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Trends in clinical trials of dengue vaccine

Abstract

Dengue is one of the most important vector-borne disease and an increasing problem worldwide because of current globalization trends. Roughly, half the world’s population lives in dengue endemic countries, and nearly 100 million people are infected annually with dengue. India has the highest burden of the disease with 34% of the global cases. In the context of an expanding and potentially fatal infectious disease without effective prevention or specific treatment, the public health value of a protective vaccine is clear. There is no licensed dengue vaccine is available still, but several vaccines are under development. Keeping in view the rise in dengue prevalence globally, there is a need to increase clinical drug and vaccine research on dengue. This paper briefly reviews on the development and current status of dengue vaccine to provide information to policymakers, researchers, and public health experts to design and implement appropriate vaccine for prophylactic intervention.

Key words: Clinical trials, dengue vaccine, global perspective

INTRODUCTION

Dengue is the most common arthropod-borne disease in humans. The global prevalence of dengue has grown dramatically in recent decades; the disease is now endemic in more than hundred countries. Dengue is estimated to affect 50–100 million people each year in the tropical and subtropical areas.^[1,2] Of these 500,000 develop into severe forms of the disease such as dengue hemorrhagic fever and dengue shock syndrome.^[3,4]

DENGUE VIRUS STRUCTURE

Dengue fever, including dengue hemorrhagic fever and dengue shock syndrome, is caused by four antigenically distinct dengue viruses DENV-1, DENV-2, DENV-3, and DENV-4 belonging to genus *Flavivirus* of the family *Flaviviridae*.^[4,5] These four dengue viruses are antigenically cross-reactive. *Aedes aegypti* and *Aedes albopictus* are the major vectors for dengue virus transmission.^[6] The

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Flavivirus virion consists of a nucleocapsid structure surrounded by a lipid bilayer containing an envelope (E) glycoprotein and a nonglycosylated membrane (M) protein. The E protein is the major surface protein with a role in receptor binding and membrane fusion, is the major immunogen during *Flavivirus* infection. The M protein is found in infected cells as a glycosylated precursor, pre-membrane (prM) protein. The other nonstructural proteins are NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. The similarity in antigenic structure of the four types of DENV is closely related to the similar manifestations of dengue diseases.^[7]

MANAGEMENT OF DENGUE FEVER

The affected patients develop high fever, headache, and muscle and joint pain, from which almost all cases recover, whereas dengue hemorrhagic fever patients develop plasma leakage and hemorrhagic manifestations, which may lead to shock.^[8] Currently, management of dengue virus infections relies on control measures targeting personnel prophylactic measures, environmental management, and source reduction.^[9,10]

DENGUE VACCINE RESEARCH AND TRIALS

Vaccines are considered as one of the major contributions of the 20th century and one of the most cost-effective public health interventions. In the situation of growing and potentially fatal infectious disease without effective prevention or specific treatment, the value of a protective vaccine is clear. There is no licensed dengue vaccine is available still, but some vaccines are under development, including live attenuated virus vaccines, live chimeric virus vaccines, inactivated virus vaccines, live recombinant DNA, and subunit vaccines as shown in Figure 1.

Sixty years back, efforts to develop a dengue vaccine was with attempts to prevent virus transmission using infectious human plasma treated with ox virus grown in live mosquitoes and inactivated with formalin.^[11] Schlesinger

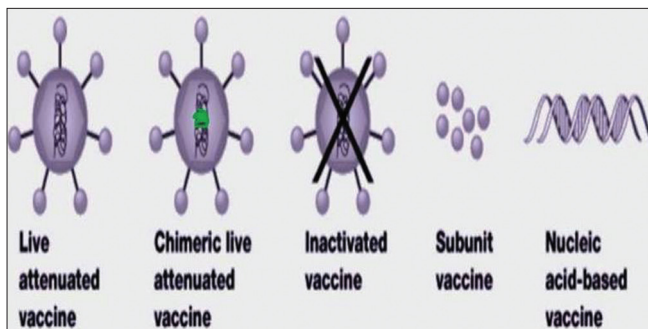


Figure 1: Types of dengue vaccine

et al. and Sabin made the first attempt to immunize using mouse-passaged live-attenuated DENV-1 and -2 viruses in 1956.^[12,13] Mahidol University and Sanofi Pasteur tried to develop live-attenuated virus dengue vaccine candidates using primary dog kidney (PDK) cell passage in 2004; the Walter Reed Army Institute of Research and GlaxoSmithKline Biologicals also used PDK passage to attenuate vaccine virus strain candidates in.^[14,15] The US National Institutes of Allergy and Infectious Diseases attenuated DENV strains by targeted mutagenesis; the resulting DENV strains served as chimeric backbones.^[16,17]

DENGUE VACCINE CLINICAL TRIALS – GLOBAL PERSPECTIVES

Despite intense research efforts over more than 60 years, no dengue vaccine is commercially available.^[10,18] This paper briefly gives the current status of dengue vaccine development globally to provide information to policy makers, researchers, public health experts to design and implement appropriate vaccine as a prophylactic intervention.

We used clinical drug trial registry of US and did an Analytical study of Dengue Vaccine Trials registered in clinicaltrials.gov from January 1, 2003, to July 3, 2013. Search was done using “Advanced search” at “search terms” and “conditions.” Data collected were subjected to descriptive analysis using Microsoft Excel software. Results were given in percentage comparison.

A total number of study registered in clinical trial registry is 183,504. The number of studies for vaccines is 4032 which accounts for 2.5% of the total clinical trials which is shown in Figure 2. Out of 4032 vaccine trials, sixty studies were registered for dengue vaccine. Among it, 31 trials in are in Phase 1, 23 trials in Phase 2, and 6 trials in Phase 3 of

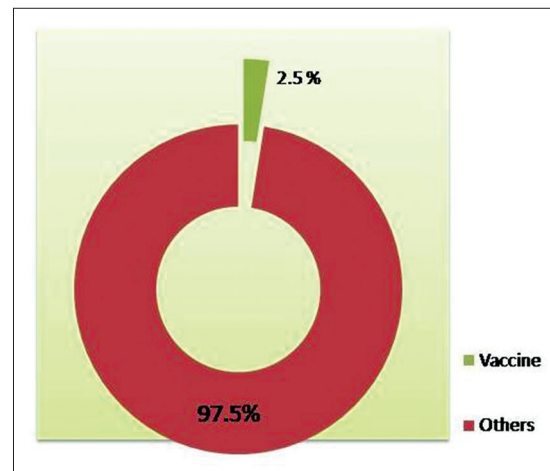


Figure 2: Percentage of vaccine trials registered in clinical trials.gov

development. The different types of dengue vaccine under clinical trials are shown in Figure 3.

DISCUSSION

Live attenuated virus vaccines contain weakened viruses that can induce adaptive immune responses to both structural and nonstructural proteins. Tetravalent vaccine would be highly desirable for a safe and effective dengue vaccine as immunization with a single type of dengue virus may present a risk of increased disease severity to later infection with a different type of dengue virus.^[19-21]

Live chimeric virus vaccines are the most advanced product, in which specific proteins from one virus are substituted for those of another virus. For dengue vaccine, chimeric viruses are constructed by exchanging the prM/E genes of each of DENV1-4 for homologous genes of the yellow fever virus strain 17D. In Phase 2 studies, the tetravalent CVD vaccine appeared safe.^[22,23] Sanofi Pasteur is in advanced clinical development (Phase 3) of a chimeric yellow fever dengue vaccine, to enter clinical endpoint trials.^[24,25] Currently, one chimeric dengue vaccine trial is carried out in India.^[26]

Inactivated virus vaccines have two advantages over live virus vaccines; there is no possibility of reverting to virulence and can induce balanced immune responses. Recent advances in genetic engineering technology have stimulated research on dengue vaccine using live recombinant DNA and subunit vaccines.^[27] The challenges in the development of dengue vaccine are the four dengue serotypes circulate globally, so the vaccine must be tetravalent.^[28] Neutralizing titers to all four viruses need to be attained despite the previous immune status of the vaccinated individuals.

CONCLUSION

The global burden of dengue is significant, and the existing clinical trials for dengue vaccines are lower in the global

context. Vaccination would be an immense value and an essential tool in prevention and control of dengue. Keeping in view the rise in dengue prevalence globally, there is a great need to increase vaccine research on dengue with applications of novel technologies for vaccine development and expansion of vaccine developers with the prospective to provide clinical benefit.

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Conflicts of interest

There are no conflicts of interest.

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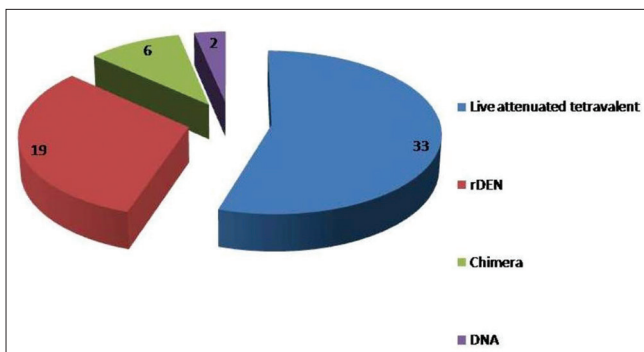


Figure 3: Number of dengue vaccines in clinical trials

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