NEWS

Creatures of Our Own Making

After millions of years of coexistence, the lives of humans and mosquitoes have become intricately intertwined. The mosquito's ability to exploit almost any type of water—natural ponds and marshes or human creations such as irrigation ditches and used tires—is testimony to its evolutionary ingenuity

To say that the malaria-carrying mosquito *Anopheles gambiae* is well adapted to its role as a human parasite is like saying that Pavarotti is a pretty good singer.

An. gambiae, native to tropical Africa, is just one of about 60 anopheline mosquitoes throughout the world that can transmit human malaria. But its unrelenting focus on human ways has made it a prodigy as a disease vector. *An. gambiae* typically breed in temporary, sunlit puddles and pools of a kind found in particular near human habitations and usually directly associated with humans' agricultural modification of the landscape: the water that collects in irrigation ditches and even the small puddles created where livestock have depressed the soil with their hooves. Adult *An. gambiae* mosquitoes are commonly found sheltering in huts during the heat of the day. At night they emerge from their resting spots and, lured by the odor of human feet and other scents (see p. 90), home in on their preferred prey.

The exquisite apparatus that the female employs to penetrate the skin of its victim is less like a simple needle than one of the "complex devices surgeons snake through a body to perform remote-control surgery," observes Andrew Spielman of Harvard School of Public Health in Boston, a leading mosquito researcher. At the end of the mosquito's slender proboscis are two pairs of cutting stylets that slide against one another to slice through the skin—"like a pair of electric carving knives," Spielman writes in a mesmerizingly gory description of mosquitoes at work in his recent book, *Mosquito: A Natural History of Our Most Persistent and Deadly Foe*.

Once through the skin, the mosquito's proboscis begins probing for a tiny blood vessel. If it does not strike one on the first try, the mosquito will pull back slightly and try again at another angle through the same hole in the skin. Inside the proboscis are two hollow tubes, one that injects saliva into the microscopic wound and one that withdraws blood. The mosquito's saliva includes a combination of antihemostatic and anti-inflammatory enzymes that disrupt the clotting process and inhibit the pain reaction—the better not to get swatted—during the minute and a half or so while the insect is feeding. (Only later does the leftover saliva provoke an allergic reaction that often leaves the characteristic raised welt of the mosquito bite.) Spielman believes that the suite of enzymes produced by particular species of mosquitoes is closely tailored to the biochemistry of its chosen hosts. *An. gambiae* thus probably produces enzymes that work best against the clotting and inflammatory biochemical pathways of its preferred target: humans.

Although humans have been around for only a couple of million years, mosquitoes have always been with us—"us" being that fraternity of mammals, birds, reptiles, and no doubt dinosaurs, bound together by common victimhood at the hands, or rather the proboscises, of the members of the family

Blood feast. Using two stylets, an *Anopheles gambiae* slices through human flesh in search of a meal.

Mass murderer
Anopheles gambiae

The main vehicle for the deadliest malaria parasite, Plasmodium falciparum*, these mosquitoes contribute to the death of more than a million people a year.*

credit: CDC

Distribution: Tropical Africa.
Breeding habitat: Shallow pools and puddles—often in hoofprints and tire ruts—near human dwellings.
Feeding: Bites humans almost exclusively; has an apparent penchant for smelly feet.
Diseases: Also transmits the O'nyong-nyong virus and worms that cause lymphatic filariasis, a disfiguring and incapacitating disease.

Anopheles gambiae

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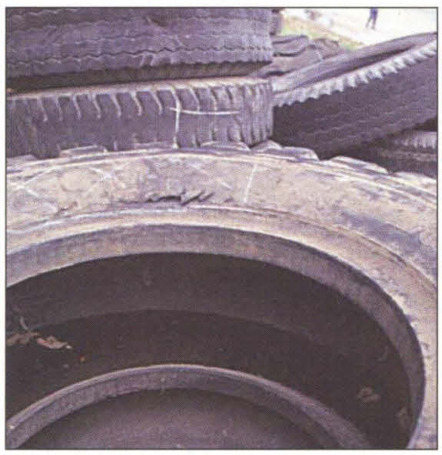
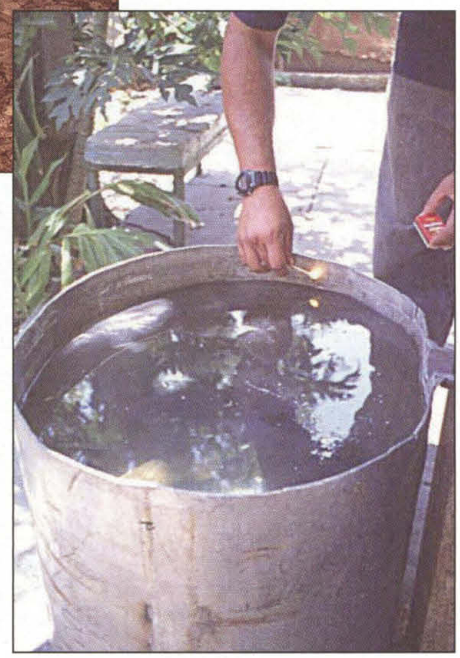
Culicidae. The word mosquito comes from the Spanish or Portuguese meaning "little fly," which is both apt description and good taxonomy. Mosquitoes are members of the order Diptera, the earliest "true" flies. Nora Besansky of the University of Notre Dame in Indiana, an expert on mosquito evolution, estimates that the divergence between the mosquito lineage and the "higher" flies such as *Drosophila* took place about 250 million years ago. The oldest known mosquito fossil, preserved in Canadian amber, dates from about 76 million to 79 million years ago; and, notes entomologist Thomas Zavortink of the University of California, Davis, an expert on mosquito taxonomy, "it's a perfectly good mosquito; it's not something that looks halfway between a mosquito and something else." Zavortink concludes: "When you put it all together, I'd say mosquitoes have to have evolved 160 [million] to 205 million years ago."

Over the eons since, mosquitoes have charted an impressive record of adaptation, diversification, and spread. The 5-cm-thick *Catalog of the Mosquitoes of the World* lists a couple of thousand species; adjusting for new discoveries, the total comes to about 3500 known and identified species throughout the world. Zavortink has estimated, however, that "we probably know only a quarter of the species" of mosquitoes actually in existence. (He hastens to add, "Maybe I'm wrong and it's half." Either way, that's a lot of mosquitoes.)

Although people commonly think of mosquitoes as being particularly associated with swamps or steaming tropical jungles, they are found in practically every habitat and climate zone on Earth, from the equator to the Arctic. The Arctic, in fact, is home to some of the most suffocating mosquito populations on the planet, albeit only for a few brief weeks of the year when the surface waters of the tundra melt. Dead caribou have been found completely exsanguinated, their blood literally sucked dry by swarms of ravenous mosquitoes that beset the still-warm corpses. The one nonnegotiable demand in the mosquito life cycle is that all mosquito larvae need to live in water, where they feed upon aquatic microorganisms as they develop. But the ability of the mosquito family to exploit suitable bodies of water in climates ranging from deserts to mountaintops (mosquitoes have been found at an elevation of 2400 meters in the Himalayas) is a staggering testimony to evolutionary ingenuity. The water can be fresh, salt, brackish, or sewage; it can be found in ponds, lakes, streams, bogs, marshes, ditches, puddles, barrels, birdbaths, tree holes, or even the leaves of the pitcher plant. Dozens or even hundreds of different mosquito species may exist in the same geographical area, each exploiting a slightly different niche among the panoply of damp places.





Nonnegotiable demand. Mosquitoes must have water to lay their eggs, but various species have adapted to whatever sources are available, be they natural ponds, used tires, or water barrels. Lighted gasoline (*right*) can kill mosquito larvae.

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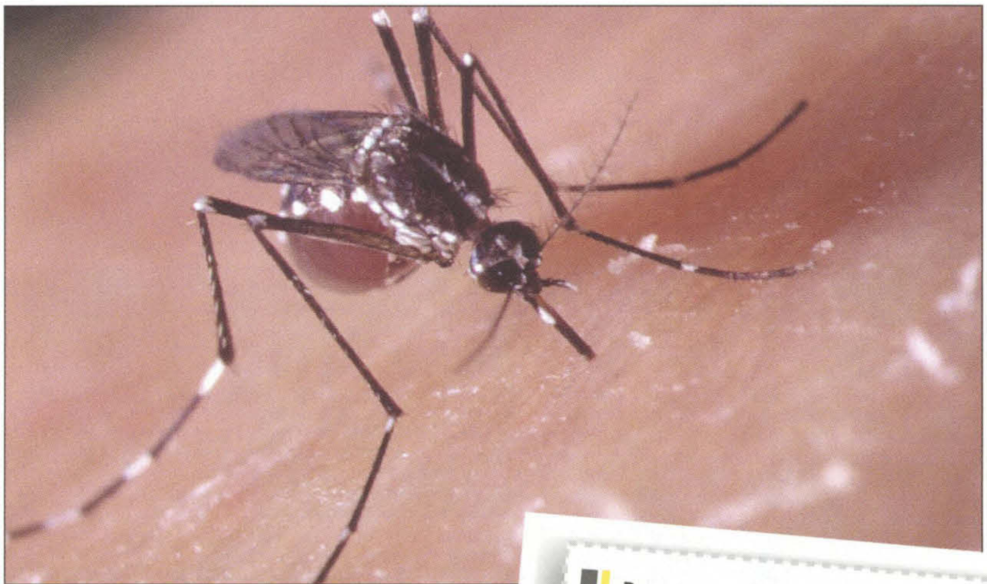
Coexisting mosquito species have also found ways to spread out ecologically within an environment: by concentrating on different hosts; by being generalists or specialists; by adopting different search and attack strategies; and by being active at different times of day. As a general rule, the mosquito species that are active during the day tend to use visual cues rather than odor to find their victims. They cue in on motion and tend to be fairly nonselective in their targets. (Odors are very specific to individual species, whereas a lot of animals move.) The infamous New Jersey mosquito, *Ochlerotatus sollicitans*, attacks like a Stuka dive-bomber from directly above, usually biting the head or upper body of its victim, and even chases victims who try to run away. Other common North American mosquitoes occupy distinct niches. The common house mosquito, *Culex pipiens*, implicated recently as a major vector of West Nile virus in the United States, feeds at night and strikes birds, livestock, and people; it appears to be attracted generally by heat and carbon dioxide. The dengue and yellow-fever mosquito *Aedes aegypti* feeds in morning and late afternoon and is "semidomesticated" in its habits, breeding almost exclusively in water that collects in small artificial containers around human habitations and preferring the blood of humans to that of other animals. The swamp mosquito *Culiseta melanura*—the major carrier of the deadly viral disease eastern equine encephalitis—breeds in subterranean pockets of water that form under tree roots and feeds almost exclusively on birds. A few mosquito species have adapted to the competition by eschewing blood altogether; *Toxorhynchites* mosquitoes live off nectar.

The unifying theme in this diversity, says Spielman, is that "mosquitoes are well adapted to a very unstable, transient environment. They're the first organism in and the first out of a newly created body of water." Not only do transient water bodies—those that form in tree cavities or seasonal waterways, for instance—provide an opportunity for breeding that might not otherwise exist in a dry region, but even in moist and temperate areas they offer the further advantage of helping mosquitoes evade predators. Mosquito eggs and larvae are extremely vulnerable to predation. But in small, temporary



Bone breaker
Aedes aegypti

credit: ARS

Transmits yellow fever and dengue, a rapidly spreading viral disease that causes excruciating joint and muscle pain (it's dubbed "breakbone fever") that can, in some forms, progress to a deadly hemorrhagic syndrome.

Distribution: Tropical and subtropical regions across the globe.
Breeding habitat: Water-containing trash and water-storage vessels.
Feeding: Like *Anopheles gambiae*, it strongly prefers human hosts.
Diseases: Also transmits Chikungunya and Sindbis viruses, both of which cause severe fever, rash, and arthritic pain.

Aedes aegypti

puddles or seasonally filled ditches, they can finish their 1- to 2-week development into pupae and adults before other carnivorous insects appear on the scene. Small, transient pools are also free of such formidable predators as fish. Some mosquitoes, notably the *Aedes* species, lay their eggs on the moist edge of a receding, seasonal stream or pool or a partially filled artificial container. The eggs stay moist for a day or two while the embryo develops, but then further development is placed on hold as the water evaporates. When rains later raise the water level, the resulting reduction in oxygen tension immediately triggers the eggs to hatch—within literally half a minute.

The other way mosquitoes cope with predators is through the strength that comes in numbers, and that's where blood-feeding comes in. In some aquatic insect species, such as mayflies, adults emerge from pupation lacking even functional mouthparts: The adults breed and die quickly, without ever feeding. But to acquire the nutrients needed to produce the hundreds of eggs that a single female mosquito can lay, some concentrated form of energy is required. Even in blood-feeding species of mosquito, it is only the female that does so. The few micrograms of blood she sucks from her host represent three times her own weight and constitute a nutrient-rich bonanza that is scarcely available in such concentrated form elsewhere in nature. In general, notes Zavortink, the mosquito species that do not feed on blood occupy a habitat where the larvae live in nutrient-rich environments and so can accumulate the needed supply of egg-laying nutrients before reaching adulthood. Further proof of the connection between blood and abundant reproduction is found among the variant subpopulations of *C. pipiens*: Spielman found that some *C. pipiens* subpopulations do not feed on blood and lay about 60 to 80 eggs only once in their lifetime. Other variants feed on blood repeatedly and produce as many as 400 eggs per blood meal. This "adaptive polymorphism," as Spielman describes it, enables the species "to thrive whether or not there is a host available."

The role that human behavior and modification of the environment have played in the evolution of the mosquito—and of the many diseases that mosquitoes can transmit to humans, among them yellow fever, malaria, dengue, West Nile virus, encephalitis, and elephantiasis—is extraordinarily complex. In recent centuries human travel, trade, and development have repeatedly introduced species to new habitats and, for that matter, created entirely new habitats. *Ae. aegypti* was brought to the New World in the 17th century, along with yellow fever, probably in the water casks of slave ships that sailed from Africa. In the 1970s, the Asian tiger mosquito *Ae. albopictus* was inadvertently carried to Texas amid shipments of used tires. *Ae. albopictus* is a tree-hole–breeding species, and the water that accumulates in a dismounted tire offers a perfect artificial counterpart to its natural habitat. The tiger mosquito does not appear to be a significant disease vector in North America, but it is notoriously aggressive, attacking in daylight.

On a local scale, recent human modification of the environment may also have dramatic consequences for the interaction of human and mosquito. Having been introduced into South American rainforests, *Ae. aegypti* began to occupy its natural habitat of tree holes, high in the forest canopy. Spielman says one can walk through such rainforests for kilometer upon kilometer without encountering mosquitoes at all. But that is only as long as the forest remains intact. When trees are felled, the mosquitoes are abruptly brought to the forest floor—and into contact with people.

The few decades that *Ae. albopictus* has been breeding in used automobile tires, or even the few centuries that *Ae. aegypti* has been breeding in water barrels or other such niches inadvertently created by modern commerce and land-use patterns, are too short to have had a major impact on mosquito evolution. But intriguing genetic evidence points to a significant human role in the recent evolution of the African malaria vector *An. gambiae* and other closely related species. Indeed, the potent niche that human beings and human modifications of the landscape represent seems to have driven a burst of speciation that, Besansky and some other researchers believe, is continuing even now—and that genetic analyses on the molecular level are capturing as it unfolds (see p. 87).

In the 1960s entomologists realized that what had been believed to be the single species *An. gambiae* is actually a complex of seven closely related "cryptic" species. These seven species cannot be distinguished "by eyeballing them," Besansky notes, but significant differences appear in their DNA sequences. There is a high degree of breeding isolation among these molecularly distinct species. There is also a high degree of feeding specialization: Among the seven are some (such as

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An. gambiae "proper") that concentrate almost exclusively on humans and others (such as *An. quadriannulatus*) that feed almost exclusively on animals.

Similarly, another major African malaria vector, *An. funestus*, is part of a subgroup of four very closely related sister species. *An. funestus* alone among them specializes in human hosts; it is found almost exclusively resting inside human dwellings and feeding on human blood. Indeed, most of the world's 60 anopheline mosquitoes that are human malaria vectors (out of the 500 or so *Anopheles* mosquito species in all) belong to similar complexes or groups of extremely closely related species.

Mitochondrial DNA analysis suggests that *An. gambiae* and *An. funestus* diverged about 4 million to 6 million years ago, which, Besansky notes, is approximately when human and chimpanzee also diverged. "Until quite recently, humans haven't been around on the planet in sufficient density that a mosquito would choose to specialize to such an extent" as *An. gambiae* and *An. funestus* do, she observes. "So you can at least speculate that it was the rise of human density and the accompanying environmental modification that triggered these bursts of diversification throughout the anopheline species."

Molecular analysis of different populations within *An. gambiae* proper suggests that further speciation is occurring even now. Two molecular forms have been identified within *An. gambiae* proper, the M and S forms (see Coluzzi Report at www.sciencemag.org/cgi/content/abstract/1077769 and Della Torre Viewpoint on p. 115). Analysis of the sperm found in impregnated females shows that only about 1% of matings occur between members of the two different forms. Moreover, striking behavioral differences exist between the two populations. The S form, which is found throughout tropical Africa, breeds in rain-dependent temporary puddles. The M form, which is found only in West Africa, breeds preferentially in humanmade environments such as irrigation ditches. These ditches typically remain filled with water for much longer periods of the year than do puddles. In other words, the M form appears to be an "incipient species that is taking advantage of habitats man has created," Besansky says. Its emergence has had the effect of "extending the reach" of *An. gambiae*—and of the malaria parasite it carries—"both physically and temporally," Besansky says: *An. gambiae* is penetrating into regions that were previously too dry to support it at all, and it is extending the seasons of the year during which it can breed, even in areas where it was previously found.

The fine-tuned adaptation of anopheline mosquito species such as *An. gambiae* and *An. funestus* to preying upon humans seems to clearly explain why these are such important vectors of human malaria. In the laboratory, all of the seven species that make up the *An. gambiae* complex can be infected with malaria. Yet in the wild, only those species that attack humans carry the parasite. The reason is largely a matter of mathematics. To successfully transmit the disease from one human to another, a mosquito has to have a high probability of biting an infected human being ("focused feeding") and also has to live long enough to bite another uninfected human being after the parasite has undergone the necessary stage of development within the mosquito's gut. A mosquito that "wastes" some of its bites on nonhumans will be a much less efficient vector of a human pathogen.

The mathematics of vector-borne disease transmission produces some fascinating and not always intuitive results. The population density of a vector is actually far less significant in determining how efficiently it spreads disease than are the factors of focused feeding and longevity.

Beginning a century ago, the United States began an antimosquito war that continues to this day; every state and many counties and districts have "mosquito control" authorities that spray insecticides, drain ditches and swamps, and even distribute mosquito-eating fish to pond owners. Their work has been remarkably effective in reducing populations of nuisance mosquitoes. But the elimination of once-endemic diseases such as malaria, yellow fever, and denguelike fevers from North America occurred largely as a result of changes in human behavior that reduced human contact with mosquitoes, not through specific control or elimination of the disease vectors themselves. Indeed, temperate North America and Europe are still home to significant populations of perfectly efficient malaria, dengue, and yellow-fever vectors. Paul Reiter, a medical entomologist at the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, notes that "we associate malaria with the tropics only because we've forgotten—because we've *relegated* malaria to the tropics."

Reiter, who has extensively researched the history of vector-borne diseases—he is also CDC's point man on the West Nile outbreak—notes that malaria was regularly found as far north as Canada and Scandinavia in the 19th century. It was endemic in England even during the unusually cold weather of the "Little Ice Age" of the 17th century. Severe outbreaks of yellow fever occurred in Philadelphia repeatedly in the 17th

Suspended animation. *Culex* mosquitoes lay their eggs one at a time and then glue hundreds together to form a raft.

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Disease monger

Culex quinquefasciatus (Southern house mosquito)

credit: CDC

Dominant vector of lymphatic filariasis, a disease caused by threadlike parasitic worms. Filariasis, which has infected some 120 million people worldwide, can lead to genital damage and elephantiasis.

Distribution: Tropical and subtropical regions across the globe.
Breeding habitat: Mainly in drains, cesspits, and other polluted water bodies.
Feeding: Mammals, including people, and birds.
Diseases: Also transmits St. Louis encephalitis and probably West Nile virus.

Culex quinquefasciatus

and 18th centuries; in the 1793 outbreak, 5000 people died—a tenth of the city's population. Philadelphia was also the site of the first recorded outbreak of denguelike fever in America, in 1780. The United States was declared malaria-free only in 1954; Holland achieved that status only in 1970.

Yet the incidence of malaria began to decline dramatically in the industrializing nations toward the end of the 19th century, well before mosquito-control programs began—indeed, before mosquitoes were recognized as the carriers of the disease. Better housing and sanitation played a significant part, but nothing did as much as the advent of one remarkably simple device in the early 20th century: the window screen. Breaking the chain of transmission was the crucial factor. If each infected person transmitted the disease on average to fewer than one other person, the epidemic would be broken and the population of the disease-causing organisms would not be able to sustain itself. That is what ultimately happened. As Spielman notes, the mosquito survived, but the parasite it transmitted did not.

Reiter's studies of history and his current-day field research on mosquitoes have convinced him that recent dire warnings of a resurgence of vector-borne disease due to global warming have at best a dubious basis in scientific fact. "Obviously, climate and weather are important," he says. But countless mosquito species, including many perfectly efficient disease vectors, are capable of surviving cold winters, either by hibernating in basements or other sheltered areas or in the form of impervious eggs. "In the end, human behavior and the economic conditions of people are probably the most important factors" in determining the distribution of vector-borne diseases, he argues. Reiter points to the striking example of dengue along the Rio Grande: From 1980 to 1999, there were 64 cases in Texas versus 62,514 in the three Mexican states on the other side of the river. Yet the population of dengue-carrying *Ae. aegypti* is actually *greater* on the U.S. side. The crucial difference is that in Mexican towns and cities, window screens are rare and people are constantly out on the streets exposed to the disease carriers. But "on the streets in Texas, you're lucky if you see someone dashing between their air-conditioned vehicle and their air-conditioned house," as Reiter puts it.

The close triangular association among humans, mosquito species such as *An. gambiae* and *Ae. aegypti*, and the diseases they carry has led to some speculation that the pathogens might be influencing the evolution of mosquitoes in ways that make them more effective disease carriers and vectors. But most experts believe that is not the case; rather, the parasites are merely opportunistic piggybackers that are exploiting the preexisting close relationship between mosquitoes and humans. Spielman points out, too, that at least some of the mosquito-borne pathogens are harmful not only to the human or animal host but to the mosquito vector as well, notably the various filarial worms (responsible for elephantiasis in humans and heartworm in dogs), whose larvae, to avoid being harmed by the mosquito's digestive tract, burrow out of the gut and into the wing muscles, where they develop. (They subsequently burrow their way to the mosquito's mouthparts, breaking out as it feeds and so gaining entry to the host's bloodstream.) Thus, if anything, there should be a selective pressure that tends toward mosquitoes' resisting the role of disease carrier.

Spielman speculates, however, that in a paradoxical way, humans—the ultimate victims of diseases such as malaria—might themselves create selective pressures that help keep the rates of malaria infection and transmission high. Spielman notes that where malaria is endemic, the resident population tends to have developed immunity to the disease. Although infection rates are high, incidence of disease symptoms is low; even infants are protected to a significant degree by passive immunity acquired from antibodies in their mothers' milk. An invading enemy, however, would not only be quite likely to be infected but also be quite likely to succumb to the disease. "These 'diseases of the enemy' like dengue and malaria protect the residents of stably infected sites," Spielman argues. "A lot of the things that mosquitoes transmit *are* nasty, and they're that way on purpose—to keep visitors away."

So, as with many aspects of this close and troubling relationship between humans and mosquitoes, the fault may lie less with them than with us. **–STEPHEN BUDIANSKY**

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Globalist

Aedes albopictus
(Asian tiger mosquito)

Fastest spreading mosquito in the world; extremely well adapted to living around people. Known to travel in used tires.

credit: CDC

Distribution: Rural and green urban areas, almost worldwide.
Breeding habitat: Water-containing trash.
Feeding: Aggressive daytime biter of humans, domestic and wild animals, and birds.
Diseases: Believed to spread dengue and La Crosse encephalitis; may occasionally transmit eastern equine encephalitis, St. Louis encephalitis, and West Nile virus.

Aedes albopictus

A simple solution. On the Texas side of the Rio Grande, window screens effectively block dengue, a mosquito-borne disease. On the Mexican side, where screens are scarce and many activities occur outdoors, the incidence of dengue is far higher.

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