

DENGUE: THE NEXT VACCINE-PREVENTABLE INFECTIOUS DISEASE ?

Lang J

Travel & Endemic Vaccines R&D Program Leader, Sanofi Pasteur, France. Associate Vice President, Research & Development.

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LA DENGUE SERA-T-ELLE LA PROCHAINE MALADIE INFECTIEUSE À BÉNÉFICIER D'UNE PRÉVENTION VACCINALE ?

RÉSUMÉ • La dengue connue il y a un siècle en tant que maladie tropicale évoluant par épidémie périodique tous les 3 à 5 ans en Asie du sud-est est devenue un problème de santé mondial qui pourrait se placer en tête de liste des maladies les plus importantes transmises à l'homme par les moustiques. Touchant presque tous les pays tropicaux ou subtropicaux, ce virus est désormais endémique dans plus de 100 pays où des cas sont observés toute l'année et près de 2,5 milliards d'individus sont à risque. La forte expansion de cette infection dans le monde au cours des 20 à 30 dernières années a déclenché beaucoup de recherches pour développer un vaccin. Sanofi Pasteur, qui de longue date contribue activement à la lutte contre cette maladie, s'est engagé à mettre au point et à faire homologuer un vaccin bien toléré et efficace contre la dengue. Les progrès importants réalisés ces dernières années permettent d'espérer que ces efforts aboutiront dans un avenir proche.

MOTS-CLÉS • Dengue - Vaccin contre la dengue - Vaccin 17D contre la fièvre jaune - Développement de vaccins - Maladies tropicales.

ABSTRACT • From a tropical disease of Southeast Asia occurring in epidemics every three to five years a century ago, dengue has evolved to become what is arguably the most important mosquito-borne disease in humans worldwide. Virtually all tropical and subtropical countries are affected and the virus is now endemic in over 100 countries where it causes year-round disease and places 2.5 billion people at risk. The dramatic global expansion of the disease over the last 20-50 years has stimulated research for a vaccine. Sanofi Pasteur, a longstanding partner in these efforts, is committed to developing and licensing a safe and effective vaccine to fight dengue. The considerable progress made in the last few years strongly suggests that such a vaccine is now within reach.

KEY WORDS • Dengue - Dengue vaccine - Yellow Fever 17 D vaccine - Vaccine Development - Tropical Diseases.

AN EXPANDING TROPICAL AND SUBTROPICAL DISEASE

Dengue disease is caused by any one of four variants, or serotypes, of the dengue virus, a member of a same the Flaviviridae family. This family of viruses causes diseases such as yellow fever, Japanese encephalitis, or West Nile fever. The mosquitoes responsible for spreading dengue—primarily *Aedes aegypti*—are ideally suited to living alongside humans in today's increasingly urbanized world. Unlike the *Anopheles* mosquito that spreads malaria, *Aedes aegypti* is an urban-dwelling, day-biting insect that breeds in any natural or man-made container able to collect water, including water cisterns, plant pots, discarded food containers etc. The global development of dengue and the spread of this mosquito vector are intimately linked. In recent decades unprecedented population growth and unplanned urbanization, combined with increasing human migration and travel, and possibly global warming, have all contributed to extend the geographic range of dengue. According to the World Health Organisation (WHO), more than 100 countries in Africa, the Americas,

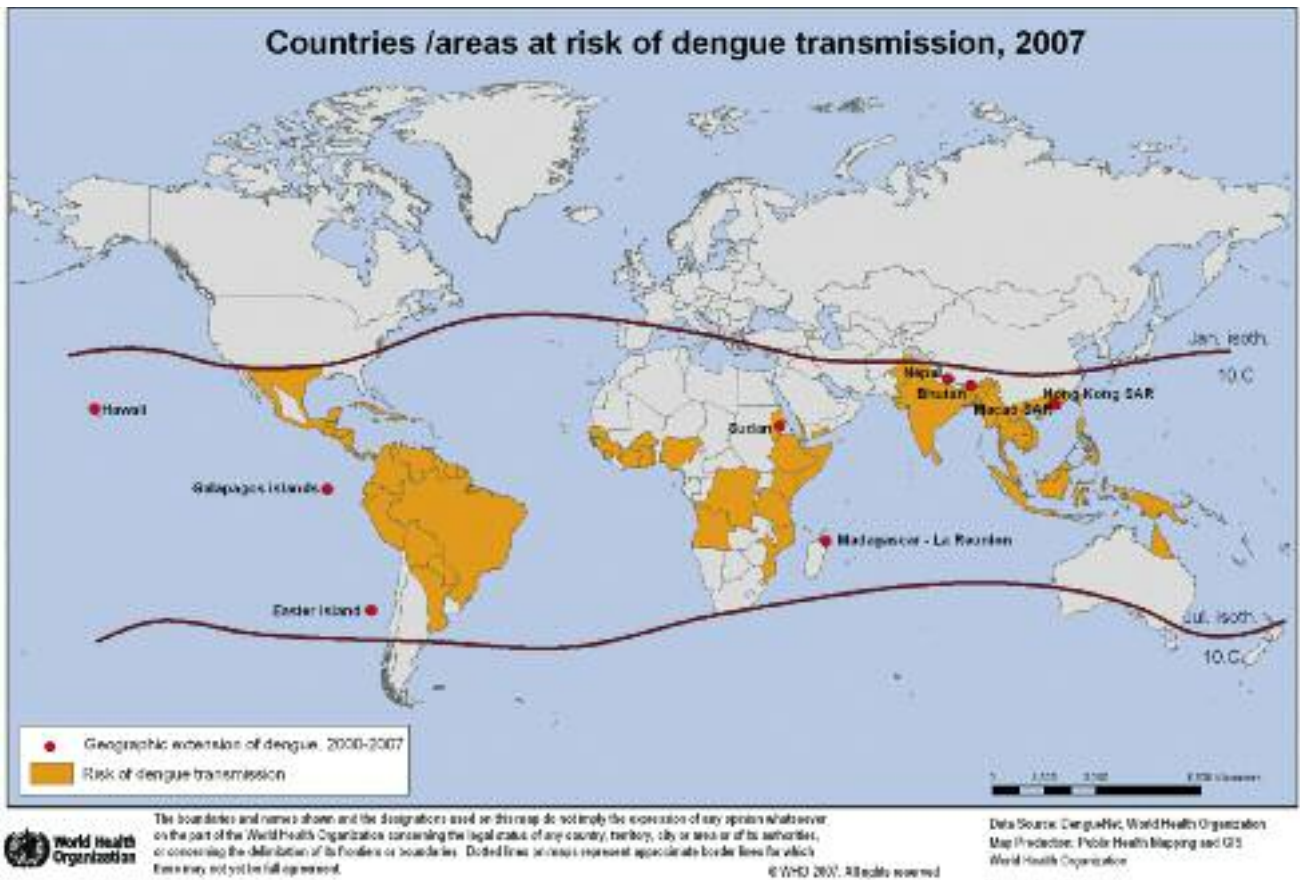
the Eastern Mediterranean, Southeast Asia and the Western Pacific are now affected (Fig. 1). Around 2.5 billion people are at risk from dengue, with 50 million cases of disease and 500,000 hospitalizations reported every year. The number of reported cases of dengue in the Americas alone rising from 335,000 in 1995, to 650,000 in 2001 and 890,000 in 2007 (1). The fatality rate is thought to be 2.5% in absence of appropriate treatment in an intensive care unit setting.

The only preventive measures against dengue currently available are individual mosquito protection or mosquito eradication programs. Both are expensive, difficult to maintain and of questionable efficacy in the long term. In this environment, vaccination is the sole means of safe and cost-effective disease prevention.

DENGUE'S SPECTRUM OF DISEASE

Typically, infection results in dengue fever, with sudden high fever, incapacitating headache, muscle and bone pain, as well as eye pain and rash, sometimes with residual weakness lasting two to three weeks. Infection can also cause a milder, flu-like fever, or can even be asymptomatic. At the opposite end of the spectrum, illness can progress to dengue hemorrhagic fever (DHF), characterized by bleeding (inclu-

• Correspondance : jean.lang@sanofipasteur.com



ding skin hemorrhaging, bleeding nose or gums) and increased vascular permeability resulting in circulatory disturbances such as hypotension and tachycardia. These latter manifestations can lead to shock (dengue shock syndrome) and death, particularly in the absence of appropriate treatment.

All four dengue serotypes cause disease, and recovery results in immunity, presumably life-long, against re-infection by the same serotype, but not against the other serotypes. As a result, individuals can, over time, become infected several times, each time by a different serotype. In endemic areas where all four serotypes co-circulate, the brunt of the disease is felt by children. Indeed, an estimated 90% of patients with severe disease are children no older than 15 years.

WHAT'S THE COST OF DENGUE

The true costs, human and economic, of dengue remain poorly documented. Nevertheless, healthcare workers in endemic countries know that the disease burden is significant, particularly during the large, frequent epidemics that sweep through these countries. During such epidemics, dengue causes significant social disruption, as well as a peak demand on local medical resources, precisely in those areas where these resources are already the most strained. In addition to the loss of life and the hospitalization (which typically

lasts five to six days) and treatment costs severe cases, there is the cost of lost work and productivity associated with the care at home of sick children, and the cost of mosquito control programs. One study has estimated the cost of dengue in children in Southeast Asia to be comparable with that of meningitis, twice that of hepatitis B and one third that of HIV/AIDS in the same region (2).

DENGUE VACCINE DEVELOPMENT: A MAJOR PUBLIC HEALTH AND TECHNOLOGICAL CHALLENGE

No licensed vaccine is yet available, but promising candidates are in development. Dengue vaccine development has been recognized as a priority by global policy makers and national authorities as exemplified by the WHO's Dengue Vaccine Development Guidelines and the support of the Bill and Melinda Gates Foundation through a grant to the Pediatric Dengue Vaccine Initiative (PDVI) (3).

As dengue serotypes can cause severe disease in young children, a dengue vaccine for use in infants must be tetravalent, i.e., provide protection against all four serotypes. Protection should also ideally be long-lasting.

When dengue vaccine research first started more than 20 years ago, the first to show promise in humans were live attenuated vaccines based on tried and tested techno-

logy first used by Louis Pasteur for his rabies vaccine and used to develop many of the vaccines we use today. This involves multiple serial passages of the wild viruses in cell culture with the objective of selecting an attenuated virus, i.e., one that has lost its ability to cause illness, but still stimulates a protective immune response. The challenge of achieving a satisfactory balance between attenuation and immunogenicity is four-fold greater for a tetravalent dengue vaccine (by definition, a cocktail of four) as very different individual attenuated vaccines is required. Furthermore, while an individual vaccine virus may show good results when given alone, it may perform poorly when injected into a human host simultaneously with other viruses as a tetravalent mixture, as the viruses can interfere or compete with each other. Indeed, the effect of this competition was evident in early trials as vaccinated individuals mounted an immune response preferentially against only one or two dengue serotypes. Responses against the other strains were much lower than when given alone. These vaccines were also found to not be as safe as first thought, possibly due to under-attenuation of some of their components (i.e., one or more of the culture-passaged viruses selected for development into a vaccine may have retained some slight ability to cause illness).

While other research groups are persevering with cell-culture passaged live attenuated vaccines, the difficulties outlined above of deriving vaccine strains displaying the right balance of attenuation (safety) and immunogenicity, with no interference when combined into a tetravalent mixture, have led Sanofi Pasteur to abandon this traditional approach in favor of a more promising and more recent technology.

Several alternative vaccine technologies are being explored (including DNA vaccines, adenoviruses, reverse genetics-attenuated vaccines, adjuvanted sub-unit proteins, shuffling of envelope proteins, or combinations of these), most of which are at very early stages. The most advanced Sanofi Pasteur tetravalent dengue vaccine candidate is based on the use of recombinant technology. This technology allows the immunogenic properties of each of the four dengue serotypes (determined by the proteins expressed on the surface of the viral particles) to be combined with the well characterized attenuation profile of an established yellow fever vaccine, the so-called YF-17D vaccine strain. The combination is made possible by the structural similarity of the dengue and YF-17D viral genomes, and is the fruit of a research collaboration between Sanofi Pasteur and Acambis who licensed exclusively this technology. The resulting dengue vaccine strains retain only the internal workings of YF-17D, notably the genetically stable genes responsible for replication, and do not encode or express the original yellow fever envelope proteins. One of the major advantages of this technique is that the similarity of the non-structural genes in these four recombinant dengue vaccine strains reduces the risk of interference or competition between strains when presented as a tetravalent vaccine. Indeed, recent clinical trial results with this recombinant tetravalent dengue vaccine in US adults show

for the first time an immune response against all four serotypes in all vaccinees with a tetravalent dengue vaccine given with a suitable regimen.

WHAT ARE THE REMAINING CHALLENGES?

As with any new vaccine, the two biggest challenges from a clinical point of view are to show that the vaccine has a satisfactory safety profile in the target population, in this case primarily children in endemic countries, and to demonstrate that the vaccine protects against disease.

Phase 2 clinical trials of this recombinant tetravalent dengue vaccine have been completed in US adults, as well as in adults, adolescents and children in Mexico and the Philippines. While the data from these studies are still under analysis, the preliminary results shared with the global scientific community show that the safety of the vaccine is satisfactory in these different populations. The next challenge will be to evaluate vaccine safety in a much larger sample of individuals, in particular in the population that will be considered high priority for immunization once a vaccine is licensed.

Clinical researchers base the potential of candidate vaccines to protect against dengue based on serum immune responses assessed *in vitro*. The serological test used in dengue clinical trials is a functional one (i.e., it tests the ability of a serum to neutralize virus, rather than «simply» detecting or quantifying the amount of antibodies in a serum sample). So although there is no immune correlate of protection in humans, it is hoped that the encouraging responses observed so far will translate into a real protection against disease.

The next phase of the clinical development program, scheduled to start later this year, will aim to answer these questions of large scale safety and vaccine efficacy in the field by giving the vaccine to a very large number of children living in a dengue endemic area and following them closely to monitor for dengue disease. This will be the first time that a tetravalent dengue vaccine reaches this stage of clinical development. Early submission for licensure of the vaccine is anticipated for 2012 if these trials are successful. The availability of this vaccine would prove to be the turning point in the management of this rapidly-expanding tropical disease, providing the public health authorities and the international community with the means of preventing millions of cases of disease each year.

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3. For more information, see the PDVI website: <http://www.pdvi.org/>