adaptation measures as above.	Adaptation is feasible as above.
	Vector and pathogen development rates increase with temperature; vector longevity decreases.	Altered disease transmission rates.	Develop and implement adaptation measures as above.	Adaptation is feasible as above.
	The frequency of extreme high rainfall events has increased.	Future rainfall patterns are likely to vary regionally, affecting vector phenology.	Develop and implement adaptation measures that are resilient to variation in rainfall.	Adaptation is feasible as above.
Travel and trade	Air travel has increased greatly over the past decade, with more north-south travel. The volume of trade has increased by 3- to 4-fold from 1980 to 2000.	International travel and globalization of trade should accelerate, with resultant increases in the spread of vectors and pathogens.	Reduce the incidence of disease in developing countries, strengthen sanitary measures on shipping and aircraft, and increase the integrity of border security in importing countries.	Adaptation is feasible as above, but emphasis needs to be on reducing sources of infection in developing countries.
Urbanization	Human population has increased from ≈1.5 to 6 billion in the last century, and there has been a strong move into cities.	Human population growth and urbanization will continue in the developing world, intensifying disease transmission rates.	Improve sanitation and public health facilities, and increase the standard of living in developing countries to enable adaptation measures to be implemented.	Adaptation is feasible as above.
Land use	Water storage, irrigation, and deforestation have increased hugely in recent decades.	Accelerating water storage and use of irrigation; major problems arising with supply, disposal, and quality of water, providing vector-breeding sites. Deforestation continues to provide new breeding sites.	Design water storage facilities to avoid shallow water, use drip irrigation, build water disposal infrastructure in cities.	A huge, expensive challenge, but with multiple benefits.

vectors in housing, and changes in human behavior patterns. (iii) Build the adaptive capacity of communities to be more flexible and responsive to changing conditions. (iv) Adopt holistic approaches to account for unforeseen as well as intended consequences of human actions in cultural, economic, and environmental dimensions. (v) Adopt a knowledge-based approach to the management of vector-borne diseases, based on comprehensive decision support systems (Fig. 14). Place emphasis on clarifying the causes of problems rather than on treating the symptoms (179). (vi) Manage surface water in cities and in agriculture to reduce breeding sites for insect, molluscan, and crustacean vectors of disease. (vii) Strengthen international sanitary procedures for movement of human pathogens and vectors around the world. (viii) Avoid intrusions into old-growth forests. (ix) Protect natural biodiversity to ensure that natural enemies of vectors are encouraged. (x) Support research (134) to clarify likely trends by collecting baseline data, define the biological and genetic processes involved, and their relationships with environmental variables by using mechanistic computer simulation models, build a knowledge base and predictive tools for adaptation, and create new protective products and services for resource-poor communities.

The key to reducing societal vulnerability to the health impacts of climate change is to enhance existing public health infrastructure and intervention programs (121, 224). Sustainable management strategies for vector-borne diseases must either create or preserve herd immunity or implement sustainable preventative measures. When programs fail after extended periods, the scene is set for epidemics of disease among populations that have lost their immunity. Even with sustainable technologies, human societies will remain vulnerable to vector-borne diseases as long as there is a risk of an interruption in the protective program. This only emphasizes the cruel reality for many people in the developing countries that are either socially or economically unstable. In the longer term, only improved living conditions will deliver a sustained reduction in vulnerability to environmental health hazards.

CONCLUSIONS

Global change is a vast field that covers most human endeavors, and so it is impossible to cover the topic comprehensively in a single review such as this. The rates of change of all aspects of human and environment-related actions are accelerating. This gives rise to numerous opportunities for unexpected or enhanced risks from vector-borne diseases, arising from the interaction between different types of change such as climate, patterns of travel, unplanned expansion of megacities, and intensification of agriculture. There are increasing risks of the spread of vector-borne diseases from developing to developed countries as globalization further accelerates the pace of movement of goods and people around the world. Already there is a trend of increasing global incidence of severe diseases such as malaria and dengue fever. This has arisen largely from declining public health infrastructures, development of resistance to drugs and insecticides, and reliance on reactive treatment rather than prevention.

On the other hand, there are examples where large-scale interventions have been successful in greatly reducing the incidence of vector-borne diseases, such as onchocerciasis in West Africa and Japanese encephalitis in East Asia.

Acknowledging the gross simplifications, a summary of the current status of knowledge and beliefs about future trends in relation to vector-borne diseases under global change is given in Table 9. There are significant uncertainties surrounding some of the risks, but for others the trends are clear and the outcomes are predictable. This should be enough to galvanize the global community to restore public health systems, reinstate preventative measures, and take up the opportunities to reduce the risks of spread of these diseases.

Adaptation must be based on a sound understanding of the causes of changed transmission patterns in each situation, in other words on an understanding of the whole vector-pathogen-host-environment system. This calls for a systems approach with comprehensive and testable predictive models to remove the subjectivity from qualitative judgements. Adaptation measures must be culturally, economically, and environmentally sustainable, and they must be able to retain their effectiveness in the face of strong environmental variation or social disturbance; i.e., they must be robust. Biological approaches based on either host resistance or natural enemies tend to be more robust because they have in-built flexibility and avoid the need for extra contributions by human management, which is so often the weakest link.

The vulnerability of communities depends as much on their capacity to prevent or respond to increases in disease transmission as it does on the risks themselves. Therefore, the key to reducing the incidence of vector-borne diseases is to increase the standards of living in developing countries and the allocation of resources to preventative measures in both developing and developed countries. A distinction needs to be made between growth and development (17). Growth in the density of human populations and their associated demands for resources and production of wastes has natural limits. It is ultimately limited by land for food production, water, renewable and nonrenewable resources, and social stability. Development, on the other hand, refers to improvements in human health and personal development. The success of globalization in advancing living standards by providing services that enhance health and well-being, rather than material goods, will play a large part in reducing the vulnerability of disadvantaged communities. A global focus on provision of public health facilities and preventative measures rather than material consumption will be a faster route to reducing the incidence of vector-borne diseases and one step toward saving the human race and the world's biological life from future catastrophe.

ACKNOWLEDGMENTS

My thanks to Rod Mahon and Richard Russell and two anonymous referees for helpful comments on the draft manuscript. Rick Bottomley assisted with the bibliography and illustrations, and Gunter Maywald provided support for the CLIMEX model.

REFERENCES

1. **Abaru, D. E.** 1985. Sleeping sickness in Busoga, Uganda, 1976–1983. Trop. Med. Parasitol. **36:**72–76.
2. **Agudelo-Silva, F., and A. Spielman.** 1984. Paradoxical effects of simulated larviciding on production of adult mosquitoes. Am. J. Trop. Med. Hyg. **33:**1267–1269.
3. **Akhtar, R., and A. J. McMichael.** 1996. Rainfall and malaria outbreaks in western Rajasthan. Lancet **348:**1457–1458.

4. **Akogbeto, M., and S. Yakoubou.** 1999. Resistance of malaria vectors to pyrethroids used for impregnated bednets, Benin, West Africa. Bull. Soc. Pathol. Exot. **92:**123–130.
5. **Allan, R., J. Lindesay, and D. Parker.** 1996. El Niño southern oscillation and climatic variability. CSIRO Publishing, Collingwood, Australia.
6. **Allan, R., S. Nam, and L. Doull.** 1998. MERLIN and malaria epidemic in north-east Kenya. Lancet **351:**1966–1967.
7. **Amerasinghe, F. P., P. H. Amerasinghe, J. S. M. Peiris, and R. A. Wirtz.** 1991. Anopheline ecology and malaria infection during the irrigation development of an area of the Mahaweli project, Sri Lanka. Am. J. Trop. Med. Hyg. **45:**226–235.
8. **Anderson, J. F., T. G. Andreadis, C. R. Vossbrinck, S. Tirrell, E. M. Wakem, R. A. French, A. E. Garmendia, and H. J. Van Kruiningen.** 1999. Isolation of West Nile virus from mosquitoes, crows, and a Cooper's hawk in Connecticut. Science **286:**2331–2333.
9. **Andrewartha, H. G., and L. C. Birch.** 1954. The distribution and abundance of animals. University of Chicago Press, Chicago, Ill.
10. **Anonymous.** 1996. Four TDR diseases can be eliminated: TDR News **49:** 1–5.
11. **Anonymous.** 1998. Dengue in the WHO western Pacific region. Wkly. Epidemiol. Rec. **73:**273–280.
12. **Anonymous.** 2000. World development report 1999/2000. World Bank, Washington, D.C.
13. **Anonymous.** 2001. *In* T. Damstra, 50 years later, refugee flight on the rise, international support waning. Refugee reports. U.S. Committee for Refugees **22:**1–9.
14. **Anonymous.** 2001. World urbanization prospects. The 2001 revision. ESA/P/WP.173. United Nations, Geneva, Switzerland.
15. **Anonymous.** 2001. Zapping mosquitoes with biopesticides. Pestic. News **54:**9.
16. **Arthington, A. H., and L. N. Lloyd.** 1989. Introduced poeciliids in Australia and New Zealand, p. 333–348. *In* G. K. Meffe and F. F. Snelson, Jr. (ed.), Ecology and evolution of livebearing fishes (Poeciliidae). Prentice-Hall, Inc., Englewood Cliffs, N.J.
17. **AtKisson, A.** 1999. Believing Cassandra. Chelsea Green Publishing Co., White River Junction, Vt.
18. **Baker, R. H. A., C. E. Sansford, C. H. Jarvis, R. J. C. Cannon, A. MacLeod, and K. F. A. Walters.** 2000. The role of climatic mapping in predicting the potential geographical distribution of non-indigenous pests under current and future climates. Agric. Ecosyst. Environ. **82:**57–71.
19. **Bang, Y. H.** 1985. Implications in the control of malaria vectors with insecticides in tropical countries of south east Asia. J. Commun. Dis. **17:**199–218.
20. **Barbazan, P., T. Baldet, F. Darriet, H. Escaffre, D. H. Djoda, and J. M. Hougard.** 1998. Impact of treatments with *Bacillus sphaericus* on *Anopheles* populations and the transmission of malaria in Maroua, a large city in a savannah region of Cameroon. J. Am. Mosq. Control Assoc. **14:**33–39.
21. **Barbour, A. G., and D. Fish.** 1993. The biological and social phenomenon of Lyme disease. Science **260:**1610–1616.
22. **Barnett, J. B., T. Colborn, and M. Fournier.** 1996. Consensus statement from the work session on 'chemically induced alteration in the developing immune system'. The wildlife/human connection. Environ. Health Perspect. **104**(Suppl. 4)**:**807–808.
23. **Barrera, R., M. E. Grillet, Y. Rangel, J. Berti, and A. Ache.** 1999. Temporal and spatial patterns of malaria reinfection in northeastern Venezuela. Am. J. Trop. Med. Hyg. **61:**784–790.
24. **Barrett, J. C.** 1989. Tsetse control, land use and livestock in the development of the Zambezi Valley, Zimbabwe: some policy considerations. Network paper 19—African Livestock Policy Analysis Network: International Livestock Centre for Africa, Addis Ababa, Ethiopia.
25. **Bateman, C.** 2000. Flood disease control—moving smartly to save lives. South Afr. Med. J. **90:**330–331.
26. **Becker, C. M.** 1990. The demo-economic impact of the AIDS pandemic in sub-Saharan Africa. World Dev. **18:**1599–1619.
27. **Beer, J., W. Mende, and R. Stellmacher.** 2000. The role of the sun in climate forcing Q. Sci. Rev. **19:**403–415.
28. **Bence, J. R.** 1982. Some interactions of predaceous insects and mosquitofish *Gambusia affinis:* a review of some recent results. Bull. Soc. Vector Ecol. **7:**41–44.
29. **Bennett, K. E., K. E. Olson, M. D. Munoz, I. F. Fernandez-Salas, J. A. Farfan-Ale, S. Higgs, W. C. Black, and B. J. Beaty.** 2002. Variation in vector competence for dengue 2 virus among 24 collections of *Aedes aegypti* from Mexico and the United States. Am. J. Trop. Med. Hyg. **67:**85–92.
30. **Bergquist, N. R.** 2002. Schistosomiasis: from risk assessment to control. Trends Parasitol. **18:**309–314.
31. **Bergquist, N. R., and D. G. Colley.** 1998. Schistosomiasis vaccines: research to development. Parasitol. Today **14:**99–104.
32. **Bia, F. J.** 1992. Malaria prophylaxis: taking aim at constantly moving targets. Yale J. Biol. Med. **65:**329–336.
33. **Bjorkman, A., and P. A. Phillips-Howard.** 1990. The epidemiology of drug-resistant malaria. Trans. R. Soc. Trop. Med. Hyg. **84:**177–180.
34. **Bodker, R., W. Kisinza, R. Malima, H. Msangeni, and S. Lindsay.** 2000. Resurgence of malaria in the Usambara mountains, Tanzania, an epidemic of drug-resistant parasites. Global Change Hum. Health **1:**134–153.
35. **Booman, M., D. N. Durrheim, K. LaGrange, C. Martin, A. M. Mabuza, A. Zitha, F. M. Mbokazi, C. Fraser, and B. L. Sharp.** 2000. Using a geographical information system to plan a malaria control programme in South Africa. Bull. W. H. O. **78:**1438–1444.
36. **Bouma, M. J., and C. Dye.** 1997. Cycles of malaria associated with El Niño in Venezuela. JAMA **278:**1772–1774.
37. **Bouma, M. J., C. Dye, and H. J. Van der Kaay.** 1996. Falciparum malaria and climate change in the Northwest Frontier Province of Pakistan. Am. J. Trop. Med. Hyg. **55:**131–137.
38. **Bouma, M. J., R. S. Kovats, S. A. Goubet, J. St. H. Cox, and A. Haines.** 1997. Global assessment of El Niño's disaster burden. Lancet **350:**1435–1438.
39. **Bouma, M. J., G. Poveda, W. Rojas, D. Chavasse, M. Quinones, J. Cox, and J. Patz.** 1997. Predicting high-risk years for malaria in Colombia using parameters of El Niño Southern Oscillation. Trop. Med. Int. Health **2:**1122–1127.
40. **Bouma, M. J., H. E. Sondorp, and H. J. Van der Kaay.** 1994. Health and climate change. Lancet **343:**302.
41. **Bouma, M. J., and H. J. van der Kaay.** 1996. The El Niño Southern Oscillation and the historic malaria epidemics on the Indian subcontinent and Sri Lanka: an early warning system for future epidemics? Trop. Med. Int. Health **1:**86–96.
42. **Bradshaw, W. E., and C. M. Holzapfel.** 2001. Genetic shift in photoperiodic response correlated with global warming. Proc. Natl. Acad. Sci. USA **98:** 14509–14511.
43. **Brenner, R. J., D. A. Focks, R. T. Arbogast, D. K. Weaver, and D. Shuman.** 1998. Practical use of spatial analysis in precision targeting for integrated pest management. Am. Entomol. **44:**79–101.
44. **Bruce-Chwatt, L. J.** 1968. Movements of populations in relation to communicable diseases in Africa. East Afr. Med. J. **45:**266–275.
45. **Bruce-Chwatt, L. J.** 1985. Mosquitoes, malaria and war, then and now. J. R. Army Med. Corps **131:**85–99.
46. **Bruce-Chwatt, L. J.** 1987. Malaria and its control: present situation and future prospects. Annu. Rev. Public Health **8:**75–110.
47. **Bruce-Chwatt, L. J.** 1988. History of malaria from prehistory to eradiation, p. 1–59. *In* W. H. Wernsdorfer and I. McGregor (ed.), Malaria: principles and practice of malariology, vol. 2. Churchill Livingstone, Edinburgh, United Kingdom.
48. **Bryan, J. H., D. H. Foley, and R. W. Sutherst.** 1996. Malaria transmission and climate change in Australia. Med. J. Aust. **164:**345–347.
49. **Burgos, J. J., S. I. Curto de Casas, R. U. Carcavallo, and I. G. Giron.** 1994. Global climate change influence in the distribution of some pathogenic complexes malaria and Chagas' disease in Argentina. Entomol. Vectores **1:**69–78.
50. **Burgos, J. J., S. I. Curto de Casas, R. U. Carcavallo, and A. Martinez.** 1994. Malaria and global climate change in Argentina. Entomol. Vectores **1:**123–135.
51. **Cai, W., P. H. Whetton, and B. Pittock.** 2001. Fluctuations of the relationship between ENSO and northeast Australian rainfall. Climate Dyn. **17:**421–432.
52. **Calvin, W. H.** 1998. The great climate flip-flop. Atlantic Monthly **281:**47–64.
53. **Chan, N. Y., K. L. Ebi, F. Smith, T. F. Wilson, and A. E. Smith.** 1999. An integrated assessment framework for climate change and infectious diseases. Environ. Health Perspect. **107:**329–337.
54. **Chandre, F., F. Darrier, L. Manga, M. Akogbeto, O. Faye, J. Mouchet, and P. Guillet.** 1999. Status of pyrethroid resistance in *Anopheles gambiae sensu lato.* Bull. W. H. O. **77:**230–234.
55. **Chatfield, C.** 1995. Model uncertainty, data mining and statistical inference. J. R. Stat. Soc. Ser. A **158:**419–466.
56. **Chitsulo, L., D. Engels, A. Montresor, and L. Savioli.** 2000. The global status of schistosomiasis and its control. Acta Trop. **77:**41–51.
57. **Christie, M.** 1954. A method for the study of larval populations of *Anopheles gambiae* and other pool-breeding mosquitoes. Annu. Trop. Med. Parasitol. **48:**271–276.
58. **Cleaver, H.** 1997. Malaria and the political economy of public health. Int. J. Health Serv. **7:**557–579.
59. **Coetzee, M., D. W. K. Horne, B. D. Brooke, and R. H. Hunt.** 1999. DDT, dieldrin and pyrethroid insecticide resistance in African malaria vector mosquitoes: an historical review and implications for future malaria control in southern Africa. S. Afr. J. Sci. **95:**215–218.
60. **Colborn, T., D. Dumanoski, and J. P. Myers.** 1996. Our stolen future: are we threatening our fertility, intelligence and survival? A scientific detective story. Dutton, New York, N.Y.
61. **Colwell, R., P. Epstein, D. Gubler, M. Hall, P. Reiter, J. Shukla, W. Sprigg, E. Takafuji, and J. Trtanj.** 1998. Global climate change and infectious diseases. Emerg. Infect. Dis. **4:**451–452.
62. **Cook, G. C.** 1992. Effect of global warming on the distribution of parasitic and other infectious diseases: a review. J. R. Soc. Med. **85:**688–690.
63. **Coope, G. R.** 1995. The effects of quarternary climate changes on insect populations: lessons from the past, p. 29–48. *In* R. Harrington and N. E.

Stork (ed.), Insects in a changing environment. Academic Press, Ltd., London, United Kingdom.
64. **Coosemans, M., and J. Mouchet.** 1990. Consequences of rural development on vectors and their control. Ann. Soc. Belge Med. Trop. **70:**5–23.
65. **Coosemans, M., and A. Van Gompel.** 1998. Arthropods vectors of diseases. What is the risk for travellers of being bitten? Of being contaminated? Bull. Soc. Pathol. Exot. **91:**467–473.
66. **Coosemans, M., M. Wery, B. Storme, L. Hendrix, and P. Mfisi.** 1984. Epidémiologie du paludisme dans la plaine de la Ruzizi, Burundi. Ann. Soc. Belge Med. Trop. **64:**135–158.
67. **Cox, C. B., and P. D. Moore.** 2000. Biogeography: an ecological and evolutionary approach. Blackwell Science, Malden, Mass.
68. **Craig, M. H., R. W. Snow, and D. le Sueur.** 1999. A climate-based distribution model of malaria transmission in sub-Saharan Africa. Parasitol. Today **15:**105–111.
69. **Crisp, T. M., E. D. Clegg, R. L. Cooper, W. P. Wood, D. G. Anderson, K. P. Baetcke, J. L. Hoffmann, M. S. Morrow, D. J. Rodier, J. E. Schaeffer, L. W. Touart, M. G. Zeeman, and Y. L. Patel.** 1998. Environmental endocrine disruption: an effects assessment and analysis. Environ. Health Perspect. **106**(Suppl. 1)**:**11–56.
70. **Cross, E. R., and K. C. Hyams.** 1996. The potential effect of global warming on the geographical and seasonal distribution of *Phlebotomus papatasi* in Southwest Asia. Environ. Health Perspect. **104:**724–727.
71. **Crowley, T. J.** 2000. Causes of climate change over the past 1000 years. Science **289:**270–277.
72. **Curtis, C. F.** 1996. Options for the control of malaria vectors. Pestic. Outlook **7:**20–24.
73. **Curtis, C. F., N. Hill, and S. H. Kasim.** 1993. Are there effective resistance management strategies for vectors of human disease? Biol. J. Linn. Soc. **48:**3–18.
74. **Curtis, C. F., J. E. Miller, M. H. Hodjati, J. H. Kolaczinski, I. Kasumba, and I. Denholm.** 1998. Can anything be done to maintain the effectiveness of pyrethroid-impregnated bednets against malaria vectors? Philos. Trans. R. Soc. Lond. Ser. B **353:**1769–1775.
75. **Dai, A., K. E. Trenberth, and T. R. Karl.** 1998. Global variations in droughts and wet spells—1900–1995. Geophys. Res. Lett. **25:**3367–3370.
76. **Damstra, T., S. Barlow, A. Bergman, R. Kavlock, and G. Van Der Kraak.** 2002. Global assessment of the state-of-the-science of endocrine disruptors. World Health Organization, Geneva, Switzerland.
77. **Dansgaard, W., S. J. Johnsen, H. B. Clausen, D. Dahljensen, N. S. Gundestrup, C. U. Hammer, C. S. Hvidberg, J. P. Steffensen, A. E. Sveinbjornsdottir, J. Jouzel, and G. Bond.** 1993. Evidence for general instability of past climate from a 250-kyr ice-core record. Nature **364:**218–220.
78. **Darriet, F., P. Guillet, R. N'Guessan, J. M. C. Doannio, A. Koffi, L. Y. Konan, and P. Carnevale.** 1998. Impact of resistance of *Anopheles gambiae s.s.* to permethrin and deltamethrin on the efficacy of insecticide-treated bednets. Med. Trop. **58:**349–354.
79. **Das, P. K., and D. D. Amalraj.** 1997. Biological control of malaria vectors. Indian J. Med. Res. **106:**174–197.
80. **Defries, R. S., L. Bounoua, and G. J. Collatz.** 2002. Human modification of the landscape and surface climate in the next fifty years. Global Change Biol. **8:**438–458.
81. **Deubel, V., and F. Rodhain.** 1999. Climate variations and dengue fever: direct and indirect impacts. Med. Maladies Infect. **29:**289–295.
82. **Dhanapala, A. H.** 1998. Sensitivity of malaria potential transmission to climate change in Sri Lanka. Asian Profile **26:**283–292.
83. **Diaz, H. F., and N. E. Graham.** 1996. Recent changes in tropical freezing heights and the role of sea surface temperatures. Nature **383:**152–155.
84. **Dobson, A.** 1992. Global warming and potential changes in host-parasite and disease-vector relationships, p. 201–217. *In* R. Carper, R. L. Peters, and T. E. Lovejoy (ed.), Global warming and biological diversity. Yale University Press, New Haven, Conn.
85. **Douthwaite, R. J.** 1992. Non-target effects of insecticides used in tsetse control operations. World Anim. Rev. **70–71:**8–14.
86. **Easton, A.** 1999. Outbreak of Japanese encephalitis hits Malaysia. Br. Med. J. **318:**893.
87. **El-Rahim, I. H. A. A., U. A. El-Hakim, and M. Hussein.** 1999. An epizootic of Rift Valley fever in Egypt in 1997. Rev. Sci. Tech. Off. Int. Epizoot. **18:**741–748.
88. **Epstein, P. R.** 1998. Global warming and vector-borne disease. Lancet **351:**137.
89. **Epstein, P. R.** 2000. Is global warming harmful to health? Sci. Am. **283:**50–57.
90. **Epstein, P. R., H. F. Diaz, S. Elias, G. Grabherr, N. E. Graham, W. J. M. Martens, E. Mosley-Thompson, and J. Susskind.** 1998. Biological and physical signs of climate change: focus on mosquito-borne diseases. Bull. Am. Meteorol. Soc. **79:**409–417.
91. **Eskow, E., R. Vemkitesh, S. Rao, and E. Mordechai.** 2001. Concurrent infection of the central nervous system by *Borrelia burgdorferi* and *Bartonella henselae.* Evidence for a novel tick-borne disease complex. Arch. Neurol. **58:**1357–1363.
92. **Etya'Ale, D. E.** 1998. Mectizan as a stimulus for development of novel partnerships: the international organization's perspective. Ann. Trop. Med. Parasitol. **92**(Suppl. 1)**:**S73–S77.
93. **Failloux, A. B., M. Vazeille, and F. Rodhain.** 2002. Geographic genetic variation in populations of the dengue virus vector *Aedes aegypti.* J. Mol. Evol. **55:**653–663.
94. **Falkenmark, M.** 1997. Meeting water requirements of an expanding world population. Philos. Trans. R. Soc. Lond. Ser. B **352:**929–36.
95. **Farquhar, G. D.** 1997. Carbon dioxide and vegetation. Science **278:**1411.
96. **Fischer, G., and G. K. Heilig.** 1997. Population momentum and the demand on land and water resources. Philos. Trans. R. Soc. Lond. Ser. B. **352:**869–889.
97. **Focks, D. A., R. J. Brenner, D. D. Chadee, and J. H. Trosper.** 1999. The use of spatial analysis in the control and risk assessment of vector-borne diseases. Am. Entomol. **45:**173–183.
98. **Focks, D. A., E. Daniels, D. G. Haile, and J. E. Keesling.** 1995. A simulation model of the epidemiology of urban dengue fever: literature analysis, model development, preliminary validation, and samples of simulation results. Am. J. Trop. Med. Hyg. **53:**489–506.
99. **Foo, L. C., T. W. Lim, and R. Fang.** 1985. Rainfall, abundance of *Aedes aegypti* and dengue infection in Selangor, Malaysia. Southeast Asian J. Trop. Med. Public Health **16:**560–568.
100. **French, J. B., W. L. Schell, J. J. Kazmierczak, and J. P. Davis.** 1992. Changes in population density and distribution of *Ixodes dammini* Acari: Ixodidae. J. Med. Entomol. **295:**723–728.
101. **Gaines, S. D., and M. W. Denny.** 1993. The largest, smallest, highest, lowest, longest, and shortest: extremes in ecology. Ecology **74:**1677–1692.
102. **Gardon, J., N. Gardon-Wendel, D. Ngangue, J. Kamgno, J. P. Chippaux, and M. Boussinesq.** 1997. Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for *Loa loa* infection. Lancet **350:**18–22.
103. **Garfield, R. M.** 1989. War-related changes in health and health services in Nicaragua. Soc. Sci. Med. **28:**669–676.
104. **Garfield, R. M., E. Prado, J. R. Gates, and S. H. Vermund.** 1989. Malaria in Nicaragua: community-based control efforts and the impact of war. Int. J. Epidemiol. **18:**434–439.
105. **Garnham, P. C. C.** 1948. The incidence of malaria at high altitudes. J. Natl. Malaria Soc. **7:**275–284.
106. **Garrett, L.** 1996. The return of infectious disease. Foreign Affairs **75:**66–79.
107. **Georghiou, G. P.** 1994. Principles of insecticide resistance management. Phytoprotection **75**(Suppl.)**:**51–59.
108. **Ghebreyesus, T. A., M. Haile, K. H. Witten, A. Getachew, A. Medhin, A. Yohannes, S. W. Lindsay, and P. Byass.** 2000. Household risk factors for malaria among children in the Ethiopian Highlands. Trans. R. Soc. Trop. Med. Hyg. **94:**17–21.
109. **Gillett, J. D.** 1989. The maintenance and spread of insect-borne disease by the agency of man, p. 35–46. *In* M. H. Service (ed.), Demography and vector-borne diseases. CRC Press, Inc., Boca Raton, Fla.
110. **Githeko, A. K., S. W. Lindsay, U. E. Confalonieri, and J. A. Patz.** 2000. Climate change and vector-borne diseases: a regional analysis. Bull. W. H. O. **78:**1136–1147.
111. **Githeko, A. K., M. W. Service, C. M. Mbogo, and F. K. Atieli.** 1996. Resting behaviour, ecology and genetics of malaria vectors in large-scale agricultural areas of western Kenya. Parassitologia **38:**481–489.
112. **Glantz, M. H.** 1991. The use of analogies in forecasting ecological and societal responses to global warming. Environment **33:**10–15.
113. **Go, V., J. Garey, M. S. Wolff, and B. G. T. Pogo.** 1999. Estrogenic potential of certain pyrethroid compounds in the MCF-7 human breast carcinoma cell line. Environ. Health Perspect. **1–7:**173–177.
114. **Gonidec, G., P. Fauran, and G. Le Gonidec.** 1981. Arbovirus diseases of the south-western Pacific. Med. Trop. **41:**85–92. (In French.)
115. **Gossling, S.** 2002. Global environmental consequences of tourism. Global Environ. Change **12:**283–302.
116. **Gouteux, J., and M. Jarry.** 1998. Tsetse flies, biodiversity and the control of sleeping sickness. Structure of a *Glossina* guild in southwest Cote d'Ivoire. Acta Oecol. **19:**453–471.
117. **Gratz, N. G.** 1999. Emerging and resurging vector-borne diseases. Annu. Rev. Entomol. **44:**51–75.
118. **Greenland, D. J., P. J. Gregory, and P. H. Nye.** 1998. Land resources and constraints to crop production, p. 39–55. *In* J. C. Waterlow, D. G. Armstrong, L. Fowden, and R. Riley (ed.), Feeding a world population of more than eight billion people: a challenge to science. Oxford University Press, Oxford, United Kingdom.
119. **Gregory, P. J., J. S. I. Ingram, B. Campbell, J. Goudriaan, L. A. Hunt, J. J. Landsberg, S. Linder, M. Stafford-Smith, R. W. Sutherst, and C. Valentin.** 1999. Managed productions systems, p. 229–270. *In* B. Walker, W. Steffen, J. Canadell, and J. Ingram (ed.), The terrestrial biosphere and global change. Implications for natural and managed ecosystems. Cambridge University Press, Cambridge, United Kingdom.
120. **Gryseels, B.** 2000. Schistosomiasis vaccines: a devils' advocate view. Parasitol. Today **16:**46–48.
121. **Gubler, D. J.** 1998. Climate change: implications for human health. Health Environ. Digest **12:**54–56.

122. **Gubler, D. J.** 1998. Dengue and dengue hemorrhagic fever. Clin. Microbiol. Rev. **11:**480–496.
123. **Gubler, D. J.** 1998. Resurgent vector-borne diseases as a global health problem. Emerg. Infect. Dis. **4:**442–450.
124. **Guzman, M. G., and G. Kouri.** 2002. Dengue: an update. Lancet Infect. Dis. **2:**33–42.
125. **Haines, A.** 1998. Global warming and vector-borne diseases. Lancet **351:** 1737–1738.
126. **Haines, A., A. J. McMichael, and P. R. Epstein.** 2000. Environment and health. 2. Global climate change and health. Can. Med. Assoc. J. **16:**729–734.
127. **Hales, S., S. Kovats, and A. Woodward.** 2000. What El Niño can tell us about human health and global climate change. Global Change Hum. Health **1:**66–77.
128. **Hales, S., P. Weinstein, Y. Souares, and A. Woodward.** 1999. El Niño and the dynamics of vectorborne disease transmission. Environ. Health Perspect. **107:**99–102.
129. **Hales, S., P. Weinstein, and A. Woodward.** 1996. Dengue fever epidemics in the South Pacific: driven by El Niño Southern Oscillation? Lancet **348:** 1664–1665.
130. **Hancock, J., et al.** 1996. The Macroeconomic impact of HIV/AIDS, p. 111–128. *In* S. Forsythe and B. Rau (ed.), AIDS in Kenya: socio-economic impact and policy implications. FHI/AIDSCAP, Washington, D.C.
131. **Handman, E.** 2001. Leishmaniasis: current status of vaccine development. Clin. Microbiol. Rev. **14:**229–243.
132. **Hanna, J. N., S. A. Ritchie, D. A. Phillips, J. Shield, M. C. Bailey, J. S. Mackenzie, M. Poidinger, B. J. McCall, and P. Mills.** 1996. An outbreak of Japanese encephalitis in the Torres Strait, Australia, 1995. Med. J. Aust. **165:**256–260.
133. **Hargrove, J. W.** 2000. A theoretical study of the invasion of cleared areas by tsetse flies Diptera: Glossinidae. Bull. Entomol. Res. **90:**201–209.
134. **Harvell, C. D., C. E. Mitchell, J. R. Ward, S. Altizer, A. P. Dobson, R. S. Ostfeld, and M. D. Samuel.** 2002. Climate warming and disease risks for terrestrial and marine biota. Science **296:**2158–2162.
135. **Hawley, W. A.** 1988. The biology of *Aedes albopictus.* J. Am. Mosq. Control Assoc. **4:**1–39.
136. **Hay, S. I., J. Cox, D. J. Rogers, S. E. Randolph, D. I. Stern, G. D. Shanks, M. F. Myers, and R. W. Snow.** 2002. Climate change and the resurgence of malaria in the East African highlands. Nature **415:**905–909.
137. **Reference deleted.**
138. **Hay, S. I., J. A. Omumbo, M. H. Craig, and R. W. Snow.** 2000. Earth observation, geographic information systems and *Plasmodium falciparum* malaria in subSaharan Africa. Adv. Parasitol. **47:**173–215.
139. **Heilig, G. K., G. Fischer, and H. van Velthuizen.** 2000. Can China feed itself? An analysis of China's food prospects with special reference to water resources. Int. J. Sustain. Dev. World Ecol. **7:**153–172.
140. **Houghton, J. T., L. G. Meira Filho, B. A. Callander, N. Harris, A. Kattenberg, and K. Maskell.** 1996. Climate change 1995: the science of climate change. Contribution of working group I to the Second Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge University Press, Cambridge, United Kingdom.
141. **Huang, C. H.** 1982. Studies of Japanese encephalitis in China. Adv. Virus Res. **27:**71–101.
142. **Hughes, L.** 2000. Biological consequences of global warming: is the signal already. TREE **15:**56–61.
143. **Ijumba, J. N., and S. W. Lindsay.** 2001. Impact of irrigation on malaria in Africa: paddies paradox. Med. Vet. Entomol. **15:**1–11.
144. **Intergovernmental Panel on Climate Change.** 2001. Climate change 2001. Third Assessment Report. Cambridge University Press, Cambridge, United Kingdom.
145. **Intergovernmental Panel on Climate Change.** 2001. Technical summary. Climate change 2001. Impacts, adaptation and vulnerability. A report of working group II of the Intergovernmental Panel on Climate Change. IPCC, World Meteorological Office, Geneva, Switzerland.
146. **International Plant Protection Convention.** 1997. International Plant Protection Convention 1997: Secretariat of the International Plant Protection Convention. [Online.] Food and Agriculture Organization, Rome, Italy. http://www.fao.org/ag/agp/agpp/pq/default.htm.
147. **Jetten, T. H., and D. A. Focks.** 1997. Potential changes in the distribution of dengue transmission under climate warming. Am. J. Trop. Med. Hyg. **57:** 285–297.
148. **Jetten, T. H., W. J. M. Martens, and W. Takken.** 1996. Model simulations to estimate malaria risk under climate change. J. Med. Entomol. **33:**361–371.
149. **Jetten, T. H., and W. Takken.** 1994. Anophelism without malaria in Europe. A review of the ecology and distribution of the genus *Anopheles* in Europe. Wageningen Agricultural University Papers, Wageningen, The Netherlands.
150. **Jobin, W.** 1999. Dams and disease: ecological design and health impacts of large dams, canals and irrigation systems. E. and F. N. Spon Ltd., London, United Kingdom.
151. **Jones, R. N.** 2000. Analysing the risk of climate change using an irrigation demand model. Clim. Res. **14:**89–100.
152. **Kamimura, K.** 1998. Studies on the population dynamics of the principal vector mosquito of Japanese encephalitis. Med. Entomol. Zool. **49:**181–185.
153. **Kanesa-thasan, N.** 1998. Development of dengue vaccines: an overview. Indian Pediatr. **35:**97–100.
154. **Karl, T. R., P. D. Jones, and R. W. Knight.** 1993. A new perspective on global warming: asymmetric trends of daily maximum and minimum temperatures. Bull. Am. Meteorol. Soc. **74:**1007–1023.
155. **Karl, T. R., R. W. Knight, and N. Plummer.** 1996. Trends in high-frequency climate variability in the twentieth century. Nature **377:**217–220.
156. **Kelly-Hope, L. A., B. H. Kay, D. M. Purdie, and G. M. Williams.** 2002. The risk of Ross River and Barmah Forest virus disease in Queensland: implications for New Zealand. Aust. N. Z. J. Public Health **26:**69–77.
157. **Keoleian, G. A., and D. Menerey.** 1994. Sustainable development by design: review of life cycle design and related approaches. Air Waste **44:**645–668.
158. **Kinley, D. H.** 1998. Aerial assault on the tsetse fly. Environment **40:**14–18, 40–41.
159. **Kitron, U.** 1998. Landscape ecology and epidemiology of vector-borne diseases—tools for spatial analysis. J. Med. Entomol. **35:**435–445.
160. **Knols, B. G. J., and W. Takken.** 1998. The wide-scale use of impregnated bednets for malaria control in Africa: impact on mosquitoes. Proc. Sect. Exp. Appl. Entomol. Neth. Entomol. Soc. **9:**15–22.
161. **Knudsen, A. B.** 1995. Geographic spread of *Aedes albopictus* in Europe and the concern among public health authorities. Eur. J. Epidemiol. **11:**345–348.
162. **Kondrachine, A. V., and P. I. Trigg.** 1997. Global overview of malaria. Indian J. Med. Res. **106:**39–52.
163. **Kovats, R. S.** 2000. El Niño and human health. Bull. W. H. O. **78:**1127–1135.
164. **Kovats, R. S., D. H. Campbell-Lendrum, A. J. McMichael, A. Woodward, and J. S. Cox.** 2001. Early effects of climate change: do they include changes in vector-borne disease? Philos. Trans. R. Soc. Lond. Ser. B **356:**1057–1068.
165. **Kovats, R. S., A. Haines, R. Stanwell-Smith, P. Martens, B. Menne, and R. Bertollini.** 1999. Climate change and human health in Europe. Br. Med. J. Clin. Res. Ed. **318:**1682–1685.
166. **Kovats, S., and A. Haines.** 1995. The potential health impacts of climate change: an overview. Med. War **11:**168–178.
167. **Krimsky, S.** 2000. Hormonal chaos. The scientific and social origins of the environmental endocrine hypothesis. John Hopkins University Press, Baltimore, Md.
168. **Kriticos, D. J., and P. R. Randall.** 2001. A comparison of systems to analyse potential weed distributions, p. 61–79. *In* R. H. Groves, F. D. Panetta, and J. G. Virtue (ed.), Weed risk assessment. CSIRO, Melbourne, Australia.
169. **Kuhn, K. G.** 1999. Global warming and leishmaniasis in Italy. Bull. Trop. Med. Int. Health **7:**1–2.
170. **Kullman, L.** 2002. Rapid recent range-margin rise of tree and shrub species in the Swedish Scandes. J. Ecol. **90:**68–77.
171. **Lacey, L. A., and C. M. Lacey.** 1990. The medical importance of riceland mosquitoes and their control using alternatives to chemical insecticides. J. Am. Mosq. Control Assoc. **2**(Suppl.)**:**1–93.
172. **Lane, R. S., J. Piesman, and W. Burgdorfer.** 1991. Lyme borreliosis: relation of its causative agent to its vectors and hosts in North America and Europe. Annu. Rev. Entomol. **36:**587–609.
173. **Laurance, W. F.** 2001. Future shock: forecasting a grim fate for the earth. TREE **6:**531–533.
174. **Laventure, S., J. Mouchet, S. Blanchy, L. Marrama, P. Rabarison, L. Andrianaivolambo, E. Rajaonarivelo, I. Rakotoarivony, and J. Roux.** 1996. Rice, a source of life and death on the Madagascan plateaux. Cah. Etudes Rech. Francophones/Sante **6:**79–86.
175. **Lawton, J., and R. May.** 1995. Extinction rates. Oxford University Press, Oxford, United Kingdom.
176. **Legner, E. F.** 1995. Biological control of Diptera of medical and veterinary importance. J. Vector Ecol. **20:**59–120.
177. **Lenorman, T., D. Bourguet, T. Guillemaud, and M. Raymond.** 1999. Tracking the evolution of insecticide resistance in the mosquito *Culex pipiens.* Nature **400:**861–864.
178. **Leveque, C.** 1990. The impact of vector control on the aquatic environment. Ann. Parasitol. Hum. Comp. **65**(Suppl. 1)**:**119–124.
179. **Lewis, W. J., J. C. van Lenteren, S. C. Phatak, and J. H. I. Tumlinson.** 1997. A total system approach to sustainable pest management. Proc. Natl. Acad. Sci. USA **94:**12243–12248.
180. **Li, Y. S., A. C. Sleigh, A. G. P. Ross, G. M. Williams, M. Tanner, and D. P. McManus.** 2000. Epidemiology of *Schistosoma japonicum* in China: morbidity and strategies for control in the Dongting Lake region. Int. J. Parasitol. **30:**273–281.
181. **Lifson, A. R.** 1996. Mosquitoes, models, and dengue. Lancet **347:**1201–1202.
182. **Lim, B. L.** 1986. Filariasis in Indonesia: a summary of published information from 1970–1984. Trop. Biomed **3:**193–210.
183. **Linacre, E.** 1992. Climate data and resources: a reference and guide. Routledge, London, United Kingdom.

184. **Lindblade, K. A., E. D. Walker, A. W. Onapa, J. Katungu, and M. L. Wilson.** 1999. Highland malaria in Uganda: prospective analysis of an epidemic associated with El Niño. Trans. R. Soc. Trop. Med. Hyg. **93:**480–487.
185. **Lindblade, K. A., E. D. Walker, A. W. Onapa, J. Katungu, and M. L. Wilson.** 2000. Land use change alters malaria transmission parameters by modifying temperature in a highland area of Uganda. Trop. Med. Int. Health **5:**263–274.
186. **Lindgren, E.** 1998. Climate change, tick-borne encephalitis and vaccination needs in Sweden—a prediction model. Ecol. Modelling **110:**55–63.
187. **Lindgren, E., and R. Gustafson.** 1998. Climate and tick-borne encephalitis in Sweden. Conserv. Ecol. **21:**5.
188. **Lindgren, E., L. Talleklint, and T. Polfeldt.** 2000. Impact of climatic change on the northern latitude limit and population density of the disease-transmitting European tick *Ixodes ricinus.* Environ. Health Perspect. **108:**119–123.
189. **Lindsay, S. W., and M. H. Birley.** 1996. Climate change and malaria transmission. Ann. Trop. Med. Parasitol. **90:**573–588.
190. **Lindsay, S. W., R. Bodker, R. Malima, H. A. Msangeni, and W. Kisinza.** 2000. Effect of 1997–98 El Niño on highland malaria in Tanzania. Lancet **355:**989–990.
191. **Lindsay, S. W., and A. Joyce.** 2000. Climate change and the disappearance of malaria from England. Global Change Hum. Health **1:**184–187.
192. **Lindsay, S. W., and W. J. M. Martens.** 1998. Malaria in the African highlands: past, present and future. Bull. W. H. O. **76:**33–45.
193. **Lindsay, S. W., L. Parson, and C. J. Thomas.** 1998. Mapping the ranges and relative abundance of the two principal African malaria vectors, *Anopheles gambiae sensu stricto* and *An. arabiensis,* using climate data. Proc. R. Soc. London Ser. B **265:**847–853.
194. **Lindsay, S. W., and C. J. Thomas.** 2000. Mapping and estimating the population at risk from lymphatic filariasis in Africa. Trans. R. Soc. Trop. Med. Hyg. **94:**37–45.
195. **Linthicum, K. J., A. Anyamba, C. J. Tucker, P. W. Kelley, M. F. Myers, and C. J. Peters.** 1999. Climate and satellite indicators to forecast Rift Valley fever epidemics in Kenya. Science **285:**397–400.
196. **Loder, N.** 2000. Royal Society warns on hormone disruptors. Nature **406:**4.
197. **Loevinsohn, M. E.** 1994. Climatic warming and increased malaria incidence in Rwanda. Lancet **343:**714–718.
198. **Lortholary, O., J. Robert, and J. Le Bras.** 1994. Epidemiology of drug resistant *Plasmodium falciparum* malaria. Ann. Med. Interne **145:**429–432.
199. **Maciel, A., A. Rocha, K. B. F. Marzochi, Z. Medeiros, A. B. Carvalho, L. Regis, W. Souza, T. Lapa, and A. Furtado.** 1996. Epidemiological study of bancroftian filariasis in Recife, northeastern Brazil. Mem. Inst. Oswaldo Cruz **91:**449–455.
200. **Mackenzie, J., M. Lindsay, and P. Daniels.** 2000. The effect of climate on the incidence of vector-borne viral diseases in Australia: the potential value of seasonal forecasting, p. 429–452. *In* G. L. Hammer, N. Nicholls, and C. Mitchell (ed.), Applications of seasonal climate forecasting in agricultural and natural ecosystems. The Australian experience. Kluwer Academic Publishers, Dordrecht, The Netherlands.
201. **Maelzer, D., S. Hales, P. Weinstein, M. Zalucki, and A. Woodward.** 1999. El Niño and arboviral disease prediction. Environ. Health Perspect. **107:**817–818.
202. **Maguire, T.** 1994. Do Ross River and dengue viruses pose a threat to New Zealand? N. Z. Med. J. **107:**448–450.
203. **Malakooti, M. A., K. Biomndo, and G. D. Shanks.** 1998. Re-emergence of epidemic malaria in the highlands of Western Kenya. Emerg. Infect. Dis. **4:**671–676.
204. **Marco, G. J., R. M. Hollingworth, and W. Durham.** 1987. Silent spring revisited. American Chemical Society, Washington, D.C.
205. **Martens, P.** 1998. Health and climate change: modelling the impacts of global warming and ozone depletion. Earthscan Publications Ltd., London, United Kingdom.
206. **Martens, P.** 1999. How will climate change affect human health? Am. Sci. **87:**534–541.
207. **Martens, P., and L. Hall.** 2000. Malaria on the move: human population movement and malaria transmission. Emerg. Infect. Dis. **6:**7–13.
208. **Martens, P., R. S. Kovats, S. Nijhof, P. de. Vries, M. T. J. Livermore, D. J. Bradley, J. Cox, and A. J. McMichael.** 1999. Climate change and future populations at risk of malaria. Global Environ. Change **9:**S89–S107.
209. **Martens, W. J. M., T. H. Jetten, and D. A. Focks.** 1997. Sensitivity of malaria, schistosomiasis and dengue to global warming. Climate Change **35:**145–146.
210. **Martens, W. J. M., T. H. Jetten, J. Rotmans, and L. W. Niessen.** 1995. Climate change and vector-borne diseases: a global modelling perspective. Global Environ. Change **5:**195–209.
211. **Martens, W. J. M., L. W. Niessen, J. Rotmans, T. H. Jetten, and A. J. McMichael.** 1995. Potential impact of global climate change on malaria risk. Environ. Health Perspect. **103:**458–464.
212. **Martin, P. H., and M. G. Lefebvre.** 1995. Malaria and climate: sensitivity of malaria potential transmission to climate. AMBIO **XXIV:**200–209.
213. **Massad, E., and O. P. Forattini.** 1998. Modelling the temperature sensitivity of some physiological parameters of epidemiologic significance. Ecosyst. Health **4:**119–129.
214. **Matola, Y. G., G. B. White, and S. A. Magayuka.** 1987. The changed pattern of malaria endemicity and transmission at Amani in the eastern Usumbara mountains, northeastern Tanzania. J. Trop. Med. Hyg. **90:**127–134.
215. **Matsuoka, Y., and K. Kai.** 1994. An estimation of climate change effects on malaria. J. Global Environ. Eng. **1:**1–15.
216. **Maxwell, C. A., C. F. Curtis, H. Haji, S. Kisumku, A. I. Thalib, and S. A. Yahya.** 1990. Control of Bancroftian filariasis by integrating therapy with vector control using polystyrene beads in wet pit latrines. Trans. R. Soc. Trop. Med. Hyg. **84:**709–714.
217. **Mayer, J. D.** 2000. Geography, ecology and emerging infectious diseases. Soc. Sci. Med. **50:**937–952.
218. **McCarroll, L., M. G. Paton, S. H. P. P. Karunaratne, H. T. R. Jayasuryia, K. S. P. Kalpage, and J. Hemingway.** 2000. Insecticides and mosquito-borne disease. Nature **407:**961–962.
219. **McCarty, J. P.** 2001. Ecological consequences of recent climate change. Conserv. Biol. **15:**320–331.
220. **McMichael, A. J.** 1997. Integrated assessment of potential health impact of global environmental change: prospects and limitations. Environ. Model. Assess. **2:**129–137.
221. **McMichael, A. J.** 2000. The urban environment and health in a world of increasing globalization: issues for developing countries. Bull. W. H. O. **78:**1117–1126.
222. **McMichael, A. J., and A. Haines.** 1997. Global climate change: the potential effects on health. Br. Med. J. Clin. Res. Ed. **315:**805–809.
223. **McMichael, A. J., A. Haines, R. Sloff, and S. Kovats.** 1996. Climate change and human health. World Health Organization, Geneva, Switzerland.
224. **McMichael, A. J., and R. S. Kovats.** 2000. Climate change and climate variability: adaptations to reduce adverse health impacts. Environ. Monit. Assess. **61:**49–64.
225. **Mellor, P. S.** 1998. Climate change and the distribution of vector borne diseases with special reference to African horse sickness virus, p. 439–454. Towards livestock disease diagnosis and control in the 21st century. Proceedings of an International Symposium on Diagnosis and Control of Livestock Diseases Using Nuclear and Related Techniques. International Atomic Energy Agency (IAEA), Vienna, Austria.
226. **Mockenhaupt, F. P., J. May, U. Bienzle, and C. G. Meyer.** 1997. Drug-resistant malaria. Dtsch. Med. Wochenschr. **122:**1293–1297.
227. **Modiano, D., V. Petrarca, B. S. Sirima, I. Nebie, G. Luoni, F. Esposito, and M. Coluzzi.** 1998. Baseline immunity of the population and impact of insecticide-treated curtains on malaria infection. Am. J. Trop. Med. Hyg. **59:**336–340.
228. **Molyneux, D. H.** 1997. Patterns of change in vector-borne diseases. Ann. Trop. Med. Parasitol. **91:**827–839.
229. **Mouchet, J., and J. Brengues.** 1990. Vector-borne diseases and vector control at the public health-agriculture interface. Bull. Soc. Pathol. Exot. **83:**376–393.
230. **Mouchet, J., and P. Carnevale.** 1997. Impact of environmental changes on vector-borne diseases. Cah. Etudes Rech. Francophones/Sante **7:**263–269.
231. **Mouchet, J., S. Manguin, J. Sircoulon, S. Laventure, O. Faye, A. W. Onapa, P. Carnevale, J. Julvez, and D. Fontenille.** 1998. Evolution of malaria in Africa for the past 40 years: impact of climatic and human factors. J. Am. Mosq. Control Assoc. **14:**121–130.
232. **Mulla, M. S., G. Majori, and A. A. Arata.** 1979. Impact of biological and chemical mosquito control agents on nontarget biota in aquatic ecosystems. Residue Rev. **71:**121–173.
233. **Murray-Smith, S., and P. Weinstein.** 1993. A time bomb in north Queensland: a case report of introduced malaria south of the nineteenth parallel. Comm. Disease Intell. **17:**211–213.
234. **National Oceanic and Atmospheric Administration.** 1999. An experiment in the application of climate forecasts: NOAA-OGP activities related to the 1997–98 El Niño event. Office of Global Programs, United States Department of Commerce, Boulder, Colo.
235. **New, M., M. Hulme, and P. Jones.** 1999. Representing twentieth-century space-time climate variability. I. Development of a 1961–90 mean monthly terrestrial climatology. J. Climate **12:**829–856.
236. **Newton, P., and N. White.** 1999. Malaria: new developments in treatment and prevention. Annu. Rev. Med. Select. Top. Clin. Sci. **50:**179–192.
237. **Nicholls, N.** 1986. A method for predicting Murray Valley encephalitis in southeast Australia using the Southern Oscillation. Aust. J. Exp. Biol. Med. Sci. **64:**587–594.
238. **Nicholls, N.** 1993. El Niño-Southern Oscillation and vector-borne disease. Lancet **342:**1284–1285.
239. **Omumbo, J. A., S. I. Hay, S. J. Goetz, R. W. Snow, and D. J. Rogers.** 2002. Updating historical maps of malaria transmission intensity in East Africa using remote sensing. Photogramm. Eng. Remote Sens. **68:**161–166.
240. **Ostfeld, R. S., and F. Keesing.** 2000. Biodiversity and disease risk: the case of Lyme disease. Conserv. Biol. **14:**722–728.
241. **Packard, R. M., and P. Gadelha.** 1994. A land filled with mosquitoes: Fred L. Soper, the Rockefeller Foundation, and the *Anopheles gambiae* invasion of Brazil. Parassitologia **36:**197–213.

242. **Pant, C. P., and N. G. Gratz.** 1979. Malaria and agricultural development. Outlook Agric. **10:**111–115.
243. **Parmesan, C., and G. Yohe.** 2003. A globally coherent fingerprint of climate change impacts across natural systems. Nature **421:**37–42.
244. **Parry, M., and T. Carter.** 1998. Climate impact and adaptation assessment. Earthscan, London, United Kingdom.
245. **Parry, M. L., and M. Livermore.** 1999. A new assessment of the global effect of climate change. Global Environ. Change **9**(Suppl. Issue).
246. **Patz, J. A.** 2001. Public health risk assessment linked to climatic and ecological change. Hum. Ecol. Risk Assess. **7:**1317–1327.
247. **Patz, J. A., M. Hulme, C. Rosenzweig, T. D. Mitchell, R. A. Goldberg, A. K. Githeko, S. Lele, A. J. McMichael, and D. Le Sueur.** 2002. Regional warming and malaria resurgence. Nature **420:**627–628.
248. **Patz, J. A., and S. W. Lindsay.** 1999. New challenges, new tools: the impact of climate change on infectious diseases. Curr. Opin. Microbiol. **2:**445–451.
249. **Patz, J. A., M. A. McGeehin, S. M. Bernard, K. L. Ebi, P. R. Epstein, A. Grambsch, D. J. Gubler, P. Reiter, I. Romieu, J. B. Rose, J. M. Samet, and J. Trtanj.** 2000. The potential health impacts of climate variability and change for the United States: executive summary of the report of the health sector of the US National Assessment. Environ. Health Perspect. **108:**367–376.
250. **Patz, J. A., K. Strzepek, S. Lele, M. Hedden, S. Greene, B. Noden, S. I. Hay, L. Kalkstein, and J. C. Beier.** 1998. Predicting key malaria transmission factors, biting and entomological inoculation rates, using modelled soil moisture in Kenya. Trop. Med. Int. Health **3:**818–827.
251. **Pearce, F.** 1990. High and dry in the global greenhouse. New Sci. **128:**34–37.
252. **Peters, W.** 1989. Changing pattern of antimalarial drug resistance. J. R. Soc. Med. **82**(Suppl. 17)**:**10–11.
253. **Peyton, E. L., S. R. Campbell, T. M. Candeletti, M. Romanowski, and W. J. Crans.** 1999. *Aedes Finlaya japonicus japonicus* Theobald, a new introduction into the United States. J. Am. Mosq. Control Assoc. **15:**238–241.
254. **Phillips, R. S.** 2001. Current status of malaria and potential for control. Clin. Microbiol. Rev. **14:**208–226.
255. **Porter W. P., J. W. Jaeger, and I. H. Carlson.** 1999. Endocrine, immune, and behavioral effects of aldicarb (carbamate), atrazine (triazine) and nitrate (fertilizers) mixtures at groundwater concentrations. Toxicol. Ind. Health **15:**133–150.
256. **Poveda, G., W. Rojas, M. L. Quinones, I. D. Velez, R. I. Mantilla, D. Ruiz, J. S. Zuluaga, and G. L. Rua.** 2001. Coupling between annual and ENSO timescales in the malaria-climate association in Colombia. Environ. Health Perspect. **109:**489–493.
257. **Prasittisuk, C., and C. F. Curtis.** 1982. Absence of effects of insecticides on susceptibility of anophelines to *Plasmodium yoelii nigeriensis.* Southeast Asian J. Trop. Med. Public Health **13:**127–132.
258. **Prothero, R. M.** 1977. Disease and mobility: a neglected factor in epidemiology. Int. J. Epidemiol. **6:**259–267.
259. **Prothero, R. M.** 2001. Migration and malaria risk. Health Risk Soc. **3:**19–38.
260. **Pépin, J.** 1997. Zaire (Congo): resurgence of trypanosomiasis ("patients within borders"). Lancet **349**(Suppl. 3)**:**10–11.
261. **Ramirez, J. A., and B. Finnerty.** 1996. CO_2 and temperature effects on evapotranspiration and irrigated agriculture. J. Irrigation Drainage Eng. **122:**155–163.
262. **Randolph, S. E., and D. J. Rogers.** 1997. A generic population model for the African tick *Rhipicephalus appendiculatus.* Parasitology **115:**265–279.
263. **Raymond, M., A. Callaghan, P. Fort, and N. Pasteur.** 1991. Worldwide migration of amplified insecticide resistance genes in mosquitoes. Nature **350:**151–153.
264. **Reeves, W. C., J. L. Hardy, W. K. Reisen, and M. M. Milby.** 1994. Potential effect of global warming on mosquito-borne arboviruses. J. Med. Entomol. **31:**323–332.
265. **Reiter, P.** 1988. Weather, vector biology, and arboviral recrudescence, p. 245–255. *In* T. P. Monath (ed.), The arboviruses: epidemiology and ecology. CRC Press, Inc., Boca Raton, Fla.
266. **Reiter, P.** 1996. Global warming and mosquito-borne disease in USA. Lancet **348:**622.
267. **Reiter, P.** 1998. Global-warming and vector-borne disease in temperature regions and at high altitude. Lancet **351:**839–840.
268. **Reiter, P.** 2000. Biting back. New Sci. **167:**41–43.
269. **Reiter, P.** 2000. From Shakespeare to Defoe: malaria in England in the little ice age. Emerg. Infect. Dis. **6:**1–11.
270. **Reiter, P.** 2001. Climate change and mosquito-borne disease. Environ. Health Perspect. **109**(Suppl. 1)**:**141–161.
271. **Remme, J. H. F., F. Binka, and D. Nabarro.** 2001. Toward a framework and indicators for monitoring Roll Back Malaria. Am. J. Trop. Med. Hyg. **64:**76–84.
272. **Richie, T. L., and A. Saul.** 2002. Progress and challenges for malaria vaccines. Nature **415:**694–701.
273. **Ritchie, S. A., and W. Rochester.** 2001. Wind-blown mosquitoes and introduction of Japanese encephalitis into Australia. Emerg. Infect. Dis. **7:**900–903.
274. **Robbins A. H., M. D. Borden, B. S. Windmiller, M. Niezgoda, L. C. Marcus, S. M. O'Brien, S. M. Kreindel, M. W. McGuill, A. Jr. DeMaria, C. E. Rupprecht, and S. Rowell.** 1998. Prevention of the spread of rabies to wildlife by oral vaccination of raccoons in Massachusetts. J. Am. Vet. Med. Assoc. **213:**1407–1412.
275. **Rocha e Silva, E. O., D. M. V. Wanderley, and V. L. C. C. Rodrigues.** 1998. *Triatoma infestans:* importance, control and elimination of the species in the State of Sao Paulo, Brazil. Rev. Soc. Bras. Med. Trop. **31:**73–88.
276. **Rodhain, F.** 1996. Worldwide situation of dengue. Bull. Soc. Pathol. Exot. **89:**87–90.
277. **Roger, P. A., I. Simpson, R. Oficial, S. Ardales, and R. Jimenez.** 1994. Effects of pesticides on soil and water microflora and mesofauna in wetland ricefields: a summary of current knowledge and extrapolation to temperate environments. Aust. J. Exp. Agric. **34:**1057–1068.
278. **Rogers, D. J.** 1995. Remote sensing and the changing distribution of tsetse flies in Africa, p. 177–193. *In* R. Harrington and N. E. Stork (ed.), Insects in a changing environment. Academic Press, Ltd., London, United Kingdom.
279. **Rogers, D. J., and S. E. Randolph.** 1993. Distribution of tsetse and ticks in Africa: past, present and future. Parasitol. Today **9:**266–271.
280. **Rogers, D. J., and S. E. Randolph.** 2000. The global spread of malaria in a future, warmer world. Science **289:**1763–1766.
281. **Rogers, D. J., and S. E. Randolph.** 2002. A response to the aim of eradicating tsetse from Africa. Trends Parasitol. **18:**534–536.
282. **Root, T. L., J. T. Price, K. R. Hall, S. H. Schneider, C. Rosenzweig, and J. A. Pounds.** 2003. Fingerprints of global warming on wild animals and plants. Nature **421:**57–60.
283. **Rosatte, R. C., C. D. MacInnes, R. T. Williams, and O. Williams.** 1997. A proactive prevention strategy for raccoon rabies in Ontario, Canada. Wild. Soc. Bull. **25:**110–116.
284. **Rosen, L., D. J. Gubler, and P. H. Bennett.** 1981. Epidemic polyarthritis (Ross River) virus infection in the Cook Islands. Am. J. Trop. Med. Hyg. **30:**1294–1302.
285. **Russell, B. M., L. E. Muir, P. Weinstein, and B. H. Kay.** 1996. Surveillance of the mosquito *Aedes aegypti* and its biocontrol with the copepod *Mesocyclops aspericornis* in Australian wells and gold mines. Med. Vet. Entomol. **10:**155–160.
286. **Russell, R. C.** 1998. Mosquito-borne arboviruses in Australia: the current scene and implications of climate change for human health. Int. J. Parasitol. **28:**955–969.
287. **Sabatini, A., V. Raineri, G. Trovato, and M. Coluzzi.** 1990. *Aedes albopictus* in Italy and the possible spread of this species in the Mediterranean area. Parassitologia **32:**301–304.
288. **Schapira, A., P. F. Beales, and M. R. Halloran.** 1993. Malaria: living with drug resistance. Parasitol. Today **9:**168–174.
289. **Schofield, C. J.** 1991. Vector population responses to control interventions. Ann. Soc. Belge Med. Trop. **71**(Suppl. 1)**:**201–217.
290. **Schoute, J. F. T., P. A. Finke, F. R. Veeneklaas, and H. P. Wolfert.** 1995. Scenario studies for the rural environment. Kluwer Academic Publishers, Dordrecht, The Netherlands.
291. **Serufo, J. C., A. M. Souza, V. A. Tavares, M. C. Jammal, and J. G. Silva.** 1993. Dengue in the south-eastern region of Brazil: historical analysis and epidemiology. Rev. Saude Publica **27:**157–167.
292. **Service, M. H.** 1989. Demography and vector-borne diseases. CRC Press Inc., Boca Raton, Fla.
293. **Shanks, G. D., and J. J. Karwacki.** 1991. Malaria as a military factor in Southeast Asia. Mil. Med. **156:**684–686.
294. **Shanks, G. D., Kiomndo K., S. I. Hay, and R. W. Snow.** 2000. Changing patterns of clinical malaria since 1965 among a tea estate population located in the Kenyan highlands. Trans. R. Soc. Trop. Med. Hyg. **94:**253–255.
295. **Snow, K.** 1999. Malaria and mosquitoes in Britain: the effect of global climate change. Eur. Mosq. Bull. **4:**17–25.
296. **Snow, R. W.** 2000. The burden of malaria: understanding the balance between immunity, public health and control. J. Med. Microbiol. **49:**1053–1055.
297. **Southgate, V. R., L. A. T. Tchuente, M. Sene, D. DeClercq, A. Theron, J. Jourdane, B. L. Webster, D. Rollinson, B. Gryseels, and J. Vercruysse.** 2001. Studies on the biology of schistosomiasis with emphasis on the Senegal river basin. Mem. Inst. Oswaldo Cruz **96:**75–78.
298. **Southwood, T. R. E.** 1977. Habitat, the templet for ecological strategies? J. Anim. Ecol. **46:**337–365.
299. **Spielman, A., U. Kitron, and R. J. Pollack.** 1993. Time limitation and the role of research in the worldwide attempt to eradicate malaria. J. Med. Entomol. **30:**6–19.
300. **Stoute, J. A., and W. R. Ballou.** 1998. The current status of malaria vaccines. Biodrugs **10:**123–136.
301. **Strobel M., and I. Lamaury.** 2001. Dengue fever—a review. Rev. Med. Interne **22:**638–647.
302. **Sutherst, R. W.** 1983. Variation in the numbers of the cattle tick, *Boophilus microplus* (Canestrini), in a moist habitat made marginal by low temperatures. J. Aust. Entomol. Soc. **22:**1–5.
303. **Sutherst, R. W.** 1993. Arthropods as disease vectors in a changing environment, p. 124–145. *In* J. V. Lake, G. R. Bock, and K. Ackrill (ed.), Environ-

mental change and human health. John Wiley & Sons, Chichester, United Kingdom.
304. **Sutherst, R. W.** 1998. Implications of global change and climate variability for vector-borne diseases: generic approaches to impact assessments. Int. J. Parasitol. **28:**935–945.
305. **Sutherst, R. W.** 2000. Climate change and invasive species—a conceptual framework, p. 211–240. *In* H. A. Mooney and R. J. Hobbs (ed.), Invasive species in a changing world. Island Press, Washington, D.C.
306. **Sutherst, R. W.** 2000. Climate variability, seasonal forecasting and invertebrate pests—the need for a synoptic view, p. 381–397. *In* G. L. Hammer, N. Nicholls, and C. Mitchell (ed.), Applications of seasonal climate forecasting in agricultural and natural ecosystems. The Australian experience. Kluwer Academic Publishers, Dordrecht, The Netherlands.
307. **Sutherst, R. W.** 2001. The vulnerability of animal and human health to parasites under global change. Int. J. Parasitol. **31:**933–948.
308. **Sutherst, R. W., and H. N. Comins.** 1979. The management of acaricide resistance in the cattle tick, *Boophilus microplus* (Canestrini) (Acari: Ixodidae), in Australia. Bull. Entomol. Res. **69:**519–540.
309. **Sutherst, R. W., J. Ingram, and H. Scherm.** 1998. Global change and vector-borne diseases. Parasitol. Today **14:**297–299.
310. **Sutherst, R. W., J. Ingram, T. Yonow, H. Scherm, and K. Sutton (ed.).** 1998. Global change impact assessment approaches for vectors and vector-borne diseases. GCTE Working Document no. 27. GCTE Office, Oxford, United Kingdom.
311. **Sutherst, R. W., and G. F. Maywald.** 1985. A computerised system for matching climates in ecology. Agric. Ecosyst. Environ. **13:**281–299.
312. **Sutherst, R. W., G. F. Maywald, and B. L. Russell.** 2000. Estimating vulnerability under global change: modular modelling of pests. Agric. Ecosyst. Environ. **82:**303–319.
313. **Sutherst, R. W., G. F. Maywald, and D. B. Skarratt.** 1995. Predicting insect distributions in a changed climate, p. 59–91. *In* R. Harrington and N. E. Stork (ed.), Insects in a changing environment. Academic Press, Ltd., London, United Kingdom.
314. **Sutherst, R. W., G. F. Maywald, T. Yonow, and P. M. Stevens.** 1999. CLIMEX. Predicting the effects of climate on plants and animals. CD-ROM and user guide. CSIRO Publishing, Melbourne, Australia.
315. **Sutherst, R. W., T. Yonow, S. Chakraborty, C. O'Donnell, and N. White.** 1996. A generic approach to defining impacts of climate change on pests, weeds and diseases in Australasia, p. 281–307. *In* W. J. Bouma, G. I. Pearman, and M. R. Manning (ed.), Greenhouse: coping with climate change. CSIRO Publishing, Melbourne, Australia.
316. **Tadei, W. P., B. D. Thatcher, J. M. M. Santos, V. M. Scarpassa, I. B. Rodri, and M. S. Rafael.** 1998. Ecologic observations on anopheline vectors of malaria in the Brazilian Amazon. Am. J. Trop. Med. Hyg. **59:**325–335.
317. **Tauber, M. J., C. A. Tauber, and S. Masaki.** 1986. Seasonal adaptations of insects. Oxford University Press, Oxford, United Kingdom.
318. **Taubes, G.** 1997. Apocalypse not. Science **278:**1004–1006.
319. **Tellier, X., J. Steffan, and A. Buhlmann.** 1991. Mechanisms of resistance to insecticides and acaricides. Practical consequences. Rev. Med. Vet. **142:** 657–667.
320. **Thakare, J. P., S. R. Shenoy, V. S. Padbidri, C. S. Rajput, D. P. Karmarkar, and S. S. Deo.** 1999. Japanese encephalitis in Sangli district, Maharashtra. Indian J. Med. Res. **109:**165–166.
321. **Thompson, L. G.** 1999. Ice core evidence for climate change in the tropics: implications for our future. Q. Sci. Rev. **19:**19–35.
322. **Tigertt, W. D., and D. F. Clyde.** 1976. Drug resistance in the human malarias. Antibiot. Chemother. **20:**246–272.
323. **Tilman, D., J. Fargione, B. Wolff, C. D'Antonio, A. Dobson, R. Howarth, D. Schindler, W. H. Schlesinger, D. Simberloff, and D. Swackhamer.** 2001. Forecasting agriculturally driven global environmental change. Science **292:** 281–284.
324. **Toole, M. J., and R. J. Waldman.** 1997. The public health aspects of complex emergencies and refugee situations. Annu. Rev. Public Health **18:**288–312.
325. **Topouzis, D., and J. de Guerny.** 1999. Sustainable agricultural/rural development and vulnerability to the AIDS epidemic. FAO and UNAIDS. UNAIDS Best Practice Collection, Geneva, Switzerland.
326. **United Nations Environment Programme.** 1999. Gobal environment outlook 2000. United Nations Environment Programme, Geneva, Switzerland.
327. **Utzinger, J., Y. Tozan, and B. H. Singer.** 2001. Efficacy and cost-effectiveness of environmental management for malaria control. Trop. Med. Int. Health **6:**677–687.
328. **van den Hurk, A. F., S. A. Ritchie, A. Ingram, and R. D. Cooper.** 1998. The first report of *Anopheles farauti sensu stricto* below the nineteenth parallel at Mackay, Queensland. Med. J. Aust. **169:**89–90.
329. **van der Hoek, W., Sakthivadivel, R., Renshaw, M., Silver, J. B., Birley, M. H., and Konradsen, F.** 2001. Alternate wet/dry irrigation in rice cultivation: a practical way to save water and control malaria and Japanese encephalitis? IWMI research report no. 47. [Online.] International Management Institute, Silverton, South Africa. http://www.cgiar.org/iwmi/pubs/pub 047/RR047.htm.
330. **Van Emden, H. F., and D. B. Peakall.** 1996. Beyond silent spring: integrated pest management and chemical safety. Chapman and Hall Ltd., London, United Kingdom.
331. **Vulule, J. M., R. F. Beach, F. K. Atieli, J. M. Roberts, D. L. Mount, and R. W. Mwangi.** 1994. Reduced susceptibility of *Anopheles gambiae* to permethrin associated with the use of permethrin-impregnated bednets and curtains in Kenya. Med. Vet. Entomol. **8:**71–75.
332. **Walker, J.** 1998. Malaria in a changing world: an Australian perspective. Int. J. Parasitol. **28:**947–953.
333. **Watts, J.** 1999. Malaysia-Japanese encephalitis outbreak leads to military intervention. Lancet **353:**1075.
334. **Weidhaas, D. E., and D. A. Focks.** 2000. Management of arthropodborne diseases by vector control, p. 539–563. *In* B. F. Eldridge and J. D. Edman (ed.), Medical entomology: a textbook on public health and veterinary problems caused by arthropods. Kluwer Academic Publishers, Dordrecht, The Netherlands.
335. **Weihe, W. H.** 1991. Human well-being, diseases, and climate, p. 352–359. *In* J. Jager and H. L. Ferguson (ed.), Climate change: science, impacts and policy. Proceedings of the Second World Climate Conference. Cambridge University Press, Cambridge, United Kingdom.
336. **Weintraub, P.** 2001. The bitter feud over LYMErix. Big pharma takes on the wrong little osp. [Online.] http://news.bmn.com/hmsbeagle/106/notes /feature3.
337. **Weintraub, P.** 2001 Tick menagerie [Online.] http://news.bmn.com/hmsbeagle /115/notes/feature2.
338. **Wellde, B. T., D. A. Chumo, D. Waema, and M. J. Reardon.** 1989. A history of sleeping sickness in Kenya. Ann. Trop. Med. Parasitol. **83**(Suppl. 1)**:**1–11.
339. **Wernsdorfer, W. H.** 1991. The development and spread of drug-resistant malaria. Parasitol. Today **7:**297–303.
340. **Wernsdorfer, W. H.** 1994. Epidemiology of drug resistance in malaria. Acta Trop. **56:**143–156.
341. **Wernsdorfer, W. H., and D. Payne.** 1991. The dynamics of drug resistance in *Plasmodium falciparum.* Pharmacol. Ther. **50:**95–121.
342. **Wery, M., and M. Coosemans.** 1980. Drug resistance in malaria. Ann. Soc. Belge Med. Trop. **60:**137–162.
343. **Whitby, M.** 1997. Drug resistant *Plasmodium vivax* malaria. J. Antimicrob. Chemother. **40:**749–752.
344. **White, G. B.** 1989. Malaria p. 1–22. *In* Geographical distribution of arthropod-borne diseases and their principal vectors. World Health Organization, Geneva, Switzerland.
345. **White, N. J.** 1998. Drug resistance in malaria. Br. Med. Bull. **54:**703–715.
346. **Wigley, T. M. L.** 1985. Impact of extreme events. Nature **316:**106–107.
347. **Wilson, M. E.** 1995. Travel and the emergence of infectious diseases. Emerg. Infect. Dis. **1:**39–46.
348. **Woodward, A., S. Hales, and P. Weinstein.** 1998. Climate change and human health in the Asia Pacific region: who will be the most vulnerable? Climate Res. **11:**31–38.
349. **World Health Organization.** 1986. Resistance of vectors and reservoirs of disease to pesticides. 10th report of the WHO Expert Committee on Vector Biology and Control. WHO Tech. Rep. Se. **737:**1–87.
350. **World Health Organization.** 1990. Potential health effects of climatic change. WHO report WHO/PEP/90/10. World Health Organization, Geneva, Switzerland.
351. **World Health Organization.** 2001. Global water supply and sanitation assessment 2000 report. 1. Water supply statistics. 2. Water resources development. 3. Sanitation statistics. I. WHO/UNICEF Joint Monitoring Programme for Water Supply and Sanitation. World Health Organization and UNICEF, Geneva, Switzerland.
352. **World Resources Institute.** 1996. World resources: a guide to the global environment. The urban environment. 1996–97. World Resources Institute, Washington, D.C.
353. **Reference deleted.**
354. **Wu, N., L. X. Qin, G. H. Liao, W. M. Zhou, W. K. Geng, Y. M. Shi, Y. Tan, and K. R. Zhao.** 1993. Field evaluation of bednets impregnated with deltamethrin for malaria control. Southeast Asian J. Trop. Med. Public Health **24:**664–671.
355. **Wu, Y. C., Y. S. Huang, L. J. Chien, T. L. Lin, Y. Y. Yueh, W. L. Tseng, K. J. Chang, and G. R. Wang.** 1999. The epidemiology of Japanese encephalitis on Taiwan during 1966–1997. Am. J. Trop. Med. Hyg. **61:**78–84.
356. **Ye-ebiyo, Y., R. J. Pollack, and A. Spielman.** 2000. Enhanced development in nature of larval *Anopheles arabiensis* mosquitoes feeding on maize pollen. Am. J. Trop. Med. Hyg. **63:**90–93.
357. **Yu, Z. N., and L. S. Yu.** 1990. Large-scale field evaluations of larvicidal preparation of *Bacillus thuringiensis* H-14 for mosquito control in town and rural environment in China. Bull. Soc. Vector Ecol. **15:**189–195.
358. **Zulueta, D. J., C. D. Ramsdale, and M. Coluzzi.** 1975. Receptivity to malaria in Europe. Bull. W. H. O. **52:**109–111.