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## UPDATES IN DENGUE FEVER : TREATMENT &amp; VACCINATION

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In the last 50 years dengue has spread from being present in a handful of countries to being endemic in 128 countries. A recent report by World Health Organization (WHO) on the dengue situation in the Western Pacific Region showed that there is a significant increase of dengue cases from 2014 to 2015. According to the report, in Malaysia alone, there were **111,285 cases** of dengue with **301 deaths** (data as of 5th December 2015). This is **16.3% higher** compared to the same reporting period of 2014 (n=95,693). From 29th November to 5th December 2015, 2,119 dengue cases were reported, which is higher than the previous week (n=2,087). The iDengue portal by Ministry of Health Malaysia showed a total of 11,215 of new dengue cases were reported from 3rd-25th January 2016 with 23 deaths. The top 3 states with the highest reported cases were Selangor (5488), Johor (1791), and WP Kuala Lumpur (897) cases.

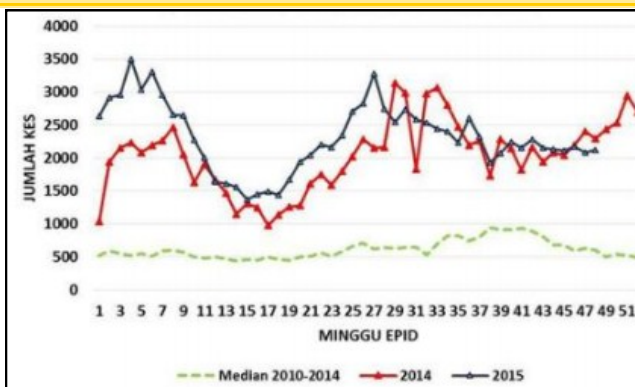
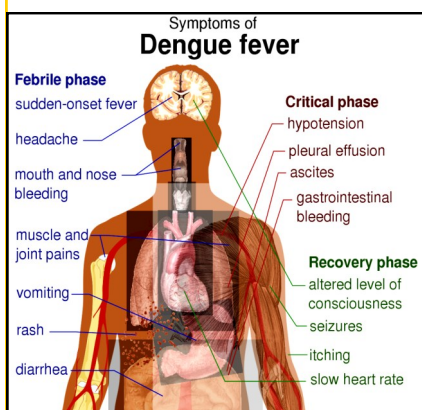


Fig 1: No of dengue cases per week 2014-2015, Dept of Health



Dengue fever is caused by the Dengue viruses (DENV) with 4 different serotypes; namely the DENV-1, DENV-2, DENV-3 and DENV-4. DENV can cause a wide range of diseases in humans, from Dengue Fever (DF) to a life-threatening syndrome called Dengue Hemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS). The DENV is transmitted between people by infected **female mosquitoes** mainly *Aedes aegypti* and to lesser extent, *Aedes albopictus*. Symptoms usually begin 4–7 days and last for up to 10 days. Deadly complication could occur due to plasma leaking, fluid accumulation, respiratory distress, severe bleeding, or organ impairment. Other symptoms are spiking temperature (40°C), severe headache, pain behind the eyes, muscle and joint pains, nausea & vomiting, swollen glands, rash, abdominal pain, mild bleeding manifestation (nose or gum bleed, petechiae, or easy bruising).

There is no specific medicine to treat dengue infection. Pain relievers such paracetamol or tramadol are given to relieve pains and fever. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen, naproxen and aspirin are avoided as it may worsen the bleeding. Rehydration with plenty of clear fluid is crucial in management of dengue fever. However, clinical studies by Institute Medical Research (IMR) published in April 2013 showed that consumption of *Carica* papaya leaf juice induced rapid increase in platelet count in patients with Grade 1 and Grade 2 dengue fever as well as the fatal dengue haemorrhagic fever. The randomized controlled trial (RCT) study was conducted in Hospital Tuanku Ampuan Rahimah (HTAR) Klang among 228 dengue patients. Patients who were given **50g of fresh Carica papaya juice for 3 consecutive days showed significant platelet improvement.**

There have been ongoing news about the development of vaccine to prevent dengue. Currently there are 6 ongoing development of dengue vaccine. In December 2015, Sanofi Pasteur announced that they have developed Dengvaxia® (CYD-TDV); the first vaccine to be licensed in the world for the prevention of dengue after almost 2 decades of research. It consists all four serotypes of virus (DENV 1-4) for population age 9 to 45 years old living in endemic areas. The vaccination schedules consist of 3 doses given 6 months apart (0/6/12 month). As of 27th January 2016, 3 countries have approved the vaccine ie Mexico, Philippines and Brazil.

Dengvaxia® is a chimeric tetravalent dengue vaccine consist of live attenuated yellow fever virus 17D strain with structural genes replaced with the corresponding dengue structural genes. It was shown to reduce dengue due to all four serotypes in two-thirds of the participants and prevent 8 out of 10 hospitalizations due to dengue; and up to 93% of severe dengue cases.

In Malaysia, the recent dengue outbreak in 2013 showed that the predominant strain of the dengue fever is by DENV-2<sup>6</sup> especially in Johor and Terengganu. However the predominant serotype in East Malaysia (Sabah & Sarawak) is DENV-4. The information on dengue serotype according to areas is important as studies shown that the level of coverage and protection varies between serotype. The Dengvaxia® vaccine is reported to give 77.7% of protection against DENV-4, but only 42.3% against DENV-2; hence its effectiveness for population in DENV-2 predominant areas remain debatable and requires further local studies.

In a nutshell, the trial results showed that the dengue vaccine is effective as preventive interventions against dengue. The strains distribution varies in Malaysia but its predominant strains are DENV-1 and DENV-2 which dengue vaccine showed the lowest efficacy against dengue. Despite that, it is found to be 88 % effective against severe dengue and reduction in hospitalization rate. Although the vaccine is yet to reach Malaysian shore and the cost of vaccine is yet to be determined, its role in National Immunization Schedule warrants a local cost-effective study to support its use. In the mean time, everyone has to play their role in the community to prevent the spread of dengue by reducing mosquito habitat. This can be achieved by eliminating the mosquito breeding places such as periodic draining or removal of artificial containers or standing waters.

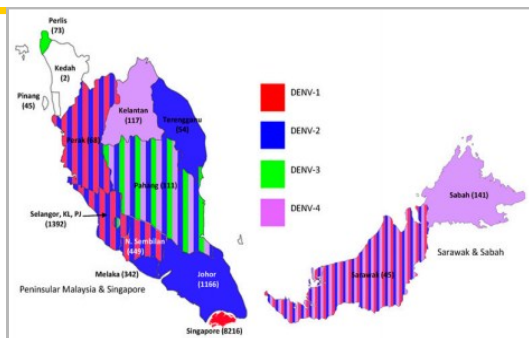


Fig 2: Serotype determination in 2013 (Dominance of a single serotype by more than 50% is denoted by a single color).

#### Report by Sanofi Pasteur on efficacy and safety profile of Dengue Vaccine: Phase III study in Asia

- ◆ The primary endpoint was achieved with 56.5% of vaccine efficacy against symptomatic dengue in children aged 2 to 14 years old after 3 doses scheduled vaccination.
- ◆ There were 88.5% reduction of Dengue Haemorrhagic Fever and two thirds reduction in hospitalization observed.
- ◆ 1% children in the vaccine group and 1% of those in the control group had serious adverse events that happened within 28 days of vaccination. Serious adverse events were consistent with medical disorders in this age group and were mainly infections and injuries.

#### Report by Sanofi Pasteur on efficacy and safety profile of Dengue Vaccines: Phase III study in Latin America

- ◆ Overall, vaccine efficacy against all dengue serotypes combined was estimated 60.8% . In the study, 397 cases of virologically-confirmed dengue were diagnosed. There was statistically significance protection, however the level of protection varies between serotypes.
  - i. DENV-1 : 50.3%
  - ii. DENV-2 : 42.3%
  - iii. DENV-3 : 74.0%
  - iv. DENV-4 : 77.7%
- ◆ The vaccine efficacy against severe dengue was estimated to be 95% but the total number of severe cases in the trial was relatively small.
- ◆ There was no evidence of an increase in serious adverse events in the trial, which included follow up for 13 months after the three-dose series.

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