

Dengue Fever Epidemic Potential as Projected by General Circulation Models of Global Climate Change

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Climate factors influence the transmission of dengue fever, the world's most widespread vector-borne virus. We examined the potential added risk posed by global climate change on dengue transmission using computer-based simulation analysis to link temperature output from three climate general circulation models (GCMs) to a dengue vectorial capacity equation. Our outcome measure, epidemic potential, is the reciprocal of the critical mosquito density threshold of the vectorial capacity equation. An increase in epidemic potential indicates that a smaller number of mosquitoes can maintain a state of endemicity of disease where dengue virus is introduced. Baseline climate data for comparison are from 1931 to 1980. Among the three GCMs, the average projected temperature elevation was 1.16°C, expected by the year 2050. All three GCMs projected a temperature-related increase in potential seasonal transmission in five selected cities, as well as an increase in global epidemic potential, with the largest area change occurring in temperate regions. For regions already at risk, the aggregate epidemic potential across the three scenarios rose on average between 31 and 47% (range, 24–74%). If climate change occurs, as many climatologists believe, this will increase the epidemic potential of dengue-carrying mosquitoes, given viral introduction and susceptible human populations. Our risk assessment suggests that increased incidence may first occur in regions bordering endemic zones in latitude or altitude. Endemic locations may be at higher risk from hemorrhagic dengue if transmission intensity increases. **Key words:** *Aedes*, biological models, climate, dengue, greenhouse effect, risk assessment, virus diseases. *Environ Health Perspect* 106:147–153 (1998). [Online 3 February 1998] <http://ehpnet1.niehs.nih.gov/docs/1998/106p147-153patz/abstract.html>

An estimated 2.5 billion people are at risk from dengue infection (1), and globally, dengue viruses are one of the most important arthropod-borne viruses transmitted to humans, whether measured in terms of the number of infections or deaths (2). Cases from recent epidemics have numbered in the millions, although only a small fraction of these is reported (3). Outbreaks in urban areas infested with dengue's primary mosquito vector, *Aedes aegypti*, can involve up to 70–80% of the populations (4). Unlike yellow fever, also carried by *Aedes aegypti*, a vaccine is not available for dengue. While a bivalent vaccine developed in Thailand has undergone human trials (5), to date, a tetravalent vaccine has not been developed.

Between 250,000 and 500,000 cases of dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS), the more severe form of the disease, occur yearly throughout the world, and the case fatality rate can be as high as 40% without treatment (6) or 1–5% with appropriate fluid replacement therapy (7). In Southeast Asia, DHF/DSS appeared in the 1950s. In the Americas, dengue and DHF/DSS reemerged during the late 1970s (4,8). In Latin America during 1995 alone, there were 284,483 reported cases of dengue, of which 7,850 cases were diagnosed as DHF/DSS and resulted in 106 deaths (Pan

American Health Organization, personal communication).

Transmission of dengue viruses is influenced by climate, among many other factors (3,9). Infectious agents that require cold-blooded invertebrate species in order to complete their life cycle are particularly sensitive to subtle changes in temperature. Dengue transmission is largely confined to tropical and subtropical regions because freezing temperatures kill overwintering larvae and eggs of *Ae. aegypti* mosquitoes (10). Also, temperature strongly affects pathogen replication, maturation, and period of infectivity, as laboratory data suggest that the extrinsic incubation period (or viral development rate) shortens nonlinearly with higher temperatures, increasing the proportion of mosquitoes that become infectious at a given time (11,12). Also, elevated temperatures can shorten insect survival time or disrupt pathogen development.

Given the relationship between temperature and dengue transmission, the possibility of climate change implores us to raise new questions about potential augmentation in the spread of this disease. The United Nations Intergovernmental Panel on Climate Change (IPCC) has suggested that by the year 2100 the average global temperature may rise by 2.0°C (range, 1.0–3.5°C) (13). This projected

rate of increase in temperature is fourfold that of the past century, over which time a 0.5°C rise in global mean surface temperature has resulted from a 30% increase in atmospheric CO₂ (14). Relevant to infectious disease distribution, minimum temperatures are now increasing at a disproportionate rate compared to average and maximum temperatures (15), and this trend is predicted to continue under climate change scenarios. Such conditions may allow dengue and other climate-sensitive vector-borne diseases to extend into regions previously free of disease, or they may exacerbate transmission in endemic parts of the world.

While several studies have demonstrated the climate sensitivity of determinants of dengue fever transmission (9–11,16–18), they do not provide a quantitative assessment of the impacts of global climate change. In this study, we used simulation analysis to project the temperature-related alteration in potential dengue transmission resulting from global climate change scenarios of the IPCC. We focused on the influence of temperature on the dynamics of viral transmission for a given infected mosquito population; the change in mosquito population densities that could also be anticipated from heavier precipitation accompanying warming is dependent on numerous site-specific parameters and so is not practical for this global study. Here, we present a scenario-based modeling approach as an important first step towards quantifying potential alteration in dengue transmission as a result of climate change.

Materials and Methods

We applied climate model outputs to the vectorial capacity (VC) model of disease transmission (19) using well-validated, climate-related parameters previously used in a

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dengue transmission simulation model (20). These dengue-specific parameters embedded within the vectorial capacity model were linked, as described by Martens (21,22), to monthly averaged outputs of temperature generated from three general circulation models (GCMs) of climate change.

Dengue transmission modeling. The basic reproduction rate R_0 (R_0), a commonly used term to predict epidemic dynamics of infectious diseases, represents the vectorial capacity multiplied by the length of time that a person remains viremic, in the case of dengue. This term yields the average number of secondary human infections produced from one infected person among a susceptible human population. If $R_0 = 1$, disease is likely to persist; if its value is <1 , the disease will tend to die out.

We focus on the VC equation that contains all parameters of R_0 except for duration of viremia, which is relatively constant. The equation defines the mean number of potential contacts infected by a mosquito population per infectious person per unit time:

$$VC = mbca^2 p^n / -\ln(p)$$

where m is the number of female mosquitoes per person, b is the probability that an infectious mosquito transmits dengue while biting a susceptible human, c is the probability that a mosquito acquires a dengue infection while biting a viremic human, a is the number of bites per person per day, n is the duration of the extrinsic incubation period (EIP), and p is the survival rate of the mosquito.

Vector density (m) is strongly related to environmental conditions. Rearranging the VC equation in terms of m , while setting VC to 1, allows calculation of the number of mosquitoes per person necessary to maintain viral transmission and thus determination of the critical density threshold of a vector population necessary to maintain viral transmission (23,24). This represents the average number of female mosquitoes per person necessary for an infectious human case to give rise to one new case of dengue in a susceptible population.

Epidemic potential. Our outcome measure, epidemic potential (EP), is simply the reciprocal of the critical density threshold. Increases in epidemic potential indicate that conditions are suitable for fewer vectors to effectively potentiate epidemic spread in a given area where *Ae. aegypti* and the virus exist; as EP rises, conditions favor a greater chance of viral transmission per mosquito. EP serves as a summary parameter that can be used as a comparative index to estimate the effect that changing ambient temperature has on potential dengue transmission risk, given a mosquito population and viral introduction.

In determining our global maps of dengue EP, we used an arbitrary cut-off value of 0.1 for current EP that define regions to include in our analysis. This exclusionary criteria was followed to reduce bias towards large change that would result from using infinitesimal EP values as denominators in regions currently at near-zero risk for dengue.

Dengue-specific parameters. Dengue-specific variables influencing EP values were derived from the relationships used in the container-inhabiting mosquito simulation

model (CIMSIM) coupled with the dengue transmission simulation model (DENSIM). Together, CIMSIM and DENSIM incorporate virtually all of the commonly recognized factors influencing the dynamics of dengue viruses in the urban setting. The entomological model, CIMSIM, is a dynamic life-table simulation model that produces mean-value estimates of key parameters for all cohorts of a single species of *Aedes* mosquito within a representative 1-hectare area. CIMSIM maintains information on abundance, age, development with respect to temperature and size, weight, fecundity, gonotrophic status, and adult survival.

In DENSIM, the entomological factors passed from CIMSIM are used to determine the biting mosquito population. The survival and emergence values dictate the dynamic size of the population within DENSIM while the gonotrophic development and weight estimates influence the rate at which these females bite. Temperature and titer of virus in the human influence the EIP in the mosquito. The infection model accounts for the development of virus within individuals and its passage between both populations (20). Assumptions used in the EP index (Table 1) were based on well-referenced entomological factors and transmission factors described in more detail in these validated dengue models of Focks et al. (20,25,26).

Temperature sensitivity varies between parameters used in the simulation models. In areas with suitable temperatures and rainfall or domestically maintained containers, the EIP is the parameter that most influences month-to-month transmission

Table 1. Assumptions used in the Dengue Epidemic Potential Model

Parameter (temperature dependent)	Default value	Contributing factors	Reference
Mosquito survival probability	0.89/day ^a	Temperature, humidity, and food availability	(26,49–51)
EIP	6–39 days	Very temperature dependent. Based on temperature-dependent enzyme kinetic model	(12,52,53)
Probability of mosquito infected from viremic human blood meal	0.45	Viral titer in blood meal ^b (viral titer contributes to EIP)	(12,20)
Biting rate on humans, based on: Duration gonotrophic cycle	74–250 hr ^c	Very temperature dependent. Based on blood meal digestion rate at 25°C determined by enzyme kinetics model	(42,54–56)
Number blood meals per cycle	1.1–2.0	Inversely related to female wet weight and directly related to larval development rate, e.g., faster development yields smaller adults ^d	(16,57)
Alternate host per feeding attempt	2.8 persons ^e	Based on four attempts per replete feed × 0.6 probability of different human host per attempt	(20)
Blood meals	90% human	<i>Aedes aegypti</i> is extremely homophilic	(58)

EIP, extrinsic incubation period.

^aWithin the viable temperature range of 6°C and 40°C (16,59).

^bAssumes infectious period of host to approximate 5 days (3,47).

^cSubsequent cycles are only 0.58 duration of first cycle (25).

^dAdult female wet weight derived from multiplying larval weight by 1.655 (16).

^eCalculated as 1.0, for first human encounter, plus three more attempts with 0.6 probability of biting different human host each time.

dynamics (20). The hypothesis explaining seasonality of DHF in Bangkok, Thailand, points primarily to temperature effects on EIP (27). Also near the equator in Iquitos, Peru, seasonality in transmission is driven by only a 1–2°C fluctuation in temperature. At this location, this slight temperature differential did not significantly influence larval development, length of gonotrophic cycle, or female size (and subsequent probability of multiple feeding); only the influence of temperature on EIP was significant. The temperature/EIP relationship probably accounts for approximately 75–85% of the variability in transmission (D.A. Focks, personal communication).

Climate scenarios. The climate change scenarios used in this study were created by modeling changes in documented current climate conditions according to the results of three transient general circulation models (GCMs). The climate scenarios referred to in this study were recommended for use by the United Nations IPCC Working Group on Impacts Assessment. Changes in baseline temperature data for the period 1931–1980 (28) were modeled according to the results of the GCMs developed by the Max Planck Institute in Germany (ECHAM1-A) (29), the United Kingdom Meteorological Office (UKTR) (30), and the Geophysical Fluid Dynamics Laboratory (GFDL89) in the United States (31). Output values (contained within grid boxes) approximate an area resolution of 250 km horizontally and 1 km vertically in the atmosphere (13), although this varies somewhat by GCM and by latitude. The main uncertainties include aspects of cloud radiative properties, coupling dynamics between the atmosphere and oceans, and detailed localized land processes.

For comparative analysis and evaluation of the modeling approach, we selected five cities that are representative of differing climates and dengue transmission: Bangkok; San Juan, Puerto Rico; Mexico City, Mexico; Athens, Greece; and Philadelphia, Pennsylvania. The baseline temperature used for these cities was derived from the National Oceanic and Atmospheric Administration (NOAA) Baseline Climate Dataset for the period 1961–1990 (32).

Results

In the dengue EP model, as temperatures increased the accelerated development rate of the virus and the increased mosquito biting rate dominated up to a temperature of 40°C, at which point potential transmission dropped sharply (Fig. 1).

Our EP model for Bangkok peaked during April through May (Fig. 2A). With an estimated 3-month duration of the log

growth phase, this suggests a peak in human cases during July and August. In Thailand, cases of dengue are reported from all provinces throughout the year, and transmission is seasonal, with the peak number of cases country wide occurring in July and August (33), or approximately 2–3 months after our calculated peak in EP. This time lag between peak EP and reported human cases matched the transmission growth phase of 2–3 months for this region, as determined by Focks et al. (20).

Transmission also occurs year-round in Puerto Rico, with some 55% of all cases occurring in September through December (34). While rainfall is related to mosquito breeding in southwestern Puerto Rico, in most other areas there are numerous water-filled artificial containers that make breeding largely independent of precipitation (35). Temperature elevation in San Juan, as projected by the three GCMs, may result in a longer period of enhanced transmission (Fig. 2B).

Mexico City, although surrounded by endemic dengue, has historically been free of dengue transmission by virtue of the city's altitude (2,485 m) and cool climate (36). Although temperatures in Mexico City do not preclude mosquito breeding, they are sufficiently cold to extend the extrinsic incubation period, preventing viral transmission. While the city has a low epidemic potential throughout the year, our EP model showed a relative increase around April (Fig. 2C), a finding consistent with current climate influences that also make April the most likely month for dengue transmission.

Athens and Philadelphia are nonendemic cities that have historically experienced epidemic outbreaks of dengue (9,37). Our projections suggest that transmission of introduced virus could occur in these cities (Fig. 2D and 2E). In the EP model, the transmission growth phase lasted for about 1 month. An elevation of the epidemic potential for both cities was projected under the three climate change scenarios; actual transmission, of course, would depend on the presence of other factors.

The three GCMs projected similar patterns of global change in dengue EP (Fig. 3). According to the three models, warming would average 1.16°C, a value close to the IPCC best estimate for around the year 2050 (38). The three maps of EP reflect the capacity for a given mosquito population to transmit dengue per geographic locale or GCM grid box (these maps are not intended to predict the expected change in *Aedes* mosquito distribution). Globally, the largest area change would occur in temperate regions. Tropical and

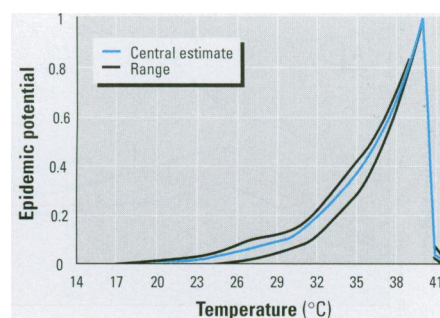


Figure 1. Epidemic potential (valued 1 as a maximum) for *Flavivirus*. Within the viable temperature range of 6–40°C, the central estimate applies a survival probability of 0.89. The range of survival probabilities used for epidemic potential determination was from 0.96 to 0.76. Reprinted with permission from Kluwer Academic Publishers (48).

subtropical regions would experience an increase in EP to a lesser extent or would remain unchanged.

For developing countries, these maps generated from the three GCMs indicate upward changes in potential infectious disease transmission. On aggregate, this increase in potential risk varied between 31 and 47% for these regions. The specific GCMs yielded the following increases: ECHAM1-A, 47% (37–74%); UKTR, 31% (24–47%); and GFDL89, 45% (35–69%).

Discussion

Our study is one of the first to use GCMs, the most highly developed climate models available (13), to estimate the potential contribution of climate change to vectorial capacity for dengue. Using GCMs, we found that epidemic potential increased with a relatively small temperature rise, indicating that fewer mosquitoes would be necessary to maintain or spread dengue in a vulnerable population. In hyperendemic tropical regions, disease transmission may be saturated, and patterns of human migration of susceptible individuals are likely to be more important to overall transmission than are climate factors. In these regions, our EP model may overestimate the effect of climate change.

By contrast, in temperate areas our model may underestimate the change in transmission potential. Our analysis of EP shows the influence of climate on viral transmission efficacy or dynamics, given a discrete infected mosquito population. The change in mosquito densities that could be anticipated to shift with global warming is not assessed in this study. On the other hand, public health infrastructure in temperate (usually developed) countries tends to reduce the actual risk posed by elevated dengue transmission potential. The dengue transmission model of Focks et al. (20) can

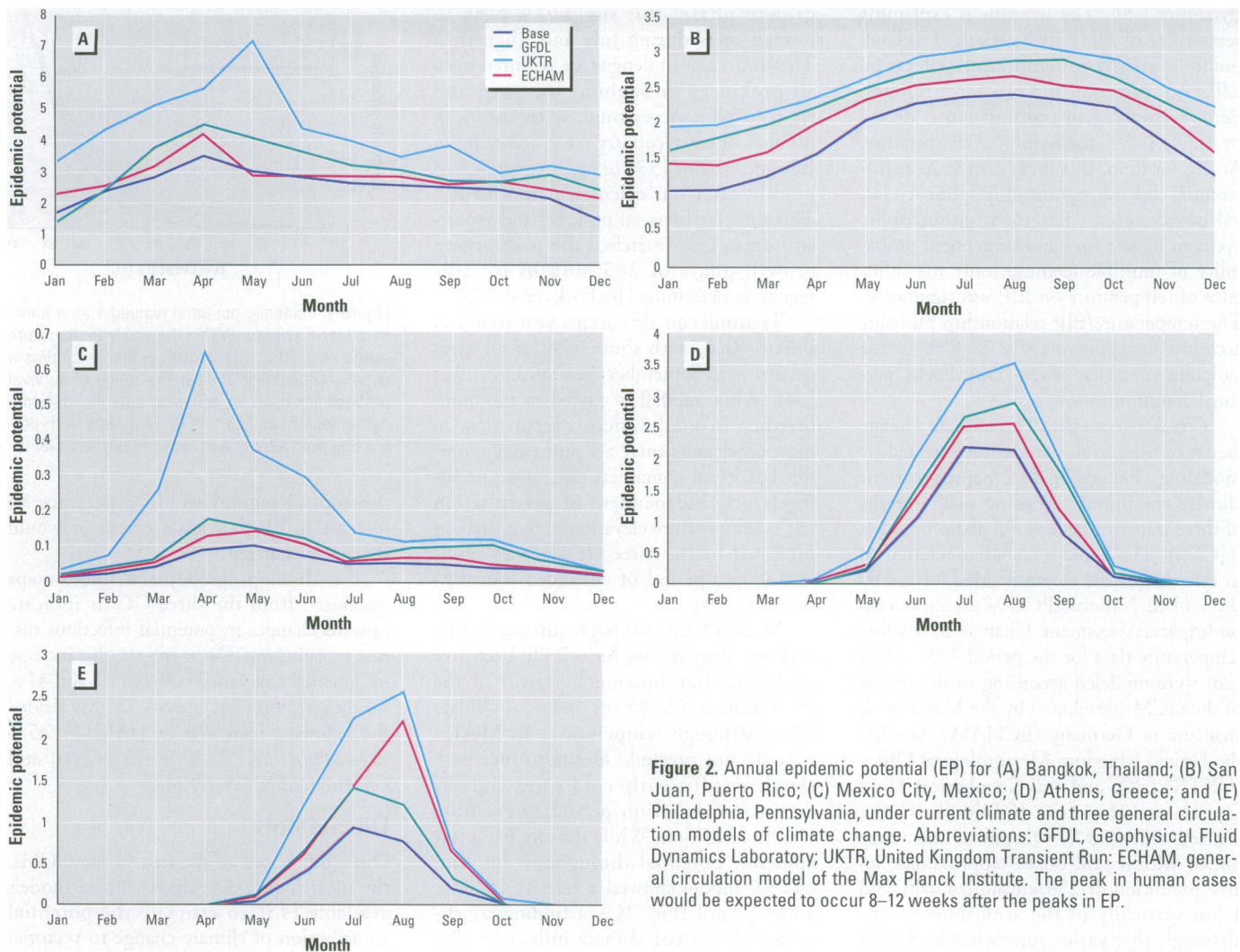


Figure 2. Annual epidemic potential (EP) for (A) Bangkok, Thailand; (B) San Juan, Puerto Rico; (C) Mexico City, Mexico; (D) Athens, Greece; and (E) Philadelphia, Pennsylvania, under current climate and three general circulation models of climate change. Abbreviations: GFDL, Geophysical Fluid Dynamics Laboratory; UKTR, United Kingdom Transient Run; ECHAM, general circulation model of the Max Planck Institute. The peak in human cases would be expected to occur 8–12 weeks after the peaks in EP.

be parameterized to incorporate site-specific data (including mosquito density determination), allowing for more localized and comprehensive risk assessment more applicable to the local rather than global level.

Our model simulation is probably most accurate for nonendemic regions currently bordering endemic areas. These fringe zones represent places where humans and *Ae. aegypti* often co-exist, but where temperature may limit disease transmission. Natural or human circumstances also may prevent transmission from rising to the level necessary to cause detectable epidemics under current conditions. If introduced, however, dengue infection among these new populations could be extensive because inhabitants of these regions lack immunity from past exposures.

Precipitation was excluded from the analysis for several reasons. While rainfall does affect mosquito population densities in some parts of the world, in the literature there is no evidence that rainfall influences

adult survival. Our study addresses transmission potential of a given mosquito population size. EP is sensitive to temperature and is derived directly from vectorial capacity equations to determine the efficacy by which a given number of mosquitoes can transmit dengue, maintaining endemic transmission. Because we are modeling transmission dynamics rather than the changing size of mosquito populations, rainfall or mosquito breeding sites are not relevant to this particular analysis. For this same reason, temperature variability that can affect local mosquito breeding sites through evaporation does not change our results.

Mosquito population densities are quite relevant, however, to more site-specific types of field studies currently under way. Determining shifts in population size would provide a more comprehensive analysis, but is not feasible for our global assessment. Population fluctuations related to temperature and precipitation can be determined by parameterizing the dengue simulation models (CIMSIM and DENSiM) at specified

sites; this has been achieved in several locations (20), but the site-specific field data collection required is not practical for regional or global scale simulation analysis.

Additionally, some site-specific studies of *Ae. aegypti* population densities have found that domestic water storage practices or the abundance of peri-domestic breeding containers (e.g., discarded tires and small containers) are more important than rainfall. Therefore, global precipitation models may be less appropriate for dengue transmission simulation compared to malaria, for example. In most of Puerto Rico (except in the southern portion), rainfall is adequate so that the number of water-filled artificial containers is largely independent of precipitation (35). Likewise, in Bangkok, dengue transmission rates appear to be unrelated to rainfall and have been attributed instead to human-filled artificial containers (39). Considering these observations, which are compounded by the greater uncertainty in projections of regional precipitation and climate variability as compared to future temperatures (13), using

global precipitation estimates at this stage would likely lead to less meaningful results.

Assessing the health effects of climate change will require analysis on various geographical and temporal levels (40). The combination of large-scale climate modeling with small-scale, site-specific evaluation would best account for both the global dynamics of climate change and the local conditions affecting disease transmission. Computer simulation modeling can aid in management of complicated disease systems and represents an important adjunct to traditional methods of investigation (41). Modeling is particularly useful in evaluating long-term climate variability, for which prospective studies lack feasibility and historical studies lack similarity with the unprecedented accelerated climate changes projected by climatologists.

Other etiologic factors not addressed at this level of integrated modeling must ultimately be incorporated to determine human risk to dengue fever. Urbanization, population density, poverty, inadequate mosquito control, absence of water systems, and international travel or migration are among factors believed to have contributed to the current reemergence of dengue (1,8). While climate conditions contribute to epidemic spread and geographic distribution of dengue (11,42) future integrated models should attempt to account for these site-specific factors as well (43).

Our model analysis is consistent with previous epidemiological studies that have confirmed the influence of temperature on dengue occurrence, as well as the sensitivity of transmission to changing temperatures. During the 1978–1979 epidemic in Honduras, endemic dengue transmission did not occur in Tegucigalpa, where average temperatures are 4°C cooler than in the coastal lowlands (44). In Mexico, endemic dengue transmission was documented at a surprising altitude of 1,700 m during an unseasonably warm summer in 1988 (36). In Mexico in 1986, the most important predictor of dengue prevalence was the median temperature during the rainy season, with an adjusted fourfold increase observed between 17°C and 30°C (17). One inference is that, while dengue outbreaks occur during the rainy season and not during the hottest period of the year, temperature remains a key determining factor.

Previous studies of climate sensitivity of malaria have shown similar results, as would be expected in that the range of malaria is limited by temperature as well (23,45). Because dengue involves only one (or two) primary species (*Ae. albopictus* being a competent though less significant carrier at present), our global maps of dengue epidemic

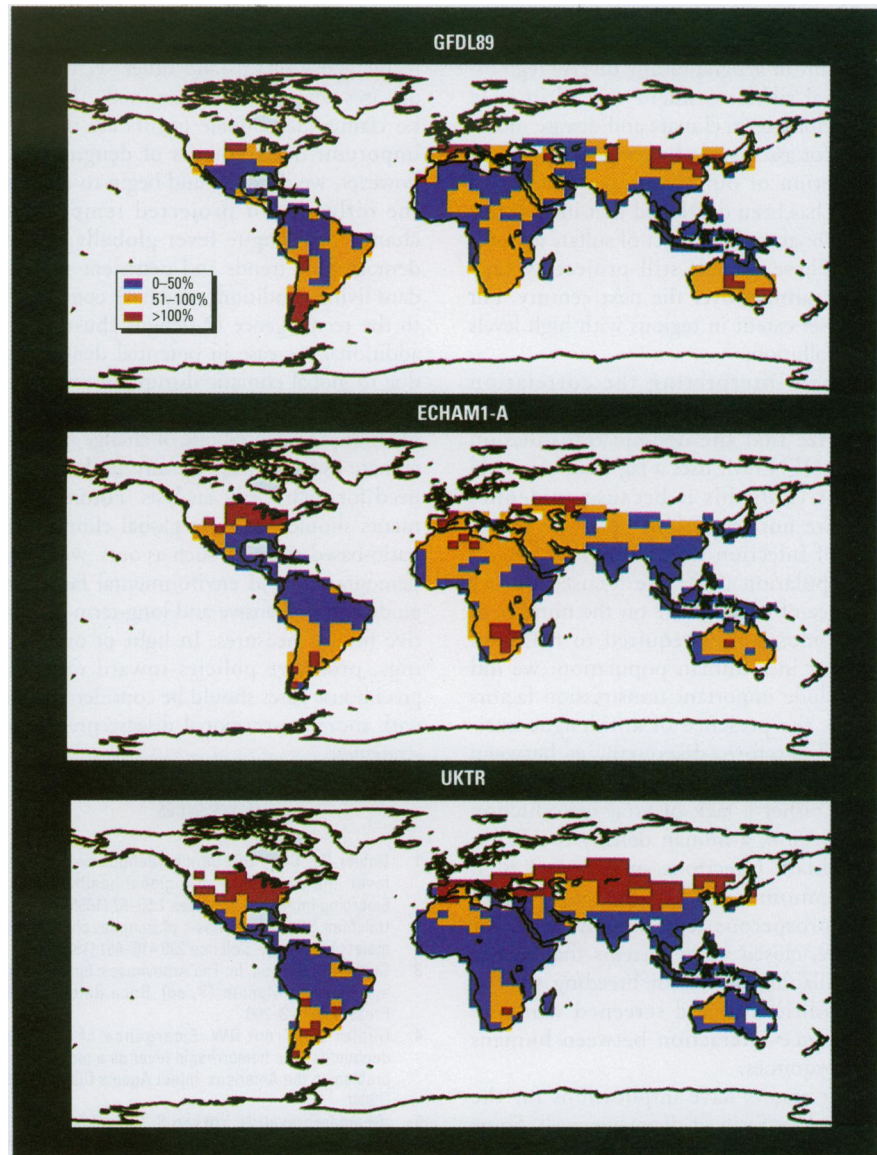


Figure 3. Changes in dengue average annual epidemic potential (EP) compared to baseline climate conditions. Projections of climate patterns were generated by the Geophysical Fluid Dynamics Laboratory (GFDL89), ECHAM1-A (model of the Max Planck Institute), and United Kingdom Transient Run (UKTR) general circulation models, calculated from monthly temperatures. The global mean temperature increase, according to these three scenarios, was 1.16°C.

potential may be more generalizable than similar assessments of malarial risk, which depends on the diverse ecology of numerous anopheline species.

Climate variability is expected with greenhouse warming, and an increase in frequency of extremely hot days above the 40°C threshold would theoretically reduce mosquito survival and subsequent transmission risk. However, there are at least two reasons that such extremes might not diminish survival rates, as observed in the laboratory. First, there is no documentation in the literature of high temperatures adversely affecting *Aedes* mosquito survival in the field. During adverse conditions, mosquitoes seek out more suitable microclimates

(e.g., under leafy vegetation or inside drain pipes or housing). Second, an increase in water vapor is predicted as the earth is heated; higher humidity may partially offset negative impacts that desiccation could have on mosquito survival.

The temperature scenarios used in our study were not intended to encompass the full range of uncertainties attributable to varying climate sensitivities to greenhouse gases, but they do illustrate the differences of the geographical and seasonal patterns of some of the most generally accepted climate change projections available. While the three GCMs project fairly similar changes in average global temperature, they diverge on smaller geographic and temporal scales.

GCM resolution can not account for intragrid box climate variability that would be important in geographically diverse regions. Regional risk assessment will ultimately require long-term climate and disease monitoring for associated changing trends. Since completion of our analysis, a new set of GCMs has been developed that incorporate the regional cooling effect of sulfate aerosols (13). These models still project average global warming over the next century, but to a lesser extent in regions with high levels of air pollution.

When interpreting the correlation between climate and EP, it is important to recognize that the dengue transmission model, DENSiM, uses a lag time of several months (20); this is because epidemics often are not recognized until the prevalence of infection rises to perhaps 1% of the population (46). We focused on the influence of temperature on the number of female mosquitoes required to maintain the virus in a human population; we did not include important transmission factors such as the presence of antidengue antibody. Therefore, discrepancies between observed and expected values of EP may be due to either a lack of viral introduction into a region, a human density too sparse to maintain infectious spread, or a high socioeconomic level of the population. More prosperous regions may have, for example, closed water systems that reduce the availability of vector breeding sites or air conditioning and screened windows that reduce interaction between humans and mosquitoes.

Our results have implications for the more serious form of dengue as well. Some evidence suggests that DHF/DSS results from sequential infection by two of the four serotypes of the dengue virus in hyperendemic locations; other risk factors include chronological age when infected and viral strain and sequence order of inoculation (47). Climatic change, as projected by the three GCMs, may result in a longer period of intensive transmission, driving up the risk of DHF/DSS in younger populations. Two major concerns arise. First, the increasing intensity of transmission results in higher seroprevalence, thus raising the number of individuals at risk of a sequential dengue viral exposure. Second, and more important, as the age drops for persons receiving primary dengue exposure, the likelihood increases for a second exposure among the preadolescent age group most at risk for fatality from a hemorrhagic event (24).

Conclusion

While the sensitivity of dengue to climate factors is well documented, the influence of

the past century's temperature rise of approximately 0.5°C (13) on the widespread reemergence of this and other vector-borne diseases remains undetermined. We make no claims that climate factors are the most important determinants of dengue fever; however, we illustrate and begin to quantify the influence of projected temperature change on dengue fever globally. While demographic trends and persistent substandard living conditions may have contributed to the reemergence of dengue thus far, the additional increase in potential dengue risk due to global climatic disruption must now be considered. Projections by climatologists of an unprecedented rate of change in global climate over the next century underline the need for such a risk analysis. Future assessments should integrate global climate scenario-based analyses, such as ours, with local demographic and environmental factors to guide comprehensive and long-term preventive health measures. In light of our findings, proactive policies toward reducing greenhouse gases should be considered along with more conventional disease prevention strategies.

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