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War against dengue: We lack tools to win the war

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Dengue is the most rapidly increasing arthropod-borne disease globally. The disease burden has increased exponentially, doubling almost every decade from the estimated 8.3 million cases in 2010 to about 58.4 million cases in 2013.[1] The number of countries reporting dengue has also increased. Before 1970, less than 9 countries reported dengue but now it has been reported in more than 100 countries worldwide. It is transmitted by two species of *Aedes* mosquito, *Aedes aegypti* and *Ae. albopictus*.

Ae. aegypti is the principle vector and is predominantly found in urban areas. It breeds, bites and rests mainly indoors. *Ae. albopictus* which breeds, bites and rests outdoors is the main vector of dengue in rural areas but is fast encroaching into urban areas especially if there is a large percentage of vegetation. Indeed, in many parts of the greater Klang Valley of Peninsular Malaysia, *Ae. albopictus* is the dominant species.[2] *Aedes* mosquitoes do not only transmit dengue but also Yellow Fever, Chikungunya, West Nile and Zika viruses. The huge epidemic of Zika with its associated severe microcephaly among the new born in Brazil in 2015 – 2016 has brought the attention of the global scientific community to these mosquitoes and the infections they carry, which were otherwise much neglected.

The *Aedes* mosquito is a very efficient vector. It is highly domesticated and highly anthropophagic. Although its flight range can go beyond 200 meters, *Aedes* breeding is typically found either inside or within the perimeter of human dwellings. The female mosquito is a multiple biter, transferring the virus to as many human hosts during its blood feeding spree. It is also an efficient breeder where it needs only as little as a spoonful of water to lay its eggs. On top of that, *Aedes* is also a smart breeder with its "skip oviposition behaviour" whereby it will not lay all the eggs in one place but rather in multiple places in nearby surroundings, often in places oblivious to us (cryptic breeding), a smart strategy of ensuring higher chances of its survival as well as its progeny's. Transovarial transmission of dengue virus does occur in *Aedes* and mathematical modelling suggests that it may contribute to the sustenance of the virus in the population and could explain for the occurrence of outbreak immediately after a spell of rainfall.[3]

The transmission dynamics of dengue infection is a complex interaction of various factors - susceptible host, the mosquito vector, the infecting virus and the surrounding environment. The four dengue serotypes do not confer cross protection to each other and they exhibit varying virulence characteristics. Changes in the dominant circulating serotype in a particular population may trigger an outbreak caused by a different serotype.[4] Irrespective of the virulence of the serotypes, only about 25-30% of those exposed to the infection will develop clinical manifestations and a large majority are asymptomatic. The significance of those asymptomatic carriers in sustaining the transmission is not known. Dengue transmission is particularly sensitive to environmental and climatic factors. Abundance of rain and high temperature favour *Aedes* breeding and virus multiplication. *Aedes* breeding potential is closely associated with human behaviour of indiscriminate littering, building and civil infrastructure design defect, construction activities, vacant land and abundant properties. Changing dengue serotypes, climatic patterns and changes in population dynamics may explain for the cyclical nature of dengue transmission in most endemic countries, and the cycle can be in the context of week, month or year.

The general principle to effectively control and eliminate local transmission of any vector borne disease including dengue is to manage, in an integrated manner, all the four elements of transmission dynamics namely the susceptible host, the infecting agent, the vector and the environment that support the vector. Unfortunately, unlike malaria, there is a lack of effective tools to manage dengue transmission. We do not have effective antiviral drugs to treat the infected person and therefore eliminate

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the source of infection to the mosquito. The existence of asymptomatic carriers may compound the problem further though its contribution to the transmission dynamics is still not very clear. We do not have anything effective and practical to protect the susceptible host from *Aedes* mosquito bite and therefore infection. Insecticide impregnated bed-net is very effective against malaria and has contributed significantly to the declining burden of malaria globally especially among children. However, unlike the *Anopheles* mosquito that transmits malaria, *Aedes* peak biting period is when the human host is already out of bed in the early morning or still active in the late evening. Our excitement for the "rashly" registered Dengvaxia vaccine, though expensive for an affordable and sustainable mass dengue vaccination programme, is short lived because of safety issues.

In malaria we can manipulate the environment to make it less conducive for the mosquito to breed such as removing vegetation along the banks of small, slow moving streams, flushing the stream through mechanical automatic siphon, agitating large pools of water or pond or constructing bunds to prevent intrusion of brackish water which favour certain anopheline mosquitoes to breed. For *Aedes*, what is there to manipulate when as little as water in a building crack or dish washer container can support *Aedes* breeding. The only solution is through source reduction (manually removing breeding places) which has been proven effective at community level only in Cuba. Nevertheless, we place great emphasis on community empowerment and mobilisation through adopting and adapting the WHO initiated Communication for Behavioural Impact (COMBI). Thousands of COMBI have been established nationwide and funding has been provided to support this community volunteer effort. While there are good examples of success stories, in large the majority of the activities are "seasonal" when an outbreak has already occurred.

The only weapon that is widely employed to prevent dengue and to control outbreak in endemic countries is the use of insecticide against the mosquito. The conventional method of application such as thermal fogging and vehicle mounted ultra-low volume (ULV) spraying are popular activities against *Aedes* in many countries. However, the robust scientific evidence to support its effectiveness is very much lacking.[5] Many of the experimental designs to assess efficacy of fogging or ULV in the field are flawed with the use of caged mosquitoes. Despite the lack of evidence, fogging and ULV spraying continue to be employed because it is the politically correct thing to do at the moment.

Since dengue outbreaks tend to be explosive in nature and the transmission dynamics of dengue is very much influenced by human, environmental and climatic factors, several studies have attempted to develop early warning systems so that action can be taken before an outbreak occurs. While there are various mathematical and statistical modelling (including the use of artificial intelligence technique) that can predict the occurrence of the outbreak with reasonable accuracy, the usefulness of these models are limited because of the lack of effective tools to prevent and contain such an outbreak.

Rationally, the best approach would be to use *Aedes* to fight *Aedes* itself. Only *Aedes* knows *Aedes* best - where it lays eggs, where it rests and where it finds its mate. If we can manipulate *Aedes* in such a way that it helps to destroy its own species or become detrimental to the development of the dengue virus it carries, there may be hope. This is the basis for the use of transgenic *Aedes* mosquito, *Wolbachia* infection or the interest in Sterile Insect Technique which has been successfully used in agricultural industry. However, we cannot rush into applying this strategy because we need robust scientific evidence that it works. Furthermore, in public health policy decision, not only must it work, it must also be practical, affordable and cost effective to implement. We also cannot depend just on one bullet on one target, but multiple bullets on multiple targets to ensure success. The global community must invest more research on dengue to find these bullets and WHO must not treat dengue as a Neglected Tropical Disease anymore.

Dengue should be given due priority by the WHO-World Bank Special Programme on Tropical Disease Research (WHO-TDR). Investment in research on dengue will pay, the same way we now reap the benefit of decades of research on malaria.

Keywords: Dengue, Aedes, transmission dynamics, vector control

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