Comparative modelling of dengue vaccine impact

WHO modelling working group
Overview

- Groups and models contributing
- Model fit to trial data
- Predicted health impacts of vaccination
- Health-economic outputs
- Conclusions
Groups and models
## Groups & models

<table>
<thead>
<tr>
<th>Group</th>
<th>Model type</th>
<th>Fitted to trial</th>
<th>Vectors</th>
<th>Trans $\propto$ symptoms</th>
<th>Demography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanofi Pasteur</td>
<td>Deterministic non-spatial</td>
<td>Yes (both, pre LTFU)</td>
<td>Yes</td>
<td>Yes</td>
<td>Brazil</td>
</tr>
<tr>
<td>Johns Hopkins + Univ Florida</td>
<td>Deterministic non-spatial</td>
<td>Yes (both)</td>
<td>Yes</td>
<td>Yes</td>
<td>Brazil</td>
</tr>
<tr>
<td>Imperial College London</td>
<td>Deterministic non-spatial</td>
<td>Yes (both)</td>
<td>Yes</td>
<td>Yes</td>
<td>Brazil</td>
</tr>
<tr>
<td>Duke Univ</td>
<td>Deterministic non-spatial</td>
<td>Calibrated</td>
<td>No</td>
<td>No</td>
<td>Brazil</td>
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<tr>
<td>Univ Florida</td>
<td>Stochastic spatial</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mexico</td>
</tr>
<tr>
<td>Univ Western Australia</td>
<td>Stochastic spatial</td>
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<td>Yes</td>
<td>No</td>
<td>Thailand</td>
</tr>
<tr>
<td>Notre Dame Univ</td>
<td>Stochastic spatial</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Peru</td>
</tr>
<tr>
<td>Exeter+Oxford Univs</td>
<td>Stochastic spatial</td>
<td>Yes (CYD14)</td>
<td>Yes</td>
<td>No</td>
<td>Generic (65 y mean lifespan)</td>
</tr>
</tbody>
</table>
Common features

- 4 serotypes – homologous and heterologous immunity
- Vectors (all but 1 model)
- Stratified by host age
- Include immunity, disease, seasonality
- Standardised outputs for this exercise
• Loose (but significant) correlation between active phase efficacy and proportion seropositive by country across CYD14 and CYD15

• Malaysia an outlier in active phase – but not in hospital phase
Comparing hospitalisation in active and hospital phases

Incl Y4 data

<table>
<thead>
<tr>
<th></th>
<th>Active phase Relative Risk</th>
<th>Y3 Hospital phase Relative Risk</th>
<th>Y4 Hospital phase Relative Risk</th>
<th>Fold increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYD15 (9-16) [Latin America]</td>
<td>0.21 (18 &amp; 43 cases)</td>
<td>0.53 (16 &amp; 15 cases)</td>
<td>0.43 (6 &amp; 7 cases)</td>
<td>2.5</td>
</tr>
<tr>
<td>CYD14 (9-14) [SE Asia]</td>
<td>0.17 (10 &amp; 30 cases)</td>
<td>0.57 (8 &amp; 7 cases)</td>
<td>0.73 (19 &amp; 13 cases)</td>
<td>3.4</td>
</tr>
<tr>
<td>CYD14 (2-8) [SE Asia]</td>
<td>0.44 (30 &amp; 34 cases)</td>
<td>1.58 (19 &amp; 6 cases)</td>
<td>1.19 (38 &amp; 16 cases)</td>
<td>3.6</td>
</tr>
</tbody>
</table>

- Relative risk of hospitalisation increased ~3 fold in both <9s and >9s in both CYD 14 and 15, comparing Y1+Y2 with Y3
- Y4 data broadly consistent with Y3 – slight indication of reduced relative risk in 2-5s, increased in 9-11s (esp in CYD14)
- Cumulative relative risk of hospitalisation for Y1-4 now >1 for 2-5s, <1 for all other age groups
Vaccination primes the immune system similarly to infection:

1. Temporary high degree of cross-immunity in at least seronegative recipients
2. Seronegative recipients have secondary-like infection once cross-immunity wanes
3. Seropositive recipients have tertiary-like infection once cross-immunity wanes
Sanofi, Imperial, Hopkins, Duke & Exeter models fitted to or calibrated against phase 3 trial data for Y1-3 (other models used similar parameters)

- Y4 data not available when models fitted
- Models fitted to data do better than others, but all adequately reproduce trends
No model fully reproduces 2-5 relative risk, but 6 out of 8 show RR>1
Sanofi, UF models give 2-5y RR <1

Model calibration predates Y4 data – RR>1 in CYD14 6-11 age group not currently predicted by any model
Health impact of vaccine
Vaccination policies modelled

• **Reference** scenario: routine vaccination of 9 year olds
  - Assume 80% coverage by default, but also consider 50%
  - Examine alternative ages of vaccination between 10 and 18
  - Also examine additional effect of one-off catch-up campaign - 80% of 10-17 year olds when vaccine is first introduced

• Assume all vaccine recipients receive 3 courses
Dependence of efficacy on serostatus means that vaccination impact varies with the proportion of recipients who are seropositive.

So we examine impact in settings with 10%, 30%, 50%, 70% or 90% of 9 year olds being seropositive on average.

Proxy for dengue transmission intensity ($R_0$)
Health impact outputs

- **Symptomatic cases** – models matched to active phase trial data, so output represents all cases, not just those seeking healthcare

- **Hospitalised dengue** – impact predictions use rates similar to SE Asia/CYD14 rather than lower rates seen in CYD15/Latin America

- **Deaths** – models assume between 0.04% and 0.08% CFR (~0.5% of hospitalised cases)

- Output population impact over 30 years
Reference scenario results: Proportion averted

Routine vaccination of 9 year olds, 80% coverage – results over 30 years
Reference scenario results: proportion averted – 10 year horizon

- Vaccination introduction perturbs transmission dynamics for ~10 years, after which impacts are fairly constant (limited indirect effects overall)
- In low transmission settings, vaccination can have a short-term benefit, but impacts become negative after 10 years
Impact by serostatus at vaccination (over 30 years)

Models which reproduce 2-5y RR>1 in CYD hospital phase tend to predict negative impact on seronegative recipients in 10-50% settings.
Key sensitivities
Effect of coverage level

Compare 50% and 80% coverage – impacts scale almost linearly
Varying age of routine vaccination

Impacts positive for all models by 14 years in 30% setting
Impact of catch-up campaign

- One-off 80% coverage of 10-17 year olds
- Impact over 10 years shown - largest in 50% & 70% settings
- Catch-up prevents a similar number of DENV hospitalisations per dose of vaccine delivered as routine vaccination
Health-economic outputs
Threshold cost per vaccinated person

- Use because ICER not suited to context where health benefits can be negative
- Defined as the maximum that could be paid (for procurement and delivery) to fully vaccinate someone before vaccination stops being cost-effective

Threshold cost per course of vaccine =

Incremental cost savings as a result of vaccination

+ 

Incremental DALYs averted as a result of vaccination 

×

Threshold cost per DALY
Example threshold costs per DALY

- Rotavirus: Rheingans et al. JID 2009; 200:S16-27
Routine vaccination of 9 year olds

- Assume ‘Brazil’-like costs, 3% discounting of costs and benefits, 30 year horizon, healthcare provider perspective
- Threshold cost per vaccinated person below US$50 in most models for threshold cost per DALY<US$4000
- Threshold cost per vaccinated person roughly doubles for societal perspective
Conclusions
Conclusions

• Predicted impact of vaccination programs:
  - Routine immunisation of 9+ year olds at 80% coverage predicted to reduce dengue disease by 10-30% long-term in moderate-to-high transmission settings
  - Impact scales linearly with coverage
  - Adding 80% coverage catch-up in 10-17 year olds might achieve overall ~30-40% reduction in dengue hospitalisations over 10 years

• Key heterogeneity: variation of efficacy with serostatus:
  - Target age for vaccination should be tuned to setting - 9 years only optimal for highest transmission setting
  - 11-14 year olds a good compromise in moderate to high transmission settings
  - Vaccine unlikely to be beneficial in low transmission settings
  - Vaccination *may* increase the risk of hospitalised dengue in substantial subset of recipients (*i.e.* seronegatives) in low-to-moderate transmission settings

• In most settings and for most models, the total cost of fully vaccinating one person cannot exceed $50 for the vaccine to remain cost-effective

• Moderate and heterogeneous efficacy requires careful communication (to policy-makers, populations, )

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Caveats

• Y4 data not included – predicted impacts may be less when models fitted to Y1-4 due to increasing relative risk in older age groups

• Efficacy may vary by serotype:
  - Seen in trial endpoints, but this may reflect differing propensity between serotypes to cause disease in primary vs secondary infection
  - Impossible to model accurately without access to more finely stratified phase 3 trial data
  - Such variation unlikely to pose risks of negative outcomes

• Efficacy may vary by age:
  - Seen in trial endpoints, but can largely be explained by assuming only serostatus-dependent efficacy
  - But can’t rule out an additional causal effect of age

• These and other uncertainties may affect long term impact:
  - Need long-term follow-up
  - Early vaccination programmes/phase 4 trials need careful monitoring