Dengue control: the challenge ahead

"Vector control remains the only and most effective mode of preventing human dengue infection."

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We are still losing our global battle against dengue virus (DENV). After half a century since the beginning of its rampant spread, and despite decades of continued vector control efforts, DENV has re-emerged to become the most important human mosquito-borne viral infection. Currently, approximately 70–100 million cases of classic DENV infection are reported every year (most of them in tropical and subtropical countries), with an estimated 2.1 million cases of life-threatening disease in the form of Dengue Hemorrhagic Fever (DHF)/Dengue Shock Syndrome [1]. Over the last two decades, the number of dengue fever epidemics has increased exponentially, and the dramatic range expansion of the endemic and hyperendemic areas is indisputable [1,2]. Moreover, the global incidence of DHF and Dengue Shock Syndrome has increased 30-fold since the 1950s, and both severe manifestations are a leading cause of hospitalization in parts of Southeast Asia [1].

Increases in human population, rapid and unplanned urbanization, and human travel have contributed to the resurgence and spread of DENV infections [2]. However, it is the inadequacy of our current tools to combat the virus carrying mosquito vectors and the virus itself, together with our limited understanding of the biological, social and behavioral dimensions of virus transmission that have contributed most to our inability to contain this dengue pandemic. New approaches, tools, and methods for dengue control and prevention are desperately needed.

The development of a successful dengue vaccine remains a microbiological challenge; a full decade after promises of its imminent arrival. An effective vaccine will not only need to protect against the four circulating viral strains, but also keep a delicate balance between the immunogenicity it evokes and the attenuation of DENV pathogenicity [3]. The lack of an adequate animal model to replicate the spectrum of human dengue disease has hampered our ability to overcome those hurdles. Nonetheless, research breakthroughs over the past 10 years have yielded a myriad of candidate vaccines, including live attenuated, inactivated, chimeric and DNA-based, some of which are currently at the state of clinical testing [3]. It remains to be seen whether this decade will unveil a viable DENV vaccine.

Even with the advent of an effective DENV vaccine, issues regarding development and delivery in endemic areas will need to be carefully addressed. Questions of vaccine distribution, unit costs and licensure in areas where the burden of disease is the highest (and local economies and health infrastructures are generally weak) will need to be accounted for in the political and managerial arenas even before a candidate vaccine enters the production pipeline. Research activities will also need to be focused to assess important knowledge gaps for proper implementation of a sustainable vaccination scheme, such as the proportion of vaccine coverage needed to achieve herd immunity, the rate of virus evolution and its potential adaptability to a novel vaccine, the logistics of vaccine distribution to under-represented population segments, and the local institutional structures needed for the implementation of a vaccination program of such breadth.

Vector control remains the only and most effective mode of preventing human DENV infection. The simple notion that, by eliminating the link between humans and mosquitoes, vector-borne disease transmission can be halted has been studied and applied for almost a century. Although particular life history traits (i.e., indoor feeding and resting, artificial container breeding, and short flight range) would make *Aedes aegypti* a controllable vector, success in its sustainable control has been rare and

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mostly short-lived [4]. Unsuccessful programs are often blamed on a lack of resources, lack of political will or ineffective implementation. Equally, or even more important, is our limited understanding of the relationships between available control interventions, vector biology, human behavior and virus transmission dynamics.

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Larval control and the elimination of unused water containers represent two of the most straightforward and widely implemented control strategies. Although theoretically simple and effective when properly implemented, both methods are highly labor intensive, and prone to failure if performed in isolation or intermittently [4]. To be effectively transmitted, DENV has to survive in a female mosquito that fed on a viremic person and lived long enough to be hungry for at least a second bloodmeal (known as an 'old' female). Therefore, targeting only larval stages carries a significant limitation: it requires a significant amount of resources to kill a large proportion of the vector population that otherwise will naturally die either as larvae or as 'young' females. A recent study, however, has shown that *Ae. aegypti* themselves can be used to deliver a highly effective biochemical insecticide into larval habitats [5], a promising finding that could resolve the conflict between cost and effectiveness of classic larviciding campaigns.

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When larval control is performed in conjunction with methods targeting the adult population, interventions tend to have increased effectiveness and impact on *Ae. aegypti* and DENV transmission. A recent study has demonstrated that, when properly implemented, indoor residual insecticide spraying can prevent the occurrence and spatial propagation of DENV infections at coverages as low as 60% [6]. However, such effectiveness comes at a cost. Insecticides are expensive, applications are highly demanding and require trained staff, and pose the risk of selecting resistant *Ae. aegypti* genotypes, if not applied alternately. More research and development are needed in order to uncover novel long-lasting insecticidal molecules or insecticide delivery modes that can derive in effective and affordable vector control interventions.

The genetic control of *Ae. aegypti* has entered into a new era. After years and millions of dollars in funding, two separate groups have initiated small-scale field trials to genetically control *Ae. aegypti* populations. A British company released genetically sterile *Ae. aegypti* males equipped with a gene that kills any offspring resulting from the mating of genetically modified and wild-type mosquitoes in the island of Grand Cayman [7]. An alternative approach, led by researchers at the University of Queensland (Australia), is attempting to genetically control transmission of DENV and other pathogens, rather than the elimination of the disease-carrying vectors [8]. By releasing *Ae. aegypti* transfected with the bacterium *Wolbachia pipientis*, which enhances the mosquito's immunity to DENV and other pathogens, the research group expects to halt virus transmission once *Wolbachia* infection propagates across the wild population.

To be effective, genetic control strategies depend on a basic principle: insects bearing the desired genetic characteristic have to mix with the natural population, outcompeting normal individuals for mates. Mixing, therefore, is a function of key *Ae. aegypti* behavioral and biological traits about which there is limited knowledge, such as dispersal behavior and longevity in the wild. Other unknown factors may significantly impact the success of *Aedes aegypti* genetic control strategies. The effective ratio of genetically modified to wild-type mosquitoes that need to be released to exert fixation is still unknown. There is no conclusive evidence (partly due to the lack of long-term studies) to rule out the possibility of virus or vector adaptation to the genetically modified mosquitoes. Issues of acceptability by local communities will need to be studied across different regions and cultural settings and, more importantly, the cost–effectiveness of genetic versus classic control interventions will need to be thoroughly addressed, particularly in resource-constrained endemic areas where DENV is more prevalent. Genetic control represents a promising alternative in specific settings (i.e., developed urban environments, islands with limited *Ae. aegypti* immigration, areas with confirmed resistance of *Ae. aegypti* to modern insecticides), but whether it will become a viable option for endemic areas where DENV exerts most of its burden is not yet clear.

As important as controlling *Ae. aegypti* and DENV transmission is their early detection. The implementation of timely and effective control strategies, such as mosquito control, can be highly dependent on data generated by surveillance systems. There is a need for effective and affordable mosquito sampling and virus detection methods. Methods monitoring the productivity of containers (known as pupal surveys) require validation and do not provide information about actual DENV transmission risk. Quantifying the density of adult female *Ae. aegypti*, on the other hand, can provide information about vector abundance and fresh material for virus testing. A novel and cost-effective adult mosquito aspiration device has the potential of enhancing *Ae. aegypti* surveillance and DENV detection [9]. Similarly, the use of honey-soaked nucleic acid preservation cards represent a promising and relatively inexpensive approach to determine the occurrence of DENV transmission in the field [10]. As novel methods become available, it will be important to assess their applicability in different settings with the end goal of generating coordinated recommendations for vector surveillance that are effective and context-sensitive.

Dengue virus transmission does not occur in isolation, but is embedded within a complex fabric of human social contexts. Surprisingly, the social dimensions of transmission and control have rarely been included in dengue research. Unlike malaria, dengue is transmitted by a day-biting mosquito and, consequently, common daily routines and movement play a significant role modulating the risk of infection of individuals [11]. Moreover, the success of community-based control interventions depends on how communities are engaged in the participatory process, which is contingent to their cultural and social contexts. We have limited knowledge on social aspects of DENV epidemiology, such as the human perception and response to DENV infection, the degree up to which human mobility and social interactions affect exposure and transmission of DENV, and the human behavioral changes that need to occur to render a community-based intervention more effective and sustainable. Clearly, this is an area where multidisciplinary research is needed to fill important knowledge gaps.

The successful translation from basic knowledge into effective DENV control interventions will ultimately depend on the active collaboration and communication between researchers from different disciplines (microbiology, entomology, epidemiology, ecology, sociology, anthropology), and on the economic support from funding agencies and institutions. Only through a better understanding of the inherent (and fascinating) complexities in DENV infection and transmission will novel and more effective control tools emerge.

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