

# The burden of dengue: insights from large scale clinical studies

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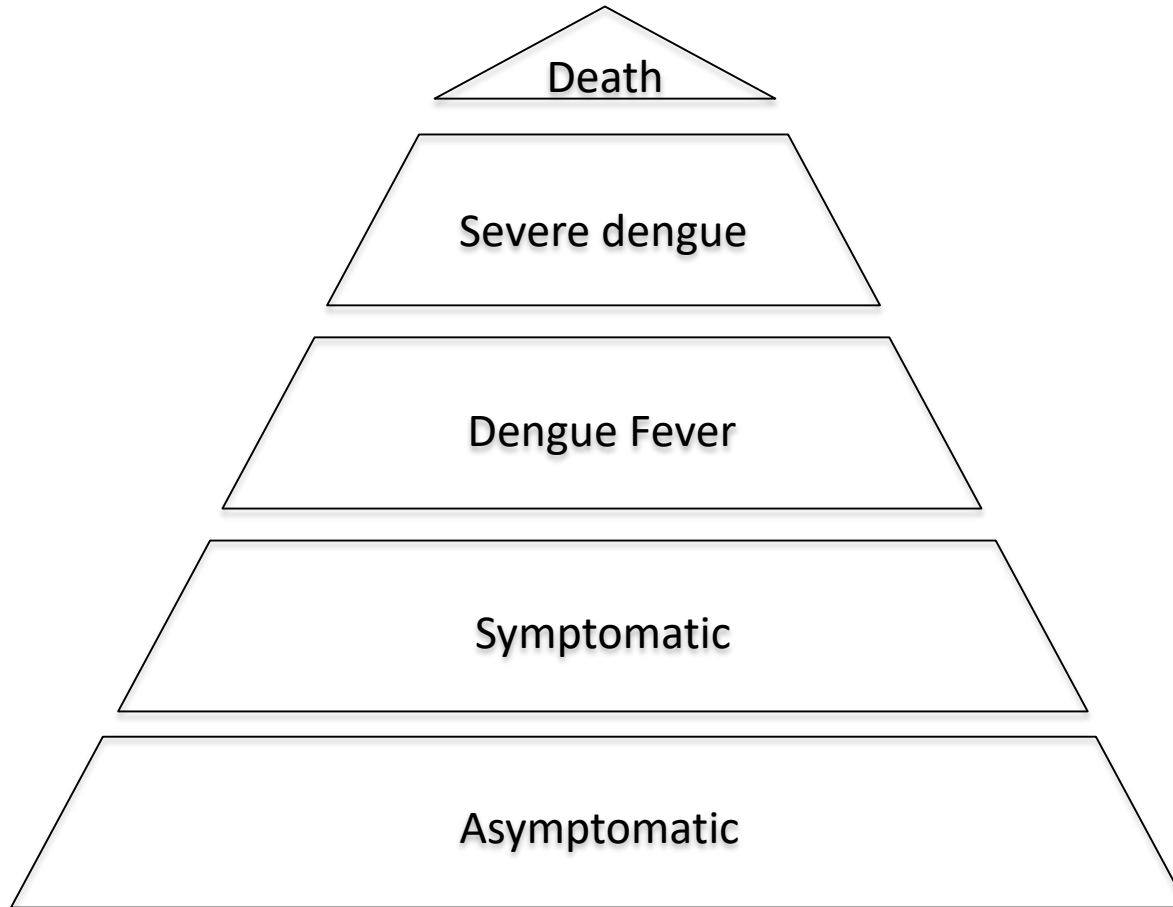


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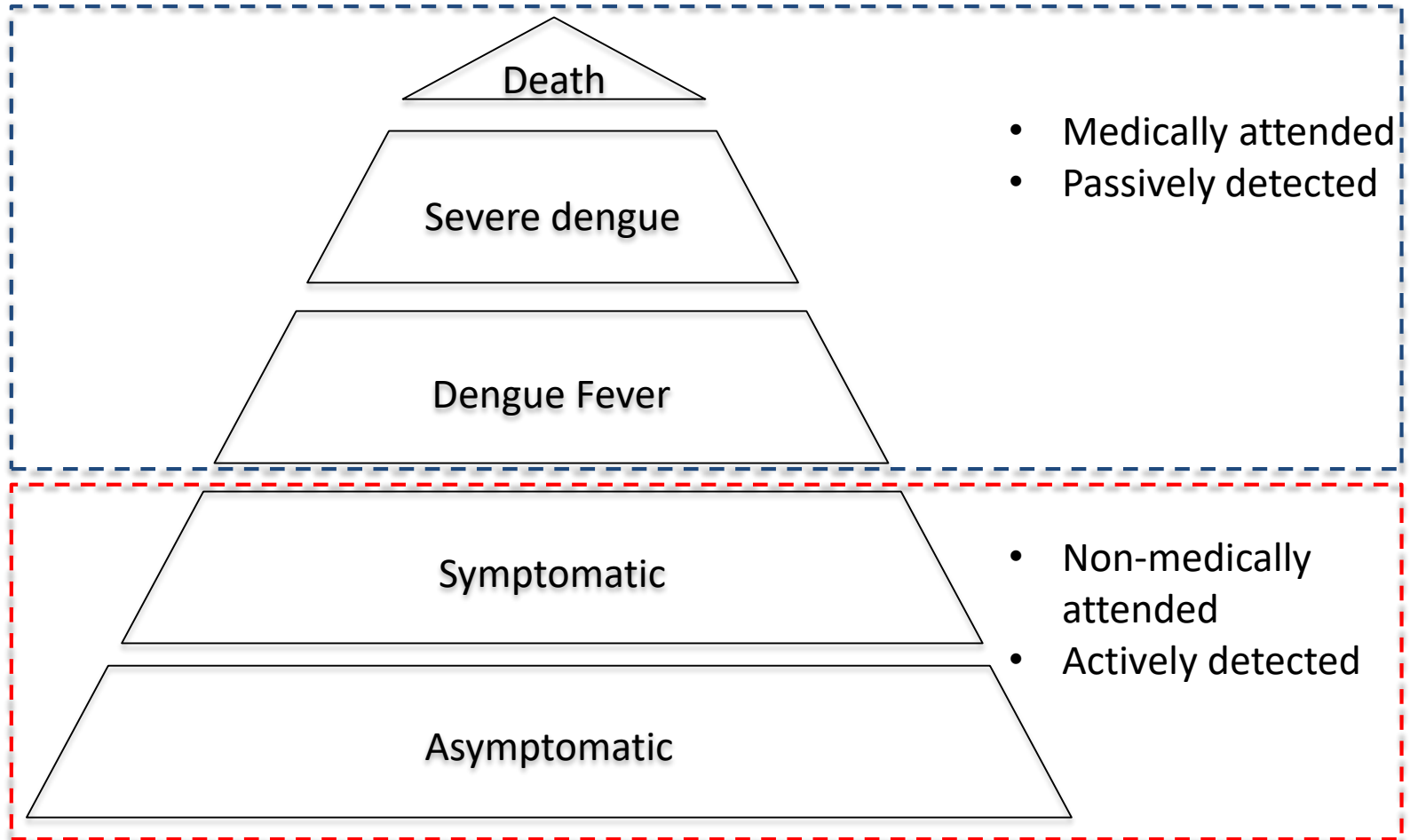
# Overview

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



# The burden of dengue

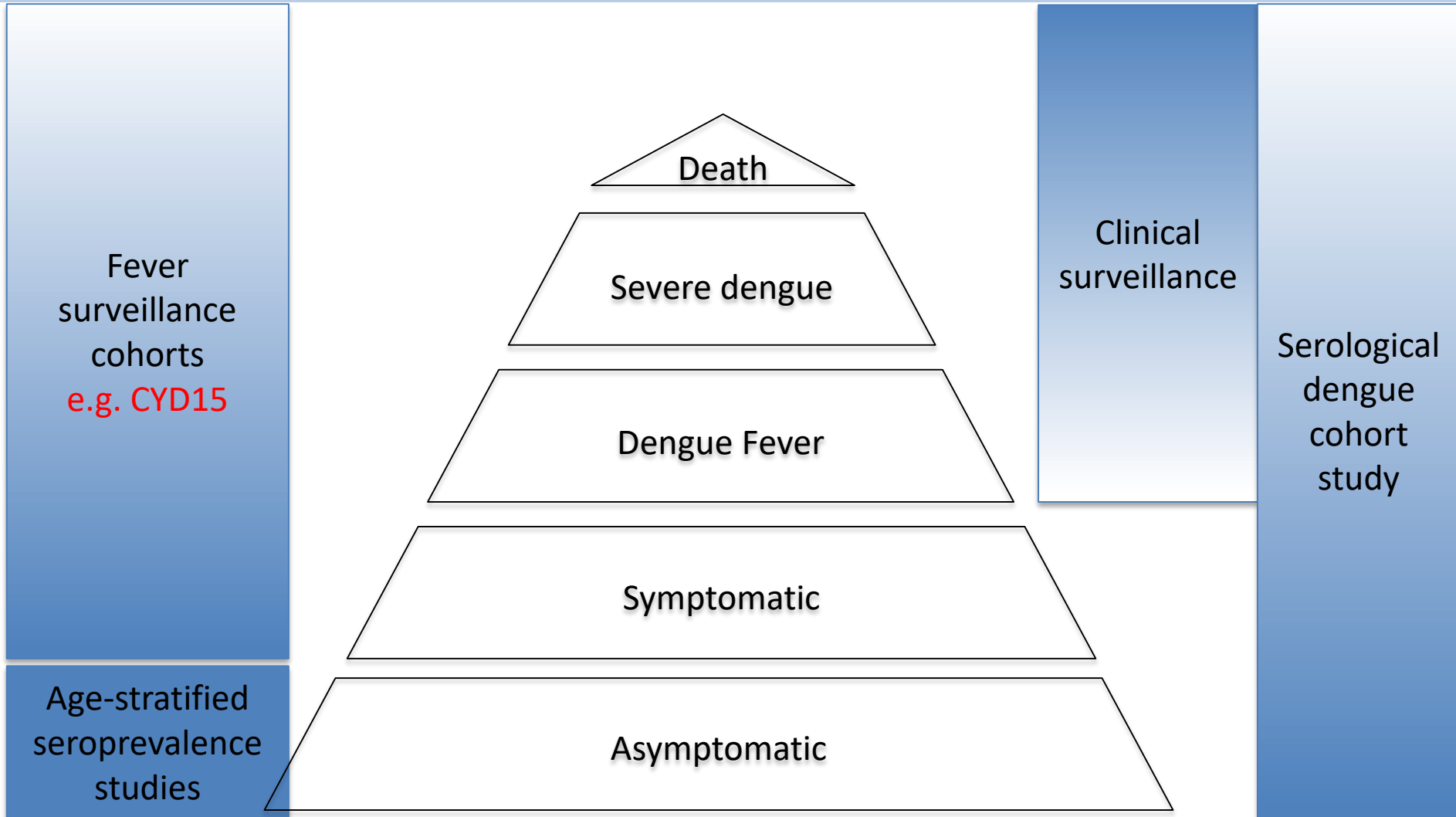


# Why is measuring burden important?

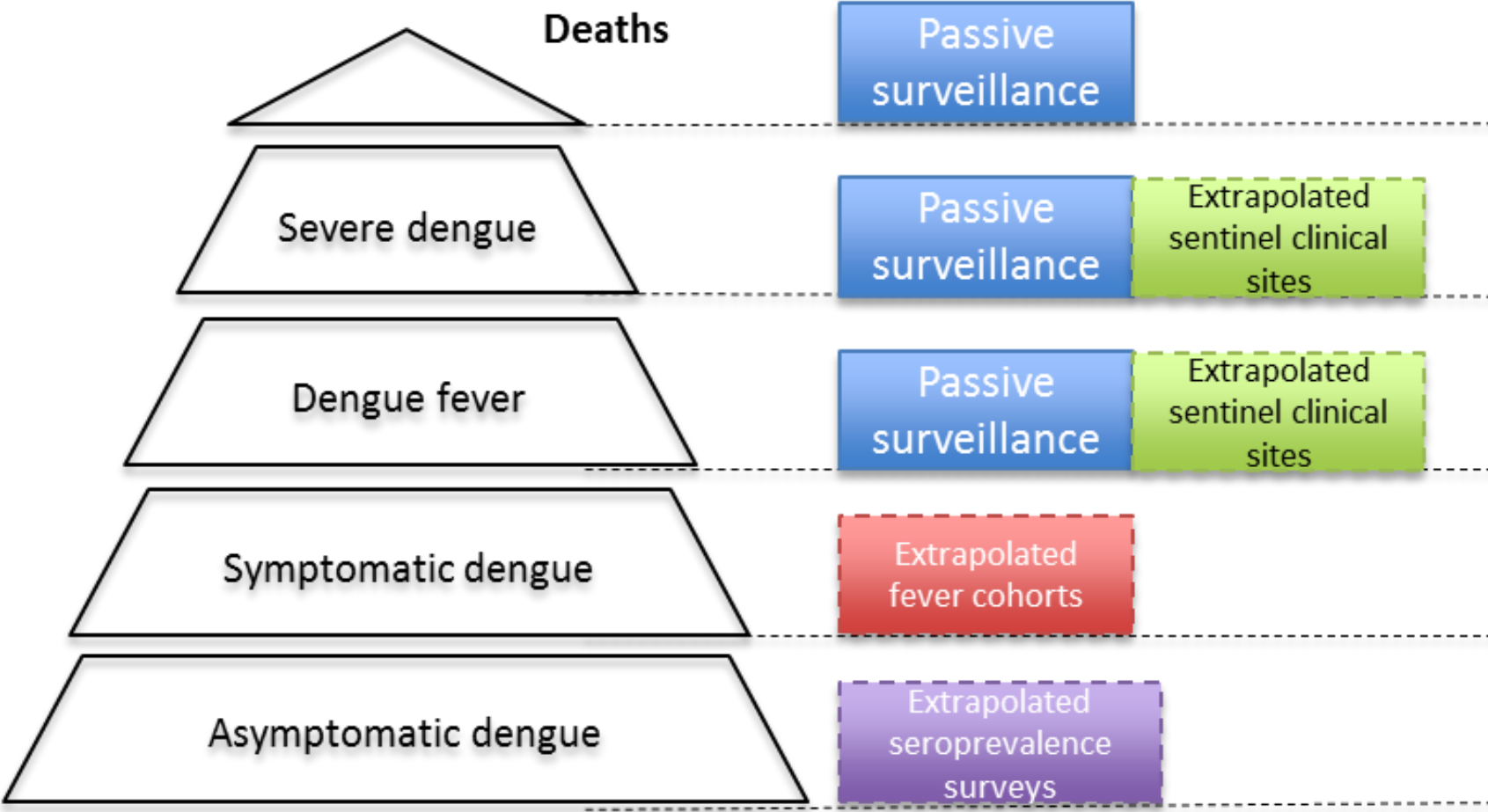
## Mapping the full spectrum of burden allows:

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



# Consensus estimates of dengue burden



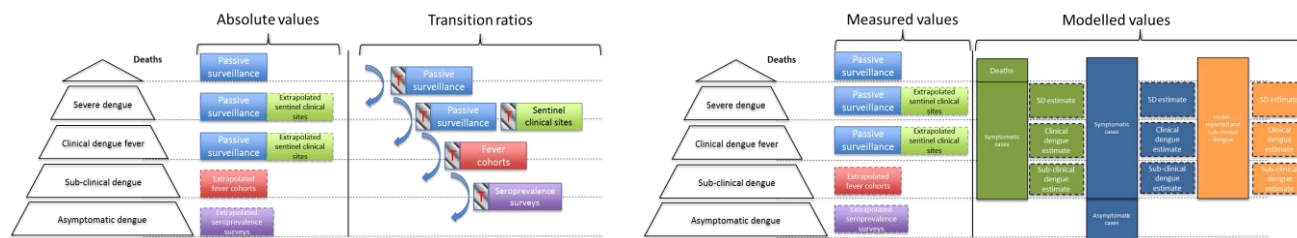
# WHO: burden estimation toolkit

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

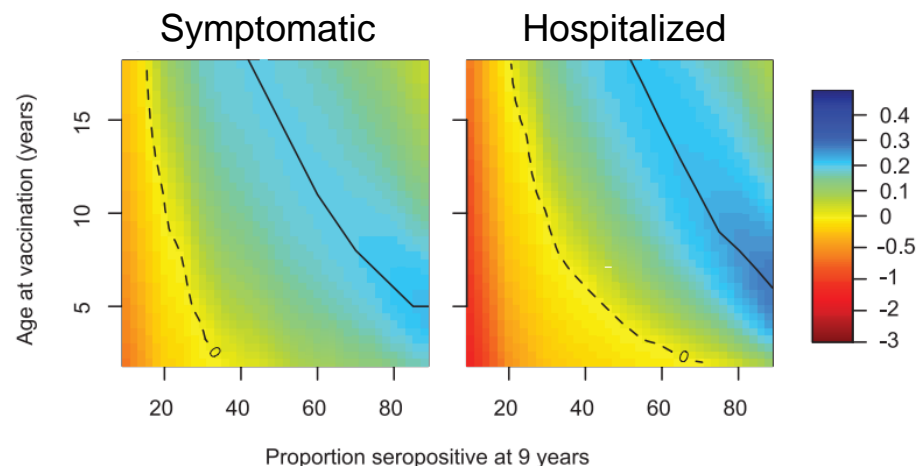
# Synergies between vaccine targeting and burden estimation

## Dengue vaccines need to be targeted

### DENGUE VACCINE

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

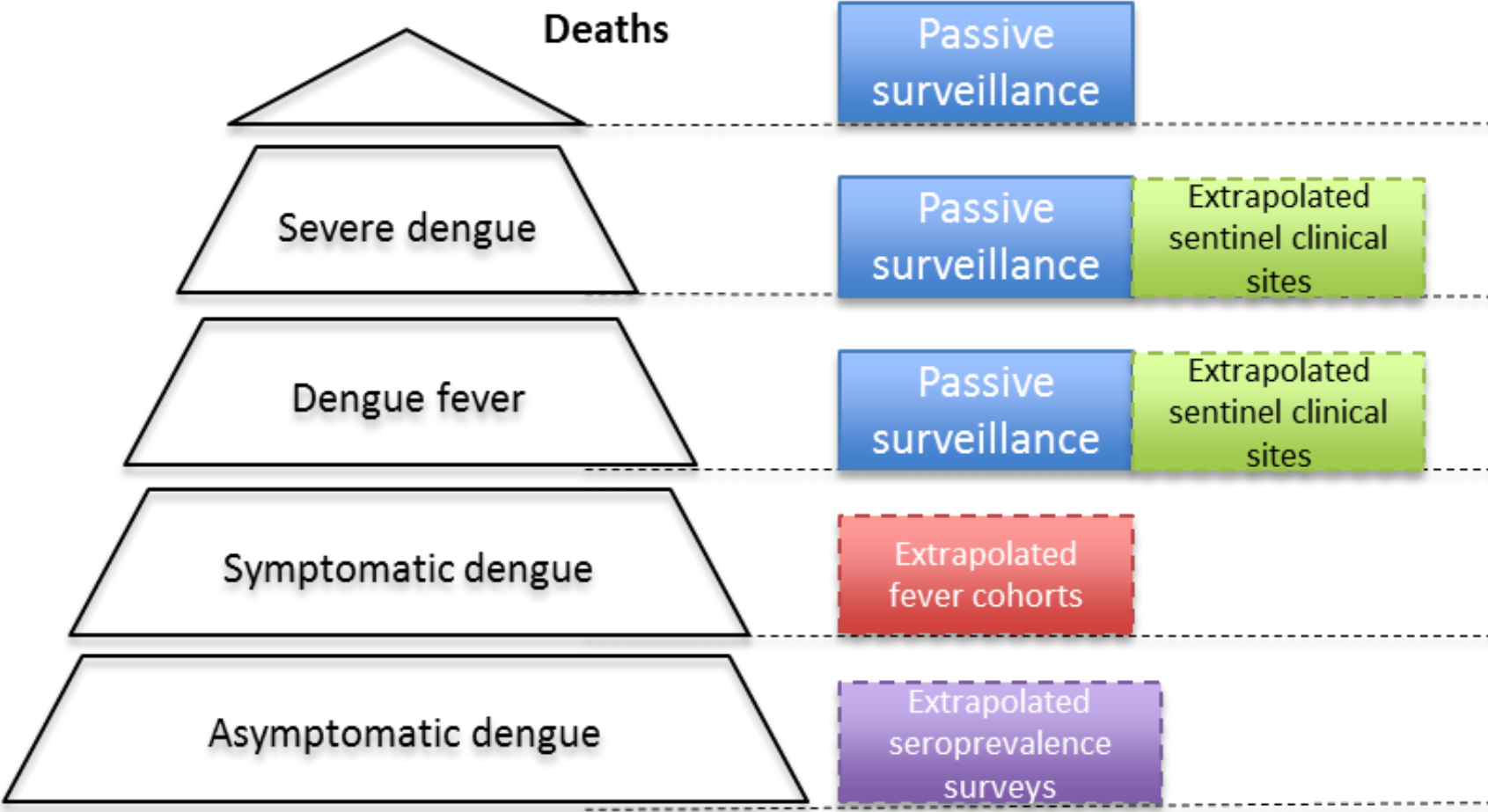
Neil M. Ferguson,<sup>1\*</sup> Isabel Rodríguez-Barraquer,<sup>2\*</sup> Ilaria Dorigatti,<sup>1</sup>  
Luis Mier-y-Teran-Romero,<sup>2</sup> Daniel J. Laydon, Derek A. T. Cummings<sup>2,3</sup>



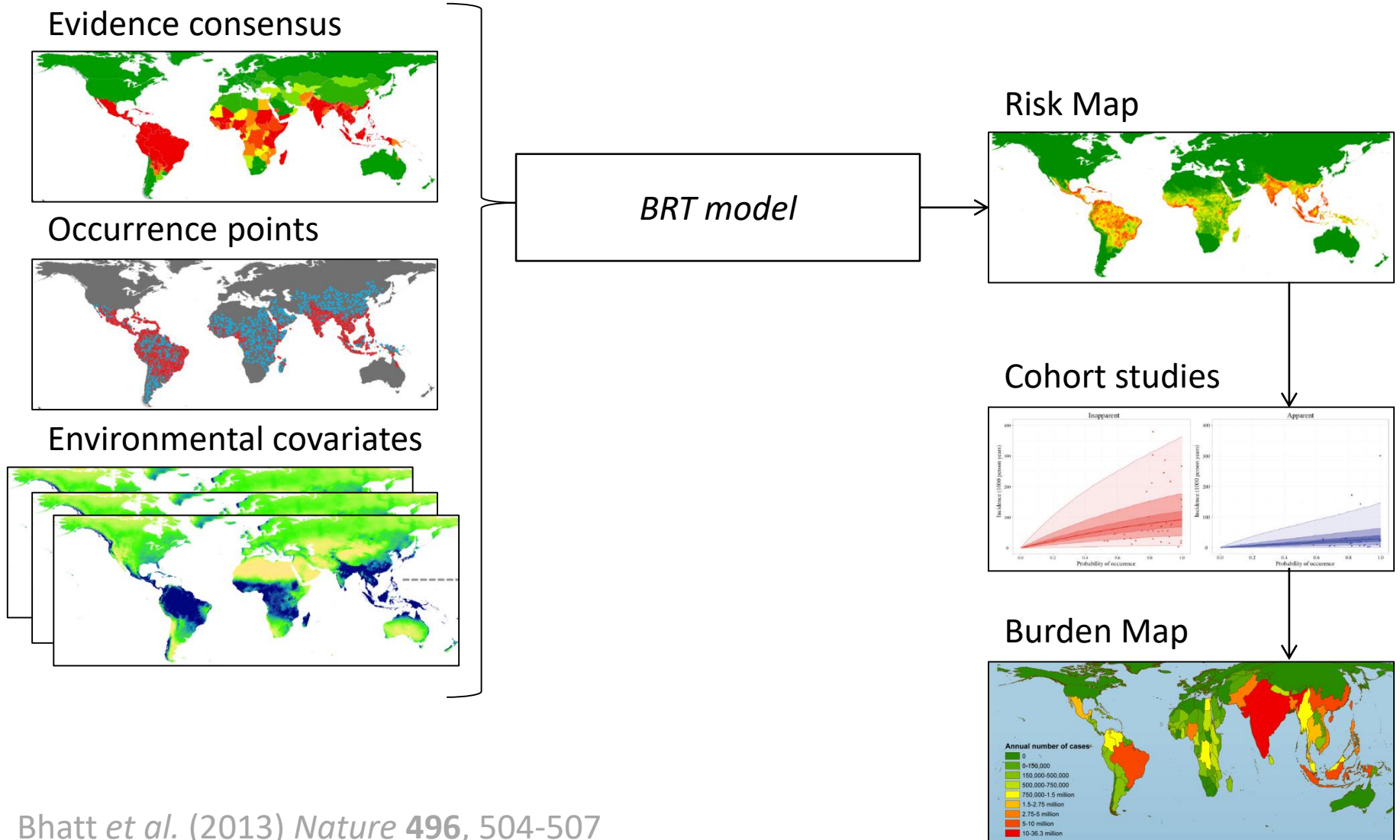
Seroprevalence surveys can be used for both:

- Optimal vaccine targeting
- Dengue burden estimation

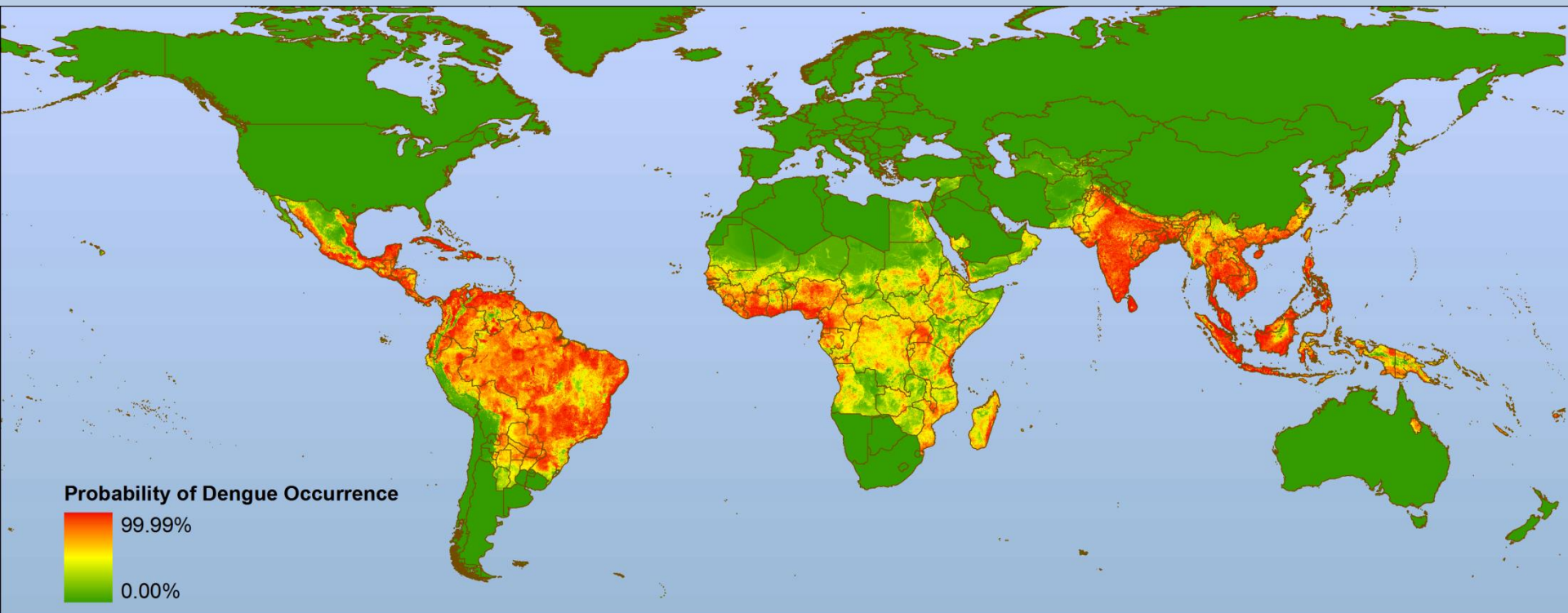
# Consensus estimates of dengue burden



# Estimating (parts) of the global burden of dengue: Infections

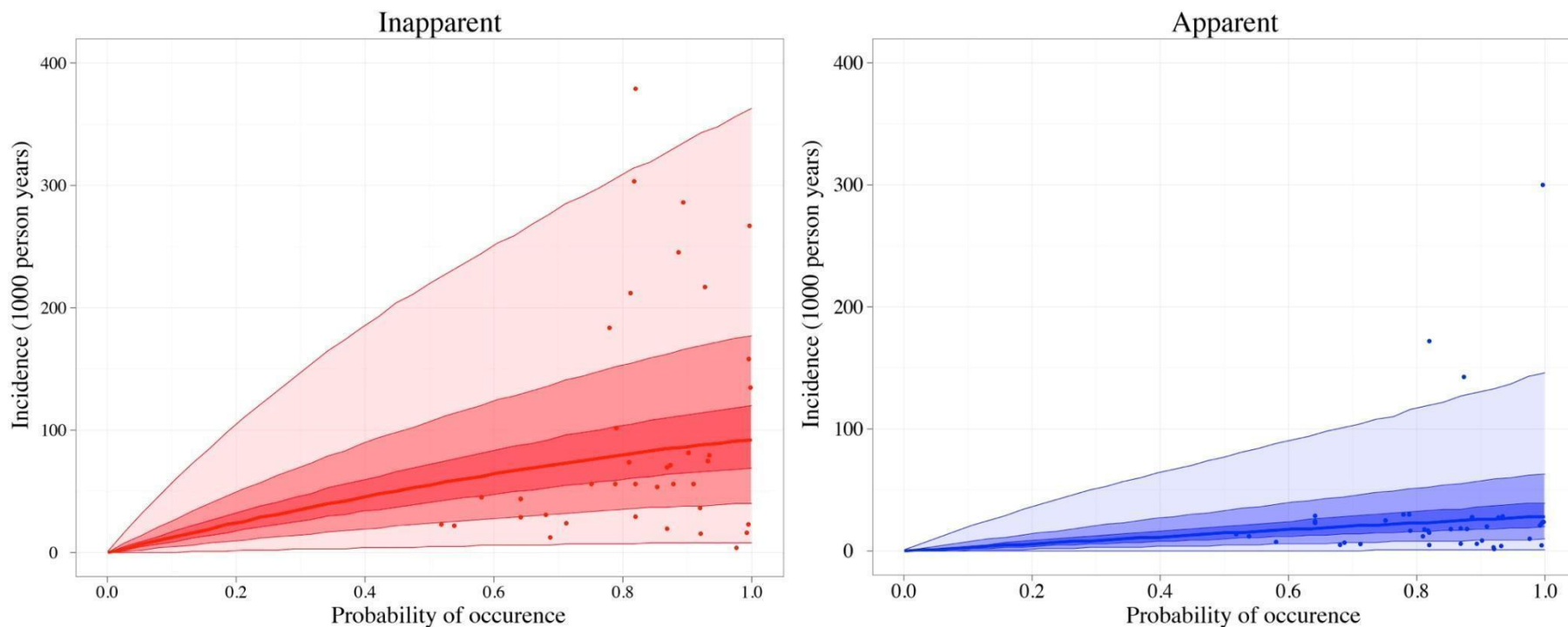


# Mapping dengue: Final risk map



- 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%)

# 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

# From maps of dengue risk to maps of dengue burden

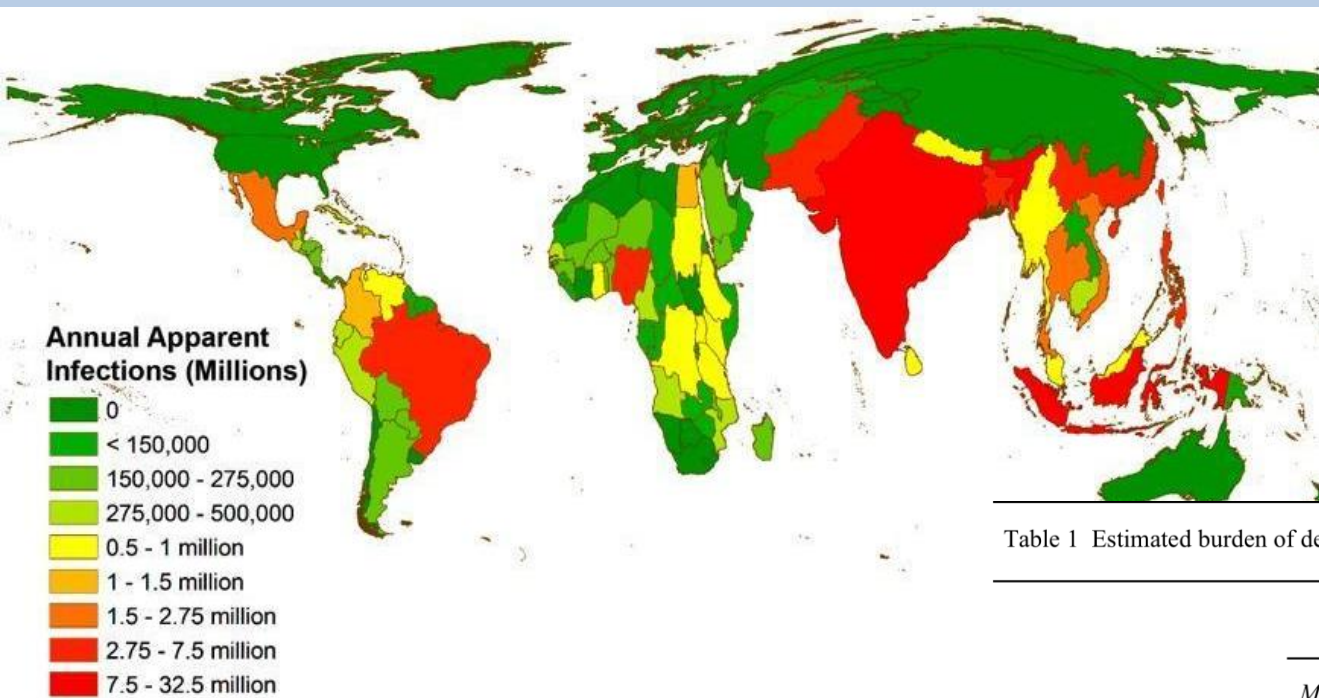
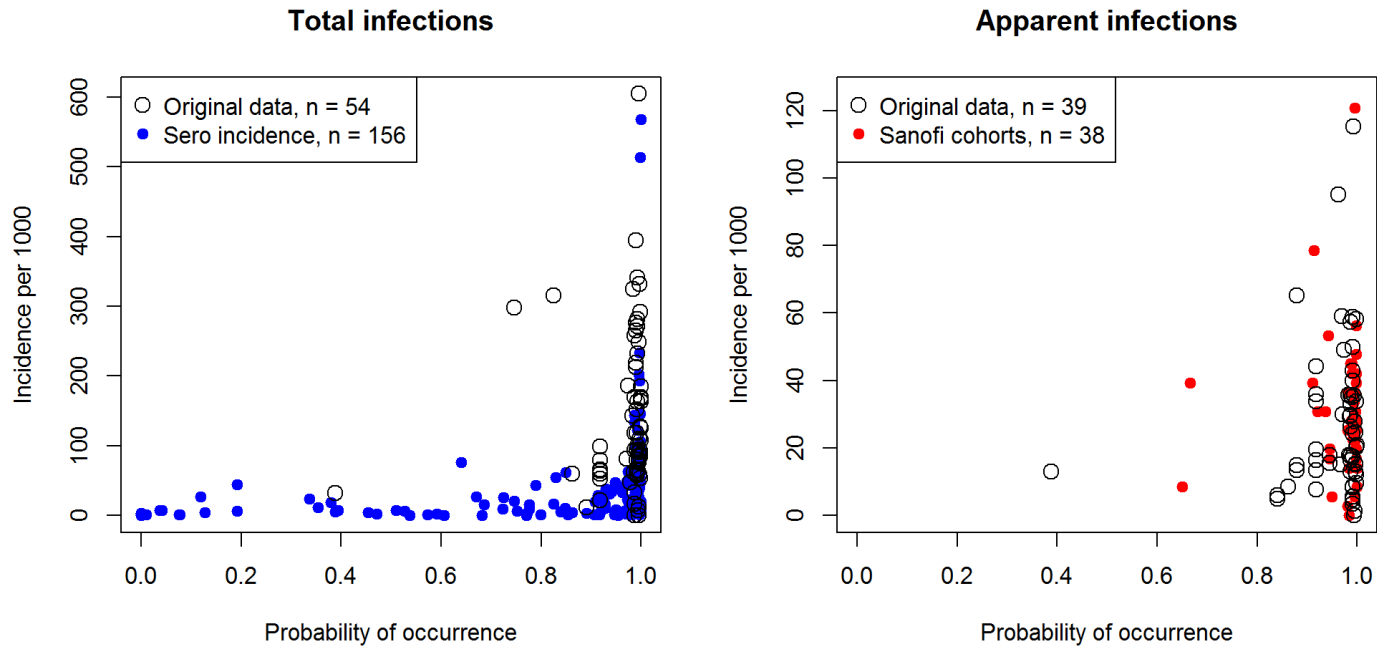


Table 1 Estimated burden of dengue in 2010, by continent

	<i>Apparent</i>	<i>Inapparent</i>
	<i>Millions (credible interval)</i>	<i>Millions (credible interval)</i>
<i>Africa</i>	15.7 (10.5 - 22.4)	48.4 (34.3 - 65.2)
<i>Asia</i>	66.8 (47.0 - 94.4)	204.4 (151.8 - 273.0)
<i>Americas</i>	13.3 (9.5 - 18.5)	40.5 (30.5 - 53.3)
<i>Oceania</i>	0.18 (0.11 - 0.28)	0.55 (0.35 - 0.82)
<b><i>Global</i></b>	<b>96 (67.1 - 135.6)</b>	<b>293.9 (217.0 - 392.3)</b>

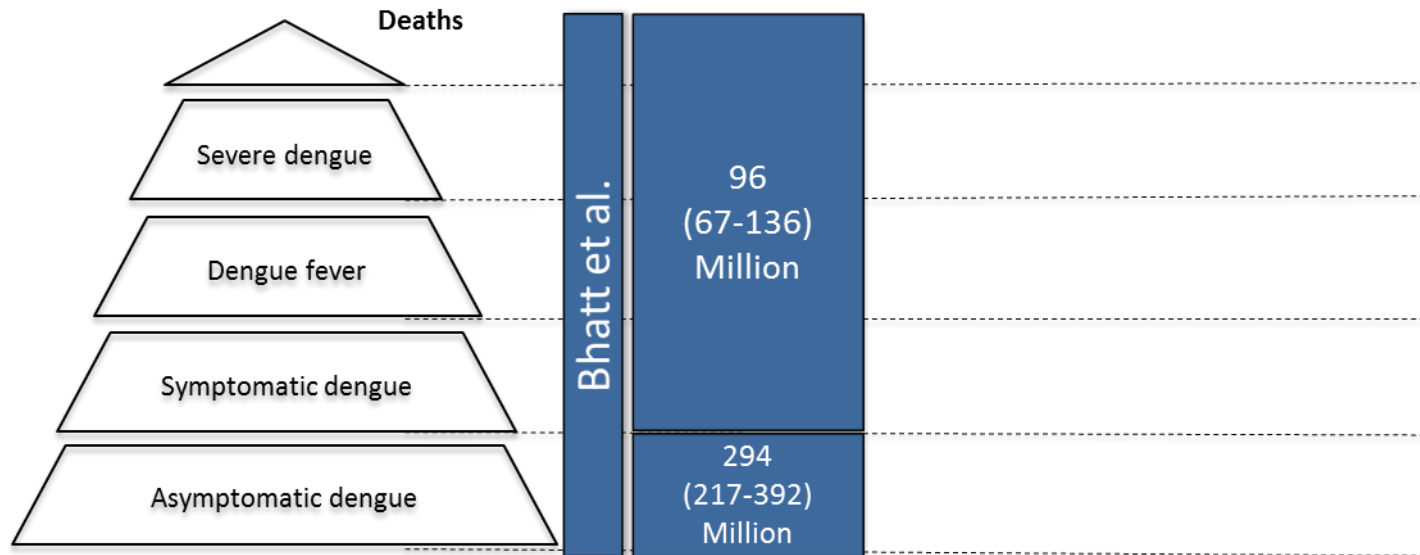
# Dengue burden in the post CYD14 and CYD15 world



- 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



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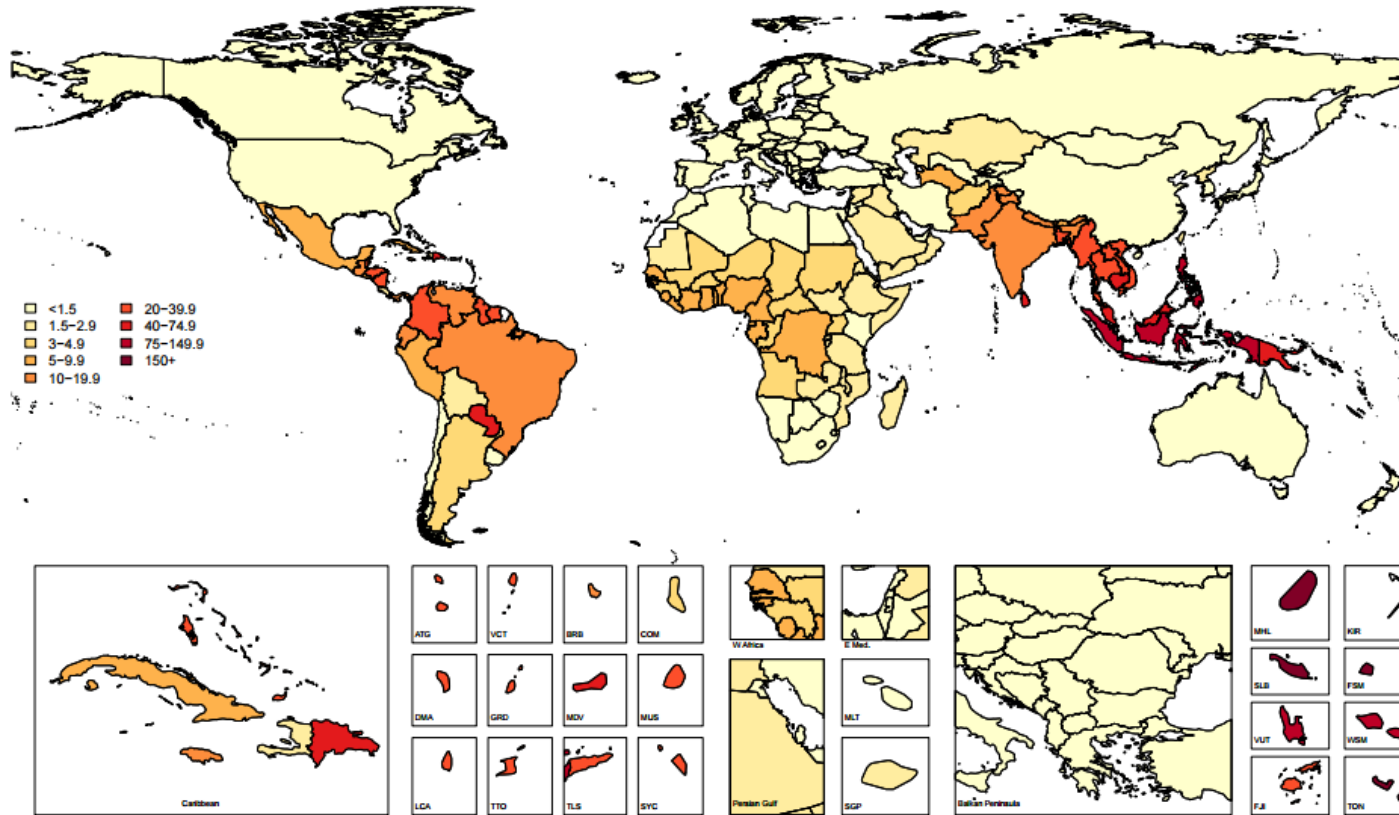
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## Modeling causes of death: an integrated approach using CODEm

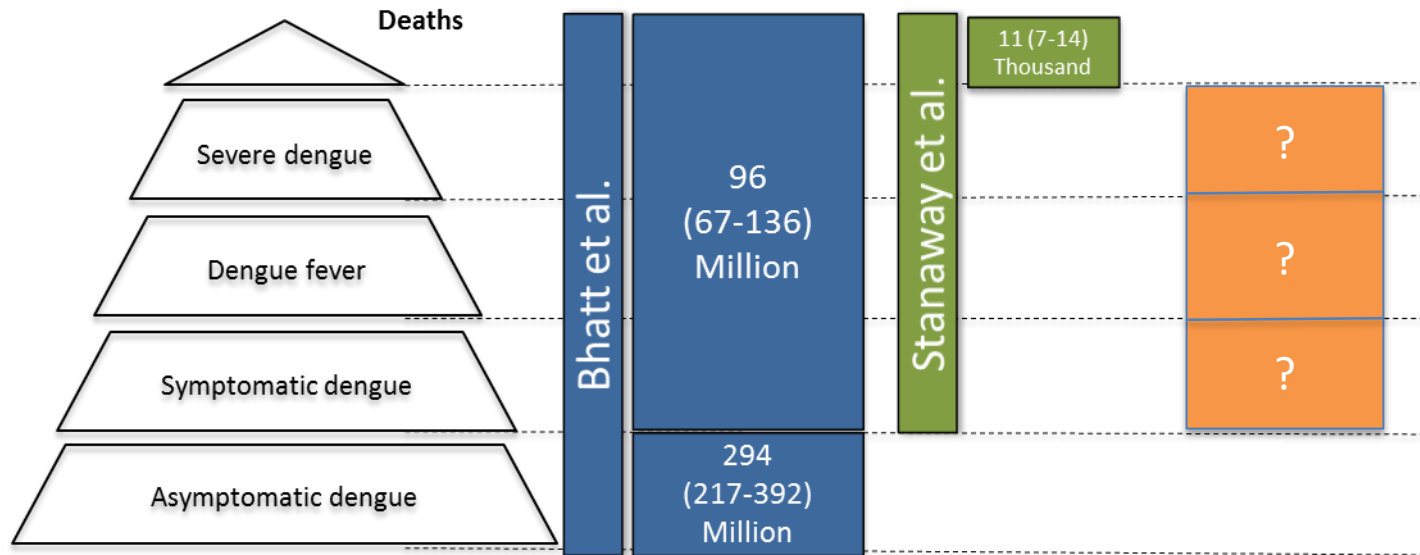
- All cause mortality data from:
  - vital registration
  - verbal autopsy
  - surveillance data
- Proportion of deaths due to dengue related to known risk factors
  - CODEm
- Dengue deaths balanced against other similar causes of death e.g. Malaria
  - CodCorrect

# Dengue mortality per 10m



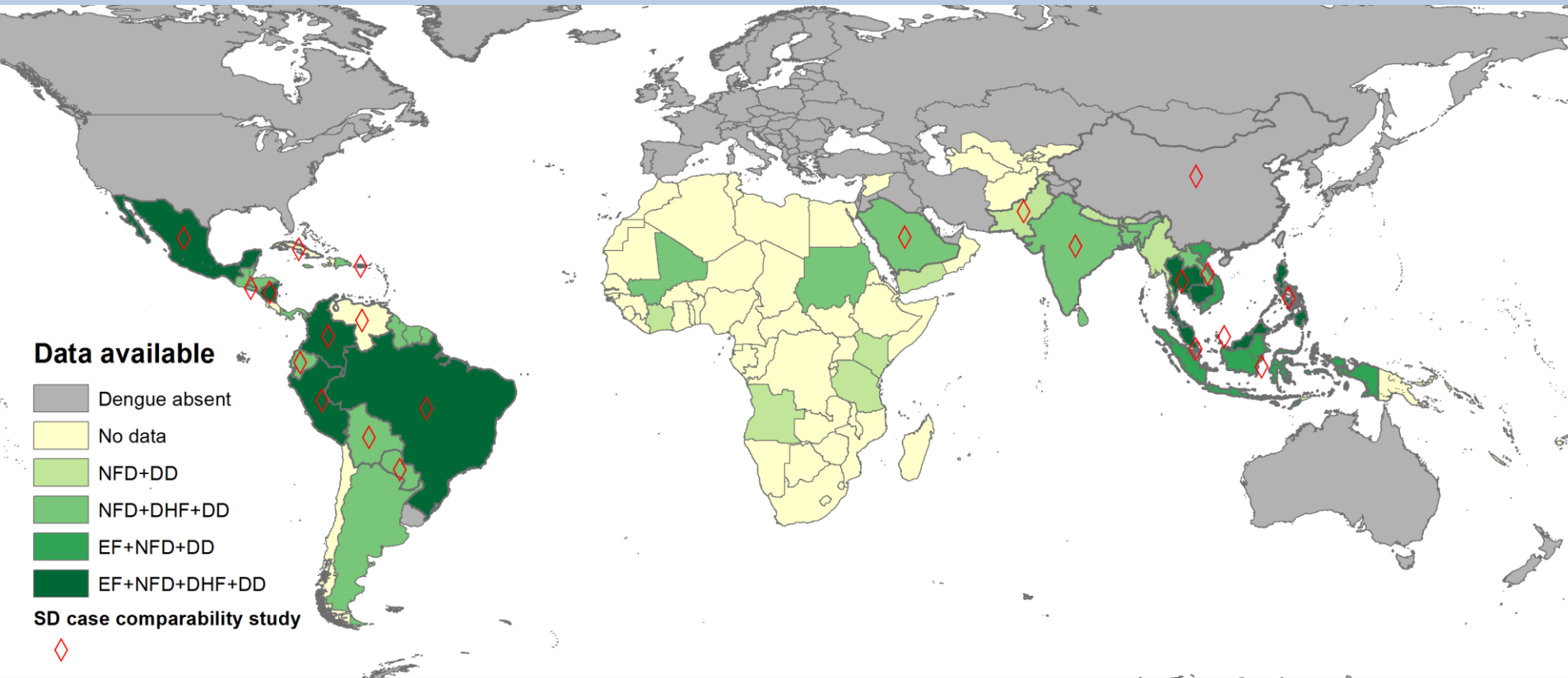
- Estimated 11,302 (6,790 – 13,722) deaths due to dengue in the year 2010
- Steadily increased since 1990 (8,277)

# 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

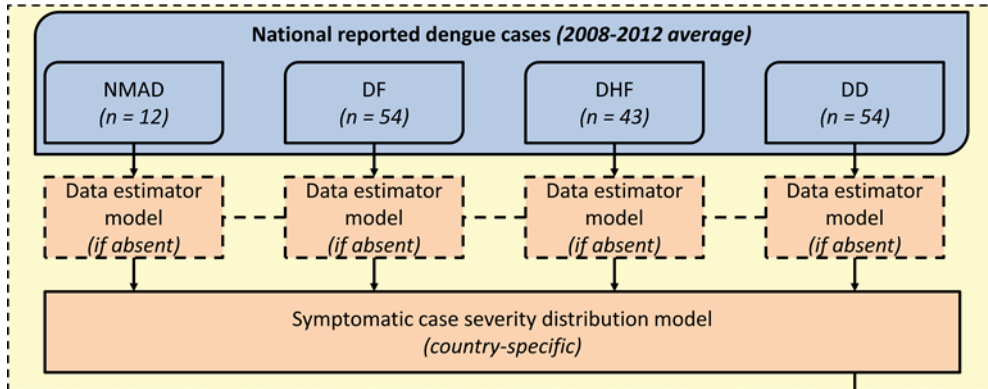
- NFD = non-fatal dengue
- DD = dengue deaths
- DHF = dengue hemorrhagic fever
- EF = expansion factor

**CYD14 and CYD15 control arm results make this a tractable problem**

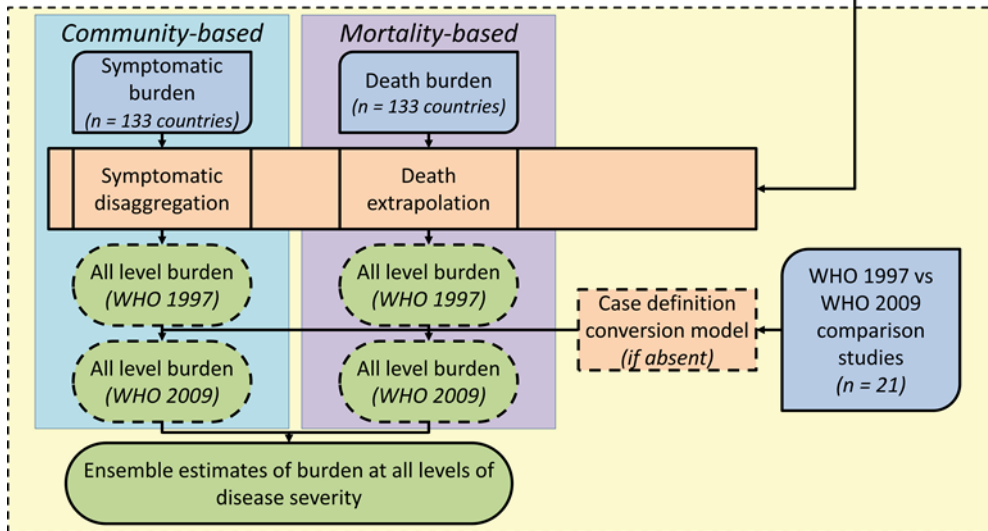
Brady *et al.* (2016), in prep  
Sarti *et al.* (2016), IJID

# Estimating clinical dengue burden: modelling

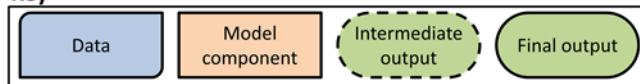
## 1. Quantifying national clinical case definitions



## 2. Converting existing estimates to all disease severity levels



### Key



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

# 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

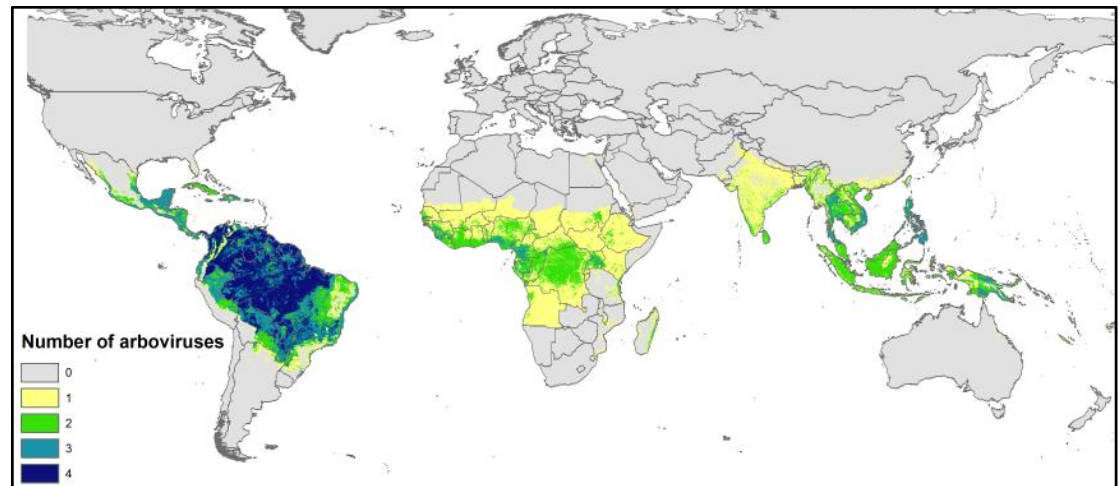
# Dengue burden in the era of chikungunya and Zika

## 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

# Acknowledgements



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**FONDATION MERIEUX**  
*Une fondation familiale dédiée à la lutte contre les maladies  
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