Dengue Vaccination Roll-out

Carl A. B. Pearson - DAIDD 2017
White Oak

Slide Set Citation: DOI:10.6084/m9.figshare.5687152

The ICI3D Figshare Collection

Goals

- apply model-thinking to public health challenges
- think about models in a collaboration
- learn about Dengue, Dengvaxia

Overview

- Audience Poll on Dengue Natural History
- Dengvaxia Trial Results, Proposed Vaccine Mechanism
- Public Health Analysis
- Application: WHO Dengvaxia recommendation
- Hindsight
- **BREAKING NEWS**

Relevant Publications

The long-term safety, public health impact, and cost-effectiveness of routine vaccination with a recombinant, live-attenuated dengue vaccine (Dengvaxia): a model comparison study. S Flasche, M Jit, I Rodriguez-Barraquer, L Coudeville, M Recker, K Koelle, G Milne, TJ Hladish, TA Perkins, DAT Cummings, and others [***CAB Pearson***]. PLoS Medicine. November 2016.

Projected Impact of Dengue Vaccination in Yucatan, Mexico. TJ Hladish, ***CAB Pearson***, DL Chao, DP Rojas, GL Recchia, H Gomez-Dantes, ME Halloran, ***JRC Pulliam***, IM Longini. PLoS Negl Trop Dis. May 2016.

Dengue: What is it?

Challenges to producing a vaccine?

Did Dengvaxia overcome those challenges?

Trial observations:

- initially efficacious against all 4 strains in all patients
- ...but waning efficacy (varying by strain)
- ...and increased risk of severe disease in young recipients, but not older patients
- later: when controlling for past dengue exposure, waning effectiveness / increased risk appears mostly for those with no past exposure

Relevant Publications, part II

Consider stopping dengvaxia administration without immunological screening. M Aguiar, SB Halstead, N Stollenwerk. Expert Review of Vaccines. December 2016 (in print, 2017).

Dengvaxia sensitizes seronegatives to vaccine enhanced disease regardless of age. SB Halstead. Vaccine. October 2017 (in print, November).

Did Dengvaxia overcome those challenges?

No.*

*qualification last year: my un-nuanced opinion, based on available evidence, Not the opinion of Sanofi Pasteur, various international bodies, any of my employers, etc.

What do we think Dengvaxia does?

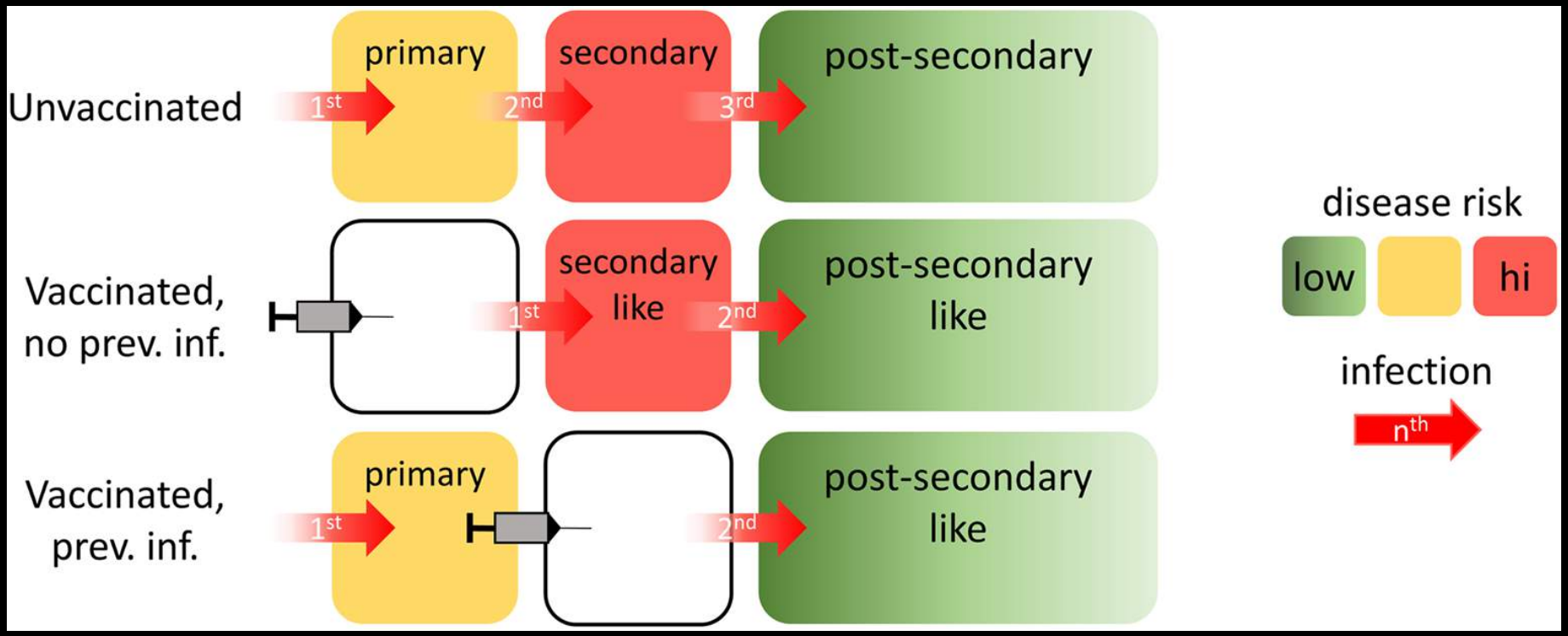


*Fig. 1 from *The Long-Term Safety…* publication mentioned at the outset.

Can Dengvaxia still be an effective tool?

- Still some efficacy and given high burden of disease, lots of value to preventing it
- Uncertainty in just how important downsides are
- Not practical to answer this question without modeling: ethical and logistical constraints, decade+ experiment scale

Modeling Public Health Interventions

Public Health Analyses

- Difference between transmission / spread model vs disease outcome models
- Incidence / prevalence relevant to dynamics, but the ultimate measures are focused differently: e.g., hospitalizations avoided, treatment cost vs intervention cost
- Necessary to model both baseline and intervention

Modeling Dengvaxia as an Intervention

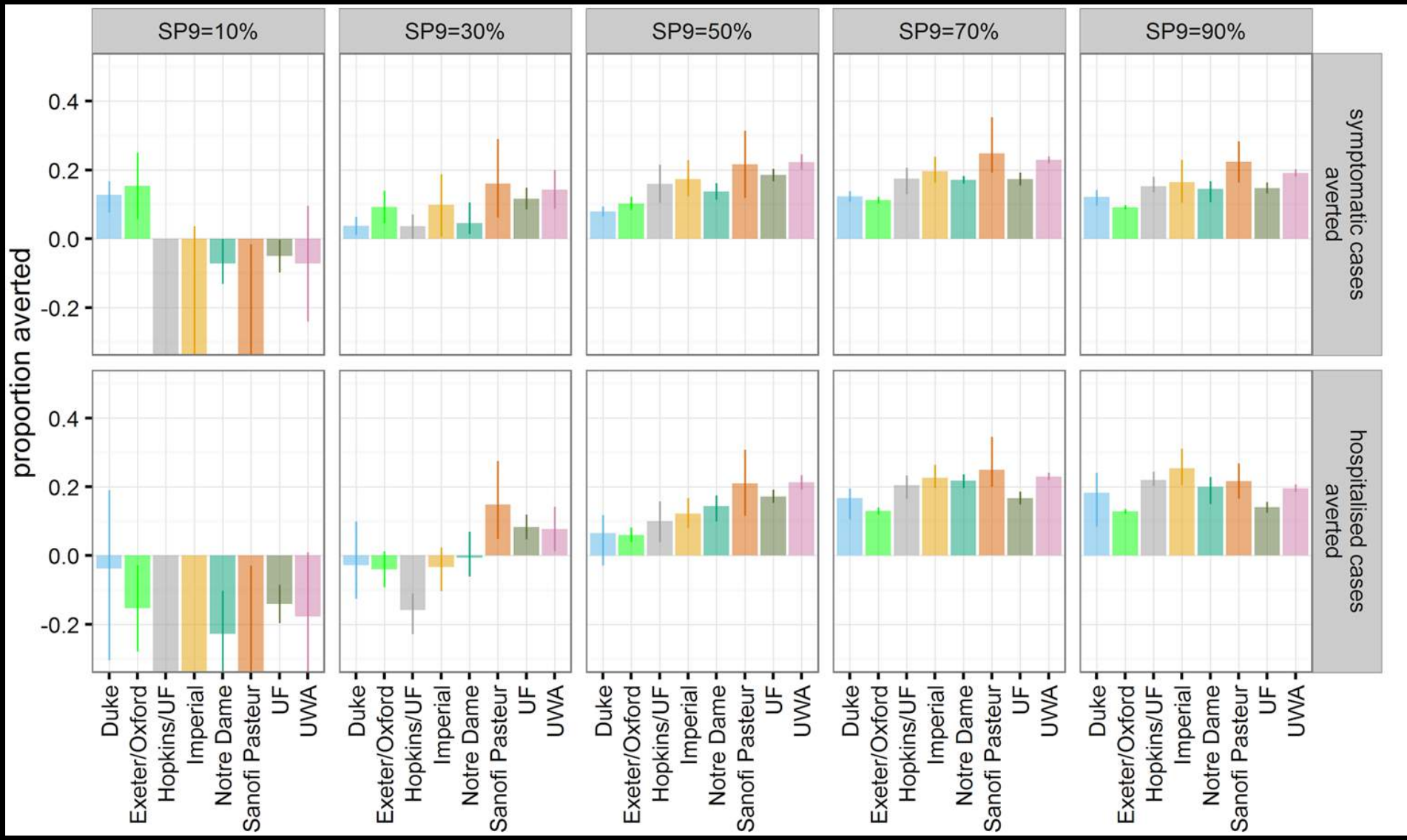
- What are the pertinent measures?
- What does the model need to accurately represent for us to assess those measures?
- What scenarios should we consider?

Modeling Dengvaxia as an Intervention: Expectations?

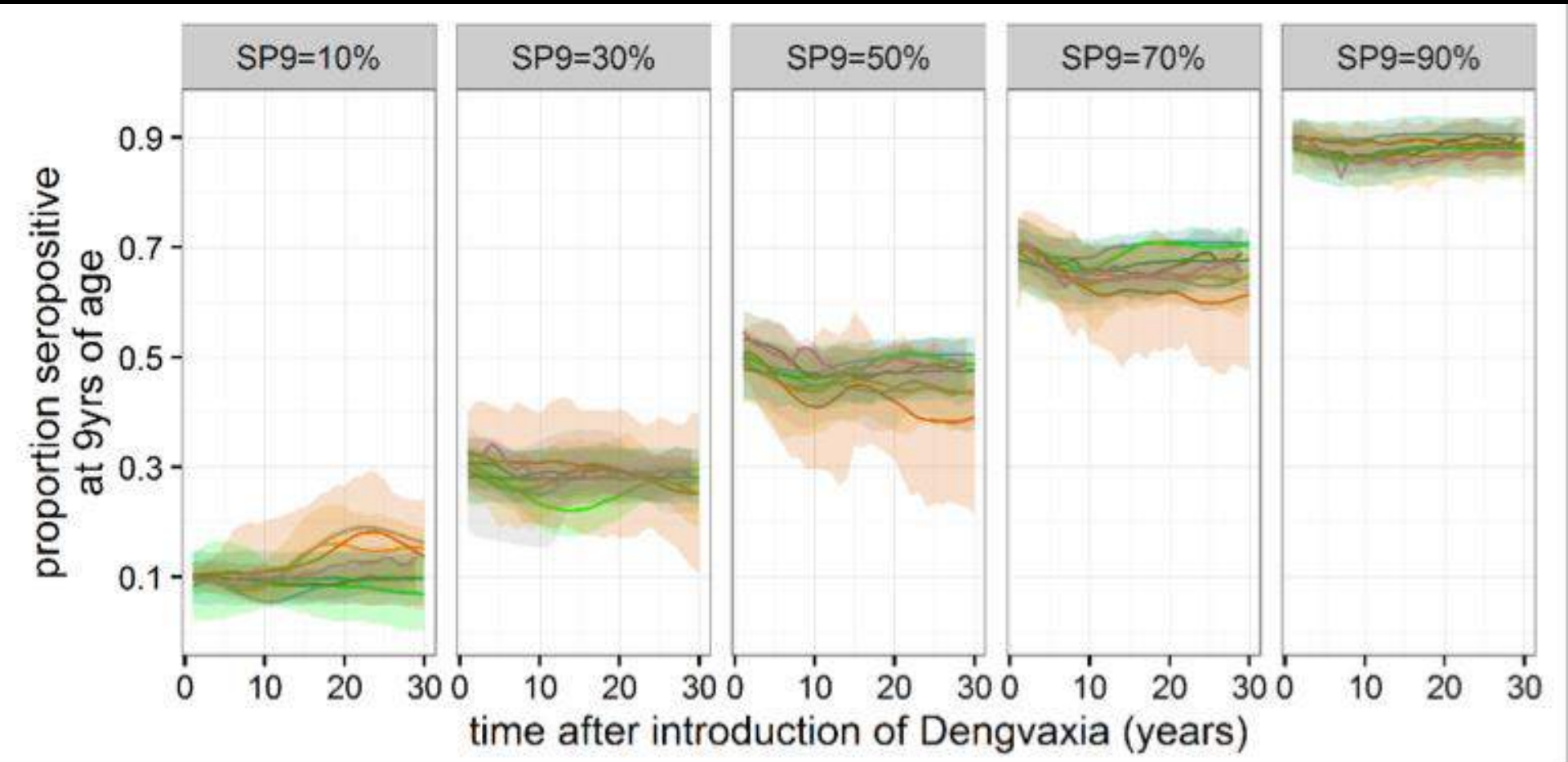
Assuming the vaccine works like a natural infection, think through the following combinations of scenarios:

- 1 vs 4 circulating strains
- Low vs High Force-of-Infection
- Vaccination in pre-school age children vs middle-school age children vs adults
- Bonus: interpolate between these scenarios

What Did We See in WHO Work?



What Did We See in WHO Work?



Public Health Conundrum

- There are clear qualitative trends in model outcomes, robust to different approaches, and consistent with the pure-reasoning model
- Most important feature: there exists a transition point between harmful and beneficial outcomes
  Modeling was key to highlighting this possibility, but: no clear agreement on the quantitative transition point.
- Models can inform (1) what to look out for in those intermediate scenarios and (2) what options are available in response to outcomes trending bad (e.g., vaccinate older)

Hindsight

- Lots dogma that any vaccine had to be tetravalent; probably a good reaction to disease enhancement
- But: in this model world, didn’t matter vaccine wasn’t tetravalent -- still had useful results
- Hindsight: had the knowledge to identify a much simpler product, but not enough questioning

Postscript, 2016

Further complications to the story: disease enhancement occur beyond just between dengue strains. There is tangible evidence that other species of flavivirus trigger this sort of immune response, e.g. W Dejnirattisai et al: “Dengue virus sero-cross-reactivity drives antibody-dependent enhancement of infection with zika virus” [1]

How might that shift harmful-beneficial point?

[1] http://www.nature.com/ni/journal/v17/n9/full/ni.3515.html

Postscript, 2017

Sanofi-Pasteur has recommended using Dengvaxia only on seropositive individuals. At least one national health organization (Phillipines) has launched legal action. The WHO revises its original recommendation (only in high seroprevalence regions) to match Sanofi-Pasteur pivot[1].

What should we make of this?

[1] http://www.who.int/immunization/diseases/dengue/q_and_a_dengue_vaccine_dengvaxia/en/

Summary

- There is a difference between scientific understanding and public health applications
- They have important overlaps but are not the same activities
- Expect to consider practicality and compromise

SOME RIGHTS RESERVED

This presentation is made available through a Creative Commons Attribution license. Details of the license and permitted uses are available at http://creativecommons.org/licenses/by/3.0/

BY

© 2016 International Clinics on Infectious Disease Dynamics and Data
Pearson C. “Dengue Vaccination Roll-out”. Clinic on Dynamical Approaches to Infectious Disease Data. DOI:10.6084/m9.figshare.5687152
For further information or modifiable slides please contact figshare@ici3d.org.

See the entire ICI3D Figshare Collection. DOI: 10.6084/m9.figshare.c.3788224.