Is it time to rollback dengue? - Mini Review

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Abstract

The past 40 years have seen a dramatic increase in the frequency, magnitude and geographic expansion of epidemic dengue, making it the most important vector-borne viral disease in the world. Mosquito control, the only option available for dengue control, has failed. New and innovative tools in the pipeline, however, may provide the opportunity to rollback this disease.

The past 40 years have seen a dramatic increase in the frequency, magnitude and geographic expansion of epidemic dengue, closely tied to the unprecedented human population growth, urbanization and globalization that have occurred during the same time period. These global trends, combined with lack of effective mosquito control, have facilitated the expansion of both the viruses and the mosquito vectors that transmit the disease, to most urban centres of the tropics. Dengue, the most important vector-borne viral disease in the world, is primarily an urban disease, with an estimated 3.6 billion people living in areas of risk and 400 million infections annually. The economic and social costs of epidemic dengue make it a devastating public health problem in the resource poor countries of the tropics [1–4].

There is neither approved vaccine nor specific drugs available for dengue, mosquito control being the only option available for disease prevention and control. Unfortunately, conventional mosquito control methods have failed in sustainable prevention of epidemic dengue [5]. The reasons for this failure are complex and beyond the scope of this paper, but include the lack of effective mosquito control tools, resources and commitment to control the disease in dengue endemic countries. That is the bad news! The good news is that the outlook for dengue control going forward is very positive. Recent dengue research has led to the development of a number of new and innovative dengue control tools, including vaccines, antiviral drugs, therapeutic antibodies, insecticides and other mosquito control tools.

The insecticides include new classes of chemicals that will provide residual activity for 6 months to a year, a characteristic that is critical to control adult mosquitoes emerging from cryptic or hidden larval habitats. Other new insecticides can be formulated as spatial repellents to prevent mosquitoes from entering selected areas or to treat both natural and artificial oviposition sites. These new insecticides have the potential to provide cost-effective adult mosquito control.

Other new and promising mosquito control tools include both genetic and biological approaches [6, 7]. The most promising genetic approach is the release of sterile male mosquitoes into a natural population to mate with wild female mosquitoes. If the sterile males are released in high enough numbers, the wild population will decrease. Sterile males can be produced by the millions and released as eggs into natural populations. Field trials have been or are being conducted in Malaysia, Cayman Islands, Brazil and Panama, all with promising results. A promising biological control tool is the infection of *Aedes aegypti* mosquitoes with a common bacterium, *Wolbachia* that naturally infects over 70% of all insects in nature, but for reasons that are unknown, not *Ae. aegypti*. Several strains of *Wolbachia* have been adapted to infect *Ae. aegypti*, causing decreased survival and decreased susceptibility to infection with dengue viruses. Field trials have been carried out in Australia showing effective spread of *Wolbachia* into the natural *Ae. aegypti* populations. Other trials in Vietnam, Indonesia, China, Colombia and Brazil are in progress.

Also exciting is the progress in dengue vaccine development [8]. There are currently six candidate dengue vaccines in the clinical trial pipeline, one in phase III, two in phase II and three in phase I (Table 1). In addition, there are numerous third-generation vaccines under development using new molecular technology. The candidate in phase III is a tetravalent chimeric vaccine constructed on the 17D yellow fever vaccine backbone manufactured by Sanofi Pasteur. The yellow fever PrM and envelope genes have been replaced with the respective genes from DENV −1, −2, −3 and −4. A phase IIB trial of this vaccine in Thailand raised concern because efficacy was low for DENV-2; however, it was safe [9]. The first phase III efficacy trial involving 10,275 children aged 2–14 years in five Asian countries has just been published, with more promising results [10]. Although the DENV-2 efficacy was still relatively low, the vaccine performed well against the other serotypes and in protecting against severe disease. The overall efficacy was 56.5%. Results from a second phase III trial in five dengue endemic countries in the Americas will be available in late 2014. Expectations are that the Sanofi vaccine will be licensed by 2017 if all goes as expected. The two vaccines in phase II trials are the Takeda (Inviragen) dengue chimeric vaccine that uses the

Table 1 The dengue vaccine pipeline by stage of clinical development

Manufacturer	Vaccine strategy	Development phase
Sanofi Pasteur	Chimeric, YF17-D backbone, DENV1-4	Phase 3
NIH/Merck	LAV + Chimeric, DENV1/4/3 Δ30; DENV2/4	Phase 2
Takeda	LAV + Chimeric, DENV2 PDK53; DENV1/2, 3/2 & 4/2	Phase 2
GSK	Killed, DENV1-4	Phase 1
NMRC	DNA, DENV1-4	Phase 1
Merck/Hawaii biotech	Subunit, DENV1-4	Phase 1 (on hold)

YF17-D, Yellow fever vaccine strain 17-D; LAV, live attenuated virus; GSK, Glaxo-Smith Kline; NIH, National Institutes of Health; NMRC, Navy Medical Research Center; PDK53, a live-attenuated DENV2 vaccine developed at Mahidol University, Thailand.

Mahidol PDK-53 DENV-2 live attenuated virus as a backbone, replacing the PrM and envelope genes with those from DENV-1, −3 and −4, and the NIH–Butantan–Merck vaccine that consists of DENV-1 and −4 viruses attenuated by a 30 nucleotide deletion in the 3′ end of the genome, a DENV-3 attenuated in the same way, but with an additional deletion, and a chimeric virus with the PrM and envelope genes of DENV-2 inserted into the attenuated DENV-4 backbone. It is anticipated that these two vaccines will be licensed by 2018 or 2019. Finally, there has been good progress in developing antiviral drugs and therapeutic antibodies for dengue viruses, which should be available in the same time frame as the vaccines.

Thus, the outlook for dengue control looks bright as several new and innovative tools will soon be available. However, it is unlikely that any one of these new tools, including vaccines, will be effective if used alone. A safe, inexpensive vaccine that is effective against all four viruses would likely be the most cost-effective way to control dengue, but there are many unknowns awaiting the introduction of dengue vaccines. As shown in the Sanofi Phase IIB and phase III trials, the vaccine may not be effective against all four viruses. Whether this will prevent their use is now being debated, but given the demonstrated priming effect of this vaccine when given to persons who have already experienced at least one dengue infection, i.e. most persons living in dengue endemic countries, it is likely that partially effective dengue vaccines can be used as important public health tools in our fight to roll back dengue. A potential barrier to the widespread use of vaccines to control dengue, however, is the lack of adequate vaccine production facilities. On the other hand, using a combination of the new tools described above in an integrated and synergistic way, sustainable control programmes might be developed that would impact dengue transmission. For example, by combining vaccines to increase herd immunity with one or more vector control tools to decrease the mosquito population, it may be possible to prevent epidemic transmission. And by integrating effective clinical diagnosis and management, perhaps using antiviral drugs, dengue might be eliminated as a public health problem.

A new organization, the Partnership for Dengue Control (PDC) was recently formed to determine the feasibility of such an integrated approach to dengue control [11]. The PDC is a global alliance of the dengue research, public health, policy, medical and scientific communities, whose goal is to bring experts from the relevant disciplines together to facilitate development of integrated control programmes targeting specific areas or countries. Although there are many scientific, political and economic barriers that must be overcome, it appears that for the first time in over 40 years, we will have the tools to succeed in rolling back dengue as a public health problem, provided we use them effectively.

References

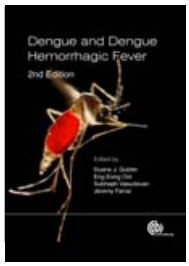
1. Alirol E, Getaz L, Stoll B, Chappuis F, Loutan L. Urbanisation and infectious diseases in a globalized world. Lancet Infectious Disease 2011;10:131–41.
2. Gubler DJ. Chapter 1: dengue viruses: their evolution, history and emergence as a global public health problem. In: Gubler DJ, Ooi EE, Vasudevan S, Farrar J, editors. Dengue and Dengue Hemorrhagic Fever, 2nd ed. CABI, London, UK; 2014. p. 1–29.
3. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, *et al.* The global distribution and burden of dengue. Nature 2013;496:504–7.
4. Shepard DS, Halasa YA, Undurraga EA. Economic and Disease Burden of Dengue. In: Gubler DJ, Ooi EE, Vasudevan S, Farrar J, editors. Dengue and Dengue Hemorrhagic Fever, 2nd ed. CABI, London, UK; 2014. p. 50–77.
5. Gubler DJ. The emergence of epidemic dengue fever and dengue hemorrhagic fever in the Americas: a case of failed public health policy. Pan American Journal of Public Health 2005;17(4):221–4.
6. Brown DM, James AA. Chapter 26: dengue vector control – new approaches. In: Gubler DJ, Ooi EE, Vasudevan S, Farrar J, editors. Dengue and Dengue Hemorrhagic Fever, 2nd ed. CABI, London, UK; 2014. p. 519–36.
7. Frentiu FD, Walker T, O'Neill SL. Chapter 27: Biological control of dengue and Wolbachia based strategies. In: Gubler DJ, Ooi EE, Vasudevan S, Farrar J, editors. Dengue and Dengue Hemorrhagic Fever, 2nd ed. CABI, London, UK; 2014. p. 537–47.
8. Halstead SB. Chapter 28: dengue vaccines. In: Gubler DJ, Ooi EE, Vasudevan S, Farrar J, editors. Dengue and Dengue Hemorrhagic Fever, 2nd ed. CABI, London, UK; 2014. p. 548–76.

9. Sabchareon A, Wallace D, Sirivichayakul C, Limkittikul K, Chanthavanich P, Suvannadabba S. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. Lancet 2012;380:1559–67.

10. Capeding MR, Tran NH, Hadinegoro SRS, Ismail HJM, Chotpitayasunondh T, Chua MN, *et al.*, the CYD14 Study Group. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebocontrolled trial. Lancet July 11, 2014. doi:10.1016/S0140-6736(14)61060-6.

11. Gubler DJ. The Partnership for Dengue Control – A new global alliance for the prevention and control of dengue. Letter to Editor, 2014. Submitted to Vaccine.

About the author



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