The burden of dengue: insights from large scale clinical studies

Dr. Oliver Brady

Centre for Mathematical Modelling of Infectious Diseases
London School of Hygiene and Tropical Medicine

X International Symposium for Latin American Experts
Brasilia, Brazil
21 September 2016
Overview

1. Why is measuring burden important?

2. Existing approaches to measure burden

3. Contribution of large-scale clinical trials and routine surveillance

4. Global estimates of the full spectrum of dengue burden

5. Dengue burden in the era of chikungunya and Zika
The burden of dengue

- Death
- Severe dengue
- Dengue Fever
- Symptomatic
- Asymptomatic
The burden of dengue

- Asymptomatic
  - Non-medically attended
  - Actively detected

- Symptomatic
  - Non-medically attended
  - Actively detected

- Dengue Fever
  - Medically attended
  - Passively detected

- Severe dengue
  - Medically attended
  - Passively detected

- Death
Why is measuring burden important?

Mapping the full spectrum of burden allows:

1. Target prevention and control activities
   – Maximize effectiveness

2. Evaluate the impact of interventions
   – If effect was smaller than expected why?

3. Track progress towards national and international goals
   – WHO 25% morbidity and 50% mortality reduction 2010-2020
The challenge

- Fever surveillance cohorts e.g. CYD15
- Age-stratified seroprevalence studies
- Clinical surveillance
- Serological dengue cohort study

Diagram:

- Asymptomatic
- Symptomatic
- Dengue Fever
- Severe dengue
- Death
Consensus estimates of dengue burden
WHO: burden estimation toolkit

Aims to:

*Improve the way countries estimate dengue burden using new and existing data*

By:

1. Standardizing passive surveillance data
2. Establishing new sentinel sites to measure the full spectrum of burden
3. Using models to extrapolate these data to estimate national burden
WHO: burden estimation toolkit

Sentinel sites for burden estimation:

– Sentinel clinical sites
  • Every case of fever receives dengue test
  • Separate reporting systems

– Fever cohorts
  • School or work-based absenteeism with follow up testing

– IgG Seroprevalence surveys
  • Age-stratified to estimate average total annual incidence

• “gold standard” sites
• Integration with existing research activities key
Synergies between vaccine targeting and burden estimation

Dengue vaccines need to be targeted

**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-Terán-Romero, Daniel J. Laydon, Derek A. T. Cummings

Seroprevalence surveys can be used for both:

- Optimal vaccine targeting
- Dengue burden estimation
Consensus estimates of dengue burden
Estimating (parts) of the global burden of dengue: Infections

Evidence consensus

Occurrence points

Environmental covariates

BRT model

Risk Map

Cohort studies

Burden Map

Bhatt et al. (2013) Nature 496, 504-507
Mapping dengue: Final risk map

- BRT showing probability of dengue presence (0-1), AUC = 0.94
- Max prec. (37%), temp. suitability (20%) and G-econ (9%) most important predictors; followed by accessibility (8%), peri-urban (8%) and urban (5%)

Bhatt et al. (2013) Nature 496, 504-507
From maps of dengue risk to maps of dengue burden

• Pair risk with paired-sera cohort studies to infer inapparent (n=54) and apparent (n=39) incidence

Bhatt et al. (2013) Nature 496, 504-507
From maps of dengue risk to maps of dengue burden

Table 1 Estimated burden of dengue in 2010, by continent

<table>
<thead>
<tr>
<th></th>
<th>Apparent</th>
<th>Inapparent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Millions (credible interval)</td>
<td>Millions (credible interval)</td>
</tr>
<tr>
<td>Africa</td>
<td>15.7 (10.5 - 22.4)</td>
<td>48.4 (34.3 - 65.2)</td>
</tr>
<tr>
<td>Asia</td>
<td>66.8 (47.0 – 94.4)</td>
<td>204.4 (151.8 – 273.0)</td>
</tr>
<tr>
<td>Americas</td>
<td>13.3 (9.5 - 18.5)</td>
<td>40.5 (30.5 – 53.3)</td>
</tr>
<tr>
<td>Oceania</td>
<td>0.18 (0.11 - 0.28)</td>
<td>0.55 (0.35 - 0.82)</td>
</tr>
<tr>
<td>Global</td>
<td>96 (67.1 - 135.6)</td>
<td>293.9 (217.0 – 392.3)</td>
</tr>
</tbody>
</table>
Dengue burden in the post CYD14 and CYD15 world

- Nearly double the data on apparent infection incidence
Estimating (parts) of the global burden of dengue

- All symptomatic estimates combined
- Difficult to validate
Estimating (parts) of the global burden of dengue: deaths

- All cause mortality data from:
  - vital registration
  - verbal autopsy
  - surveillance data

- Proportion of deaths due to dengue related to known risk factors
  - CODEm

- Dengue deaths balanced against other similar causes of death e.g. Malaria
  - CodCorrect

Dengue mortality per 10m

- Estimated 11,302 (6,790 – 13,722) deaths due to dengue in the year 2010
- Steadily increased since 1990 (8,277)

Estimating (parts) of the global burden of dengue

- Difficult to reliably measure deaths in many areas
- Still missing estimates of clinical burden (99% of dengue surveillance data)
Estimating clinical dengue burden: data

- Data available at a national level 2008-2012
  - NFD = non-fatal dengue
  - DD = dengue deaths
  - DHF = dengue hemorrhagic fever
  - EF = expansion factor

CYD14 and CYD15 control arm results make this a tractable problem

- Brady et al. (2016), in prep
- Sarti et al. (2016), IJID
Estimating clinical dengue burden: modelling

Evidence synthesis of data from:
1. Routine passive surveillance
2. Expansion factor studies
3. Treatment seeking surveys
4. Case definition comparison studies

Integrates these with the two leading dengue burden estimates

Brady et al. (2016), in prep
The full spectrum of burden: New insights

• First estimates of the full spectrum of DENV burden

• Standardized comparison of CFRs

• Impact of changing case definitions and their utility
  – Particularly for diagnosing mild dengue
Dengue burden in the era of chikungunya and Zika

Challenges
• Cross reacting diagnostics
• Misdiagnosis
• Cross immunity?

Opportunities
• Diagnostic development
• Integrated control
• Boosted economic argument

100% burden 90% burden 50% burden
Conclusion

• Measuring the full spectrum of dengue burden can be useful for:
  – Targeting new control campaigns
  – Evaluating the effectiveness of different control strategies

• Big advances in burden estimation
  – Increasingly open case data
  – Data from vaccine trials
  – New opportunities linking vaccine targeting and burden estimation

• Modelled burden estimates give insight:
  – But still many uncertainties
  – Will be iteratively updated as time goes on

• Chikungunya and Zika present new challenges to burden estimation