Dengue is the most rapidly spreading mosquito-borne viral disease in the world, associated with high morbidity and mortality. It is caused by the transmission of the dengue virus (DENV) through the bite of the infected mosquito vector, Aedes aegypti. There are 4 serotypes of DENV (1–4), and all of them circulate in Singapore. Pre-adolescents and young adults are at the highest risk of dengue in this region. In Singapore, the dengue vaccine is approved for the prevention of dengue caused by DENV 1–4 in individuals aged 12–45 years living in endemic areas. The vaccine is effective in reducing symptomatic, severe and hospitalised dengue, with clear benefits in seropositive individuals.

Keywords: Dengvaxia®; Severe Dengue; Hospitalised Dengue; Benefit–Risk Ratio; Serostatus.

OVERVIEW OF DENGUE

Background and Epidemiology

Dengue is the most rapidly spreading mosquito-borne viral disease in the world. The dengue virus (DENV) is transmitted through the bite of the infected mosquito vector, Aedes aegypti, which is mainly found in the tropical and sub-tropical regions. The dengue virus occurs as 4 distinct serotypes, DENV (1–4), all of which can cause the disease. The multilevel factorial interactions that exist between the various DENV serotypes have yet to be elucidated.

All 4 DENV serotypes circulate in Singapore. While there was an increase in DENV-3 cases in 2016, circulation of all 4 strains was noted in 2017, with a higher prevalence of DENV-2, followed by DENV-4, DENV-1, and DENV-3 (Figure 1).

Figure 1: Surveillance of DENV serotypes in Singapore in 2017

Disease Burden

According to the World Health Organization (WHO) estimates, about 390 million people are infected with dengue each year. The number of severe dengue cases requiring hospitalisation is 500,000 per year, and the mortality rate of severe dengue is about 2.5 percent. In view of these estimates, WHO has set an objective to reduce dengue mortality by 50 percent and morbidity by 25 percent by 2020. In Singapore, there is a considerable inter-annual and seasonal variability, with cyclical outbreaks occurring every 2–5 years; significant epidemic activity has been noted since 2013. A total of 13,115 cases with an average of 20 percent hospitalisations were reported in 2016. An important finding that adds to this disease burden is that about 75 percent of dengue cases are asymptomatic, and asymptomatic individuals may be exposed to more mosquitoes through their disrupted daily routines compared to symptomatic individuals, thereby contributing to a large reservoir of infection.

Population at Risk for Dengue

Most dengue infections occur in pre-adolescents and young adults. The age group of 15–44 years has been found to be consistently at the highest risk for dengue in Singapore; about 62.5 percent cases belonged to this age group from 2002 to 2014.

Severity of the Disease

The clinical spectrum of dengue is highly unpredictable. The disease is classified by WHO into two distinct categories: dengue that occurs with or without warning signs. Both of these can develop into severe dengue, characterised by plasma leakage, fluid accumulation with respiratory distress, severe bleeding, organ impairment, and subsequent hospitalisation and death. There are multiple factors affecting dengue severity, including virulence of the infecting serotype, host genetics, and age. Although antibody-dependent enhancement (ADE) has been demonstrated in vitro, and hypothesised to cause severe dengue, pre-existing in vitro ADE levels have not been shown to correlate with disease severity upon natural infection.

DENGVAXIA®: THE FIRST DENGUE VACCINE LICENSED IN THE WORLD

Overview

Dengvaxia® is the first dengue vaccine to be licensed in the world; currently, Dengvaxia® is approved in 18 countries. Over 20 years of research have been invested into the development of this recombinant, live-attenuated vaccine. Dengvaxia® is a technological advancement, developed by removing the genes coding for structural proteins (while
The development of Dengvaxia® has been robust, with about 25 clinical studies (5 phase I, 14 phase II and 6 phase III studies) conducted in more than 40,000 subjects across 15 countries. Early phase I/II clinical trials, including the phase II CYD28 trial conducted in Singapore, showed a balanced immune response of the vaccine against the 4 DENV serotypes after 3 doses and a safety/reactogenicity profile comparable to the control vaccines. In the CYD28 trial (n=1198), it was also noted that a vaccination schedule of 3 doses must be completed for attaining adequate geometric mean neutralising antibody titres (GMTs); the attained mean GMT titres were stable for up to 4 years of follow-up.

Large-scale efficacy and safety studies of Dengvaxia® have been conducted in 10 countries in more than 30,000 participants. The phase III Asian study (CYD14) was conducted in more than 10,000 children (aged 2–14 years) in five highest dengue-endemic countries in Asia, namely Vietnam, Thailand, Malaysia, Indonesia and the Philippines. This study involved two phases: a 25-month active surveillance phase for assessing the efficacy of the vaccine and a 4-year long-term follow-up (LT FU) phase for assessing the long-term safety of the vaccine. The study concluded that Dengvaxia® has a good safety profile, is effective in protecting against all 4 DENV strains and reduces the incidence of severe disease and hospital admissions. Furthermore, it was noted that the efficacy of the vaccine was higher in individuals with pre-existing dengue neutralising antibodies than in seronegative individuals, and in older age cohorts as compared to a younger population. The phase III CYD15 study was conducted in the highest dengue-endemic countries of Latin America and the Caribbean. This study had similar design and objectives as the CYD14 study and enrolled more than 20,000 subjects aged 9–16 years. The study reported that the vaccine was efficacious against virologically confirmed dengue (VCD) and severe VCD, and was associated with a clinically significant reduction in hospitalisations for VCD. Furthermore, similar to the CYD14 study, this study also reported a higher efficacy of the vaccine in seropositive versus seronegative individuals.

A meta-analysis of the results of the active surveillance phases of CYD14 and CYD15 in 13,732 subjects aged 12–16 years revealed that the vaccine was efficacious against all DENV serotypes (Figure 2). This analysis formed the basis for the approval of the vaccine in Singapore in the age group of 12–45 years. The approval of the upper age limit of 45 years, despite the availability of efficacy data only up to the age of 16 years, is based on the concept of immunological bridging. According to this theory, the mechanism of action of Dengvaxia® is based on the production of neutralising antibodies and the GMTs of antibodies after the third injection have been noted to be higher in phase II immunological studies in individuals aged 18–45 years, compared to the titres noted in CYD14 and CYD15 studies, which enrolled individuals aged up to 16 years. Therefore, it is anticipated that adults up to 45 years of age living in endemic areas will produce similar levels of antibodies and have similar levels of protection compared with the adolescent population. This concept of immunological bridging is a method cited by the WHO and used by various other vaccines.

**Table 1: Age-wise percentage of seropositive individuals in Singapore in 2016**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Proportion of population with prior exposure to dengue in Singapore (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤17</td>
<td>10</td>
</tr>
<tr>
<td>18 – 29</td>
<td>18</td>
</tr>
<tr>
<td>30 – 39</td>
<td>42</td>
</tr>
<tr>
<td>&gt;40</td>
<td>&gt;50</td>
</tr>
</tbody>
</table>

A supplementary analysis (NS1 study) of the efficacy data of the phase Ib/III studies was conducted recently to further assess the efficacy of the vaccine in individuals with or without prior dengue infection. A new assay was developed by the University of Pittsburgh and used by Sanofi for this analysis, which enabled the detection of antibodies against the dengue non-structural protein 1 (NS1). This distinguished the immune responses due to past dengue infection from those due to vaccination, thus enabling the categorisation into seropositive or seronegative at the time of receiving the first dose of the vaccine. The results showed a clear benefit in vaccinating seropositive individuals, and an unfavourable benefit–risk profile in seronegative individuals who were vaccinated (Figure 3). Despite this, the cases of severe dengue noted in seronegative vaccine recipients were primarily dengue haemorrhagic fever (DHF) grades I and II, and did not lead to shock, severe bleeding or death; recovery was noted in all patients.
The findings from this new analysis for optimising the use of Dengvaxia® based on the serological status is shown in Table 2.30

Table 2: Five-year risk of severe dengue in vaccinated/unvaccinated individuals based on serostatus

<table>
<thead>
<tr>
<th>Serostatus</th>
<th>Vaccinated:</th>
<th>Five-year risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seropositive</td>
<td>Vac-ve</td>
<td>4.8/1000</td>
</tr>
<tr>
<td>Seronegative</td>
<td>Vac +ve</td>
<td>4/1000</td>
</tr>
<tr>
<td>Seropositive</td>
<td>Vac +ve</td>
<td>1.7/1000</td>
</tr>
<tr>
<td>Seronegative</td>
<td>Vac -ve</td>
<td>1/1000</td>
</tr>
</tbody>
</table>

Based on the findings from this new analysis, a revision in the warning and adverse event section of the Dengvaxia® label has been proposed. According to this update, (1) Dengvaxia® should only be recommended when the potential benefits outweigh the potential risks (in countries with a high burden of dengue disease); and (2) vaccination should not be recommended in individuals who have not been previously infected by DENV.25

REFERENCES

Through the bite of the infected mosquito vector, *Aedes aegypti*, Dengue is the most rapidly spreading mosquito-borne viral disease. Benefit–Risk Ratio; Serostatus.

Of dengue in this region. In Singapore, the dengue vaccine is effective against all 4 DENV strains and reduces disease burden is that about 75 percent of dengue cases are reported in 2016. An important finding that adds to this epidemic activity has been noted since 2013. A total of 13,115

According to the World Health Organization (WHO) there are 4 serotypes of dengue virus occurs as 4 distinct serotypes, DENV (1–4), and have similar levels of protection compared with the non-structural protein 1 (NS1). This distinguished the immune responses due to past dengue infection from those due to leakage, fluid accumulation with respiratory distress, severe

Available at: https://www.sanofi-pasteur.com/media/Project/One-Sanofi-Pasteur/Primary-Sanofi-Pasteur/ONEDMGVA/2016/10/04/First-Dengvaxia-Pasteur-Sanofi-SA.pdf. Accessed on: 08 Mar 2018.

25. Dengvaxia® [prescribing information] Singapore: Sanofi Pasteur SA.

---

**LEARNING POINTS**

- All 4 strains of dengue virus circulate in Singapore.
- The burden of dengue disease is very high in Singapore, with cyclical outbreaks occurring every 2–5 years.
- **Dengvaxia®** is effective against all 4 dengue virus serotypes, with a significant reduction in the incidence of severe disease and hospital admissions.
- **Dengvaxia®** is more effective in seropositive as compared to seronegative individuals; vaccination increases the risk of severe dengue and hospitalisation in seronegative individuals.