Editorial

Dengue vaccine: Light at the end of the tunnel?

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A vaccine to prevent dengue disease is urgently needed. The development of a live-attenuated dengue virus vaccine has been complicated by a number of factors. Firstly, it has been difficult to develop monovalent vaccines against each of the four serotypes exhibiting satisfactory balance between attenuation and immunogenicity[1]. Secondly, an effective live-attenuated dengue virus vaccine must consist of a tetravalent formulation of components representing each serotype because multiple serotypes typically co-circulate in a region, each dengue serotype is capable of causing disease and the introduction of additional serotypes is common[2]. In addition, the association of increased disease severity (dengue haemorrhagic fever/shock syndrome) in previously infected persons undergoing an infection by a different dengue virus serotype necessitates a vaccine that will confer long-term protection against all four serotypes[3]. Thirdly, it has been difficult to formulate a tetravalent vaccine with low reactogenicity that induces a broad neutralizing antibody response against each dengue virus serotype[4]. Fourthly, a dengue vaccine must confer protection against a wide range of genetically diverse subtypes which are dispersed around the world and can be readily introduced into a new region by international travel[5].

Several promising approaches to dengue vaccine development are currently being investigated in both academic and industrial laboratories[6]. Vaccine candidates include live, attenuated vaccines obtained via cell passages or by recombinant DNA technology and subunit vaccines[7]. Decades in the making, the dengue vaccine's arrival is now in sight. While dengue vaccine development has been widespread among research institutions and pharmaceutical companies, Sanofi Pasteur, the largest vaccine developer in the world, is years ahead of the rest.

Sanofi Pasteur has been involved in the research and development of a dengue vaccine since the 1990s[8]. In 1994, a partnership was formed between Sanofi Pasteur and the Vaccine Development Centre, University of Mahidol (Bangkok - Thailand)[3]. In 2004, the classical live vaccine approach was abandoned due to reactogenicity and under-attenuation of serotype 3. Sanofi Pasteur decided to adopt a new approach, with a second generation live attenuated vaccine[8]. In 2006, they formed a partnership with Paediatric Dengue Vaccine Initiative (PDVI), a consortium working to accelerate the introduction of a dengue vaccine for children in endemic countries supported by the Bill & Melinda Gates Foundation[8]. In 2007 positive results were obtained in phase II clinical studies[8]. In 2009, Sanofi Pasteur dengue vaccine entered a paediatric clinical efficacy study in Thailand[8]. In June 2010, the U.S. FDA granted fast track status to Sanofi Pasteur dengue vaccine[8]. In October 2010, Sanofi Pasteur dengue vaccine entered phase III clinical study.

The Sanofi Pasteur tetravalent dengue vaccine candidate is composed of 4 recombinant live attenuated vaccines based on a yellow fever vaccine 17D (YFV 17D) backbone, each expressing the perimembrane and envelope genes of one of the four dengue virus serotypes[9]. Pre-clinical studies have demonstrated that the tetravalent dengue vaccine is genetically and phenotypically stable, non-hepatotropic, less neurovirulent than YFV 17D and does not infect mosquitoes by the oral route[9]. In vitro and in vivo preclinical studies also showed that the tetravalent dengue vaccine induced controlled stimulation in human dendritic cells and significant immune responses in monkeys[9]. Tetravalent dengue vaccine reactogenicity, viraemia induction and antibody responses were investigated in three Phase I trials in the USA, the Philippines and Mexico, in a two or three-dose regimen over a 12 month period. Results showed that the majority of adverse events were mild to moderate and transient in nature[9]. Viraemia was transient and low, and was not increased after initial dengue tetravalent vaccine administration, even in the case of incomplete responses[9].

The Sanofi Pasteur tetravalent dengue vaccine has been shown to induce almost full seroconversion against all four serotypes in both adults and children after two to three injections[10,11]. Furthermore, pre-existing flavivirus immunity, such as that seen in exposed populations living in dengue-endemic areas or that induced by previous vaccination against

yellow fever or Japanese encephalitis, favours a higher and more rapid immune response to the dengue vaccine without any negative effect on clinical safety or vaccine viraemia, compared with responses seen in non flavivirus immune individuals[7,9].

In February 2011 Sanofi Pasteur formed a partnership with the International Vaccine Institute to support the Dengue Vaccine Initiative (DVI), a non-profit advocacy group focused on raising awareness of dengue fever and supporting the introduction of dengue vaccination, funded by the Bill & Melinda Gates Foundation[8]. Initial efficacy results from the Thai study on thousands of children are expected in September 2012[8]. Provided the field tests are successful, Sanofi Pasteur hopes to make the vaccine commercially available in 2015.

The price of a vaccine is one of the most important factors affecting its ultimate application in developing countries. Research funded by the DVI involving an economic analysis of producing a tetravalent dengue vaccine shows that the cost could be as low as $0.20 per dose with an annual production level of 60 million doses packaged in ten-dose vials[12].

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G N Lucas
Joint Editor