

**Technology Development Board enters into an agreement with M/s Panacea BiotecPvt Ltd, New Delhi to complete the late stage development of first Indian Dengue Vaccine**

On 14<sup>th</sup> November, the Technology Development Board enters into an agreement with M/s Panacea BiotecPvt Ltd. for the late stage development including Phase II & III of the attenuated dengue vaccine. Dengue is a mosquito-borne flavivirus disease that has spread to most tropical and many subtropical areas. Caused by four closely related viruses, the Dengue viruses 1-4, there are no specific dengue therapeutics; hence prevention limited to vector control measures is the most adopted method. A dengue vaccine would therefore represent a major advance in the control of the disease.

There are many dengue vaccines under development, including live attenuated virus vaccines, live chimeric virus vaccines, inactivated virus vaccines, live recombinant, DNA, and subunit vaccines. The first vaccine Dengvaxia (CYD-TDV) by Sanofi Pasteur was registered in 2015 in Mexico. CYD-TDV is a live recombinant tetravalent dengue vaccine that has been evaluated as a 3-dose series on a 0/6/12 month schedule in Phase III clinical studies. It has been registered for use in individuals 9-45 years of age living in endemic areas. WHO Strategic Advisory Group of Experts (SAGE) has recommended that the dengue vaccine should be considered only in geographic settings with high endemicity.

**M/s Panacea BiotecPvt.Ltd., New Delhi and its Source of Technology**

Scientists at National institutes of Health (NIH), USA developed the attenuated strains of Dengue viruses that were tested in non-human primates for their safety and immunogenicity properties. The studies show that the attenuated viruses are able to replicate and trigger the generation of antibody response against each serotype, a primary requirement of a successful Dengue Vaccine. The vaccine strains did not have any adverse reactions and a challenge with respective wild type virus led to neutralization of the wild type viruses in immunized non-human primates.

As part of technology transfer, NIH USA has supplied fully characterized Virus seeds of the four Dengue Vaccine candidate viruses to PBL. Working further on this, PBL developed in-house process to produce the vaccine virus Drug Substance (DS); analytical methods to qualify the vaccine; and lyophilized formulation for longer stability.

PBL submitted a loan application to the TDB for setting up of a project envisaging “Development and commercialization of Dengue Tetravalent Vaccine (Live Attenuated, Recombinant, Lyophilized)” based on the technology licensed from NIH and perfected indigenously through in-house R&D. An agreement has been signed on 14<sup>th</sup> November 2017; and the trials are expected to be completed by 2019.



Exchanging the Loan Agreement with M/sPanacea Biotec Pvt. Ltd, New Delhi

**About Dengue Fever**

Dengue fever, also known as breakbone fever, is a viral disease characterized by severe headache, skin rash and debilitating muscle and joint pain. Currently, there is no vaccine to protect against dengue, and there is consensus on the urgent need for effective dengue vaccines, not only for those who live in endemic areas, but also for those who travel or are deployed to those areas. The development of a dengue vaccine has unique challenges. There is limited understanding of how the virus interacts with the immune system and how certain types of pre-existing immunity can exacerbate disease. Therefore, a safe and effective dengue vaccine must be tetravalent, and induce strong and long-lived protection against all 4 serotypes simultaneously in order to avoid the risk of sensitizing the vaccine recipient to severe disease.

With more than one-third of the world's population living in areas at risk for infection, dengue virus is a leading cause of illness and death in the tropics and subtropics. Medical records have shown that the Dengue fever has been around since as early as 1779. However, details on the transmission and the cause of the diseases came to light only in the 20th.

Dengue in India has dramatically expanded over the last few decades, with rapidly changing epidemiology. The first major Dengue Hemorrhagic fever outbreak in the entire nation occurred

in 1996 by dengue virus serotype 2, and after a gap of almost a decade, the country faced yet another DF outbreak in the year 2003 by dengue virus serotype 3. A dramatic increase in the number and frequency of outbreaks followed, and, at present, in most of the states of India, dengue is almost endemic. At present, all the four serotypes are seen in circulation, but the predominant serotype keeps changing. Despite this trend, surveillance, reporting, and diagnosis of dengue remain largely passive in India. More active community-based epidemiological studies with initiatives for dengue vaccine development and intensive vector control should be geared up to control the spread of dengue in India.

### **Burden of disease in India**

According to the World Health Organization, the incidence of dengue globally has shot up 30-fold in the past 50 years. The cumulative dengue diseases burden has attained an unprecedented proportion in recent times with a sharp increase in the size of human population at risk. Dengue disease presents highly complex pathophysiological, economic, and ecologic problems. One billion people (15% of the world's population) reside in India. India's population is twice that of Southeast Asia, the region that currently reports the most dengue-related deaths. A recent study done at the University of Oxford using a map-based approach to model how many dengue cases were occurring in various parts of the world, estimated that India had the largest number of dengue cases, with about 33 million apparent and another 100 million asymptomatic infections occurring annually.

Quantifying the burden of dengue is critical for policy makers to set policy priorities and make informed decisions about disease control. Surveillance for dengue has been very limited in India and reporting to the Central Government has also not been mandatory. In 2004, a World Health Organization initiative called for promoting improvement of dengue surveillance as part of the Integrated Disease Surveillance Programme in India, strengthening laboratory networking and quality assurance, and reviewing case definitions. Although improvements are being made, the current gaps in epidemiological data and surveillance mean that the burden of dengue in India probably is much higher.

A landmark 2014 study by the government's National Institute of Health and Family Welfare (NIHFW), New Delhi, found that India could have had "an annual average of 5,778,406 clinically diagnosed dengue cases, or 282 times the reported number per year" between 2006-2012.

### **Importance of Dengue Vaccine and Its need in India**

Vaccines are considered as one of the major contributions of the 20<sup>th</sup> 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.

### **Challenges to vaccine development**

Infection by one of the four dengue virus serotypes has been shown to confer lasting protection against homotypic re-infection, but only transient protection against a secondary heterotypic infection. Moreover, secondary heterotypic infection is associated with an increased risk of severe disease. This and other observations suggest an immunopathological component in dengue pathogenesis, which is referred to as immune enhancement of disease. Due to these dengue-specific complexities, vaccine development focuses on the generation of a tetravalent vaccine aimed at providing long-term protection against all virus serotypes. Additional challenges are posed by the lack of an adequate animal disease model and the resulting uncertainty around correlates of protection. In spite of these challenges, vaccine development has made remarkable progress in recent years, and the current dengue vaccine pipeline is advanced, diverse and overall promising.