Dengue Vaccine

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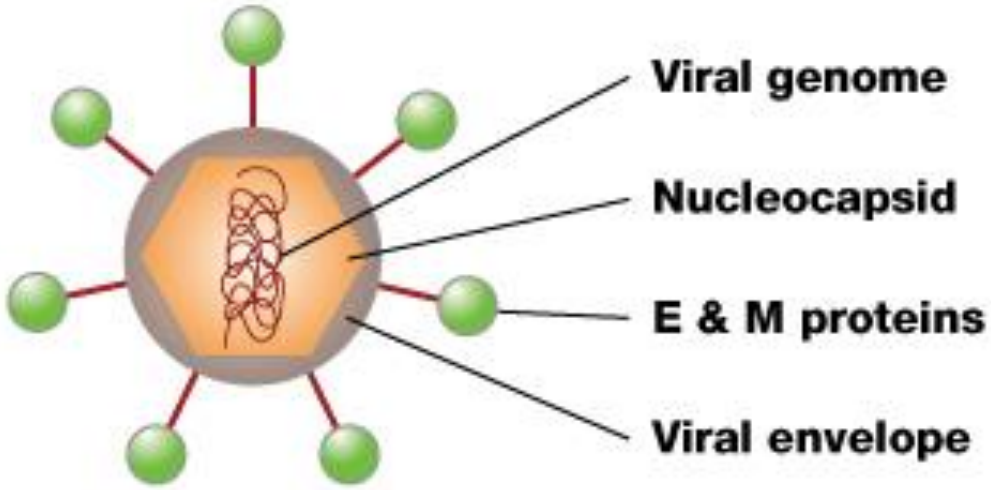
No Conflicts of interest

Dengue

- Dengue virus (DENV), a member of the genus *Flavivirus*
- Vector-borne disease transmitted predominantly by the mosquito *Aedes aegypti* (*Aedes albopictus)*
- There are 4 genetically and immunologically distinct serotypes:
  - dengue-1 virus (DENV-1), dengue-2 virus (DENV-2), dengue-3 virus (DENV-3), and dengue-4 v



Dengue Infection

- Typically
  - self-limiting illness characterized by severe “flulike” symptoms, myalgia, headache, nausea, vomiting, arthralgia, rash, and retro-orbital pain
  - however, a wide spectrum of presentation can occur:
    - respiratory and gastrointestinal symptoms common

- Severe disease is rare
  - mainly in paediatric population
  - rarely in travellers
  - classified as:
    - **dengue without warning signs** (fever and 2 of nausea/vomiting, rash, aches and pains, leukopenia and positive tourniquet test.)
    - **dengue with warning signs** (abdominal pain or tenderness, persistent vomiting , clinical fluid accumulation (ascites/pleural effusion), mucosal bleeding, lethargy/restlessness, liver enlargement > 2cm, increase in HCT with decrease in platelet count) : CRITICAL PHASE
    - **severe dengue** (shock, fluid accumulation with respiratory distress; Severe bleeding; Severe organ involvement)

Annual number of global deaths from neglected parasitic and related tropical diseases

Disease	Estimated no. of deaths
Malaria	655,000
Schistosomiasis	280,000 (Sub-Saharan Africa only)
Hookworm infection	65,000
Leishmaniasis	51,000
Amoebiasis	40,000
Dengue	21,000
Chagas disease	14,000
Trichuriasis	10,000
Liver fluke and lung fluke	<10,000
Total	1.1 million

Beaumier et al. Translational Research, 2013-09-01, Volume 162, Issue 3, Pages 144-155

Approximate number of cases of neglected parasitic and related tropical diseases

Disease	Approximate no. of cases globally
Ascariasis	800 million
Hookworm	600 million
Trichuriasis	600 million
Schistosomiasis	400–600 million
Amoebiasis	480 million
Malaria	216 million
Lymphatic filariasis	115 million
Dengue	50–500 million
Trachoma	40 million
Strongyloidiasis	30–100 million
Onchocerciasis	26 million
Liver fluke infection	24 million
Paragonimiasis	23 million
Leishmaniasis	12 million
Chagas disease	10 million

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Dengue Vaccines – why do we need them

- Significant global disease burden
  - Morbidity
  - Mortality is low
    - paediatric population
- Geographic expansion
- Economic burden
- Significant cause of morbidity and hospitalization in returned travellers

No licensed vaccine, no specific therapeutic agents and no efficient vector control

Challenges all along the way……..

- Development of a challenging vaccine:
  - 4 serotypes
  - Severe disease – safety concerns
  - `Unknowns' – immune correlates and pathogenesis
- Testing phase
  - Surprising results from vaccine trials and therefore uncertain applicability
- Good Incentives for vaccine development:
  - Important socioeconomic challenges to the development of neglected tropical diseases
    - predominantly among the poorest people living in low- and middle-income countries, there are few—if any—market incentives to develop new products, including vaccines
  - An important exception is dengue, which has also emerged in wealthy countries such as Singapore and the United States, and in coastal cities of Brazil and Southeast Asia, where large numbers of people with economic means also live.

What vaccines are in testing phases for dengue?

TetraVax-DV	Johns Hopkins University/NIH/Instituto Butantan	Phase 1 clinical testing	Live attenuated
TDEN	USAMRMC	Phase 1 clinical testing	Live attenuated
DENVax	CDC/Inviragen	Phase 1 clinical testing	Chimeric live attenuated
TV	Sanofi Pasteur	Phase 3 clinical testing	Chimeric live attenuated
TDEN-PIV	WRAIR/GSK	Phase 1 clinical testing	Inactivated purified vaccine
DENV-1 PIV	WRAIR	Phase 1 clinical testing	Inactivated purified vaccine
HBV-001 D1	Merck & Co.	Phase 1 clinical testing	Recombinant protein
TVDV	NMRC/Vical	Phase 1 clinical testing	DNA

Chimeric live attenuated dengue vaccines

- Sanofi-Pasteur is currently the furthest along in the initiative of developing a DENV vaccine
- live attenuated chimeric platform with the yellow fever virus vaccine 17D (YFV-17D) as a backbone with its membrane (*prM*) and envelope *E* genes replaced with those of the various serotypes of dengue
- 3 dose schedule: 0, 6 and 12 months
- Previous pediatric and adult trials have shown the vaccine to have no major safety issues, result in high rates of seroconversion, and it is able to induce $T_H 1$ responses.
- Recently, the results of Sanofi's Phase 2b efficacy study in Ratchaburi, Thailand, demonstrated an overall efficacy of approximately 30%.
  - This lower efficacy value is a result of the lack of immune response to 1 of the serotypes. [26] Phase 3 studies are currently ongoing.

Asia-Pacific study

- Multi-centre RCT Phase 3 study
- Five countries (Asia-Pacific)
- 10,275 children aged 2-14 years

Findings:

Per protocol:

250 cases of virologically confirmed dengue

- 47% vaccine, 53% placebo → Efficacy = 56.5%

Serotype specific efficacy:

DENV 1	DENV 2	DENV 3	DENV 4
50%	35%	78.4%	75.3%

Asia-Pacific Study

Other outcomes:

Vaccine efficacy:

- 80.0% for severe dengue after 1 or 2 injections
- 88.5% after 3 injections

For vaccine recipients: breakthrough episodes of dengue were milder, less hospitalisation, shorter median duration of hospital admission.

- 62% adverse events in vaccine group compared with 38%

Latin American study

- Multi-centre RCT Phase 3 study
- Colombia, Brazil, Mexico, Honduras, Puerto Rico
- 20,869 children between the ages of 9 and 16 years

Findings:

Per protocol: 176 cases of virologically confirmed dengue in vaccine group, 221 in placebo group

→ Efficacy = 64.7%

Latin American study

Findings:

Serotype specific efficacy:

DENV 1	DENV 2	DENV 3	DENV 4
50.3%	42.3%	74.0%	77.7%

Prevention of severe dengue: 95% efficacy

Vaccine efficacy against hospitalization: 80.3%

What's the future for the dengue vaccine?

- Who will it be used it?
  - Lower than expected efficacy for disease acquisition but less severe disease
    - paediatric population
  - 3 dose schedule will limit uptake

  - Long-term follow up of vaccinees required to understand whether waning vaccine-elicited immunity predisposes recipient to more severe outcomes

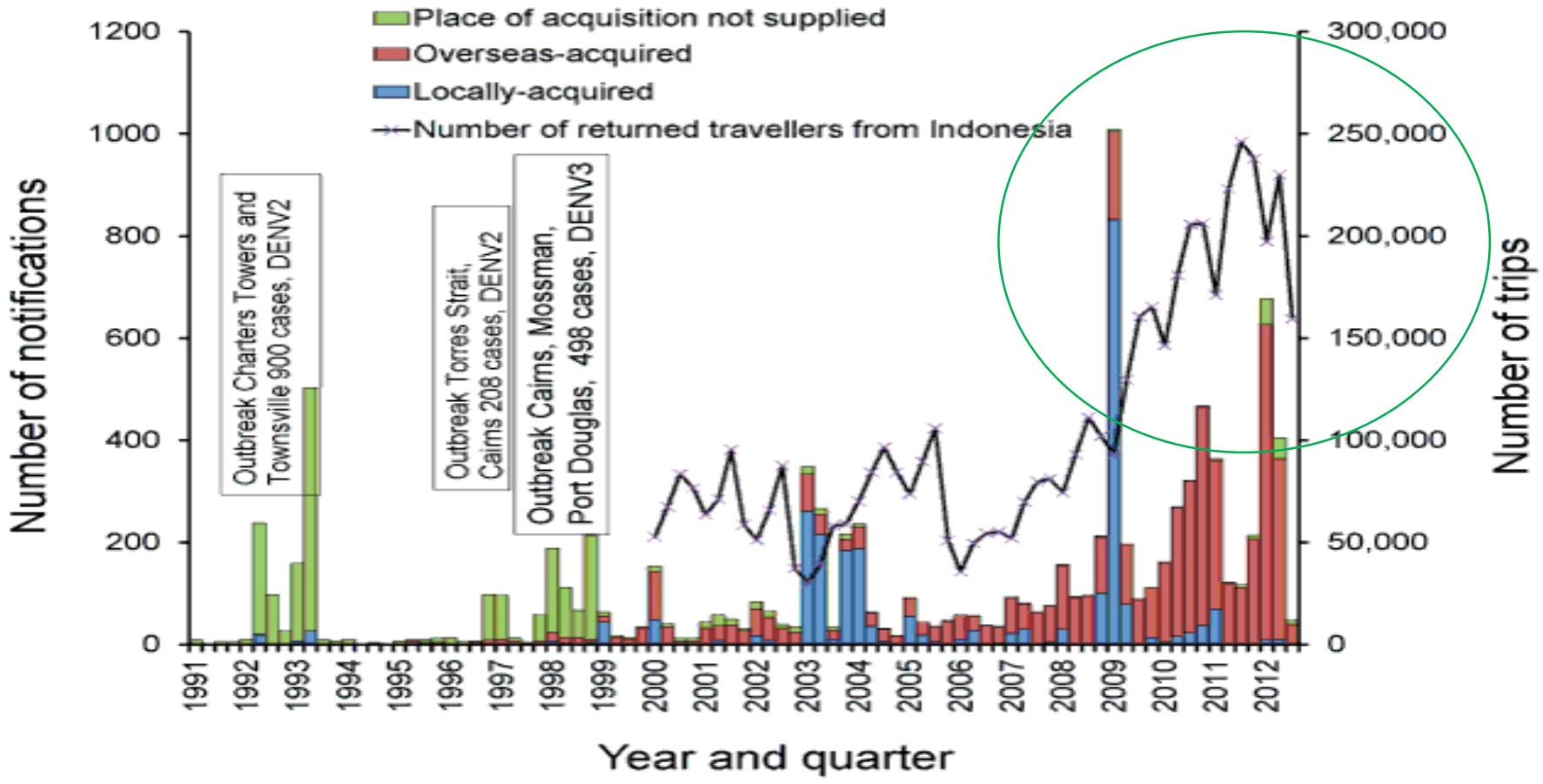
Travellers: Increasing number of overseas acquired dengue

- Overseas acquired dengue in Australia
  - 23% of all notification in 1991 – 1999
  - 93% of all notifications in 2010

- Dengue infection is a more common cause of fever in the returned traveller than malaria in travellers returning from almost all regions of the world
  - - with the exception of Sub-Saharan Africa

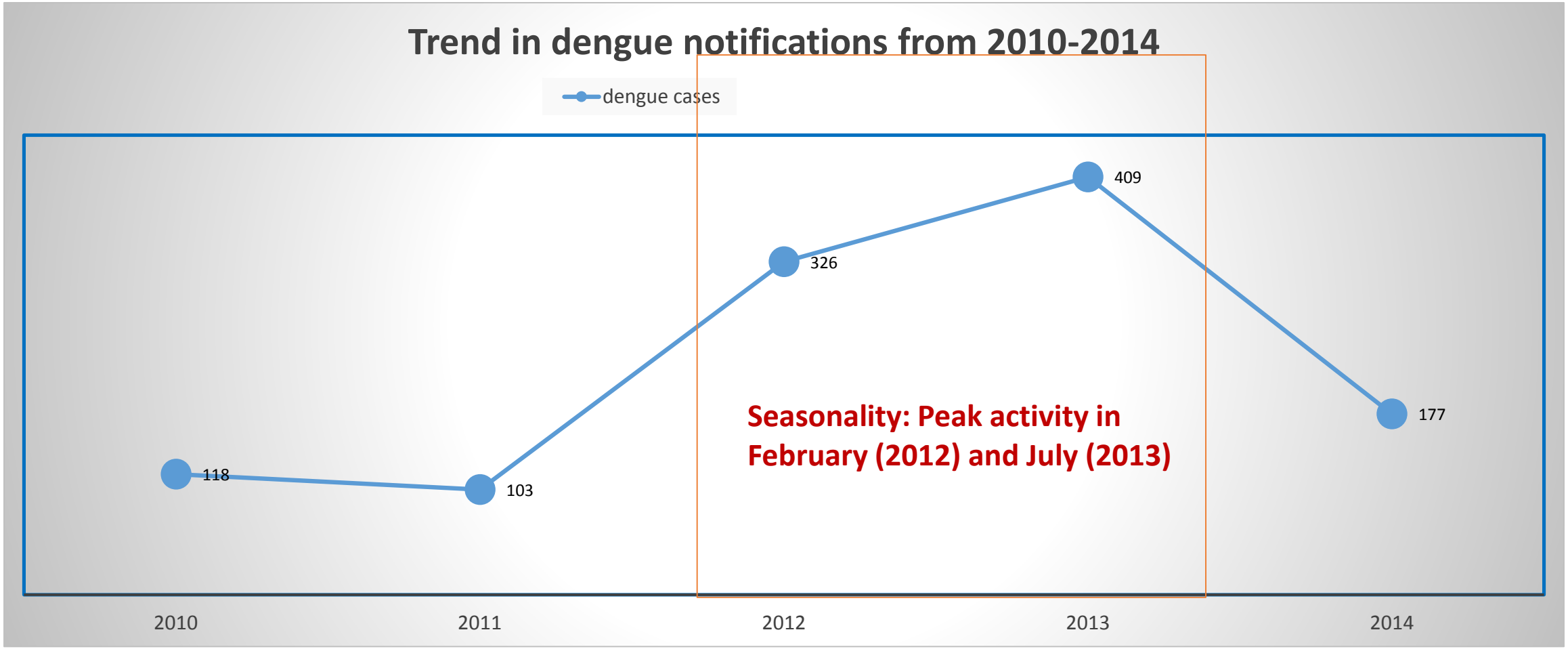
Freedman et al NEJM 2006

Increase in the number of notified cases in Australia



Knope CDI 2013

Victoria: Increased dengue notifications in 2012 & 2013



So for now:

- Ongoing research into the immunity- infection dynamics, antivirals, modification of mosquito populations

- Improved recognition (epidemiology, diagnostics)
- Triaging and fluid management

Thank you