Overview of malaria and dengue

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Malaria

*Plasmodium* parasites:
- *P. falciparum*
- *P. vivax*
- *P. ovale*
- *P. malariae*
- *P. knowlesi*

Vector: *Anopheles* mosquitoes
Global disease burden

• 300-500 million cases/year
• 1-3 million deaths
  • ~90% of deaths in Africa are of children less than 5 years old
• Economic burden of US$12 billion per year
• Most severe malaria cases are due to *P falciparum*
Anti-malarial drug resistance

Drug introduced
- Chloroquine
- Sulfadoxine pyrimethamine
- Pyronaridine
- Artemisinin
- Mefloquine
- Piperaquine
- Artesunate mefloquine
- Artesunate lumefantrine
- Dihyrdorartemesinin piperaquine
- Pyranaridine artesunate

Drug resistance detected
- Thai-Cambodia
- Thailand
- China
- Vietnam
- Thai-Cambodia
- Thai-Myanmar
- Cambodia

Adapted from *The Scientist* 2019
Vaccine made of live malaria parasites shows early success

Strategy uses a combination of parasites and medicines to generate immunity while avoiding symptoms.

Heidi Ledford
Dengue virus (DENV)

Aedes aegypti

Aedes albopictus

Katzelnick et al, Science 2015
**Dengue ± Warning Signs**

**Probable dengue**
- live in / travel to dengue endemic area.
- Fever and 2 of the following criteria:
  - Nausea, vomiting
  - Rash
  - Aches and pains
  - Tourniquet test positive
  - Leukopenia
  - Any warning sign

**Laboratory-confirmed dengue**
(important when no sign of plasma leakage)

**Warning signs***
- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargement >2 cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation and medical intervention)*

**Severe Dengue**

1. Severe plasma leakage
2. Severe haemorrhage
3. Severe organ impairment

**Criteria for Severe Dengue**

**Severe plasma leakage**
- leading to:
  - Shock (DSS)
  - Fluid accumulation with respiratory distress

**Severe bleeding**
- as evaluated by clinician

**Severe organ involvement**
- Liver: AST or ALT >= 1000
- CNS: Impaired consciousness
- Heart and other organs
## Efficacy trials of anti-dengue therapeutics

<table>
<thead>
<tr>
<th>Compound</th>
<th>Trial design</th>
<th>Primary endpoint</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
<td>Randomised, placebo controlled</td>
<td>Viremia resolution</td>
<td>None</td>
</tr>
<tr>
<td>Balaparivir</td>
<td>Randomised, double-blind, placebo controlled</td>
<td>Viral log reduction</td>
<td>None</td>
</tr>
<tr>
<td>Celgosivir</td>
<td>Randomised, double-blind, placebo controlled</td>
<td>Viral log reduction</td>
<td>None</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Randomised, double-blind, placebo controlled</td>
<td>Safety, Viral log reduction</td>
<td>Safe None</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Randomised, double-blind, placebo controlled</td>
<td>Safety</td>
<td>Good safety but no efficacy signal</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>Randomised, double-blind, placebo controlled</td>
<td>Viral log reduction</td>
<td>None</td>
</tr>
<tr>
<td>VIS513</td>
<td>Randomised, double-blind, placebo controlled (trial on-hold due to covid)</td>
<td>Viral log reduction</td>
<td>?</td>
</tr>
</tbody>
</table>
## Clinical phase dengue vaccine/candidates

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Type</th>
<th>Stage</th>
<th>Efficacy outcome</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengvaxia (Sanofi Pasteur)</td>
<td>Chimeric</td>
<td>Completed phase 3</td>
<td>Bi- to tri-valent?</td>
<td>Licensed for use in those with prior dengue infection (PDI)</td>
</tr>
<tr>
<td>TAK003 (Takeda)</td>
<td>LAV/Chimeric</td>
<td>Completed phase 3</td>
<td>Bi-valent. Possibly tri-valent.</td>
<td>No ADE thus far. Appears safe in those without PDI</td>
</tr>
<tr>
<td>TV003 (NIH/Butantan/Merck)</td>
<td>LAV/Chimeric</td>
<td>Phase 3</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>TDEN (GSK/WRAIR)</td>
<td>Inactivated</td>
<td>Phase 1</td>
<td>Poor immunogenicity</td>
<td>Abandoned</td>
</tr>
<tr>
<td>V180 (Merck)</td>
<td>Subunit</td>
<td>Phase 1</td>
<td>Poor immunogenicity</td>
<td>Abandoned</td>
</tr>
<tr>
<td>D1ME100 (US Navy)</td>
<td>DNA</td>
<td>Phase 1</td>
<td>?</td>
<td>Likely abandoned</td>
</tr>
</tbody>
</table>
The challenge of dengue control
Mosquito population and population immunity

Data from Ministry of Health, Singapore