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Global Climate Change and Infectious Diseases

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The effects of global climate change on infectious diseases are hypothetical until more is known about the degree of change in temperature and humidity that will occur. Diseases most likely to increase in their distribution and severity have three-factor (agent, vector, and human being) and four-factor (plus vertebrate reservoir host) ecology. *Aedes aegypti* and *Aedes albopictus* mosquitoes may move northward and have more rapid metamorphosis with global warming. These mosquitoes transmit dengue virus, and *Aedes aegypti* transmits yellow fever virus. The faster metamorphosis and a shorter extrinsic incubation of dengue and yellow fever viruses could lead to epidemics in North America. *Vibrio cholerae* is harbored persistently in the estuaries of the U.S. Gulf Coast. Over the past 200 years, cholera has become pandemic seven times with spread from Asia to Europe, Africa, and North America. Global warming may lead to changes in water ecology that could enhance similar spread of cholera in North America. Some other infectious diseases such as LaCrosse encephalitis and Lyme disease are caused by agents closely dependent on the integrity of their environment. These diseases may become less prominent with global warming because of anticipated modification of their habitats. Ecological studies will help us to understand more fully the possible consequences of global warming. New and more effective methods for control of vectors will be needed.

The influence of climate and the environment on infectious diseases has been a subject of debate, speculation, and serious study for centuries. Jacob Henle (*1*) stated in his 1840 treatise *On Miasmata and Contagia* "Heat and moisture favor the production and propagation of the infusoria and the molds, as well as the miasmata and contagia, therefore miasmatic-contagious diseases are most often endemic in warm moist regions and epidemic in the wet summer months." He included cholera and yellow fever among the miasmatic-contagious diseases, and indeed these two diseases may have a resurgence, as global warming materializes.

For a discussion of global climate change and its possible effect on infectious diseases, I shall deal necessarily in hypothetical terms. There is no way of knowing for certain what effect, if any, a rise in temperature and a change in rainfall patterns will have. It is feasible, however, to review the literature and point out where warmer temperatures and increased or decreased rainfall favor transmission of certain pathogenic infections; then the epidemiology of these infections can be dissected to see where the temperature and rainfall are critical to the success of the agent.

It is convenient to adopt the terminology used by Jaques May (*2*) in his book *The Ecology of Human Disease.* He considers each transmissible disease a complex. Those that involve only the causative agent and man are two-factor complexes; those that involve in addition a vector are three-factor complexes; and those that involve yet an intermediate host are four-factor complexes. The ambient temperature will have an influence on each of the factors in the complex. Many of the two-factor complexes are not limited by temperature and therefore are distributed anywhere in the world that the agent is introduced and that is inhabited by people. Examples are poliomyelitis and measles. The distribution, prevalence, and severity of these diseases are not expected to be modified by global climate change. One could argue that mortality rates of measles and poliomyelitis are higher in the tropics than in the temperate zones, and therefore these diseases will become more severe. The increased severity in the tropics is probably related to poorer socioeconomic conditions. To the extent that global warming increases poverty and its associated ills, the two-factor complexes will also be affected.

The three- and four-factor complexes by definition include the vector-borne diseases and zoonoses. Only rarely is a given vector-borne disease distributed everywhere people live. These diseases are usually limited in their distribution, either by the range of their vector, or by that of a reservoir vertebrate host. The vector and host in turn are limited in range directly or indirectly by temperature and rainfall.

Yellow Fever and Dengue

If I had to guess which vector-borne diseases would pose the greatest threat in case of global warming in North America, I would say those transmitted by *Aedes aegypti* mosquitoes—yellow fever and dengue. Both diseases are caused by viruses of the family Flaviviridae. There is a single yellow fever serotype and four serotypes of dengue. In the days of sailing ships, *Aedes aegypti* mosquitoes flourished in the water storage vessels on board and were transported each spring north to the Atlantic coastal cities. Dengue in Philadelphia was described in 1780 by Benjamin Rush, and yellow fever epidemics occurred as far north as Boston. This history is important in the context of global warming because the limiting factor in these epidemics was the onset of cold weather. *Aedes aegypti* is killed rapidly at freezing temperatures; 62% of adults died when exposed for 1 hr at 32 °F

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(*3*), and in a study in Georgia, most larvae died when average weekly ground temperature dropped to 48°F (*4*).

The northernmost winter survival of *Aedes aegypti* is now about 35° N latitude, or the latitude of Memphis, Tennessee. This distribution is predicted with global warming to move northward and encompass additional large population centers, the numbers depending on how much warming occurs. In addition, the development of mosquito larvae is faster in warm climates than cold ones, and thus with global warming, the mosquito will become a transmitting adult earlier in the season.

The extrinsic incubation period of dengue and yellow fever viruses also is dependent on temperature. Within a wide range of temperature, the warmer the ambient temperature, the shorter the incubation period from the time the mosquito imbibes the infective blood until the mosquito is able to transmit by bite. The implication is that with warmer temperatures in the United States, not only would there be a wider distribution of *Aedes aegypti* and faster mosquito metamorphosis, but also the viruses of dengue and yellow fever would have a shorter extrinsic incubation period and thus would cycle more rapidly in the mosquito. A more rapid cycle would increase the speed of epidemic spread.

Persons infected with dengue are entering the United States on a regular basis. In 1987, the diagnosis was confirmed by the Centers for Disease Control in 18 cases by laboratory examination (*5*). These persons were ill in 10 states and the District of Columbia, and all were presumably infected outside of the United States. Three of these were from Florida and Georgia, states with *Aedes aegypti*. Table 1 shows the numbers of imported cases of dengue infection over an 11-year period. All four serotypes have been recognized. Importation of dengue cases continues; as recently as 2 months before this conference, we identified dengue type 1 virus from the blood of a man returning to New Haven, Connecticut, from Thailand. We isolated the same serotype simultaneously from the blood of his travelling companion hospitalized at New York Hospital.

Another vector of dengue virus, the Asian tiger mosquito *Aedes albopictus*, has recently been introduced to the United States from Asia. This mosquito has established itself in scattered foci as far north as 42° N latitude. With global climate change, predictably this vector will become more prevalent and extend its range even further north, thus compounding the risk of dengue transmission.

One may argue that global climate change will be associated with large areas of drought, thus *Aedes aegypti* will not have sufficient water in which to breed. Paradoxically, this mosquito thrives both in wet and dry climates. In dry areas, people store water in their homes. The mosquito is domestic and breeds readily in cisterns and water storage jars.

How serious are yellow fever and dengue? Yellow fever is a febrile hemorrhagic disease characterized by hepatic and renal failure. Between 20 and 50% of victims with the severe form die, although recovery, when it occurs, is almost always complete. Dengue is usually a nonfatal illness with fever, rash, and protracted malaise. A severe form of dengue with hemorrhagic fever and shock syndrome is described principally in persons suffering a second infection with a different serotype. Most of the hemorrhagic fever cases are in children, and the case fatality rate is about 5%. An effective vaccine is available for yellow fever, but there is no specific preventive immunization for dengue.

Table 1. Dengue in the United States, 1977–1987.[a]

Year	Confirmed cases	Serotype
1977	57	
1978	52	
1979	10	
1980	45[b]	
1981	44	1,4
1982	45	1,2,4
1983	27	1,2,3,4
1984	6	1,3
1985	8	1,4
1986	33	1,2,4
1987	18	1,2,4

[a]Adapted from Centers for Disease Control (*5*); excludes Puerto Rico, U.S. Virgin Islands, and Pacific Territories.

[b]Cases were imported into the United States except for 1980 when indigenous transmission occurred.

To summarize, we know the following: *a*) *Aedes aegypti* mosquitoes are prevalent in the southern United States as far north as latitude 35° N. Temperature is a factor limiting northward spread. This species thrives in both wet and dry climates. *b*) *Aedes albopictus* mosquitoes have recently been introduced into the U.S. and range as far north as latitude 42° N. *c*) *Aedes aegypti* is an effective vector of yellow fever, and both mosquito species are effective vectors of dengue. The extrinsic incubation period of dengue and yellow fever viruses is shortened by higher ambient temperatures, leading to more rapid amplification of epidemic spread. *d*) All four serotypes of dengue virus have been introduced into the United States in recent years, and introduction is a regular occurrence that can be expected to continue. *e*) Yellow fever and dengue are serious diseases. There is no vaccine for dengue.

Cholera

Let me turn now to a very different disease, cholera. It is different because it is considered to be a two-factor complex—agent and human being. Cholera behaves ecologically, however, like a three-factor complex. There is growing evidence that a reservoir for this disease exists in bays and estuaries and that such a reservoir encompasses the Gulf Coast of the United States (*6*).

Cholera is characterized by profuse, watery diarrhea leading to loss of body salts and severe dehydration. The disease is rapidly fatal in a high percentage of patients if fluid and salt replacement is not immediately available. The causative agent of epidemic cholera is a bacterium, *Vibrio cholerae* serogroup 01, that is motile and grows aerobically at 37°C.

Cholera has been known for centuries in the delta of the Brahmaputra and Ganges rivers. Since the beginning of the nineteenth century there have been seven pandemics in which the *Vibrio cholerae* spread rapidly from endemic foci, usually in Asia, to Africa, Europe, and sometimes to North America. Once an epidemic starts, transmission is by fecal-oral spread from carriers recovered from the disease and from asymptomatic, infected persons.

Since 1973, repeated episodes of cholera in persons living in the Gulf Coast focus of Louisiana and Texas, and in persons consuming raw oysters from Louisiana, have been recorded. In August 1988, cholera occurred in a man in Colorado who ate oysters harvested in a bay off the coast of Louisiana (*7*). Between August and October of 1988, persons in five other states de-

veloped cholera, presumably from oysters harvested in the same area.

Comparison of the cholera toxin gene sequences using a DNA probe (*8*) confirmed that the strains of *Vibrio cholerae* coming from Louisiana were very similar to each other over a span of several years, and that these isolates differed from those of other parts of the world. Thus the evidence is strong that there is a continuing focus of the agent in Louisiana and that the multiple episodes of disease do not represent repeated introductions.

What does cholera have to do with global climate change? Louisiana has 40% of the coastal wetlands. With a rise in sea level and perhaps diminished river flow rates, the bays and estuaries of Louisiana can be expected to undergo major modifications. The temperature, pH, salinity, and composition of plant and animal life may well change drastically. The focus of *Vibrio cholerae* may thrive or may disappear as a result of these changes; we cannot count on its disappearance, however.

May (*2*) has plotted the areas of cholera expansion in pandemics of the nineteenth century. These were summer outbreaks and lay between summer isotherms of 60° and 80°F and summer isohyets of 2 to 4 inches per month of rain. Little is known about the relation of *Vibrio cholerae* to the ecology of estuaries harboring the agent in the United States. Colwell and associates (*9*) have made a start. So far, no aquatic animal reservoir has been found, although persistence in shellfish for several weeks has been demonstrated. A better understanding of the ecology would help us predict the effect of global climate change and prepare us to react.

Other Diseases

Dengue, yellow fever, and cholera are not the only diseases that probably will be affected. Predictions of the effects of global warming include relatively severe modifications of some of our forests. As forest habitats decline, so will many of the more fragile species of insect vectors and vertebrate hosts of parasitic, bacterial, and viral infections. We may, for instance, experience a gradual decline in prevalence of LaCrosse encephalitis virus that depends in part on tree-holes of hardwood forests for breeding of its vector, *Aedes triseriatus*, and for maintenance of its vertebrate hosts, squirrels and chipmunks. We may also experience a decline in Lyme disease, caused by *Borrelia burgdorferi*, a spirochete transmitted by the tick, *Ixodes dammini*. Tick populations are dependent in their adult stage on deer for their blood meals [although deer population reduction does not always lead to reduced tick populations (*10*)], and deer populations are dependent at least in part on forests for browsing and cover.

Finally, one must consider the possibility of emergence of new infectious diseases. New diseases have continually appeared, and there is no reason to doubt they will continue. Lyme disease, first recognized in 1975 (*11*), is now the most prevalent tick-borne disease in the United States. The agents of such diseases are not actually new. They have been present in natural wildlife cycles, and it is the ecology that changes, bringing the agent in contact with humans.

The relatively rapid ecologic changes that are now predicted set the stage for a speeding up of the process. As change occurs, creatures extend their distribution and overlap occurs. In the special case of segmented genome viruses, ecological overlap of populations creates an abundant opportunity for reassortment of genes that could increase the virulence of the progeny virus (*12*). There is no way to anticipate these events, but their potential argues for maintaining a strong biomedical infrastructure and watching closely for new diseases.

Recommendations

What can we do now to prepare for the changes in climate that are expected? I have used examples of infectious diseases that may increase in prevalence or severity. Each of these depends on a reservoir, either a vector, a vertebrate host, or an environmental source, for its maintenance. We know from experience that these diseases have the potential to become epidemic when the ecology changes. We do not know how the ecology will change over the next 50 years, nor do we know enough about the ecological factors essential for the generation of epidemics of each disease.

The first recommendation, therefore, emphasizes the importance of ecological studies. These should be multidisciplinary, involving botany (including forestry), zoology, entomology, microbiology, hydrology, climatology, and epidemiology. The information we need to project what will happen with climate change can best be acquired in the field, studying survival and adaptation, especially at the fringe of the distribution of species of plants, vertebrate animals, and arthropods. Confirmatory laboratory studies will also be needed, especially of arthropod vectors and the interaction of infectious agents with the vector. These laboratory studies will involve survival of the vector and infectious agent under changed temperature and humidity and ability of the agent to multiply or go through its development cycle in the vector under changed conditions. The ecology of water systems that harbor cholera organisms should also be studied. With the information gained, we should be in a better position to project what will happen with specific diseases after global climate change.

The second recommedation relates to arthropod-borne disease agents. We need research on the means of control of vectors. The rationale is that whatever climate and ecologic change occurs, we can anticipate an increase in some vector-borne diseases. The only generic defense (other than health education) will be control of vectors.

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