Modeling results / SDF: Routine vaccination strategy
Introduction catch-up strategy

Ira Longini, Diana Rojas, Tom Hladish
CSQUID, University of Florida, Gainesville, FL

Betz Halloran, Dennis Chao
Fred Hutchinson Research Center, University of Washington, Seattle, WA

Hector Gomez Dantes
National Institute of Public Health, Cuernavaca, México

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This talk

• Concepts in vaccine efficacy and effectiveness
• Dengue vaccines under development
• Description of individual-level, stochastic simulation model
• Potential effectiveness and impact of dengue vaccine
  • Catchup
  • Waning
• Combining dengue vaccines with vector control
Current dengue intervention use and impact modeling

• Vaccine effectiveness depends on
  • Vaccine efficacy
  • Durability of protection
  • Force of infection of each serotype
  • Mix of serotypes circulating
  • Level of immunity in the population
  • Age structure of the population
    • Change immunity patterns
    • Level of exposure
Current dengue intervention use and impact modeling

- Vector control effectiveness
  - Need for integrated vector control for established methods
  - Need to establish the relationship between vector control methods and dengue illness and infection
    - More field studies
- Biological control
  - Genetic
  - Biological, e.g., Wolbachia, copepods
Vaccine efficacy and effectiveness

• Direct effects
  – direct protective effects in person who is vaccinated

• Indirect effects
  – effects of widespread vaccination on someone who is not vaccinated

• Total Effects
  – possibly synergistic effect of being vaccinated and widespread vaccination on someone who is vaccinated

• Overall effects
  – overall population effect, say, reduction in incidence, of widespread vaccination.
Overall effectiveness and impact

- **Overall effectiveness**
  
  \[ \text{VE}_{\text{overall}} = 1 - \left( \frac{r_{\text{vac}}}{r_{\text{novac}}} \right) \]
  
  - \( r_{\text{vac}} \): overall incidence rate with vaccination campaign
  
  - \( r_{\text{novac}} \): overall incidence rate with no vaccination in a comparable population

- **VPDI}_{\text{overall}} = (\#\text{risk}) \ r_{\text{novac}} \ \text{VE}_{\text{overall}} \), cases averted

  \[ = (\#\text{risk}) \ (r_{\text{novac}} - r_{\text{vac}}) \]
Sanofi dengue vaccine so far

- Very safe
- Reasonable protection for disease with infection so far
- Longer term follow-up needed for durability of immunity and protection
- Excellent protect against severe disease
- Heterogeneity in protection
  - Serotypes
  - Prior immunity
  - Other factors?
Individual-level, stochastic, mathematical model


Model: Natural history of dengue

- Human SEIR is linked to mosquito SEI model
- Humans and mosquitoes infect each other when they are in the same setting
Model Structure: dengue model Yucatán State overview (Agent-based model)

- People stay home, or go to work or school each day
- Mosquitoes stay put or occasionally move to adjacent location each day
  
- Uninfected mosquitoes are modeled probabilistically, infected mosquitoes modeled explicitly

Model based on Chao et al (2012), PLOS NTD
Dengue eras modelled in Yucatan

- Pre-history (before 1956)
- Elimination (1956-1979)
- Fitting (1979-2013)
- Forecast (2014-2033)
Dengue in Yucatan, 1979-2013

Reported cases

- Mild disease
- Severe disease

Serotype

1
2
3
4
Households are placed within municipalities according to nighttime light output (VIIRS/NASA).

Pixel size = 430m x 460m
Households
Mosquitoes move according to Delaunay triangulation.
Observed seasonality (1995-2011)
Pr\{Rainfall\} \rightarrow \text{Mosquito population}
Temperature $\rightarrow$ Incubation Period

$EIP(T) = e^{[e^{2.9-0.08T}]+0.1}$, after Chan and Johanson (2012)
Seasonality

Fit to data using Approximate Bayesian Computation (ABC)
Timing of peak matches
Width of peak may be narrow because model’s seasonality doesn’t change
Duration of cross immunity = 2 years
Immune profile validation

95% CI bars on empirical data
Yucatan Simulation

http://peregrine.hladish.com/d3_dengue_map/mex.html
## Vaccine efficacy for simulations

### Latin America

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Vaccine Efficacy*</th>
<th>Antibody positive</th>
<th>Antibody negative</th>
<th>Overall**</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>60</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
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<tr>
<td>4</td>
<td></td>
<td>95</td>
<td>48</td>
<td>78</td>
</tr>
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</table>

* Assuming leaky vaccine effect

** Based on 60% antibody positive
Vaccination strategies

• Routine vaccination
  • Vaccination of 2, 9 or 16 year-olds every year
• Routine vaccination with one-time catchup
  • Vaccination of 2, 9 or 16 year-olds every year
  • One time catch-up up to 30
• Coverage:
  • 80% coverage for 9 year-old routine
  • 60% coverage for 10-30 year-old catchup
  • Same # doses for others
Yucatan Simulation with Vaccination

http://peregrine.hladish.com/vac_map/
Effect of durable vaccine: routine only and routine + catchup

![Graph showing annual incidence of cases per 100,000 people over time for different vaccination scenarios. The graph compares baseline, 2yo + catchup, 2yo, 9yo + catchup, 9yo, and 16yo + catchup scenarios. The y-axis represents annual incidence, and the x-axis represents time (years).]

- Black line: baseline
- Blue dashed line: 2yo + catchup
- Blue line: 2yo
- Green dashed line: 9yo + catchup
- Green line: 9yo
- Orange dashed line: 16yo + catchup
- Orange line: 16yo
Effectiveness of durable vaccine: routine only and routine + catchup

Year

Effectiveness (reduction in cases)

2yo
2yo + catchup
9yo
9yo + catchup
16yo
16yo + catchup
Cumulative severe cases (DHF/DSS) averted per 100,000 at risk

<table>
<thead>
<tr>
<th></th>
<th>Years 1-5</th>
<th>Years 1-10</th>
<th>Years 1-15</th>
<th>Years 1-20</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 yo routine</td>
<td>103</td>
<td>246</td>
<td>537</td>
<td>1010</td>
</tr>
<tr>
<td>9 yo + 10-30 catch-up</td>
<td>433</td>
<td>955</td>
<td>1504</td>
<td>2128</td>
</tr>
</tbody>
</table>
Conclusions

Routine vaccination of children

- Overall effectiveness starts near 0% and goes to 50%
- Prevent 1,000 severe cases/100,000 over 20 years

Routine vaccination of children + one time catch up to 30

- Overall effectiveness starts near 50% and goes to 75%
- Prevent 2,100 severe cases/100,000 over 20 years
Potential effects of vaccine efficacy waning
Waning Patterns

The diagram illustrates the time to 50% efficacy loss of a vaccine over different time periods since vaccination. The x-axis represents the years since vaccination, ranging from 0 to 20 years, and the y-axis shows the percentage of effectiveness (VE(t)).

- **No waning** line indicates constant effectiveness.
- **10 years** line shows a linear decrease in effectiveness over 10 years.
- **5 years** line indicates a faster decrease in effectiveness over 5 years.
- **2 years** line represents the quickest decrease in effectiveness over 2 years.

The chart demonstrates that the longer the time since vaccination, the quicker the loss of vaccine efficacy.
Effectiveness of waning vaccine, boosting: routine only

Routine vaccination of 9 year olds

Effectiveness (reduction in cases)

Year

2 yr waning
5 yr waning
10 yr waning
2 yr waning & boosting
5 yr waning & boosting
10 yr waning & boosting
no waning
Conclusions about waning

• Even longer-term waning would be problematic
  • Could make the epidemic worse
• Boosting strategies would be necessary
  • Depending on waning speed, boosting should take place at appropriate intervals
  • Vaccination with boosting strategies could be worked out using mathematical models
Vector reduction model

- Simulate past dynamics (1878-2013)
- Reduce mosquito population by 10, 25, or 50% (2014-2033)

Vector reduction ≠ vector control
Why does vector reduction lose effectiveness?

Initially:

High natural immunity + VC = small epidemics

Later:

Modest natural immunity + VC = ~normal epidemics

What if we stop?
Effectiveness of 10-year vector reduction campaign

Effectiveness (reduction in cases)

Year

10% VR
25% VR
50% VR
Vector-only conclusions

• Noise may obscure empirical effectiveness
• Vector-reduction only is ambitious/problematic
• Stop slowly
Effects of new vector reduction plus vaccination
Effectiveness of 10% vector reduction with routine vaccination

- **10% VR**
- **9 yo vaccination**
- **VR + vaccination**

Effectiveness (reduction in cases) vs Year
Vector reduction + routine vaccination

10% VR  
25% VR  
50% VR

Stable effectiveness possible
Vector reduction + routine + catchup vaccination

10% VR

25% VR

50% VR
Overall conclusions

Modest interventions not bad, may be untenable
• Vector reduction effectiveness wanes
• Routine vaccination effectiveness starts low

Combined modest interventions promising
• Increased, sustained effectiveness

Ambitious VR and catchup not needed

Cost-benefit analysis needed to find balance
Funding Sources

• Dengue Vaccine Initiative/Bill and Melinda Gates Foundation
• NIH, NIAID
  • R37 AI32042
• NIH, NIGMS
  • U54 GM111274 (MIDAS)
• Sanofi Pasteur (Phase IV studies in the Yucatan)
Gracias
Measures of Vaccine Efficacy

• $VE_S$ Vaccine Effect on Susceptibility
• $VE_P$ Vaccine Effect on Clinical Disease
  • Classical III vaccine trials
    Many times observe
    $$VE_{SP} = 1 - (1 - VE_S) (1 - VE_P)$$

• $VE_I$ Vaccine Effect on Infectiousness
• Search for immune correlates (even surrogates for VE)
Summary: CYD 15 *

- Overall VE_{SP} = 60.8% [CI: 52.0 – 68.0]**
- Overall VE_{Hosp} = 80.3% [CI: 64.7 – 89.5]
- Serotype-specific VE_{SP}
  - ST1: 50.3% [CI: 29.1–65.2]
  - ST2: 42.3% [CI: 14.0–61.1]
  - ST3: 74.0% [CI: 61.9–82.4]
  - ST4: 77.7% [CI: 60.2–88.0]
- Vaccine more efficacious in people with prior immunity compared to those who are naïve, 2 to 1 ratio, accounts for age differences in VE

Phase IIb and III vaccine trials of Sanofi Pasteur tetravalent dengue vaccine

- Phase I and II in many countries
- Phase IIb completed in Thailand (CYD23)*
- Phase III completed late 2014
  - 5 countries in SE Asia (CYD14)**
  - 5 countries in Latin America (CYD15)***

Stepped wedge cluster trial

- One-way cross-over cluster trial
- Randomized, phased introduction on a facility by facility basis until all facilities have received intervention
- Time points informed by
  - Type of disease, outcome, time to expected effect etc.
- Higher risk of bias compared to randomized control trials (RCT)
- Less efficient than RCT but more efficient than cluster trial
- Typically requires more time

Source: Matthias Egger

<table>
<thead>
<tr>
<th>ETC 1-5 (randomly selected)</th>
<th>Period (weeks)</th>
</tr>
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<tbody>
<tr>
<td>1-2</td>
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<td>9-10</td>
<td>9-10</td>
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<tr>
<td>11-12</td>
<td>11-12</td>
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Standardized data collection in all patients (treated and control)

<table>
<thead>
<tr>
<th>Active treatment</th>
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<tbody>
<tr>
<td>Control</td>
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