

Estimating the full public health value of vaccines

Optimal use of Dengue vaccines

João Bosco Siqueira Jr
Federal University of Goiás - Brazil

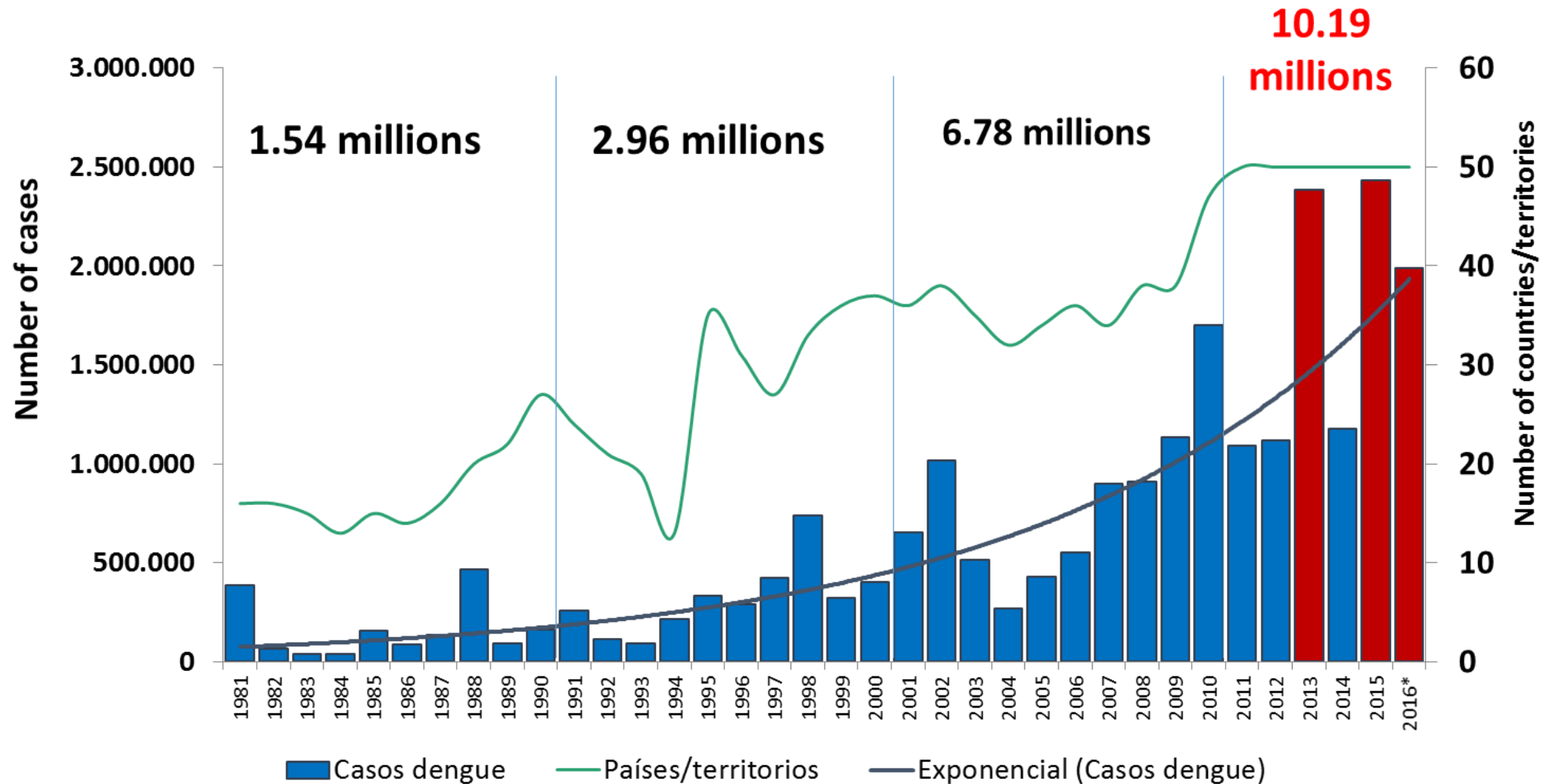
Les Pensières Fondation Mérieux Conference Center
Veyrier-du-Lac - France 5-7 December 2016



Current Dengue Control and Prevention Scenario

- **Limited success in prevention activities despite efforts from countries at national or local level**
- **Focused on vector control and social mobilization (sometimes hard to achieve)**
- **Lack of new insecticides and increasing resistance for the existing ones**

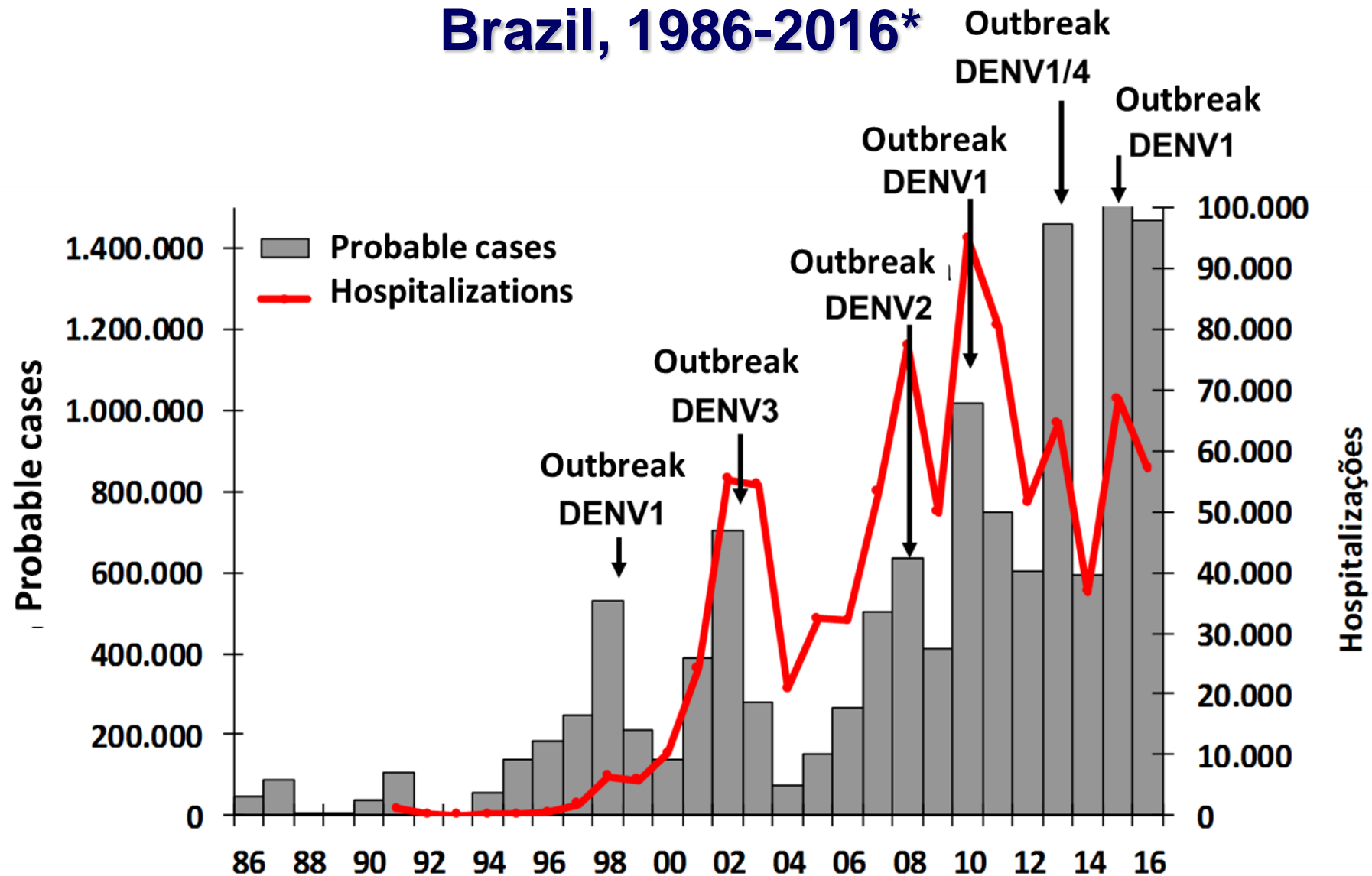
Number of Dengue Cases in the Americas by Decade, 1980 – 2016*



Kindly shared by J.L. San Martin / OPAS

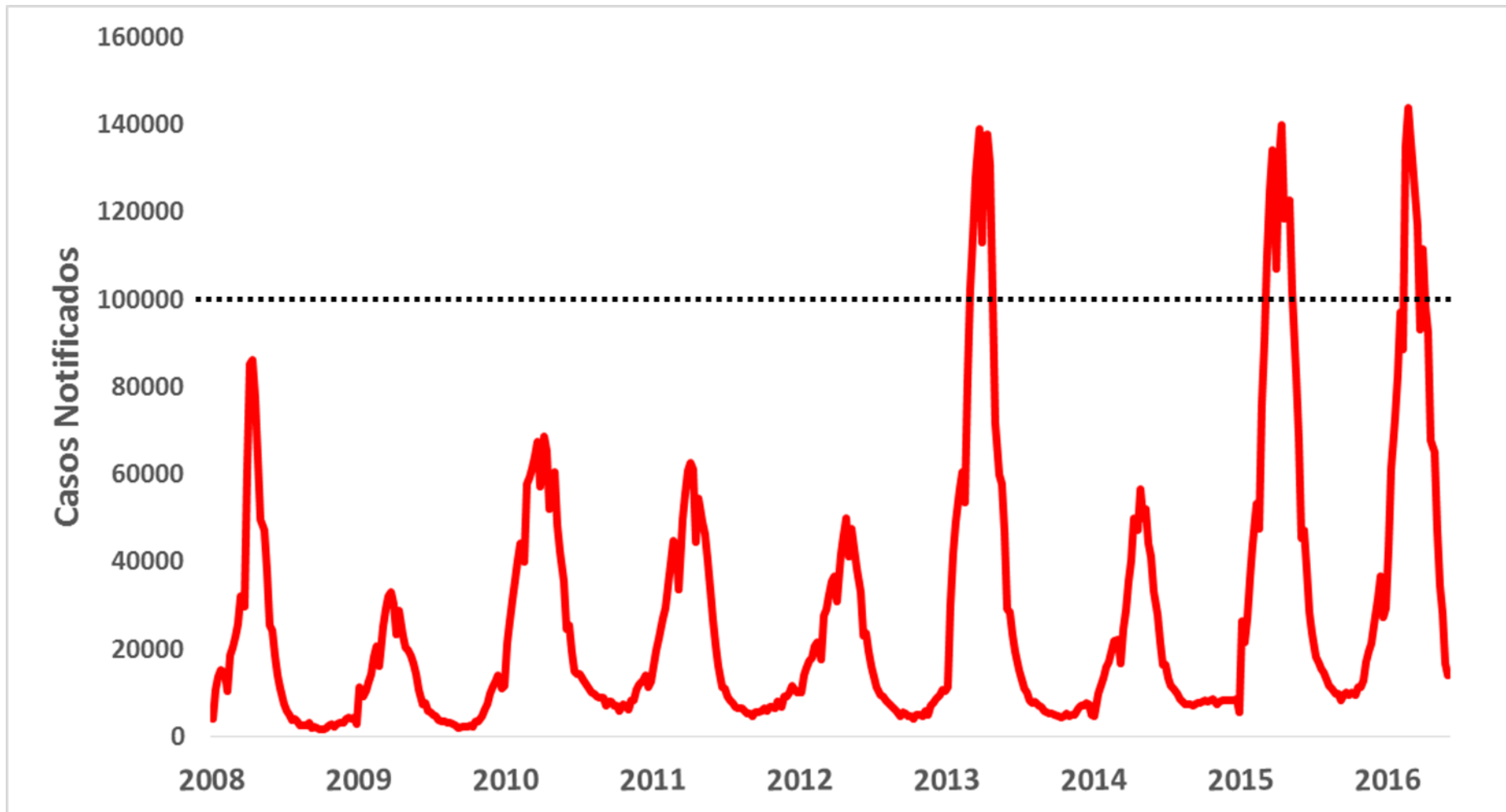
Source: Programa Regional de Dengue de la OPS/OMS
 * Hasta SE 35 del 2016

Dengue probable cases and hospitalizations, Brazil, 1986-2016*



* Preliminary data – November / 2016. Source: Sinan/SVS/MS e SIH/SAS/MS

Reported Cases by Week of Symptoms, Brazil, 2008-2016 *



*preliminary data for 2016

When I think of a dengue vaccine, what do I want?

**What can I say?
I want it all.**

Long term protection

Affordable cost and millions of doses available

High efficacy and effectiveness

Balanced protective response against each serotype

Safe

Safe

Super Safe

Easy to implement



N Engl J Med. 2015 Sep 24;373(13):1195-206. doi: 10.1056/NEJMoa1506223. Epub 2015 Jul 27.

Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease.

Hadinegoro SR, Arredondo-García JL, Capeding MR, Deseda C, Chotpitayasunondh T, Dietze R, Muhammad Ismail HI, Reynales H, Limkittikul K, Rivera-Medina DM, Tran HN, Bouckennooghe A, Chansinghakul D, Cortés M, Fanouillere K, Forrat R, Frago C, Gailhardou S, Jackson N, Noriega F, Plennevaux E, Wartel TA, Zambrano B, Saville M; CYD-TDV Dengue Vaccine Working Group.

N Engl J Med. 2015 Jan 8;372(2):113-23. doi: 10.1056/NEJMoa1411037. Epub 2014 Nov 3.

Efficacy of a tetravalent dengue vaccine in children in Latin America.

Villar L, Dayan GH, Arredondo-García JL, Rivera DM, Cunha R, Deseda C, Reynales H, Costa MS, Morales-Ramírez JO, Carrasquilla G, Rey LC, Dietze R, Luz K, Rivas E, Miranda Montoya MC, Cortés Supelano M, Zambrano B, Langevin E, Boaz M, Tornieporth N, Saville M, Noriega F; CYD15 Study Group.

Lancet. 2014 Oct 11;384(9951):1358-65. doi: 10.1016/S0140-6736(14)61060-6. Epub 2014 Jul 10.

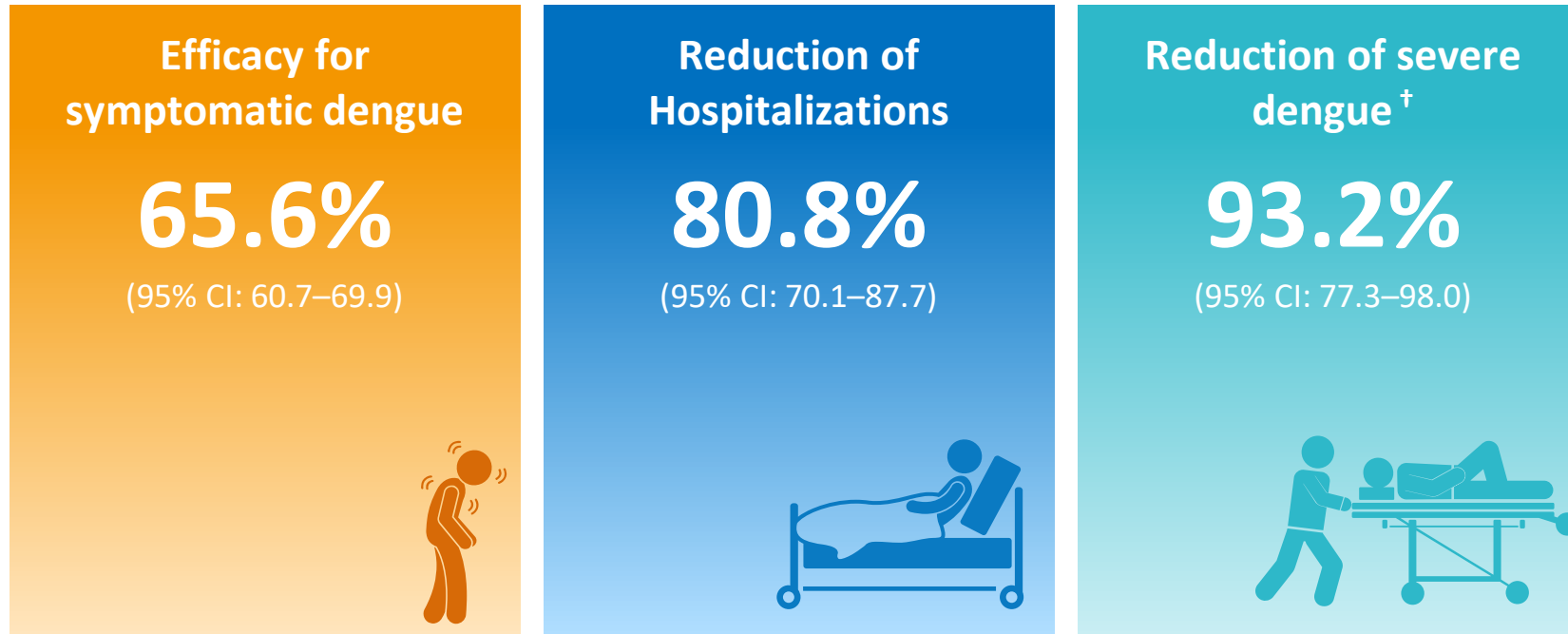
Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial.

Capeding MR¹, Tran NH², Hadinegoro SR³, Ismail HI⁴, Chotpitayasunondh T⁵, Chua MN⁶, Luong CQ², Rusmil K⁷, Wirawan DN⁸, Nallusamy R⁹, Pitisuttithum P¹⁰, Thisyakorn U¹¹, Yoon IK¹², van der Vliet D¹³, Langevin E¹⁴, Laot T¹⁵, Hutagalung Y¹⁶, Frago C¹⁶, Boaz M¹⁷, Wartel TA¹⁶, Tornieporth NG¹⁴, Saville M¹⁸, Bouckennooghe A¹⁶; CYD14 Study Group.

CYD-TDV – Efficacy Population 9 to 16 years of age

Summary of efficacy results

25 months follow up* Aggregated analysis^{‡1}



*Data come from the 2 pivotal, phase III, large-scale efficacy trials CYD14 and CYD15, which were designed to fully assess efficacy; postdose 1; ¹Full Analysis Set for Efficacy (FASE): all subjects who received at least one injection. [†]dengue hemorrhagic fever, World Health Organization 1997 criteria. CI=confidence interval; DENV=dengue virus.



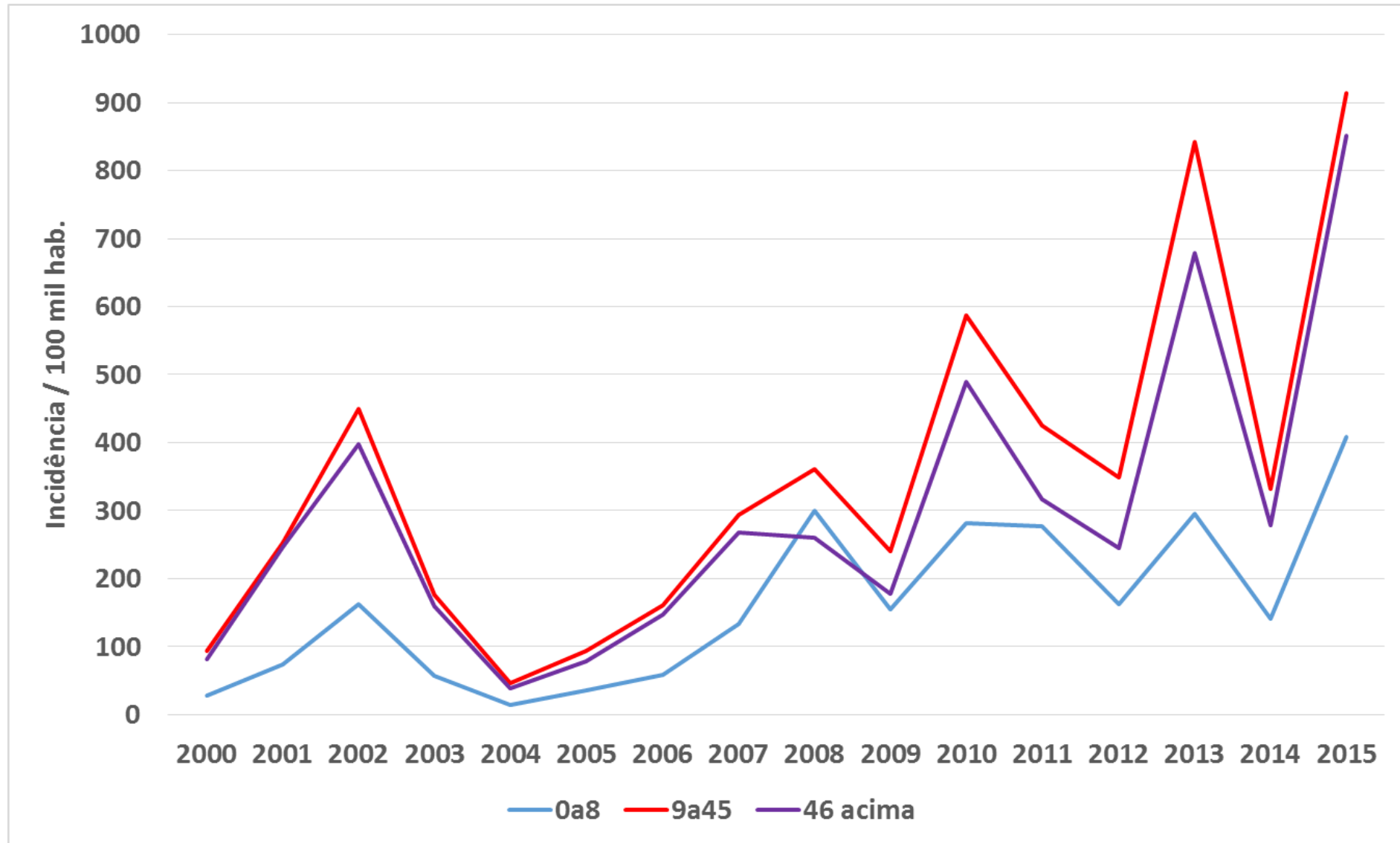
Dengvaxia[®] First Dengue Vaccine Approved in Brazil

- *Global introduction of the first Dengue Vaccine gains further momentum with this third approval in a row in an endemic country-*
- *With 1.4 million dengue cases reported this year, Brazil stands to gain tremendous value from this new dengue prevention tool -*

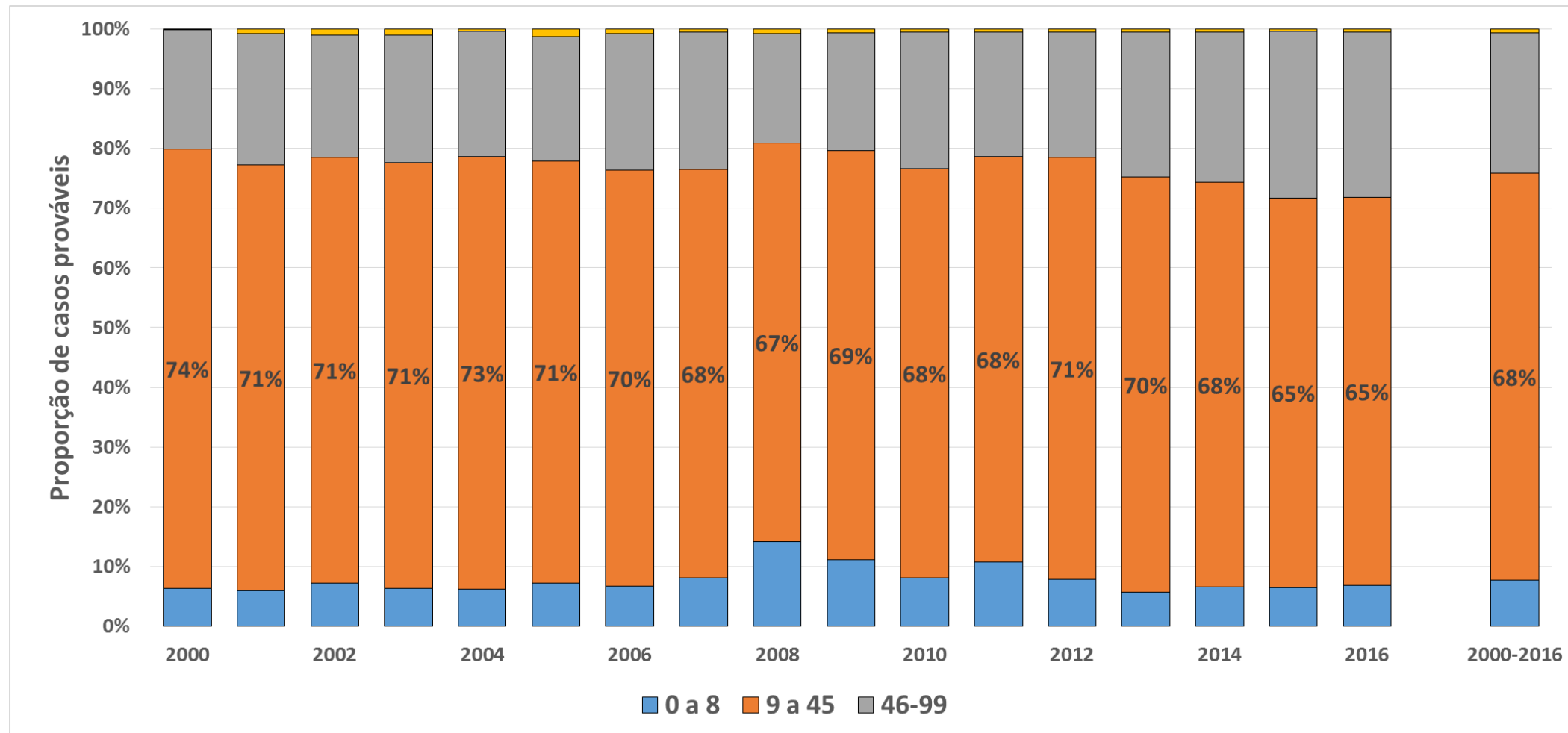
Lyon, France - December 28, 2015 - [Sanofi Pasteur](#), the vaccines division of [Sanofi](#), announced today that Brazil has granted regulatory approval to Dengvaxia[®], representing the third successful licensure of the dengue vaccine, which was also approved in Mexico and the Philippines earlier this month.

The Brazilian regulatory authorities ANVISA approved Dengvaxia[®], tetravalent dengue vaccine, for the prevention of disease caused by all four dengue types in individuals from 9-45 years of age living in endemic areas.

Dengue Incidence by Age Group, Brazil, 2000 - 2015



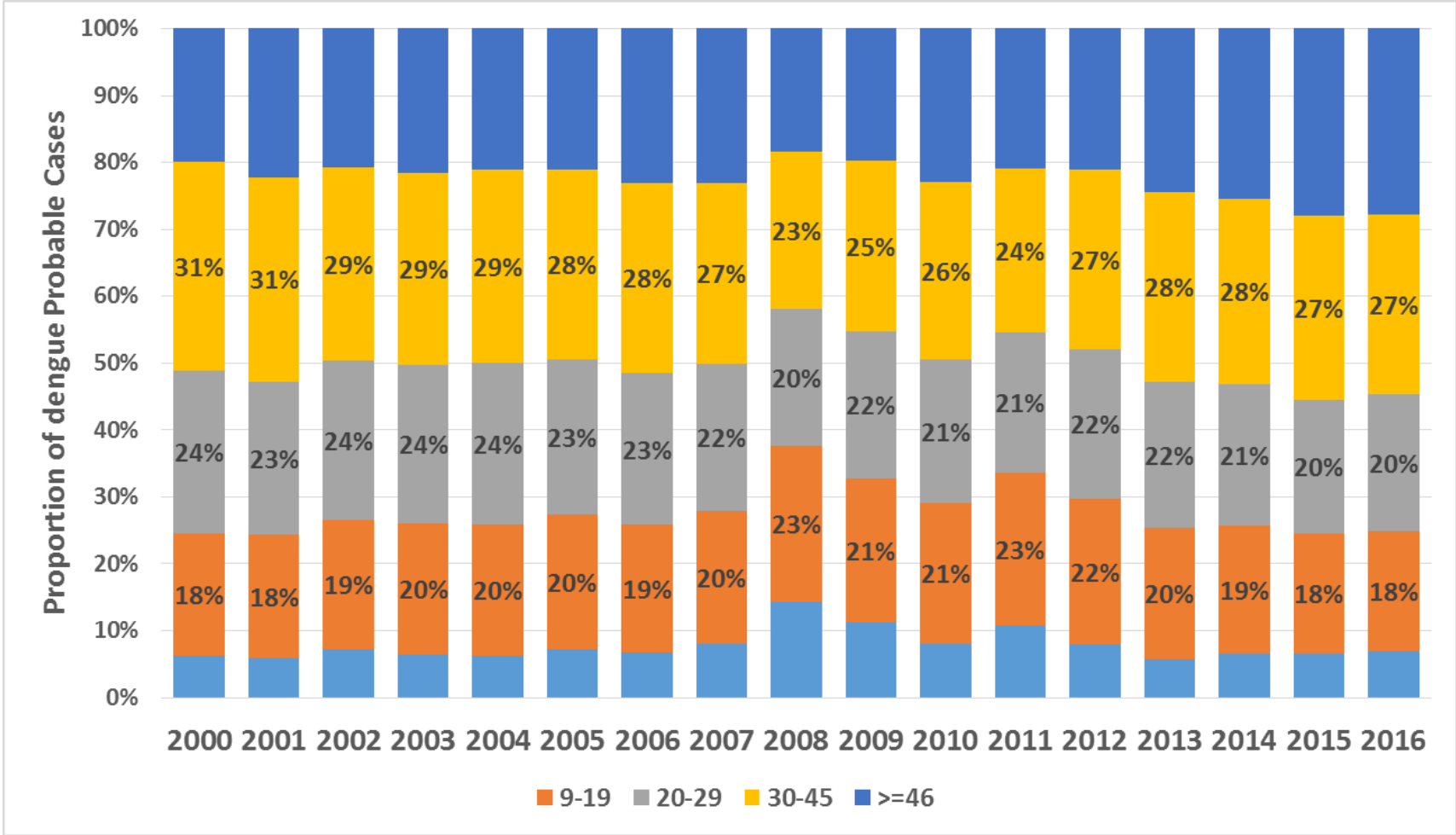
Proportion of Dengue Probable Cases by Age Group, Brazil, 2000 – 2016*



*Preliminary data for 2016.

Source: Sinan/SVS/MS

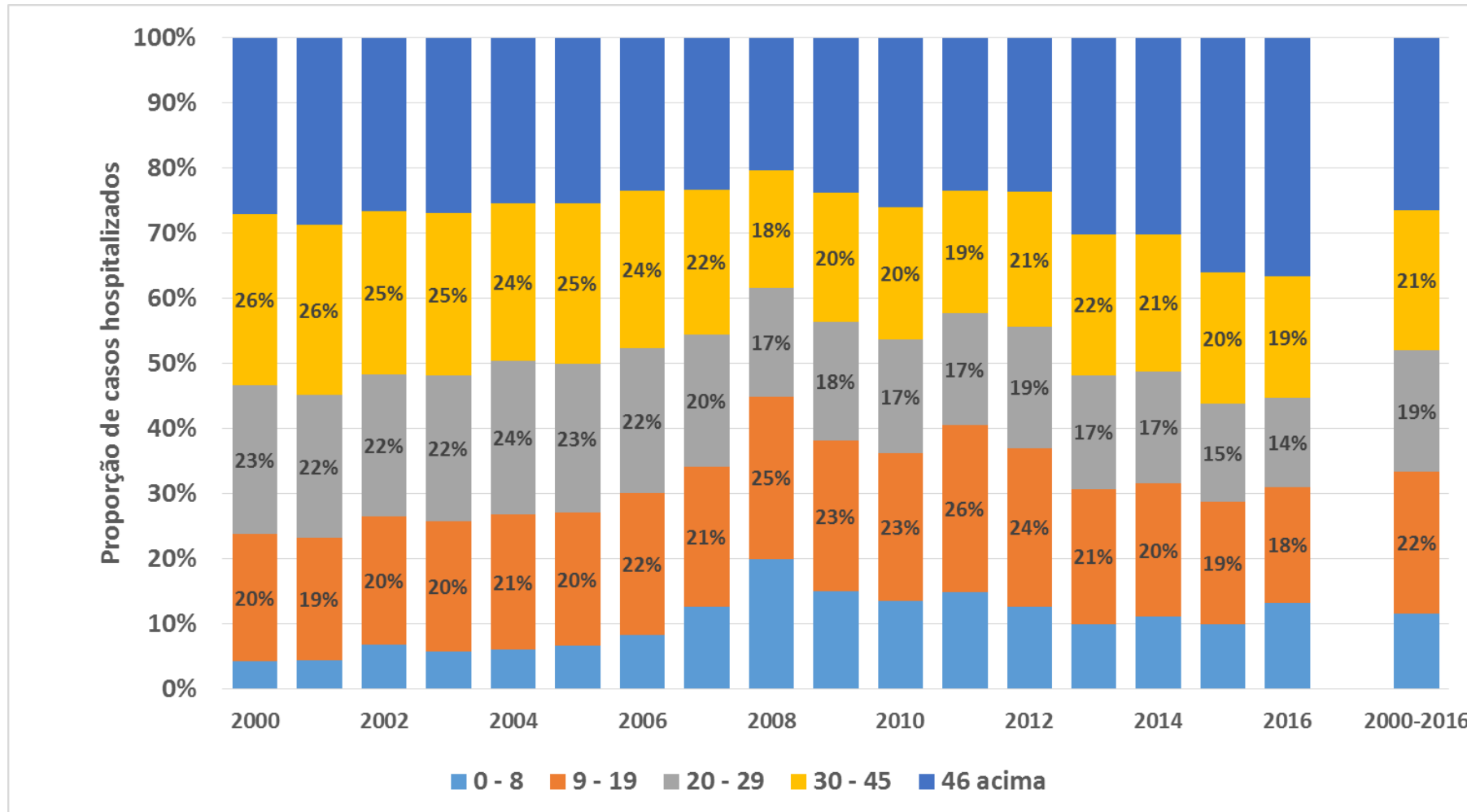
Proportion of Dengue Probable Cases by Age Group, Brazil, 2000 – 2016*



*Preliminary data for 2016.

Source: Sinan/SVS/MS

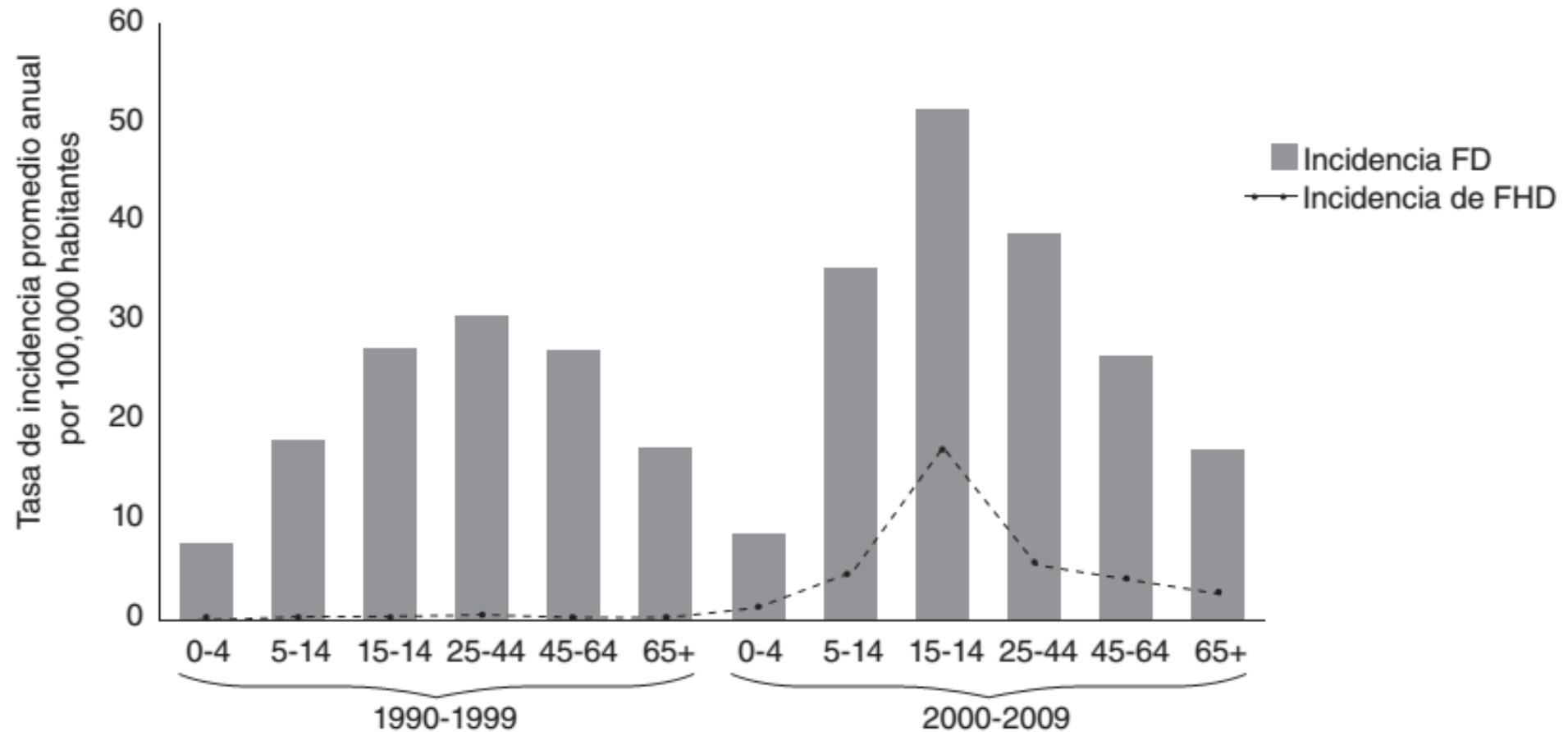
Proportion of Dengue Hospitalized Cases by Age Group, Brazil, 2000 – 2016*



*Preliminary data for 2016.

Source: SIH/SAS/MS

Dengue Incidence by age group Mexico, 1990-1999 and 2000-2009

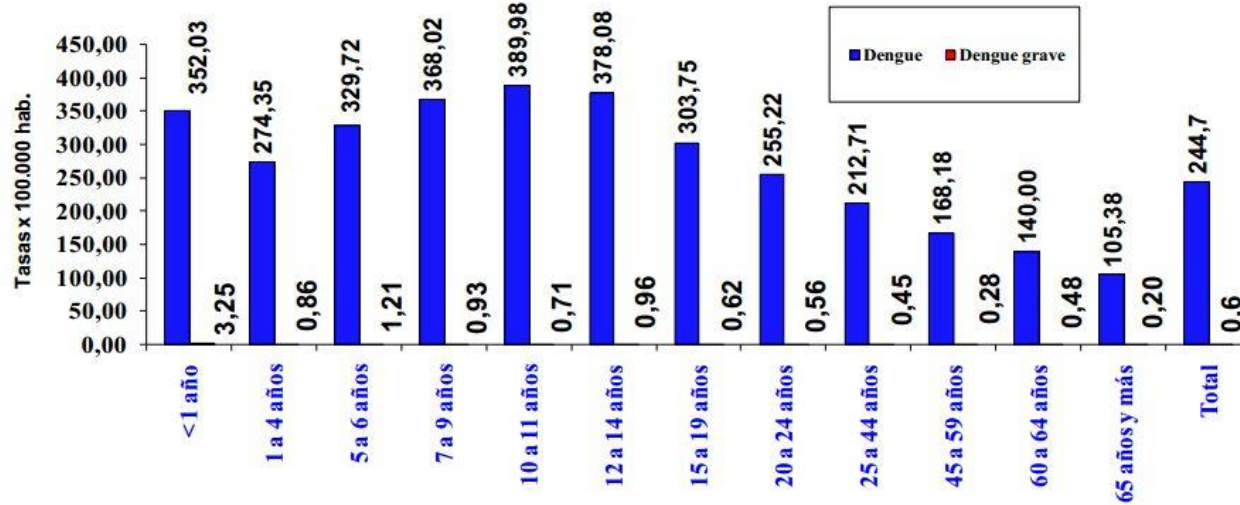


Cases by age group

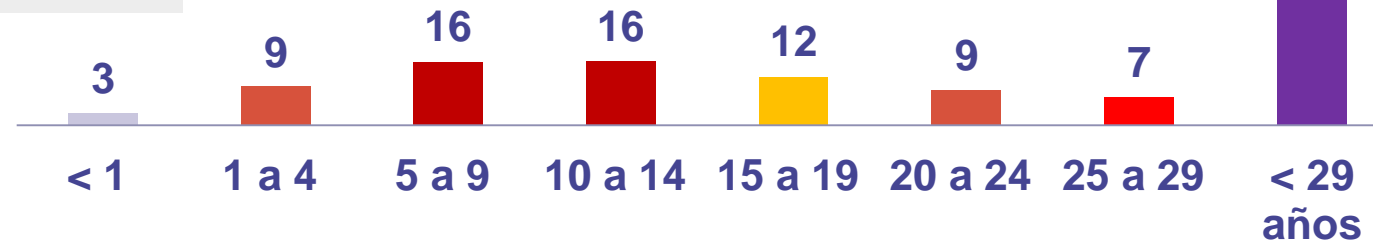
Venezuela

Dengue Incidence by age group

Gráfico N° 19
Distribución de casos probables de Dengue,
según grupos de edad, Tasa x 100.000 habitantes.
República Bolivariana de Venezuela año 2014. Semana epidemiológica N° 44.



Colombia



Porcentaje de casos de dengue en Colombia por grupo etario



**World Health
Organization**

Organisation mondiale de la Santé

Weekly epidemiological record Relevé épidémiologique hebdomadaire

29 JULY 2016, 91th YEAR / 29 JUILLET 2016, 91^e ANNÉE

No 30, 2016, 91, 349–364

<http://www.who.int/wer>

Contents

349 Dengue vaccine: WHO
position paper – July 2016

**Dengue vaccine: WHO
position paper – July 2016**

**Note de synthèse de l’OMS
sur le vaccin contre la dengue
– juillet 2016**

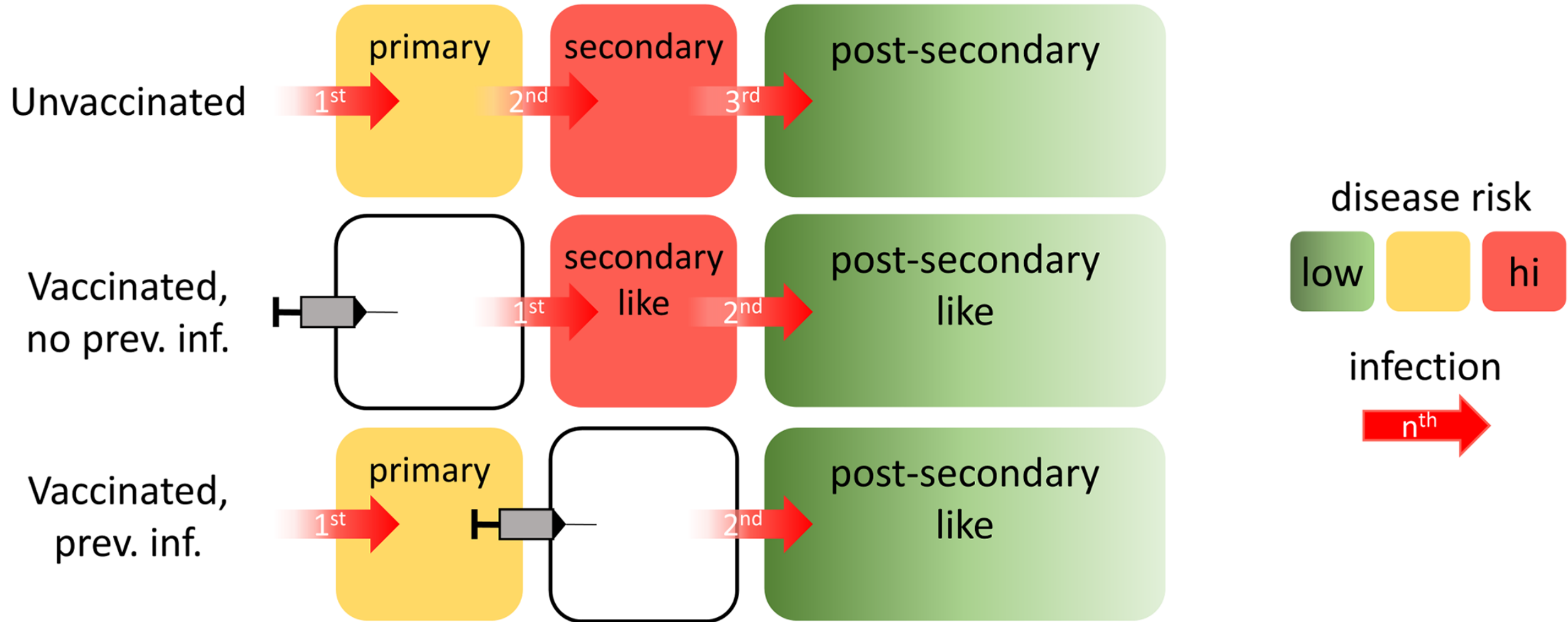
WHO Position

- Countries should only consider introduction of dengue vaccine CYD-TDV in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease.
- To maximize public health impact and cost effectiveness, age groups targeted for vaccination should have 70% or greater seroprevalence.
- Vaccine is not recommended when seroprevalence is below 50% in targeted age group.

How is the seroprevalence at 9 years of age?

- **Baseline seropositivity rate in children 9 to 12 y old in the trial settings in Asia and Latin America was between 48% (Mexico) and 91% (Colombia).**
 - **Other studies of dengue seroprevalence in endemic areas (Brazil; Thailand, Mexico, India) have found values of SP9 in the range of 40% to 81%**
 - **Ongoing study for ~70 different cities in Brazil**
-
- Symptomatic Dengue in Children in 10 Asian and Latin American Countries. *N Engl J Med.* 2016; 374: 1155–1166. doi: 10.1056/ NEJMoa1503877
 - Seroprevalence and risk factors for dengue infection in socio-economically distinct areas of Recife, Brazil. *Acta Trop.* 2010; 113: 234–240. doi: 10.1016/j.actatropica.2009.10.021
 - Revisiting Rayong: Shifting Seroprofiles of Dengue in Thailand and Their Implications for Transmission and Control. *Am J Epidemiol.* 2014; 179: 353–360. doi: 10.1093/aje/kwt256
 - Amaya-Larios IY, Martinez-Vega RA, Mayer S V., Galeana-Hernandez M, Comas-Garcia A, Sepulveda-Salinas KJ, et al. Seroprevalence of Neutralizing Antibodies Against Dengue Virus in Two Localities in the State of Morelos, Mexico. *Am J Trop Med Hyg.* 2014; 91: 1057–1065. doi: 10.4269/ ajtmh.14-0145
 - The Hidden Burden of Dengue and Chikungunya in Chennai, India. Kittayapong P, editor. *PLoS Negl Trop Dis.* 2015; 9: e0003906. doi: 10.1371/journal.pntd.0003906

Illustration of the assumed vaccine mode of action.



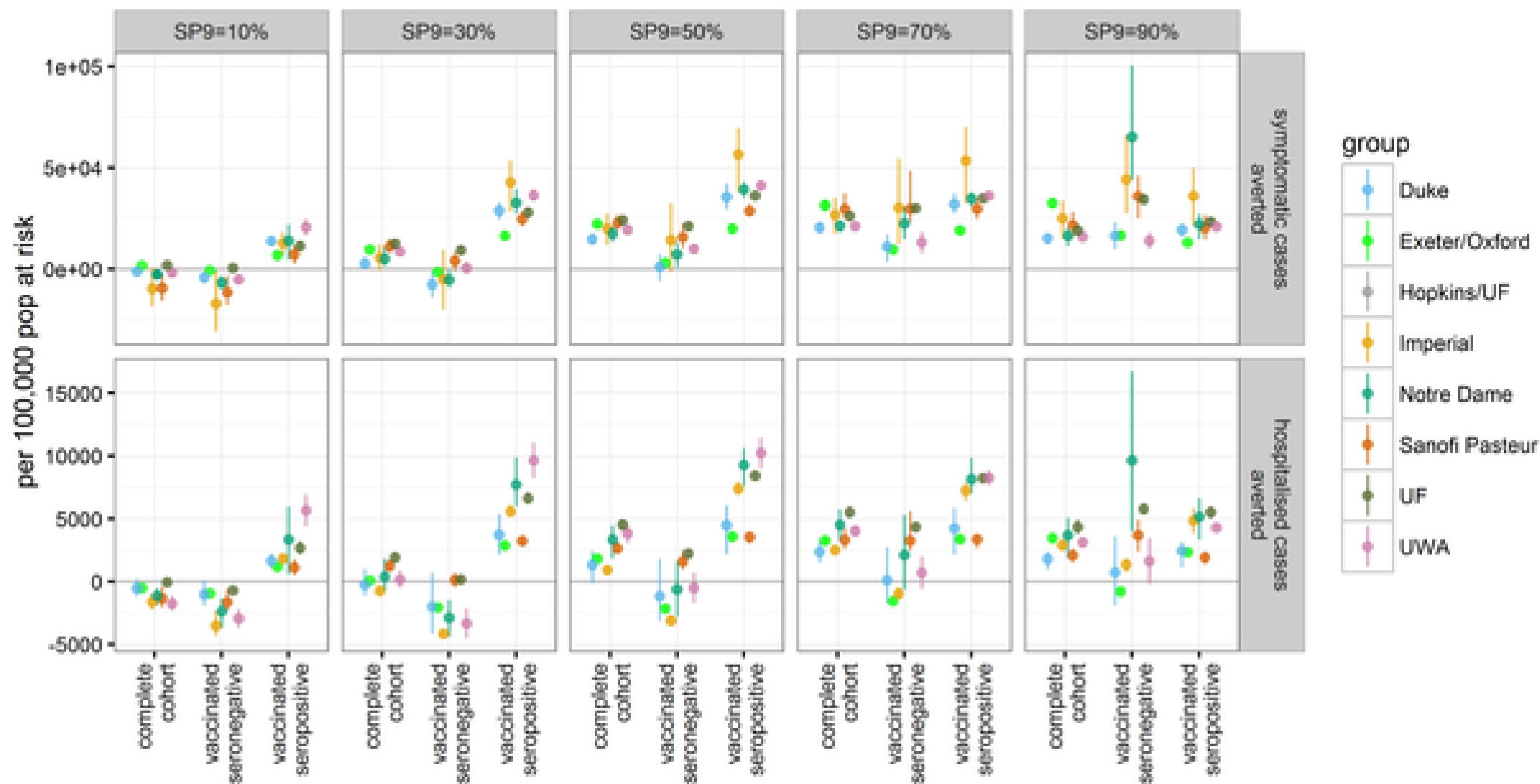
The proportion of symptomatic and hospitalised DENV cases (rows) averted within 30 y after vaccine introduction in the reference scenario for the range of transmission intensities



Flasche S, Jit M, Rodríguez-Barraquer I, Coudeville L, Recker M, et al. (2016) 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. PLOS Medicine 13(11): e1002181. doi:10.1371/journal.pmed.1002181

<http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002181>

Fig 4. The number of symptomatic and hospitalized DENV cases averted per 100,000 population in the first vaccinated cohort within 30 y after vaccination.



- **All models predicted that in settings with moderate to high dengue endemicity (SP9 > 50%), the default vaccination policy would reduce the burden of dengue disease for the population by 6%–25% (all simulations: –3%–34%) and in high-transmission settings (SP9 > 70%) by 13%–25% (all simulations: 10%– 34%)**
- **In settings with low transmission intensity (SP9 ≤ 30%), the models predicted that vaccination could lead to a substantial increase in hospitalization because of dengue**
- **Modelling reduced vaccine coverage or the addition of catch-up campaigns showed that the impact of vaccination scaled approximately linearly with the number of people vaccinated**

THE PUBLIC HEALTH VALUE OF DENGUE VACCINE

- Vaccine (2016)
- Estimating the public health importance of the CYD-tetravalent dengue vaccine: Vaccine preventable disease incidence and numbers needed to vaccinate
- Bradford D. Gessner, Annelies Wilder-Smith
- <http://dx.doi.org/10.1016/j.vaccine.2016.03.017>

G Model
JVAC-17445; No. of Pages 5

ARTICLE IN PRESS

Vaccine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

Journal homepage: www.elsevier.com/locate/vaccine

Estimating the public health importance of the CYD-tetravalent dengue vaccine: Vaccine preventable disease incidence and numbers needed to vaccinate

Bradford D. Gessner^a, Annelies Wilder-Smith^{b,c,*}

^a Agence de Médecine Préventive, Ferney-Voltaire, France
^b Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
^c Institute of Public Health, University of Heidelberg, Germany

ARTICLE INFO

Article history:
Received 28 November 2015
Received in revised form 1 March 2016
Accepted 9 March 2016
Available online xxx

Keywords:
Dengue
Dengue vaccine
CYD-TDV
Vaccine efficacy
Vaccine effectiveness
Vaccine preventable disease incidence
Number needed to vaccinate

ABSTRACT

Background: To evaluate the potential public health impact of the live attenuated tetravalent Sanofi Pasteur dengue vaccine (CYD-TDV) we analyzed data from the reported clinical trials to calculate vaccine preventable disease incidence (VPDI) and number needed to vaccinate (NNV) based on the licensure indication for persons age 9 years and above.

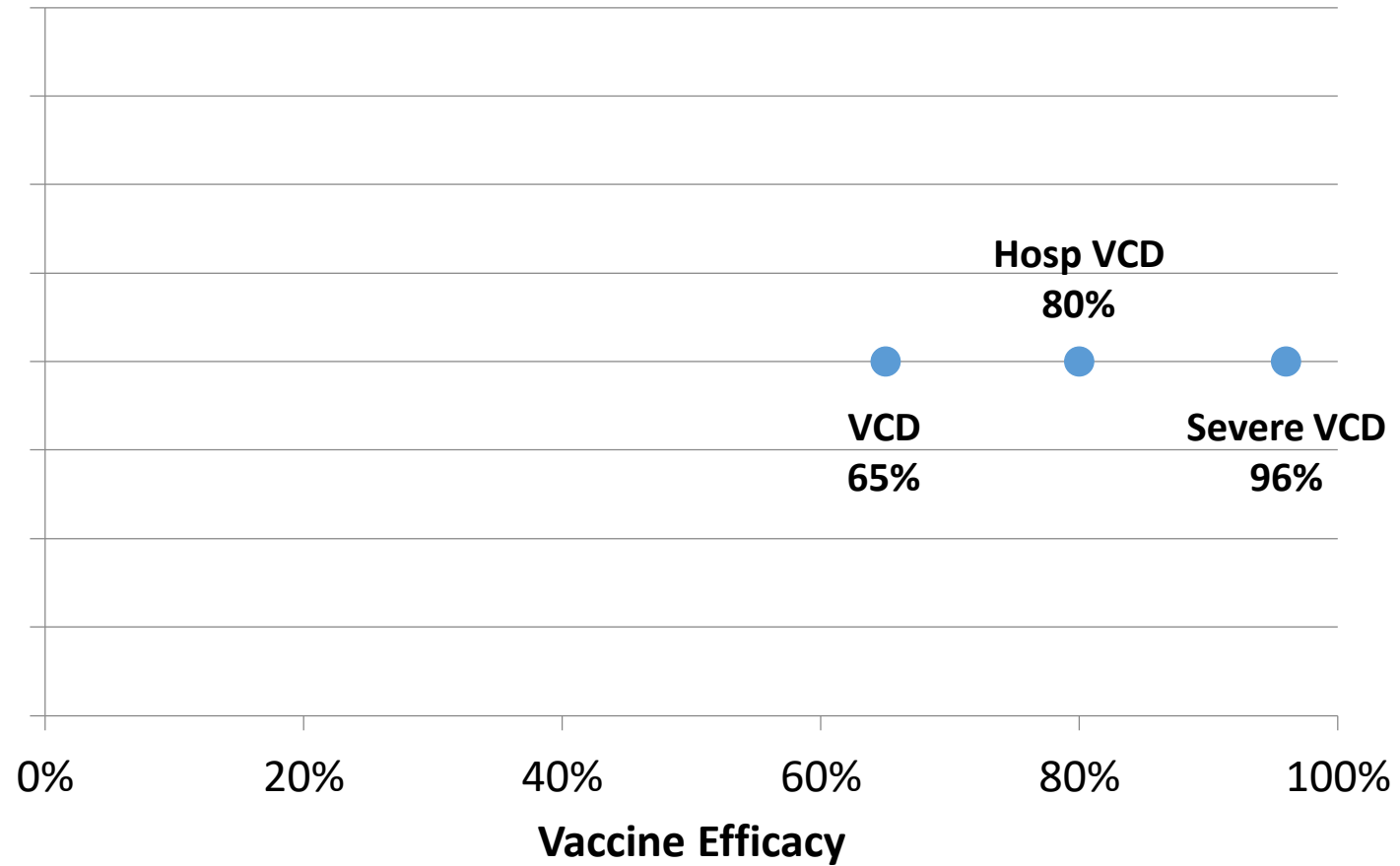
Methods: VPDI is defined as incidence in an unvaccinated population X vaccine efficacy (VE), and thus incorporates both VE and the underlying burden of disease. NNV was calculated as 100,000 divided by VPDI divided by 2-year length of study. We compared these values to data for three newer vaccines that are currently integrated into some national immunization programs in Asia and Latin America, namely pneumococcal conjugate, *Haemophilus influenzae* type b, and rotavirus vaccines.

Results: In the Asian-Pacific trial, in the first 25 months after the first dose of the dengue vaccine, CYD-TDV prevented annually 2639 cases of virologically confirmed dengue for every 100,000 persons vaccinated, for an NNV of 18. In the Latin American trial, given the overall lower annual dengue incidence compared to Asia, VPDI was 1707, and NNV 28. For the Asian-Pacific and Latin American studies, the VPDI for hospitalized virologically confirmed disease at the trials' end were 638 and 239 per 100,000 population per year, respectively, with NNVs of 75 and 201. VPDI for confirmed dengue hospitalization was higher than that for Hib vaccine against Hib meningitis or all cause severe pneumonia while lower than that for rotavirus vaccine against severe rotavirus gastroenteritis.

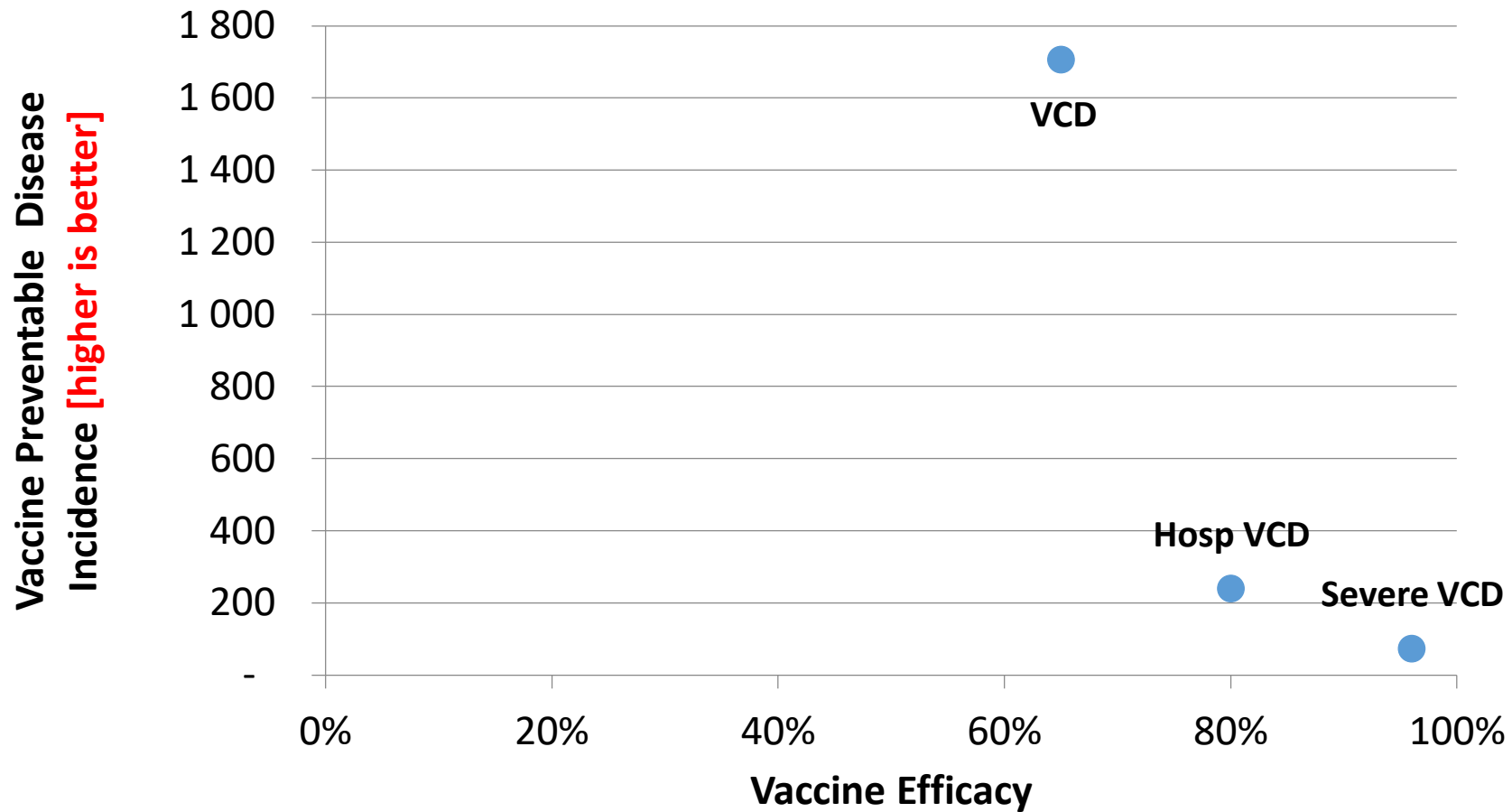
Conclusion: Our analysis found that the CYD-TDV dengue vaccine had favorable VPDI and NNV, also when compared to existing vaccines used in Latin America and Asia. VPDI and NNV varied by serotype distribution, extent of prior dengue exposure (baseline seroprevalence) and country. These findings will help policy-makers decide where and how to introduce this vaccine post-licensure.

© 2016 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

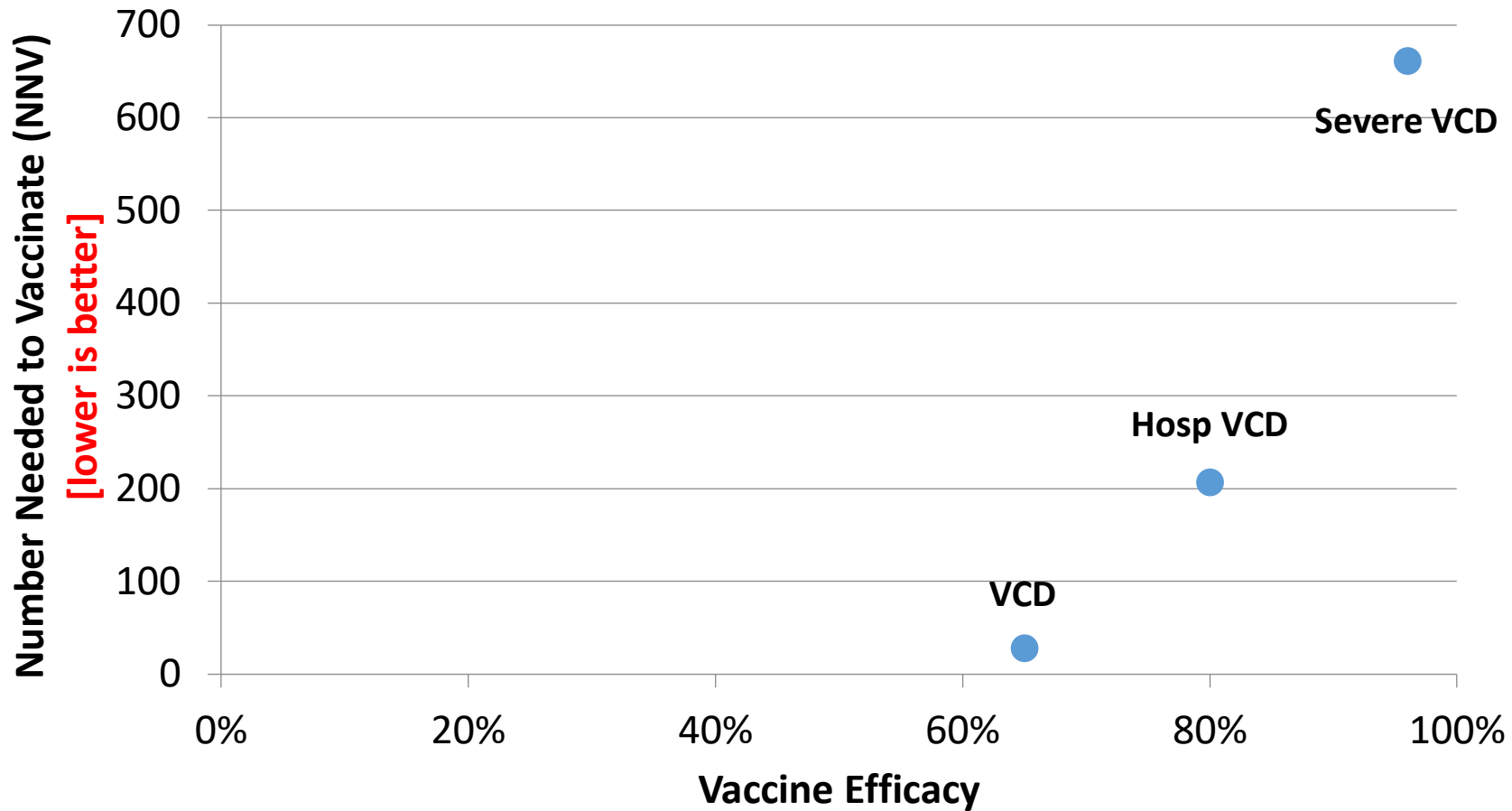
LAC Region vaccine efficacy : dengue



LAC Region: Public health impact can be greater in settings where vaccine efficacy is lower: dengue



LAC Region: Public health impact can be greater in settings where vaccine efficacy is lower: dengue



LAC Region Summary - Dengue

- **CYD-TDV shows high efficacy against severe clinical disease (96%) and health care utilization (80%)**
- **CYD-TDV also shows an ability to reduce dengue disease burden**
 - **Dengue VPDI is very high (1707)**
 - **Dengue NNV is very low (28)**
- **In addition, analyses found that the CYD-TDV dengue vaccine had favorable VPDI and NNV when compared to vaccines already used in the LAC region (Hib, rotavirus, PCV)**
- **CYD-TDV is important from different perspectives**
 - **Prevention of severe clinical disease**
 - **Reduction in health services utilization**
 - **Reduction in overall disease burden**

Conclusions

- **Vaccine is recommended for endemic areas and a negative impact on the entire population can be avoided by choosing a target age for vaccination in which average seroprevalence exceeds ~50%.**
- **Understanding any differences between naturally and vaccine-acquired immunity will be critical in assessing the overall impact of vaccination on this group**
- **To maximize the population impact of vaccination and to prevent negative impacts, it will be necessary to carefully tailor vaccination strategies to local epidemiological conditions**
- **Population serosurveys can mitigate risks in planning routine vaccination**

Obrigado



siqueirajb@gmail.com