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Outlook for a dengue vaccine

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Abstract

Dengue is an increasing medical problem in subtropical and tropical countries. The search for a safe and effective vaccine is complicated by the fact that there are four types of dengue virus and that, if a vaccine is live attenuated, it should be proven not to cause the life-threatening form of dengue, dengue haemorrhagic fever. So far one vaccine candidate, a four-valent chimeric vaccine constructed from a yellow fever vaccine strain, has reached large clinical trials and has been shown to offer protection against dengue types 1, 3 and 54 but not against dengue type 2. It is highly likely that an effective vaccine will be available in the next decade.

Keywords: Dengue, dengue vaccine, clinical trial, dengue haemorrhagic fever, dengue epidemiology
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Introduction

Dengue fever is a mosquito-borne flavivirus infection. Four serotypes of the virus have been identified and multiple infections in the same individual are common because the first dengue infection is often in childhood. The two most common vectors are *Aedes aegypti* and *Aedes albopictus*, which are both day-biters and breed near human habitations. The virus multiplies in the mosquitoes and there is no man-to--man transmission. Clinically, dengue virus causes flu-like illness with fever as the main symptom and low mortality rates. However, in about 5% of individuals who acquire a second dengue infection, dengue haemorrhagic fever with bleeding symptoms may occur and has a considerable mortality.

Epidemiologically more than half of the world's population live in areas where there is a risk for dengue infections and in the last 10 years there has been a rapid and marked increase in the number of reported dengue outbreaks in countries with tropical or subtropical climate (data from Africa are still incomplete). According to WHO there are 50–100 million dengue cases per year globally, of which 500 000 are dengue haemorrhagic fever. The total annual mortality is estimated to be about 22 000 cases. Most of the dengue cases occur in urban areas; examples are Singapore and Rio de Janeiro.

Vaccine Development

Presently there is no licensed dengue vaccine but there is a very high level of interest in afflicted countries. Several factors explain the slow rate of development of dengue vaccines. First, a vaccine should be four-valent to cover all dengue types. Second, if the vaccine is an attenuated one, the risk must be considered that the vaccine could lead to dengue haemorrhagic fever in recipients who have previously had dengue infections. Third, dengue outbreaks are seasonal and the incidence varies from year to year. Therefore studies to evaluate the efficacy of a vaccine candidate must be timed to a period with a high level of infections. Fourth, as an immuno-local correlate of protection is lacking, the efficacy of a vaccine must be based on large phase III trials. Fifth, the low mortality in dengue infections has, to some degree, been a disincentive to develop vaccines, especially as it is of major importance that an effective and safe dengue vaccine

TABLE 1. Efficacy of a tetravalent vaccine versus that of a control >28 days after three injections (per protocol analysis). Data from Sabchareon *et al.* (2)

	Dengue vaccine		Control		
	Person-years at risk	Cases	Person-years at risk	Cases	Efficacy (95% CI)
Cases	2522	45	1251	32	30.2% (−13.4–56.6)
Serotype 1	2536	9	1251	10	55.6% (−21.6–84.0)
Serotype 2	2510	31	1250	17	9.2% (−75.0–51.3)
Serotype 3	2541	1	1257	2	75.3% (−37.5–99.6)
Serotype 4	2542	0	1265	4	100% (24.8–100.0)

should be made available to the populations of endemic areas rather than becoming a tourist vaccine or a vaccine for special groups, e.g. military personnel.

Vaccine Candidates

The most common approach to development of a dengue vaccine has been to use attenuated virus. Other approaches, e.g. vaccines built on virus subunits, are in early clinical development. The candidate that has proceeded farthest is the Sanofi Pasteur tetravalent dengue vaccine (Sanofi, Lyon, France) (1). It is a chimeric vaccine constructed from a strain of yellow fever vaccine (YFV 17D) into which the prM genes of the four dengue serotypes have been inserted. Preclinical studies have shown that the vaccine stimulates human dendritic cells, that it is not hepatotropic and that it is less neurotropic than the YFV 17D vaccine. It has also been shown to induce an immune response with production of neutralizing antibodies to all four dengue serotypes (2). This dengue vaccine has been evaluated in a large phase IIB trial in Ratchaburi province in Thailand (2). The trial site had been extensively evaluated before the study (3–5) and the study was randomized, controlled and observer-blinded. More than 4000 schoolchildren aged 4–11 years were included and received either the dengue vaccine or control (rabies vaccine for the first dose and then saline/placebo) at 0, 6 and 12 months. The safety of the vaccine was shown to be excellent with no differences between vaccine recipients and controls with respect to side effects (2). Efficacy results are summarized in Table 1.

The overall protective efficacy of the vaccine was only 30%. This was due to the fact that during the study period the predominant serotype in the study population was serotype 2 and protection against that serotype was much lower than against the other three serotypes.

TABLE 2. Dengue vaccine candidates in clinical development

Developer	Type of vaccine	Development stage
Naval Medical Research Center	Plasmid DNA	Phase I
NIH	Live-attenuated	Phase II
Butantan (Brazil)	Live-attenuated	Phase II
Inviragen	Live-attenuated	Phase II
Merck	Subunit	Phase I
GSK	Live-attenuated	Phase I

Discussion

The results of the Rachaburi trial with the Sanofi tetravalent vaccine show that we still do not have a dengue vaccine proven in large studies to be safe and effective. However, large phase III studies of the Sanofi vaccine are ongoing in Australia, Asia and Latin America and the manufacturer hopes to have it licensed in 2015. Simultaneously, clinical trials have started of other dengue vaccine candidates. According to the Dengue Vaccine Initiative, a consortium including International Institute, Johns Hopkins University, the Sabin Foundation and WHO, six vaccine candidates are in clinical trials (http://www.denguevaccine.org/vaccine-development, Table 2). Of special interest are the two products that are not live-attenuated because they would not have a risk of dengue haemorrhagic fever following vaccination.

Transparency Declaration

The author declares no conflicts of interest.

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