Dengue Vaccines: Herd Immunity Considerations

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1. Introduction

2. Models of Dengue Transmission

3. Herd Immunity Considerations
   - Immune enhancement of transmission
   - Vaccine performance
   - Age effects of Vaccination
   - Basic Reproductive Number

4. Conclusions
Dengue Virus

- Mosquito-borne flavivirus
- Four antigenically distinct serotypes
- Estimated 50-100 million infections annually
- Presentation ranges from asymptomatic to severe form (DHF)
- 2° cases are 50 times as likely to have DHF
Immune Enhancement

- Dengue virus and antibody complexing with platelets and activating clotting cascade
- Plasma leakage
- Monocyte
  - Interferon γ
  - HLA-peptide
  - T-cell receptor
  - Antigen presentation
- Memory T-cell
  - Apoptosis of naive T cells
  - Expansion of low affinity cross-reactive T cells
- Platelet
  - Secretion of vasoactive cytokines: TNFα, Interleukin 2, Interferon γ
- Endothelium
  - Antibody-dependent enhancement
  - Dengue virus

Farrar, NEJM, 2009
Challenges of Vaccine Development

- Cannot contribute to immunopathogenesis
- Needs to generate neutralizing immunity to all four serotypes
  - avoid virus-to-virus interference or flavivirus interference
- Needs to create long-lasting immunity
The candidate produced by Sanofi Pasteur is soon to begin phase III trials.

This candidate is years ahead of others in development.

Status of vaccine development:

<table>
<thead>
<tr>
<th>Developer</th>
<th>Producer</th>
<th>Stage of Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acambis</td>
<td>Sanofi Pasteur</td>
<td>Pre-Clinical, Phase 1</td>
</tr>
<tr>
<td>WRAIR</td>
<td>Glaxo SmithKline</td>
<td>On hold</td>
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<tr>
<td>NIH</td>
<td>Biological E</td>
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<td></td>
<td>Butatan</td>
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<tr>
<td>Hawaii Biotech</td>
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<tr>
<td>CDC</td>
<td>InViragen</td>
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</table>
Questions

- Can vaccinations lead to increased secondary infections?
  - What are the characteristics of these vaccines?
  - What is the impact of non-immunized individuals?
- What will be the effect of the age shift on symptomatic and severe cases?
- What fraction of the population will we have to vaccinate?
Age specific model with cross immunity, immune enhancement and SEI model of vectors
Vaccine provides all or nothing immunity to all or a subset of serotypes with some probability.
Results of hypothetical vaccination 1

- $R_0 = 4, \phi = [1.5, 1.5, 1.5, 1.5], \nu = [0.5, 0.5, 0.5, 0.5]$
\( R_0 = 4, \phi = [1.5, 1.5, 1.5, 1], \nu = [0, 0, 0, 0.98] \)
Results of hypothetical vaccination 3

- $R_0 = 4$, $\phi = [1.5, 1.5, 1.5, 1.5]$, $\nu = [0, 0, 0, 0.6]$
Model was parameterized to match dominant multiannual periodicity of all serotype incidence data as well as proportion of incidence occurring at each age.
Hypothetical vaccines

Scenario 1: Single dose delivered at 1 year of age with 0.9 independent probability of generating immunity to each serotype reaching 90% of targeted children

Scenario 2: Three doses delivered at 12 months, 18 months and 24 months with 0.9 independent probability of gaining immunity to each serotype at third dose reaching 90% of targeted children

Scenario 3: Three doses delivered at 12 months, 18 months and 24 months with 0.1, 0.2 and 0.9 probability of gaining immunity to each serotype at 1st, 2nd and 3rd dose respectively reaching 90% of targeted children
## Reduction in Incidence

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Over 5 years</th>
<th>Over 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario 1</td>
<td>29.0%</td>
<td>87.1%</td>
</tr>
<tr>
<td>Scenario 2</td>
<td>18.1%</td>
<td>79.5%</td>
</tr>
<tr>
<td>Scenario 3</td>
<td>22.9%</td>
<td>84.4%</td>
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</table>
Using hospital based data from Thailand, we have found an increasing odds of DHF compared to DF upon secondary exposure with age (Fried, PloS NTDS, 2010).

Vaccine will shift average to older individuals, thus their severity will impact overall impact of vaccine.
Average age of medically attended dengue illness in Thailand has doubled in the last 15 years

During this period, the incidence of DHF has remained fairly constant
Age changes associated with Demographic Changes

- Recent increases in age specific incidence linked to demographic changes
- Aging of population has contributed to a halving of the force of infection and a doubling of the mean age of DHF cases
Changes in demography

- Birth Rate (per 1000)
- Proportion
- Year
- Age

- Changes in demography

- Immune enhancement of transmission
- Vaccine performance
- Age effects of Vaccination
- Basic Reproductive Number
Results of age specific simulations with changes in demography
Recent increases in age specific incidence linked to demographic changes

Aging of population has contributed to a halving of the force of infection and a doubling of the mean age of DHF cases
Role of Immune Individuals in Population

- Immune individuals provide blood meals
- An increase in the proportion of immune individuals reduces contact between infectious and susceptible individuals
- Reduction in contact between infectious and susceptible individuals reduces the hazard that each susceptible individual experiences
- Another example of herd immunity effects
Calculating the Basic Reproductive Number from Force of Infection

- Force of infection can be used to estimate the fraction of the population susceptible to infection.
- Apply hazard to population to estimate fraction susceptible. Use theoretical results that \( 1/(\text{fraction susceptible}) \) estimates basic reproductive number.

\[
1 = R = sR_0
\]

\[
\frac{1}{s} = R_0
\]
$R_0$ associated with more rainfall, higher temperatures and larger population density
Spatial variation in R0 suggests that 78% of the country would have to be targeted compared to 88% of the country without spatially targeting vaccine.
Conclusions

- We find through simulation that vaccines could conceivably increase transmission but only vaccines that would not be considered for licensure.
- Demographic changes have lead to herd immunity effects reducing the hazard that young people experience.
- We find spatial heterogeneity in the basic reproductive number across Thailand.
- Suggests that optimal vaccination strategies may be spatially heterogeneous.
Thank you
At equilibrium
\[ 1 = R = sR_0 \]
\[ 1/s = R_0 \]
### Using Age data to estimate the Force of Infection

Cumulative proportion of incidence of dengue by age in Bangkok

<table>
<thead>
<tr>
<th>Year</th>
<th>Cumulative Proportion</th>
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<tbody>
<tr>
<td>1985</td>
<td>0.4</td>
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<tr>
<td>1986</td>
<td>0.8</td>
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<tr>
<td>1987</td>
<td>0.6</td>
</tr>
<tr>
<td>1988</td>
<td>0.7</td>
</tr>
<tr>
<td>1989</td>
<td>0.4</td>
</tr>
<tr>
<td>1990</td>
<td>0.8</td>
</tr>
<tr>
<td>1991</td>
<td>0.6</td>
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<td>2001</td>
<td>0.6</td>
</tr>
<tr>
<td>2002</td>
<td>0.7</td>
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<tr>
<td>2003</td>
<td>0.8</td>
</tr>
<tr>
<td>2004</td>
<td>0.4</td>
</tr>
</tbody>
</table>
Estimating the Force of Infection

\[ x(a,t) = e^{-\int_0^a \sum_k \lambda_k (a-\tau, t-\tau) d\tau} \]

\[ z_i(a,t) = \left[ e^{-\int_0^a \sum_{k \neq i} \lambda_k (a-\tau, t-\tau) d\tau} \right] \left[ 1 - e^{-\int_0^a \lambda_i (a-\tau, t-\tau) d\tau} \right] \]
Fitting models to cumulative age specific incidence
Estimates of the Force of Infection

Graphs showing the trend in the force of infection over years (a) and the frequency distribution of the mean force of infection for the years 1985-2005 (b). Another graph (c) shows the percentage change in the force of infection over the same period.
Organizing a meeting in late summer of modeling groups, epidemiologists and vaccine experts.

Working meeting meant to apply multiple modeling approaches to assess Sanofi Pasteur’s candidates.