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Fighting dengue via research

I REFER to the report "Innovative research to fight dengue needed" (*The Star*, Aug 11). To say that dengue research in this country is "piecemeal" or "not serious" is far from the truth. As early as 1908, the then newly-established Institute for Medical Research (IMR), Kuala Lumpur had already conducted a survey in Port Swettenham (now Port Klang), Penang and Singapore and found that *Aedes aegypti* was an exotic species introduced via shipping lanes from tropical Africa.

From then on, research on dengue by the IMR has been actively pursed unabated. Voluminous data and abundant knowledge on dengue have been acquired and accumulated over the last 100 years through the institute's research efforts.

Research has been, and continues to be, conducted in all areas of dengue, which can broadly be classified as:

> Vector control;
> Vector bionomics (vector ecology, vector-virus interaction);
> Vector surveillance;
> Dengue diagnostics;
> Dengue treatment/management/antiviral development/vaccine;
> Dengue virus serotype/genotype surveillance/virulence;
> Human genetic factors;
> Climate change impact on dengue;
> Human behavioural research;
> Burden of disease/cost; and
> Epidemiology (outbreak prediction model).

The immense contribution of IMR to dengue research is eloquently summarised in its Bulletin No. 23 "Dengue Fever Studies in Malaysia" (1986) and updated in Bulletin No. 24 in 2014.

Recently, IMR has been designated a World Health Organisation good laboratory practices (GLP) laboratory for the evaluation of vector control products. The laboratory, one of six in Asia, is tasked with evaluating chemical control products, including repellents against dengue vectors. Nevertheless, to date, there is still no concrete evidence that use of repellents could deter dengue primarily due to the fact that not every member of the community uses repellent, and mosquito vectors would continue to bite and transmit dengue to these non-users.

With the advances in various innovative technologies to control dengue, the institute has now embarked on the application of Wolbachia to control the Aedes mosquito. Wolbachia is a parasitic bacterium found naturally in 60% to 70% of insects, spiders, nematodes, etc. After its discovery in 1924, voluminous data and numerous studies have been conducted on this micro-organism. Hence, saying that we know too little of this microbe is a misstatement.

A quick check on the medical database "PubMed" reveals that a total of 2,906 papers have been published in peer-reviewed journals on Wolbachia since 1962. With regards to its safety, there is no evidence whatsoever that Wolbachia poses any detrimental effects on humans or other animals.

In fact, Wolbachia in naturally-infected insects such as mosquitoes has no known effects on the host (mosquito) or pathogens the mosquito may have harboured. Only when Wolbachia is transferred from a host, such as a mosquito species, to another species via micro-injection of the eggs, will it inhibit replication of pathogens like dengue, zika, chikungunya or yellow fever virus.

Due to the biological uniqueness of Wolbachia, two strategies could be used to control dengue – the replacement strategy and suppression strategy.

In replacement strategy, both male and female Wolbachia-carrying *Aedes aegypti* are released into the environment to mate with their wild counterparts. All their offspring will carry Wolbachia and will therefore be free of the dengue virus. This is the strategy Malaysia uses.

In the suppression strategy, only male Wolbachia mosquitoes are released to mate with wild females. All the resulting eggs will be sterile and sustained release of such males over time will result in elimination of the wild population. This strategy is being evaluated in Singapore.

The first field release of Wolbachia-carrying *Aedes aegypti* to replace the wild population was conducted in Australia in 2011 (Hoffmann *et al*, 2011, *Nature* 476: 454-457), which was successfully conducted with the establishment of Wolbachia in the natural *Aedes aegypti* population. Dengue transmission was completely eliminated in the release areas.(O'Neill *et al*, 2018, Gates Open Res, 2:36). More recently, Zheng *et al* (2019, *Nature* 572: 56-61) successfully eliminated *Aedes albopictus* in an area in Guangdong, China using the suppression strategy. No adverse effects on environment or human population were found in all these studies.

The Malaysian Wolbachia project was launched in 2017 in which Wolbachia-infected *Aedes aegypti* were released in seven dengue hotspots in Klang Valley. After a year of release, dengue cases were significantly reduced. A report on the findings will be published in a high-impact journal.

Based on these promising results, a release programme was subsequently launched in nine dengue hotspots in the Klang Valley. The outcomes of this programme are still being monitored and will serve as the basis for future expansion of the release in more dengue hotspots.

The Wolbachia approach can be used in combination with the other multiple approaches, including use of repellents. Its advantage is that it does not require ongoing interventions once the Wolbachia mosquitoes are established. In addition, Wolbachia could effectively address the challenge of dengue transmission from asymptomatic carriers who harbour the virus without any presentation of symptoms.

Currently, it is extremely difficult to identify these carriers, who can spread the disease unknowingly after being bitten by the mosquito vectors. However, since Wolbachia-carrying mosquitoes are virus-free, virus picked up by these mosquitoes from asymptomatic carriers would not replicate and effectively block the transmission.

To date, Wolbachia is the most promising, effective, affordable and safe method of interrupting dengue transmission.

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