Policy Forum

Defining Challenges and Proposing Solutions for Control of the Virus Vector *Aedes aegypti*

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The mosquito *Aedes aegypti* is the primary vector of three important viral diseases—dengue, yellow fever, and chikungunya—and is capable of transmitting a number of others. *Ae. aegypti,* which bites during daylight, is uniquely domestic among mosquito vectors: it mates, feeds, rests, and lays eggs in and around human habitation.

Control of this mosquito should lead to control of disease, and there are well-documented historical examples of both yellow fever and dengue being eliminated or significantly reduced through *Ae. aegypti* control [1]. Construction of the Panama Canal was possible only after US Army Surgeon General William Gorgas stopped yellow fever transmission among workers by eliminating *Ae. aegypti* breeding sites. Fred Soper, of the Rockefeller Foundation, led the highly successful *Ae. aegypti* eradication program during the 1950s and 1960s that extinguished yellow fever and dengue transmission from most of Central and South America. More recently, Singapore and Cuba greatly reduced risk of dengue transmission by means of anti–*Ae. aegypti* legislation and actions. Use of the predatory crustacean *Mesocyclops* is preventing dengue transmission in parts of Vietnam [2].

Unfortunately, these successes are exceptions that were often too short-lived. Dengue has reoccupied Latin America and increases yearly; most of Southeast Asia remains highly endemic. Despite the availability of a vaccine, yellow fever outbreaks occur with dismaying frequency in Africa and Latin America. Chikungunya caused epidemics during 2005–2006 in the Indian Ocean region that were the largest yet recorded. In some

regions, such as Sudan, all three viruses coexist. The reasons for failure are numerous. Spreading urbanization increases the habitat for expanding *Ae. aegypti* populations, rapid global migration increases the potential for vector and virus dissemination, poverty hobbles the efforts of individuals and communities to carry out effective protective measures, and even when resources for control exist, they are too often ineffectively applied [3].

Summary Points

- If done properly, *Aedes aegypti* suppression is a practical method to control urban dengue, yellow fever, and chikungunya viruses.

- The goal should be to reduce adult *Ae. aegypti* populations or their interactions with humans below that which can sustain an epidemic; it is unrealistic to expect to eradicate either the vector or the viruses.

- The reason *Ae. aegypti* control is not used more widely is that most endemic countries have poorly defined goals and are unwilling to commit resources except during epidemics.

- A new paradigm for control should include focused surveillance and strategies that kill adult mosquitoes, and development and testing of products that appeal to the consumer; this could make national programs more effective and cheaper, and therefore more attractive.

- Programmatic innovations and novel products can be most effectively and efficiently developed in areas where substantial baseline information is already available (e.g., Peru, Puerto Rico, Thailand, Singapore, Indonesia, and Vietnam). This should lead to large-scale intervention project(s) of sufficient duration to determine the longer-term intervention consequences, specifically to establish if transmission can be broken.

An international panel (see Acknowledgments) met at Fort Collins, Colorado, United States, in May 2006 to critically examine why *Ae. aegypti* control has so seldom been successful in eliminating disease and to recommend measures to increase the opportunities for success. Consideration of control methods was limited to technologies now available or that could be soon developed; therefore, methods depending on genetical manipulation, such as genomic transformations and sterile male releases, were not discussed. There was unanimous agreement that elimination or significant reduction of *Ae. aegypti* populations is an effective and proven method for disease prevention. After reviewing examples of successful and failed programs, two issues especially worthy of attention were identified: (1) program design and management—specifically, sustainability, goal-setting, and surveillance/assessment—and (2)

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the need for more effective mosquito control tools.

Program Design and Management

Sustainability. Common to all successes was the ability and commitment to sustain a mosquito control program. At its most basic level, *Ae. aegypti*–borne disease can be eliminated by the simple expedient of preventing vector access to water containers necessary for immature mosquito development. But the implementation even of such a straightforward program requires careful planning, blanket coverage, and conscientious execution; to have lasting effect it must be indefinitely sustained. Effective programs had two common elements consistent with a policy of determined leadership that stressed community responsibility: (1) a vertical component, usually governmental, that initiated, planned, and oversaw the program, and (2) a horizontal component, usually householders, who helped execute control measures and permitted access to their property.

Although community participation is crucial to success, there are no apparent examples of successful efforts initiated solely at the community level [4]. Denying *Ae. aegypti* the opportunity to lay eggs or complete development in water in and around homes will work only when all members of the community participate—people who eliminate mosquito habitats are still vulnerable from neighbors who do not. In fact, participation is often high only during epidemics. No examples were found where education campaigns had lasting influence on behavior. Although "bottom-up" policy is attractive, it is unrealistic to expect it to work without strong "top-down" leadership and support. The most effective means of ensuring community participation would be arthropod control measures that are themselves attractive to the community, such as those that have broad impact by killing a wide variety of vectors and nuisance pests, not just *Ae. aegypti*.

Well-reasoned and specific public health goals will be the foundation for effective leadership. Sustainability will be enhanced by the availability of easy-to-use evidence-based decision-making tools that allow public health officials to effectively argue for policies that are scientifically based, make better use of limited resources, advocate for provision of the necessary funding, secure "buy-in" from higher levels of government, and obtain programmatic freedom for decision making.

Goals. How is success defined in an anti–*Ae. aegypti* campaign? What are the endpoints? Goals have often been undefined, ambiguous, or irrelevant. Although the ultimate objective must be to prevent disease, most current programs emphasize reduction of immature *Ae. aegypti* density, which is of little value because its relation to transmission risk is weak [5]. Goals for preventing epidemics or maintaining consistently low vector populations require different programmatic strategies and necessitate different surveillance systems. One of the most important steps for improving efficacy of *Ae. aegypti*–borne disease control programs will be development of methods for setting quantitative goals that are spatially and temporally specific. This will require a shift in thinking from the current situation, in which little interpretation is needed of prescribed entomological measures that are uniformly applied, to a new approach that calls for assessing risk against locally derived goals that are based on location-specific dynamics in epidemiology, ecology, and availability of resources. In this new scenario, it is essential to understand that entomological thresholds are dynamic and that they only make sense in the context of local epidemiology [5].

Surveillance and assessment. Surveillance is fundamental for setting goals and evaluating success. Unfortunately, except for vector eradication programs [1], current surveillance seems to play no significant role in strategically applied *Ae. aegypti*–borne disease prevention. There are epidemiological surveillance systems designed to detect introduction of novel viruses, but we are not aware of any systems that predict epidemic risk based on entomological information.

Measuring mosquito density is conceptually easier and less expensive than human diagnosis, but immature mosquito indices have a weak relation to risk from virus transmission. Methods that monitor production of late-instar larvae and pupae promise to be more informative [6,7] but require validation. Although the density of adult female *Ae. aegypti*, which transmit virus, is more closely associated with disease incidence, adults of this species are difficult to catch and rarely monitored. An inexpensive and effective *Ae. aegypti*–specific adult trap would be a significant surveillance breakthrough, and could also allow for virus testing.

It is not clear how useful any surveillance will be that does not measure the immunological status of the population at risk. Serologic assays of periodic blood samples from representative populations, including children, are impracticable in many communities. Development of noninvasive (e.g., using saliva, tears, or urine), serotype-specific, rapid, sensitive, and inexpensive methods for detection of antibodies would be a major advance for surveillance and assessment. Clinic networks that monitor and report clinical disease—syndromic surveillance—may forecast elevated risk, even though cases typically trail transmission, and subclinical or mild illness may evade detection.

There are no validated algorithms to predict, at a given location, to what extent a reduction in *Ae. aegypti* population will reduce transmission. An improved understanding of the relation of entomological factors to risk must be a priority. Information generated from surveying mosquitoes, virus, and sera needs to be synthesized into meaningful models of virus transmission risk. The complex natural history of arbovirus transmission contributes to the difficulty in setting goals and executing effective control. There is convincing evidence that mosquito-borne disease incidence is highly focal [8]. Knowing the spatial distribution of cases in a given situation and the most productive sources of adult mosquitoes would allow planners to focus limited resources. Although surveillance data, both entomological and epidemiological, have often been collected, other than in Singapore [1] and research settings, there are few instances of control programs where disparate parameters have been usefully combined. Areas identified as needing urgent research attention are (1) development of entomological thresholds for different disease control goals and (2) effective, user-friendly virus transmission models that account for variation throughout time and space.

Tools

Four areas with potentially high impact for vector control tool development

were identified based on products either currently on the market or whose development is nearly complete. They are (1) novel methods for control of immature *Ae. aegypti*, (2) novel delivery systems for adult control, (3) adult mosquito monitoring tools, and (4) quantitative assessment tools. The emphasis is on application within households or dwellings, recognizing *Ae. aegypti*'s unique habits of feeding frequently on human blood and resting indoors [9].

Novel delivery systems for adult control. It has been known since the early 1900s [10,11] that the most cost-effective means of preventing mosquito-borne disease is to target the adult vector, which transmits the pathogen. The prevailing paradigm for suppressing *Ae. aegypti*, however, targets immature mosquitoes, the vast majority of which will not survive long enough to transmit virus.

Aircraft-delivered and truck-mounted ultra-low volume spraying has limited efficacy [12] against *Ae. aegypti* because the vapor frequently does not penetrate into buildings where adult mosquitoes rest, although it is often used as a visible symbol of governmental action during emergencies. A better approach is to target adult vectors in places proximate to humans by delivering pesticides directly inside dwellings. This shifts vector population age structure to younger mosquitoes and reduces survival of infective or virus-incubating mosquitoes. Control in buildings can be accomplished with indoor residual or space spraying, but those approaches are often hampered by limited access into homes and resource limitations.

In another approach, which has been referred to as *la casa segura*, or "the safe home" (B. Beaty, personal communication), householders protect themselves in the home against a variety of vector-borne diseases and pest insects. This concept recognizes that householders in many developing countries already buy pesticides to control insects in the home. Residents in Thailand were estimated to have spent US$4–US$25/year/household on insecticides; this represents a greater amount than was spent per household on organized mosquito control [13]. There are advantages in engaging market forces to promote products, rather than relying solely on public health appeals.

Insecticide-treated materials. Insecticide-treated materials (ITMs), developed initially for malaria control, have not been sufficiently appraised against *Ae. aegypti*. In Mexico and Venezuela, lambdacyhalothrin- or deltamethrin-treated materials hung on windows and used as water jar covers significantly reduced *Ae. aegypti* densities in both intervention and controls clusters, which was attributed to community or "spill-over" effect [14]. ITMs usually enjoy high acceptance. There has been steady improvement in ITM efficacy and economy—longer-lasting chemicals and ever-improving impregnation techniques—to meet malaria demand. *Ae. aegypti*–specific ITM delivery strategies have yet to receive the attention they merit, despite their obvious promise.

Lethal ovitraps. Ovitraps are faster and less expensive, use less pesticide, and are less likely to affect non-target species than interior residual spraying. A combination of lethal ovitraps and sticky ovitraps was used in North Queensland, Australia with encouraging results (S. Ritchie, personal communication; [15]). Lethal ovitraps are essentially a black bucket containing water with an attractant infusion (0.5 grams alfalfa pellet), a cloth strip treated with a residual pyrethroid insecticide, and a plastic mesh cover ([16], adapted from [17]). Use of oviposition repellents or source reduction might push gravid females away from hard-to-control natural sites toward lethal ovitraps or ITMs; i.e., a "lure and kill" strategy. Suitability and impact of these tools needs to be evaluated in endemic areas.

Space repellents. Space repellents are volatiles that expel mosquitoes from a large cubic area without necessarily killing them. In addition to killing mosquitoes, many insecticides repel at low doses [18]. Metofluthrin (Sumitomo Chemical), a synthetic pyrethroid with spontaneous vapor action at room temperatures, has been highly lethal to mosquitoes in preliminary tests [19]. Similar in concept to ITMs, it can be formulated as compressed paper or plastic strips to be hung from ceilings [20,21]. Passive space repellents, which could be used in combination with ITMs or lethal ovitraps, might provide low-cost, long-term mosquito repellency free of an external energy source and

with minimal pesticide exposure for residents.

Novel methods for control of immature *Ae. aegypti*. An ideal larvicide would be long-lasting, have low toxicity for both humans and other non-target organisms, and persist. Products should be evaluated to account for variation in container materials (plastic, metal, clay, glass, cement, wood) and in large trials under realistic field conditions.

Pyriproxyfen, an insect growth regulator, may be the most promising larvicidal product currently available. It is effective at inhibiting adult *Ae. aegypti* emergence at concentrations of less than or equal to one part per billion [22–27], can be applied in various formulations (e.g., sticks, granules), and is cost-competitive. It is already in veterinary and agricultural use. It remains effective up to five months, longer than *Bacillus thuringiensis israelensis*, methoprene, or temephos, and is less toxic. Adult mosquitoes exposed to pyriproxyfen have decreased fecundity. Importantly, contaminated adults can disseminate lethal doses from treated to untreated sites [25,27].

Adult monitoring tools. Development of a cost-effective, field-appropriate method for estimating adult *Ae. aegypti* densities should be a priority. An adult trap would be less intrusive than current *Ae. aegypti* household surveys, require less labor, and allow for more complete coverage both spatially and temporally. Ideal characteristics of an adult trap would include low cost, ease of distribution, species exclusivity, a consistent sampling profile, and independence from electric power. An adult trap would benefit from an effective lure or attractant.

At present the best options are (1) backpack aspirators, (2) sticky ovitraps, and (3) the BG trap. Although current models of battery-powered backpack aspirators may be too expensive for most disease-endemic countries (>US$400), this is the most effective way to quickly collect large numbers of *Ae. aegypti* across different ages, sexes, and physiological statuses from large numbers of households [28–30]. In Thailand, backpack aspirators collect ~25%–30% of adult *Ae. aegypti* in a house (T. Scott and L. Harrington, unpublished data), and an individual collector can sample 25–30 households in a normal workday

[31]. The development of new, less expensive designs could extend their use into developing country settings. Sticky ovitraps [32] are an inexpensive method to collect adult *Ae. aegypti*. The sticky ovitrap consists of a plastic bucket, water, an infusion attractant, a fitted sticky surface, and a large-mesh covering. Collected mosquitoes can be identified and counted quickly; no electricity is needed, and traps can be left unattended for up to seven days. Their limitations are that they target egg laying rather than host-seeking females, and their effectiveness can be influenced by availability of natural oviposition sites. Large-scale validation studies are warranted. The BG trap is an attractant trap that requires electricity and costs US$100–US$300 per unit (http://www.biogents.com/en/index.html), which will limit its use in resource-strapped environments. It appears to be comparable in efficacy to backpack aspiration collections of *Ae. aegypti* adults [33].

Quantitative assessment tools. A critical missing component of *Ae. aegypti*–borne disease control programs is quantitative assessment tools that can convert surveillance information into decisions. It is widely accepted that local conditions drive variation in *Ae. aegypti*–borne disease transmission patterns. Except for a few notable exceptions, most dengue prevention programs do not effectively use the entomological and clinical information that they routinely collect to make decisions [34,35]. Addressing this challenge requires: (1) improved, accessible transmission models, (2) evidence-based decision software, and (3) integrated use of geographic information systems (GIS).

There cannot be universal guidelines for preventing *Ae. aegypti*–borne disease because transmission dynamics vary across local fluctuations in immunity status, characteristics of human/mosquito contact, vector ecology, and climate patterns. Only quantitative models can adequately account for these kinds of key, site-specific variables. The ideal model will be user-friendly and facilitate easy importation of local surveillance data. Models for predicting success of different control strategies and transmission thresholds are under development [36]; increased functionality, ease of use, and rigorous validation are the principal goals for

their improvement. Effective models will allow governments to make better use of limited resources by highlighting strategies and establishing priorities that are most likely to be effective.

Decision support systems (DSS) are overarching programs for synthesizing data into effective decision making. They could include models, GIS coordinates, relevant literature, and a decision tree in easily interpretable format for situation-specific advice [37]. Existing DSS for other vector-borne diseases exemplify the power of this approach [38]. For tsetse control web-based DSS, models, cost analyses, and general information on tsetse are available to assist in the planning and implementation of control operations (http://www.tsetse.org/).

GIS allows spatial display of entomological and epidemiological data and facilitates targeted interventions. Although developing GIS for a city may require an initial investment, benefits to program management and decision making are great. Base maps may exist for some municipalities. GIS software is becoming increasingly user-friendly and adaptable.

Conclusions

We hope this brief discussion will provoke a re-examination of how best to prevent dengue and other arboviruses using *Ae. aegypti* control. The universal reliance over the last 50 years on source reduction may appear logical, given the vector's domestic habitat, but obviously it is not working in most societies at risk. Dengue is more prevalent now than at any time in history. Malaria prevention, which is based on verifiable mathematical principles first derived nearly 100 years ago, preferentially targets adult mosquitoes, which transmit parasites. We recommend that far more attention should be given to methods directed toward adult rather than immature *Ae. aegypti*. Several classes of tools were identified that would make this easier. Immediate field testing and continued improvement of those ready for implementation is recommended, including those that may now be on the market. The use of various immature indices in surveillance was considered generally uninformative, and the refinement or development of more accurate indicators of risk and the means of measuring them

was emphasized. The only metric that verifies that a program is working is a decrease in disease incidence. Finally, the crucial need for political commitment was repeatedly stressed as among the most important components of a control program, regardless of the methods used. Although participation of those affected is crucial, there has never been a successful program without enlightened, adequately funded, and well-organized leadership. ∎

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