

critical countries. Zimbabwe, for example, “has doubled or tripled enrollment in medical schools,” according to Friedman, “but they haven’t increased the number of professors. This is probably going to lead to lower quality.”

Throughout Africa, innovative programs are testing approaches to ameliorating the shortage. Once effective pilot programs have been identified, scaling up will be the next hurdle: programs that are found to work on a small scale or in a particular environment may not be easy to expand or replicate.

Despite the challenges, the world has taken its first steps toward needed changes. In addition to receiving attention from the Group of Eight industrialized countries and the United Nations World Summit, the shortage of

health care workers recently inspired the American Public Health Association to pass a policy statement on “Ethical Restrictions on International Recruitment of Health Professionals to the United States.” The policy addresses the role of the United States in exacerbating the international crisis, calling on employers to adopt voluntary codes for ethical recruitment and on the government to contract only with employers who have done so. In addition, it advocates the training of greater numbers of U.S. health care professionals and more equitable distribution of those we have.

Though the worker shortage has a long history, “it’s only in the past 3 to 5 years that the political advocacy has been loud enough that this issue has been put on the political agenda,” says

the WHO’s Dayrit. He acknowledges that “there are no magic bullets” against brain drain — “eventually, the local economy competes with the global economy, and it [is] futile to try to put up barriers. Over time, people find ways around them.” Nevertheless, he says, “I have to be optimistic. What we’re doing is trying to increase the dialogue and engagement among countries and identify concrete steps . . . so that you can create a cascade of events that lead to amelioration.”

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1. World Health Organization. The world health report 2006 — working together for health. (Accessed June 1, 2007, at <http://www.who.int/whr/2006/en/index.html>.)

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## FOCUS ON RESEARCH

# Taking a Bite Out of Vector-Transmitted Infectious Diseases

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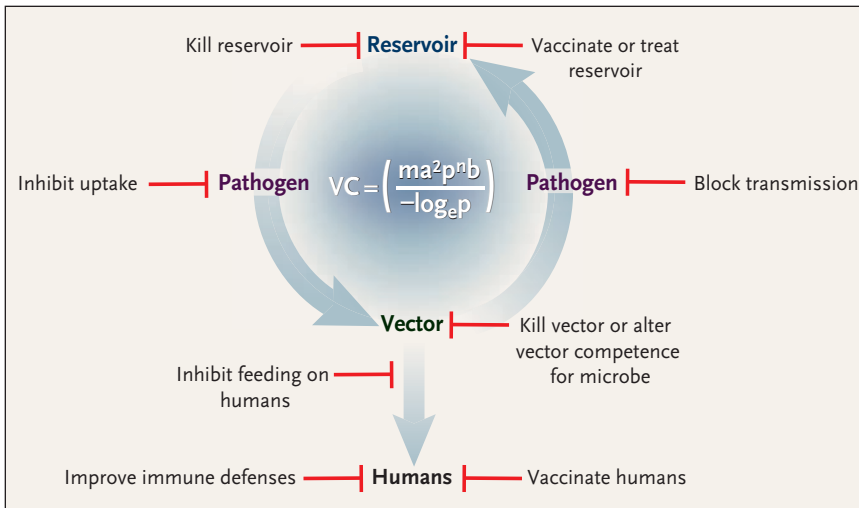
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It is hard to overstate the medical importance and burden of vector-transmitted infectious diseases. Whether the metric used is mortality (malaria, for example, kills 1 million to 2 million people annually, most of them children under 5 years of age), morbidity (more than 70 million years of healthy living are lost to malaria, Chagas’ disease, leishmaniasis, dengue fever, lymphatic filariasis, and the encephalitis viruses), or something as difficult to quantify as anxiety in a population (activities in outdoor playgrounds and high schools, for example, were moved or suspended along the south shore of

Massachusetts this past fall because of concern raised by three cases of eastern equine encephalitis), the burden of these infections is enormous.

The key elements involved in human vectorborne infectious diseases are the infectious microorganism (virus, bacterium, or parasite), the vector (mosquito, tick, or fly), and the reservoir from which the vector obtains the infection (see diagram). Control strategies for these diseases should be informed by an understanding of the complex dynamics of vector–host interactions and the ways in which the environments of both the vector and

host intersect to produce human disease. Models, including the Ross–Macdonald model (see diagram),<sup>1</sup> have been developed to permit prediction of the effects of different approaches. For example, when the reservoir is accessible, the elements of the model involving the reservoir host (a and b) can potentially be manipulated in a way that has a substantial influence on organism transmission and therefore disease burden. In contrast, when the reservoir cannot be influenced, approaches to mediating the transmission of vectorborne diseases to humans are almost exclusively dependent on affecting the rela-



### The Ross–Macdonald Model of Vectorial Capacity and Strategies to Interrupt Vector-Transmitted Infectious Diseases.

This classic mathematical model estimates vectorial capacity (VC), or the efficiency with which an arthropod vector transmits a pathogen. The density of the vector species ( $m$ ) plays a role in VC, since the more individual vectors that are present, the more likely they will be to transmit a pathogen. Control measures targeting larval stages of a vector (e.g., larvicides) are targeting  $m$ . VC is also affected by the chance that a vector will feed on a susceptible host species ( $a$ ). This variable is multiplied by itself in the model, since a vector must feed once on an infected host to acquire the pathogen and once on an uninfected host to transmit it. Interventions that reduce host–vector contact (e.g., bed nets) are targeting  $a$ . The probability that a vector, having acquired the pathogen, will live long enough to transmit it is a combination of the daily survival probability ( $p$ ) and the extrinsic incubation period ( $n$ ), or the number of days after acquiring the pathogen that are required for a vector to become capable of transmitting it. Control programs targeting adult vectors (e.g., the application of dichlorodiphenyltrichloroethane [DDT] to the walls of dwellings) affect  $p$ . Finally, VC is affected by vector competence ( $b$ ), which is the chance that when a vector feeds on an infected host it will actually acquire the pathogen and support its development to the infectious stage. This is affected by intrinsic properties of the vector and by the density of the pathogen in the infected host. Mass drug-treatment programs and schemes for the genetic modification of vectors target  $b$ . Control strategies (denoted by red bars) for vectorborne infectious diseases can target the reservoir, the pathogenic microorganism, the vector, the human host, or combinations of these elements. A slide presentation is available with the full text of this article at [www.nejm.org](http://www.nejm.org).

tive abundance ( $m$ ) and life expectancy ( $p$ ) of the insect vector.

Traditional approaches to the control of such infections have targeted two broad strategies: vaccination or chemical prophylaxis for at-risk humans, and reduction and avoidance of vectors. Vaccination has had some success for a number of vectorborne infections, including yellow fever and Japanese encephalitis. However, despite years of research and investment, vaccines for important vectorborne infections such as malaria and dengue fever remain elusive. The use of antimicrobial prophylaxis

for malaria is effective for travelers to areas where the disease is endemic but has not proven practical for residents of such areas and has led to the development of resistance to the antimicrobial agents.

In this issue of the *Journal*, Sundar and colleagues (pages 2571–2581) report on a control strategy they tested for sandfly-transmitted visceral leishmaniasis in Bihar, India, that extends the concept of antimicrobial administration by taking advantage of the local vector–host dynamics to target eradication of the reservoir. Since, on the Indian subcontinent, the

reservoir for *Leishmania donovani* is limited solely to humans (unlike the zoonotic reservoirs in South America), these investigators reasoned that mass outpatient treatment of the human reservoir population with an affordable, effective, intramuscularly administered aminoglycoside (paromomycin), coupled with a program to reduce the sandfly vector population, could be an effective control strategy for this potentially lethal disease. Their results, indicating a 94.6% cure rate that was similar to that of intravenously administered amphotericin B, has prompted the adoption by the Indian government of widespread paromomycin treatment as part of a public health program to eliminate visceral leishmaniasis from the region.

Reservoir reduction may also be a viable strategy for the control of infections for which the primary reservoir is not human. Tsao et al.<sup>2</sup> have shown that vaccination of wild mice, a major reservoir of *Borrelia burgdorferi* (the causative agent of Lyme disease), with injected recombinant outer-surface protein A can significantly reduce carriage of the organism by ticks in the subsequent year. Several research groups are now developing mechanisms for delivering vaccines to animal reservoirs, using oral baits. Oral baiting for wild-life vaccination has proven very effective in combating the non-vectorborne disease rabies. Other vectorborne infections for which wildlife vaccination strategies are being tested include *Yersinia pestis* (plague) and hantavirus.

Although reservoir-reduction strategies are becoming more prominent, most previous infection-control strategies have focused on the vector. Vector-targeted strategies are particularly

attractive, since the vectorial capacity to transmit infectious diseases to humans is related to vector density and, in an exponential way, to vector survival. Perhaps the best-known example of a successful vector-reduction strategy is the U.S. campaign to eradicate yellow fever and malaria during the construction of the Panama Canal. In that case, a comprehensive plan that included drainage of standing pools of water, cutting of grass and brush, oiling of ponds and swamps to kill larvae, and capture of indoor mosquitoes resulted in the eradication of yellow fever and a substantial reduction in cases of malaria. In the 1930s and 1940s, similar efforts toward mosquito control in the southeastern United States, as part of a program of the Tennessee Valley Authority, led to the near-eradication of endemic malaria in the United States. Insecticidal spraying with dichlorodiphenyltrichloroethane (DDT) was begun in this country in the late 1940s as part of the National Malaria Eradication Program and helped to eliminate the few remaining cases of malaria in the United States. However, although initially hailed as a panacea, spraying with DDT has not been effective at eradicating malaria worldwide. Well-publicized problems with environmental toxicity, the possibility of human carcinogenesis, and the development of resistance among insects have led to the withdrawal of DDT from widespread use.

Exciting new strategies are targeting novel components of the vector-pathogen interaction. For example, a small peptide molecule (SM1) has been shown to bind to mosquito salivary and midgut cells and to impair plasmodium development and subsequent transmission from this insect vector.

Whereas plasmodium has usually been thought of as causing disease in humans, it has become apparent that mosquitoes themselves have reason to avoid becoming infected with this parasite, since it decreases fertility. In mixed caged populations of mosquitoes, those expressing the plasmodium-resistant SM1 gradually replace wild-type, disease-transmitting mosquitoes,<sup>3</sup> raising the possibility that a genetically altered, malaria-resistant mosquito could be introduced to reduce transmission.

Targeting of the vector-human interaction with vaccines that protect against vector feeding is another new approach. Vaccination with a midgut protein of the boophilus tick, Bm86 antigen, has been shown to be effective in preventing these ticks from feeding on cattle<sup>4</sup> and has been approved for commercial use. Vaccination may also be able to prevent the transmission of pathogens either by decreasing the feeding time or by recruiting a vigorous immune defense to the site of the tick bite. The Bm86 vaccine has reduced the incidence of babesiosis in vaccinated cattle, and vaccination with a different tick salivary protein, 64TRP, has been shown to prevent the transmission of tick-borne encephalitis as effectively as a pathogen-targeted vaccine. Similarly, vaccination with a sandfly salivary protein can prevent the transmission of leishmania.<sup>5</sup> Vaccination against insect and arthropod vectors may be used alone as a strategy for protecting humans or combined with attempts at reservoir eradication.

As we enter the postgenomic era for many of the pathogens, vectors, and reservoirs of human vectorborne diseases, we are gaining a new understanding of genome-genome intersections that

are critical to the maintenance of infectious cycles. The availability of new molecular tools such as small interfering RNA (siRNA) and microarrays is allowing scientists to rapidly identify and test promising new candidates for disease-interruption strategies. These strategies offer great hope that targeting specific interactions between a pathogen and either its vector or its reservoir host may lead to new approaches that can reduce human disease with minimal disturbance of the delicate ecosystems in which these pathogens persist.



A slide presentation on the transmission of vectorborne infections can be viewed at [www.nejm.org](http://www.nejm.org).

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