Overview of a “neglected” infectious disease: dengue
Outline

• Current epidemiological trends
• Mechanisms underlying dengue transmission
• Dengue control
• Overview of recent modeling efforts
  • Drivers of serotype interactions
  • Implications for vaccines
• Discussion
Dengue in a nutshell

- Estimated 400 million annual infections worldwide
  - broad clinical spectrum of infection: silent → DF → DHF/ DHSS

- DENV single-stranded RNA virus (Flavivirus)
  - 4 antigenically-distinct serotypes
  - permanent immunity serotype-specific (?)
  - severe disease in response to sequential infection
Principally transmitted by peridomestic mosquito Aedes aegypti (also Aedes albopictus)

Blood Meals:
- females take multiple blood meals
- feed as early as 21 hours
- linked to a 4 day gonotrophic cycle
- temperature dependence:
  - flight limited below 21°C
  - conflicting biting results

Oviposition:
- laid in standing water but food availability is important
- eggs can survive great extremes: (8.9°C-43.3°C)
- activation after 1 week at 18.3°C or more

Adult Mortality:
- maximum in lab: 225 days; maximum in field: 42 days
- average in field: 15 days
- temperature dependent – 15 mins at 48.9°C ->100% mortality
  - extended periods at 40.6°C
Shifting epidemiology

Increasing case reports ...
Shifting epidemiology

Increasing severity ...

Laboratory-Confirmed DHF in the Americas Prior to 1981 vs. 1981 - 2003


Source: WHO/PAHO/CDC

DHF incidence in Americas, WHO/PAHO/CDC
Dengue in 2010

The global distribution and burden of dengue
Bhatt et al., Nature 2013
Dengue in U.S.? – Headlines from 2010

“Dengue Re-emerges in U.S., Spurring Race for Vaccine”, NY Times

“Will dengue fever spread in U.S.? Too soon to tell, experts say”, USA Today

“Miami Has First Dengue Fever Case in 50 Years”, US News

October 26 1934

DENGUE IN SOUTHEASTERN STATES

During the week ended October 13, 1934, 134 cases of dengue were reported in the State of Georgia.

On October 12, 1934, it was estimated that there were 250 cases of dengue in Miami, Fla., with very few new cases.

Public Health Reports, Oct 26 1934
... and 2013

Martin County
Introduction Summer 2013 (DENV-1)
22 local autochthonous cases

Key West
Introduction 2009-2010 (DENV-1)
~2% apparent rate

Christofferson et al., Parasites & Vectors 2014
Phylogeny of dengue viruses

Strain replacement – what determines spread of novel genotypes?
Why is dengue re-emerging?

• Increased human movement (transporting virus & initially mosquitoes)
• Rapid urbanization, poor living conditions
• No sustained effective vector control
• Absence of vaccine (until 2016 ... but see later)
What dengue case reports don’t reveal

• Tip of the iceberg – how many infections are asymptomatic?

• Serotype? Genotype?

• Individual history of infection?
  – $4! = 24$ different serotype sequences
Vector-borne Disease

Focus of pathogen transmission
Arboviruses

**Arthropod-borne viruses**

**anthroponosis**

**zoonosis**

Mosquito carriers occasionally infect humans and other mammals.

WNV mostly cycles between birds and mosquitoes.
Dengue Transmission Cycle

- Infectivity of hosts to vectors
- Probability that exposed vector survives EIP
- # bites per vector
- Infectivity of vectors to hosts
- Duration of host infection
- Host biting rate
Dengue Transmission Cycle

1/r

b

ma

c

a/g

e^{-gn}
Vectorial Capacity & Basic Reproduction Number

\[ V = \frac{ma^2 e^{-gn}}{c} \quad \implies \quad R_0 = \frac{b}{r}V \]

- \( V \): ratio of vector to host population density
- \( R_0 \): transmission probability
- \( b \): vector biting rate
- \( r \): recovery rate
- \( g \): extrinsic incubation period
- \( m \): infection probability
- \( n \): daily mortality
What processes determine maintenance and expansion of dengue?

• Human-virus interactions
  – Human susceptibility to infection & disease depends on sequence of infection, age, viral strain, etc.

• Mosquito-virus interactions
  – Viral fitness within mosquito depends on viral strain, temperature, etc.

• Non-viral factors (shaping mosquito-human contact)
  – Temporal & spatial variation (at different scales) in climate, habitat, behavior, movement
Potential mechanisms underlying dengue dynamics

Environmental:

Vector biology and virus transmission influenced by seasonality (and perhaps inter-annual variation) in climatic variables
Long-Term and Seasonal Dynamics of Dengue in Iquitos, Peru

Steven T. Stoddard¹,²*, Helen J. Wearing³, Robert C. Reiner Jr.¹,², Amy C. Morrison¹,⁴, Helvio Astete⁴, Stalin Vilcarromero⁴, Carlos Alvarez⁵, Cesar Ramal-Asayag⁶, Moises Sihuincha⁷, Claudio Rocha⁴, Eric S. Halsey⁴, Thomas W. Scott¹,², Tadeusz J. Kochel⁸, Brett M. Forshey⁴
Cases captured by clinic-based surveillance system in Iquitos, Peru between 2000–2010
Seasonal timing of epidemics – interplay of climate, human immunity, vector control & stochasticity
Dengue Control

• Vector-targeted control
  – Reduce mosquito populations
  – Reduce infectious mosquito populations
    • Shorten female life span
    • Introduce mosquito populations with reduced capacity to transmit dengue

• Human-targeted control
  – Vaccines (several in various stages of testing)
Dengue vaccine

- One vaccine Dengvaxia (CYD-TDV) developed by Sanofi Pasteur, licensed
  - live attenuated tetravalent chimeric vaccine with yellow fever backbone
- Approximately five other vaccine candidates in clinical development
  - two (developed by Butantan and Takeda) in Phase III trials

Serious concerns about whether vaccines may cause more harm than good

WHY?
Dengue replication

https://youtu.be/3LhWuaTRCME
Serotype Specific Data: Mexico

What mechanisms determine these patterns of interaction?
Potential mechanisms underlying dengue dynamics

- **Antibody response to infection**
  - antibody-dependent enhancement (ADE): wane to sub-neutralising levels, second episode of infection with heterotypic serotype may lead to enhanced viral replication (Halstead, 1970)
Ferguson et al. (1999; PNAS)

Studied two-strain model: direct transmission, no seasonality

Concluded that antibody-dependent enhancement can

1. generate persistent (sometimes chaotic) serotype dynamics, qualitatively consistent with data
2. Facilitate coexistence of serotypes
Thai dengue data

- Serotype-specific clinical data
- Aggregated DF & DHF case reports

Nisalak et al. (2003; Am J Trop Med Hyg)
Sabin's "experiments"

RESEARCH ON DENGUE DURING WORLD WAR II

ALBERT B. SABIN

Army Epidemiological Board, Preventive Medicine Division, Office of the Surgeon General

STATUS OF PROBLEM PRIOR TO WORLD WAR II

Most of the basic and significant contributions to our knowledge of dengue prior to World War II were made by honored members of the medical department of the U.S. Army. Ashburn and Craig (1) provided the evidence for the viral etiology of the disease. Siler, Hall and Hitchens (2) clearly established the period of infectivity of dengue patients for Aedes aegypti mosquitoes, the period required for the development of the virus in these mosquitoes before they could transmit the infection, as well as the very long period during which these mosquitoes were capable of transmitting dengue. Simmons, St. John and Reynolds (3) established (a) the role of Aedes albopictus in the transmission of dengue, (b) the occurrence of inapparent infection in certain monkeys under experimental and possibly also natural conditions, thus suggesting the existence of a "jungle" type of dengue fever exclusive of the human cycle, (c) the persistence of immunity to the homologous strain of virus for 13 months in human volunteers residing in an endemic region, and (d) many of the properties of the virus. It is necessary to recall, however, that the latter investigators completed their studies in 1930, before most of the important, newer virological techniques and procedures had been developed. In 1934, Snijders, Postmus and Schüffner (4) reported some immunity experiments on human beings in Holland with two different strains of virus which left the subject of immunity to dengue in a rather unsettled state. In 1936, Shortt, Rao and Swaminath (5) reported the successful cultivation of dengue virus on the chorioallantoic membrane of chick embryos, but their conclusions were not based on tests on human beings. Otherwise, little or no work was done on dengue during the period of 1930 to 1940.
Potential mechanisms underlying dengue dynamics

- **Antibody response to infection**
  - antibody-dependent enhancement (ADE): wane to sub-neutralising levels, second episode of infection with heterotypic serotype may lead to enhanced viral replication (Halstead, 1970)
  - transient cross-immunity: cross-reactive antibody levels elevated for 2-9 months following infection (Sabin, 1952)
Typical model framework

- Susceptible
- Exposed
- Infectious
- Cross-immune
- Recovered

Serotype 1

Serotype 2

Mortality
ADE: increased susceptibility

Dominant inter-epidemic period of each serotype

Dominant inter-epidemic period of aggregate cases

Correlation between serotypes

Wearing & Rohani (2006; PNAS)
Critical community size

Thai DHF data

Data from http://www.jhsph.edu/cir/dengue.html

Wearing & Rohani PNAS 2006
Dengue serotypes in Thailand

Monthly serotype-specific case counts of dengue from Queen Sirikit National Institute of Child Health in Bangkok, Thailand

Transmission model

Transmission rate in month $t$

$$I_{t,i} = r_t \cdot I_{t-1,i} \cdot S_{t-1,i} \cdot \epsilon_{t,i}$$

$$S_{t,i} = B_{t-d} + S_{t-1,i} - I_{t,i} - \delta Q_{t,j \neq i}$$

Births accounting for 4 months of maternal immunity

Loss from Susceptibles to serotype $i$ when infection with serotype $j$
Interrogating data

- Used statistical methods—based on maximum likelihood—to distinguish among different models

<table>
<thead>
<tr>
<th>average duration of cross protection</th>
<th>% protected (δ)</th>
<th>r_i^λ</th>
<th>r(t)^*</th>
<th>log-lik</th>
<th>d.f.</th>
<th>ΔAIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–902.4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>N_a</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–946.7</td>
<td>15</td>
<td>112.6</td>
</tr>
<tr>
<td>N_b</td>
<td>0</td>
<td>●</td>
<td>–</td>
<td>–882.9</td>
<td>19</td>
<td>–7.0</td>
</tr>
<tr>
<td>N_c</td>
<td>0</td>
<td>●</td>
<td>●</td>
<td>–817.2</td>
<td>41</td>
<td>–94.4</td>
</tr>
<tr>
<td>N_d</td>
<td>0</td>
<td>●</td>
<td>●</td>
<td>–781.1</td>
<td>119</td>
<td>–10.7</td>
</tr>
</tbody>
</table>

E_a = 0.77

E_b = 2.23

E_c = 1.88

E_d = 2.27

F_a = 0.48

F_b = 2.13

F_c = 2.00

F_d = 1.75

N_i = serotype-specific transmission parameters included
N_r = seasonal transmission parameters included
log-lik = log-likelihood for the given model
d.f. = degrees of freedom of the model
ΔAIC = change in Akaike Information Criterion over null model
Overall Modeling Conclusions

- **Strongest result**: models need to include temporary cross-immunity to generate best match with Thai data (see also Adams *et al.* 2006 *PNAS*)

- Suggests weak *transmission* consequences of ADE

- However, *does not* exclude a significant role for ADE in dengue *pathogenesis*
Consequences for vaccination

Figure S1: Mechanism of action of the vaccine assumed in the default model

- Unvaccinated individuals (top row of Figure S1) experience a moderate severity infection in unvaccinated individuals.
- Secondary natural infection in unvaccinated individuals.
- Primary infection, a more severe secondary infection, then mild tertiary and quaternary infections.
- Seronegative individuals who are vaccinated while still fully susceptible to dengue serotypes as is generally observed after the first natural infection.
- Immunological effect of vaccination is akin to a (silent) natural infection.
- Conversely, vaccination of individuals who have experienced one or more dengue infections (bottom row of Figure S1) boosts their immunity to levels comparable to those of individuals who have experienced two or more infections. Thus, a breakthrough infection increasing the probability of symptomatic and severe disease upon a primary infection, a more severe secondary infection, then mild tertiary and quaternary infections.
- In contrast, vaccination of individuals who have been vaccinated after their primary infection will cause symptomatic or severe disease with the same (low) probability as a tertiary infection in unvaccinated individuals.
- Secondary infection in an individual vaccinated after their primary infection will cause symptomatic or severe disease with the same (high) probability as a quaternary infection.

Materials and Methods
Model of vaccine action
Consequences for vaccination

- Assessing dengue vaccine potential using modeling

DENGUE VACCINE

Benefits and risks of the Sanofi-Pasteur dengue vaccine: Modeling optimal deployment

Neil M. Ferguson,† Isabel Rodríguez-Barraquer,∥ Ilaria Dorigatti,† Luis Mier-y-Teran-Romero,∥ Daniel J. Laydon, Derek A. T. Cummings∥

The first approved dengue vaccine has now been licensed in six countries. We propose that this live attenuated vaccine acts like a silent natural infection in priming or boosting host immunity. A transmission dynamic model incorporating this hypothesis fits recent clinical trial data well and predicts that vaccine effectiveness depends strongly on the age group vaccinated and local transmission intensity. Vaccination in low-transmission settings may increase the incidence of more severe “secondary-like” infection and, thus, the numbers hospitalized for dengue. In moderate transmission settings, we predict positive impacts overall but increased risks of hospitalization with dengue disease for individuals who are vaccinated when seronegative. However, in high-transmission settings, vaccination benefits both the whole population and seronegative recipients. Our analysis can help inform policy-makers evaluating this and other candidate dengue vaccines.

Best-fitting model: (i) second infections twice as likely to lead to symptomatic dengue as primary and (ii) ~7mo period of heterologous protection in seronegative vaccine recipients
Consequences for vaccination

1. **Low-transmission settings:** vaccination may increase incidence of more severe “secondary-like” infection plus numbers hospitalized

2. **Moderate transmission settings:** positive impacts overall, but increased risks of hospitalization with dengue disease for individuals who are vaccinated when seronegative.

3. **High-transmission settings:** vaccination benefits both whole population and seronegative recipients
Discussion

• Dengue incidence increasing
  – Underlying causes complex, likely related to changing climate, land-use and mobility

• Epidemiology of dengue complex because of associations between
  – Serotypes (via immune memory)
  – Sequence of infection (primary/secondary/tertiary)
  – Seasonality in vector biology

• Important consequences for vaccination
  – may, perversely, lead to increased disease in some settings