



VACCINOLOGY 2016

X International Symposium for Latin American Experts
September 20 - 22 | Brasília

New epidemiological perspectives coming from dengue vaccine clinical trials

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Federal University of Goiás - Brazil

X International Symposium for Latin American Experts

Organized by: Fondation Mérieux and the Latin American Society
for Pediatric Infectious Diseases (SLIPE)

Dengue Key Facts

- **The global incidence of dengue has grown dramatically in recent decades**
- **Geographic spread of both the mosquito vectors and the viruses: global resurgence of epidemic dengue disease and emergence of severe forms in the past 25 years**
- **1950s: 9 dengue-reporting countries - Now: public health concern in over 100 countries**

Source: World Health Organization

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**

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.

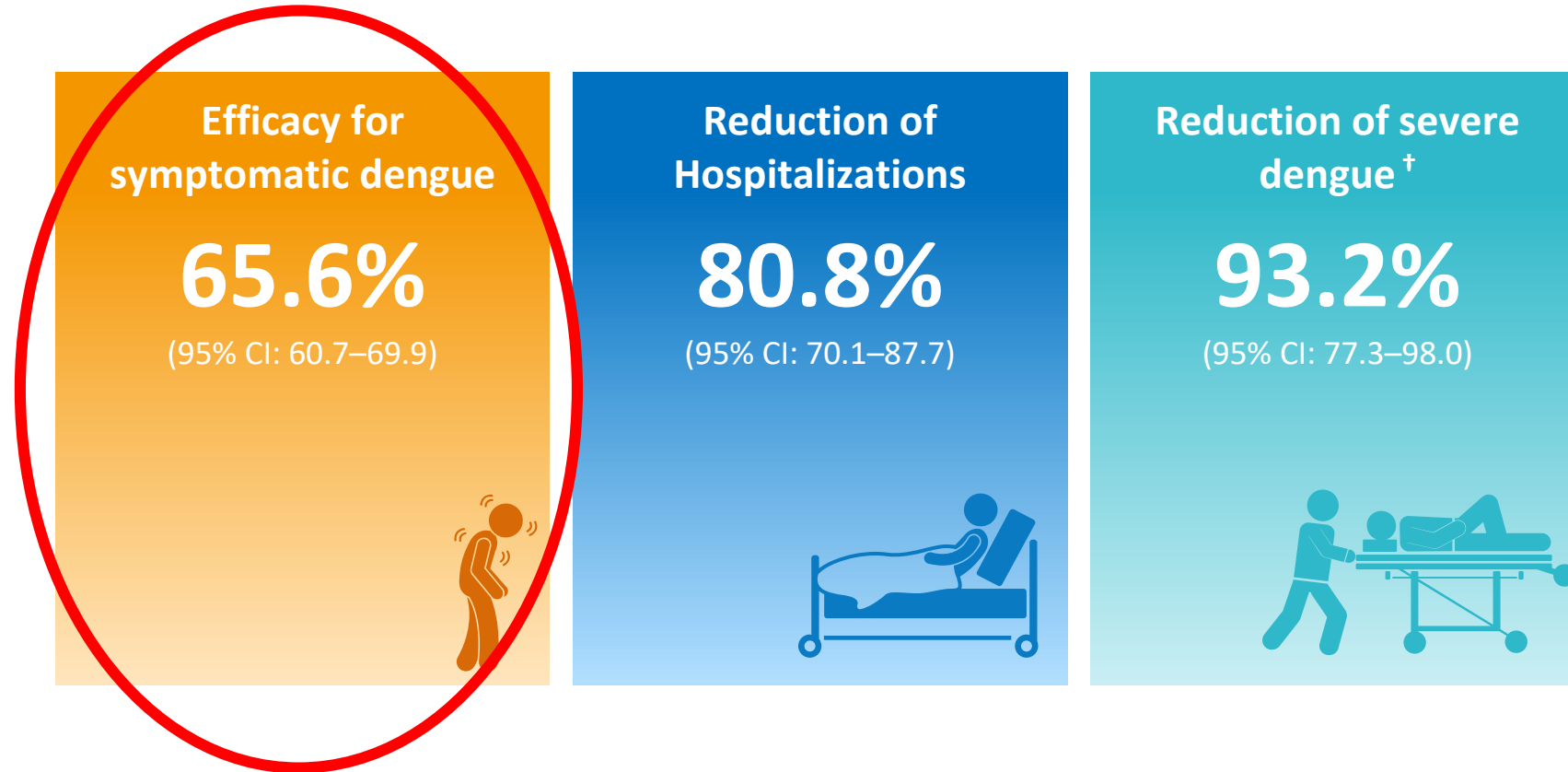
Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial.

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

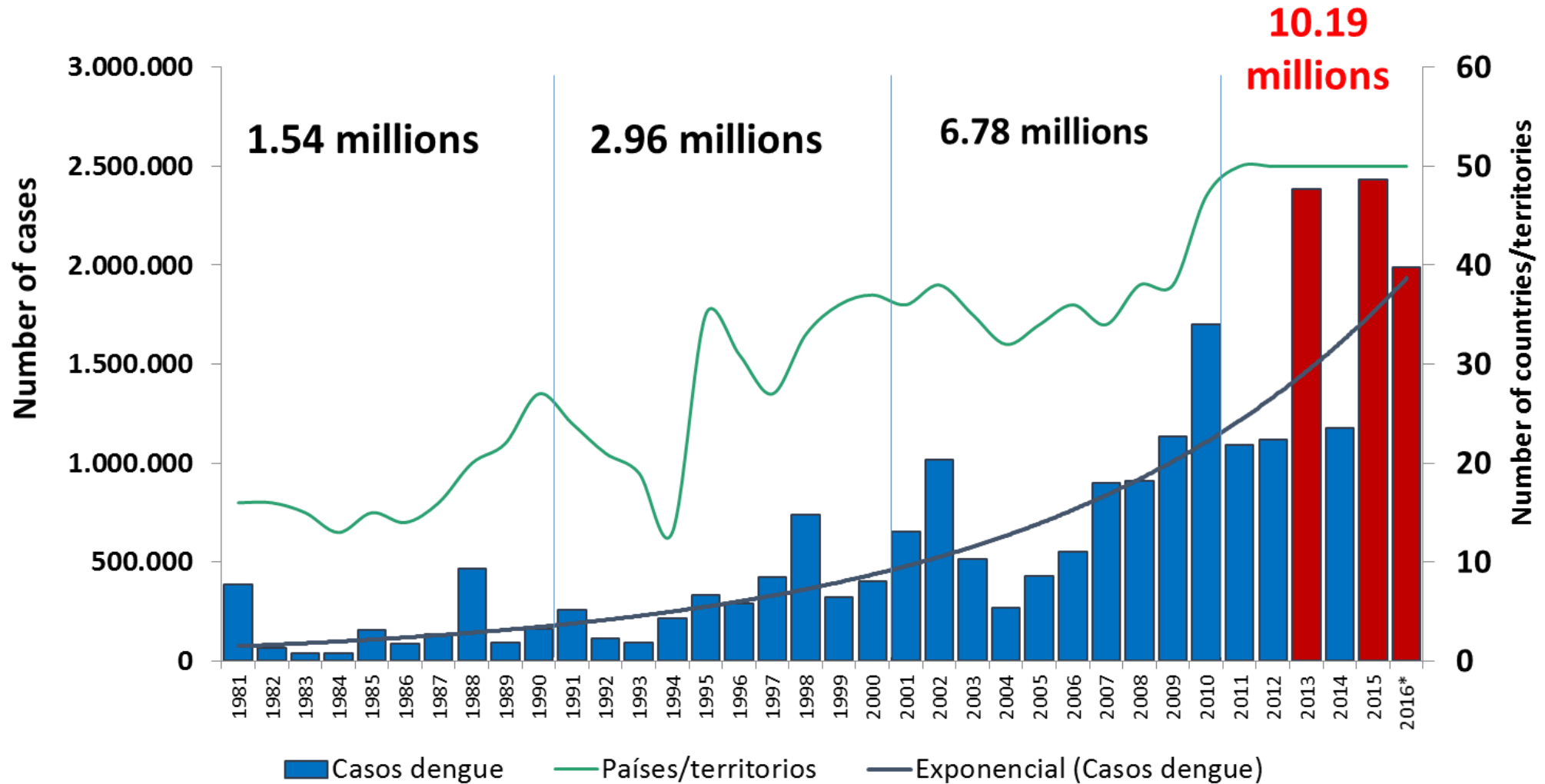
Summary of efficacy results

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; [‡]Full 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.

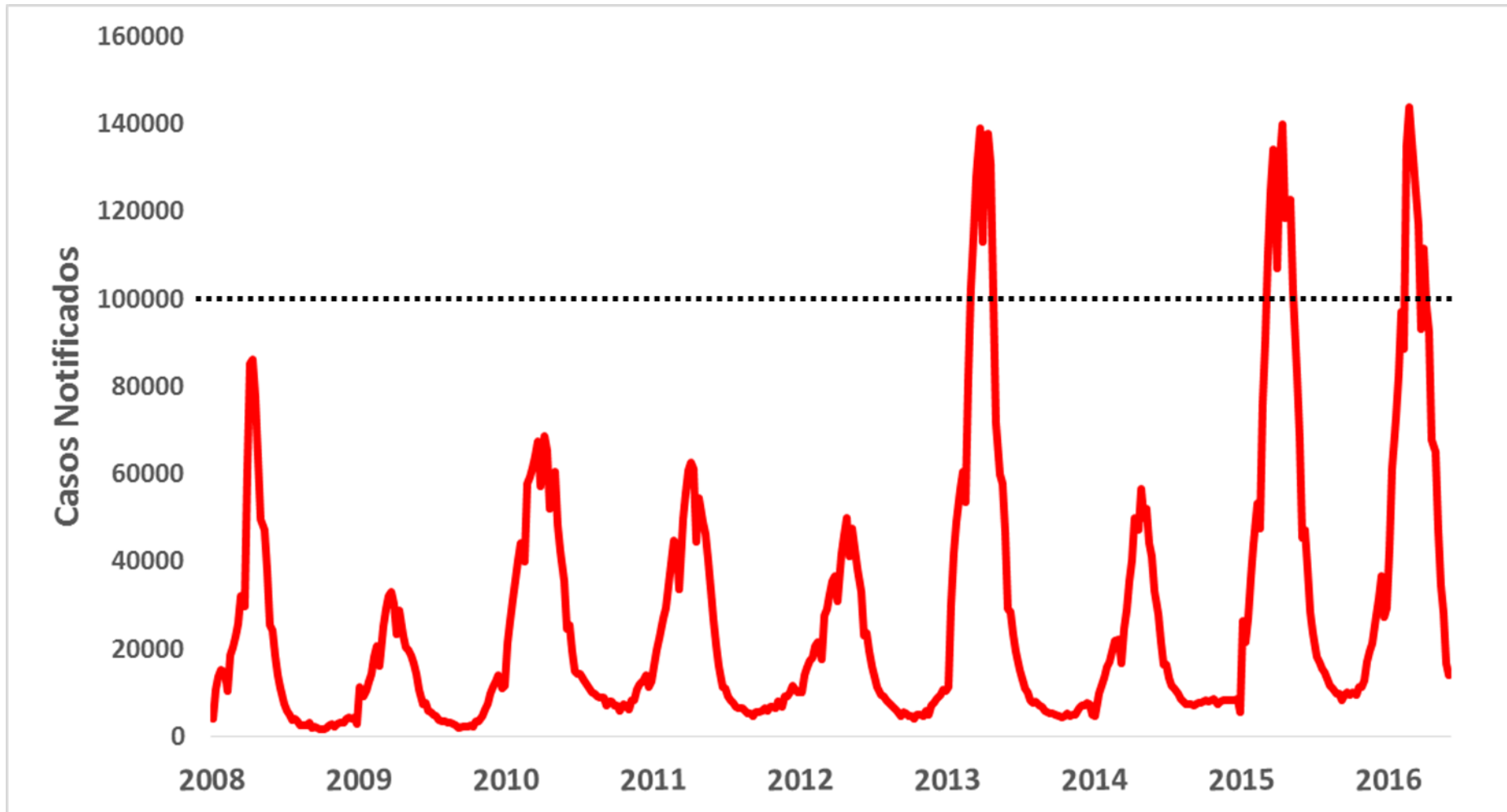
Number of Dengue Cases in the Americas by Decade, 1980 – 2016*



Kindly shared by J.L. San Martin / OPAS

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

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



*preliminar data for 2016

PRESS RELEASE



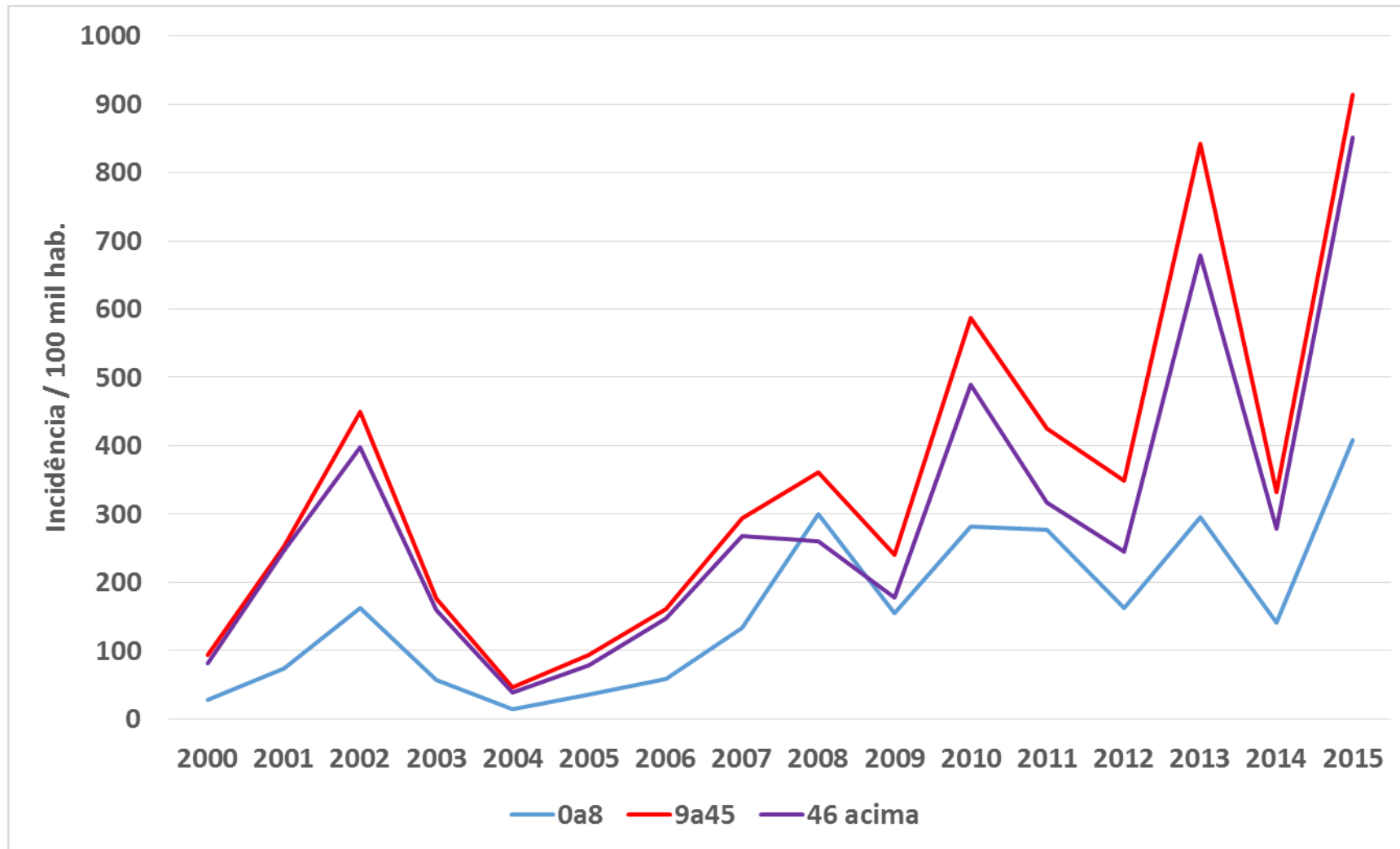
Dengvaxia[®] First Dengue Vaccine Approved in Brazil

- *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 -*

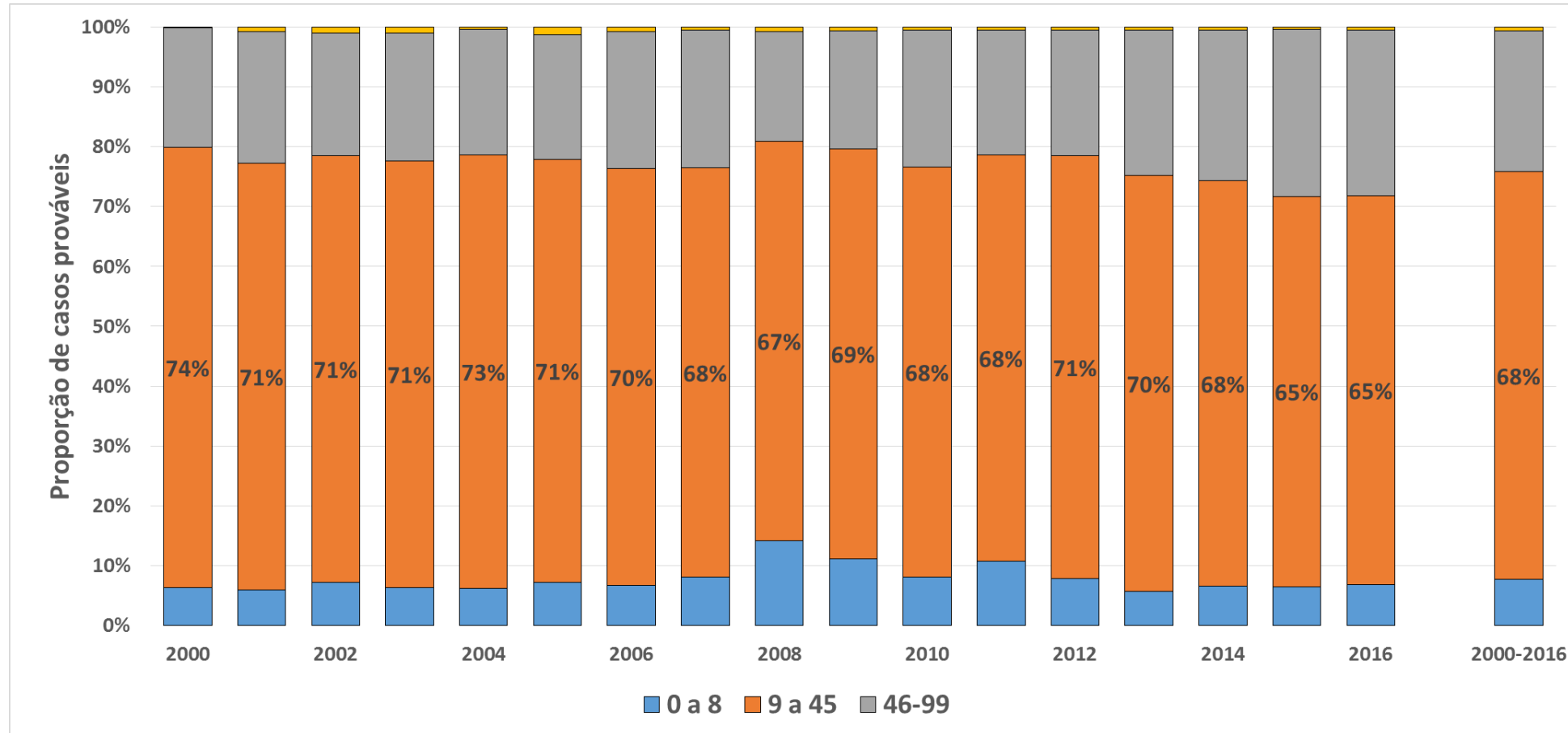
Lyon, France - December 28, 2015 - [Sanofi Pasteur](#), the vaccines division of [Sanofi](#), announced today that Brazil has granted regulatory approval to Dengvaxia[®], representing the third successful licensure of the dengue vaccine, which was also approved in Mexico and the Philippines earlier this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



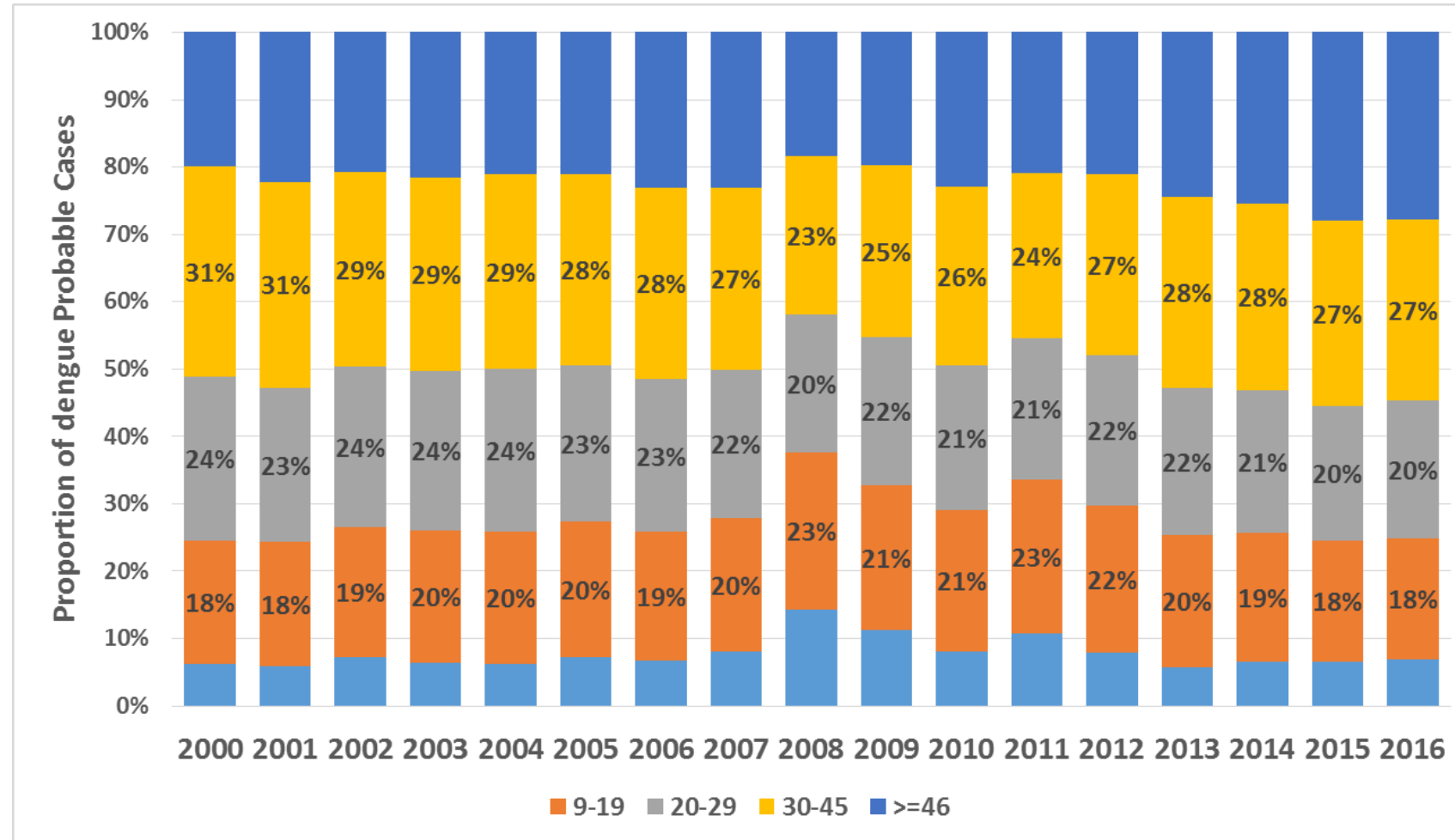
Proportion of Dengue Probable Cases by Age Group, Brazil, 2000 – 2016*



*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

A comparative study on active and passive epidemiological surveillance for dengue in five countries of Latin America

Elsa Sarti ^{a,*}, Maïna L'Azou ^b, Marcela Mercado ^c, Pablo Kuri ^d, Joao Bosco Siqueira Jr ^e, Erick Solis ^a, Fernando Noriega ^f, R. Leon Ochiai ^b

[International Journal of Infectious Diseases 44 \(2016\) 44–49](#)

RESEARCH ARTICLE

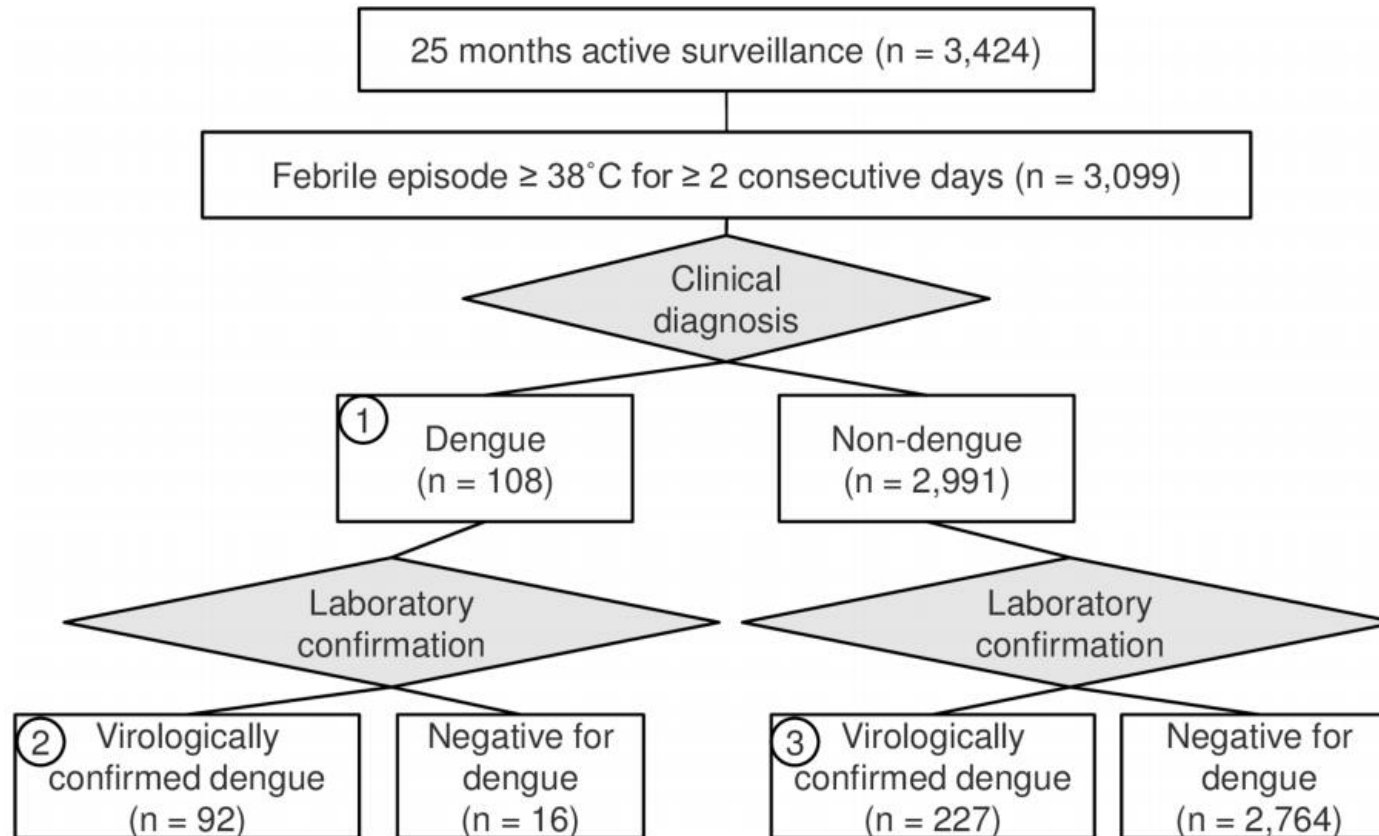
Symptomatic Dengue Disease in Five Southeast Asian Countries: Epidemiological Evidence from a Dengue Vaccine Trial

Joshua Nealon ^{1,*}, Anne-Frieda Taurel ¹, Maria Rosario Capeding ², Ngoc Huu Tran ³, Sri Rezeki Hadinegoro ⁴, Tawee Chotpitayasunondh ⁵, Chee Kheong Chong ⁶, T. Anh Wartel ¹, Sophie Beucher ¹, Carina Frago ¹, Annick Moureau ⁷, Mark Simmerman ¹, Thelma Laot ¹, Maïna L'Azou ⁸, Alain Bouckenoghe ¹

- **Control groups from phase III studies:**
- **Acute febrile illness and virologically confirmed dengue (VCD)**
 - **3,424 children, 2 to 16 years of age, in Asia (Indonesia, Malaysia, the Philippines, Thailand, and Vietnam) from June 2011 through December 2013**
 - **6,939 children, 9 to 18 years of age, in Latin America (Brazil, Colombia, Honduras, Mexico, and Puerto Rico) from June 2011 through April 2014.**
 - **Acute febrile episodes were determined to be VCD by means of a detection of NS1 antigen by ELISA and dengue viral RNA by RT-PCR.**
 - **Episodes of fever 38°C on 2 consecutive days were recorded and clinically diagnosed as DF or DHF based on 1997 WHO guidelines**

- **Sub-national passive dengue surveillance data from districts, provinces, or cities encompassing each clinical trial center were retrieved from official government surveillance systems or from personal communications**
- **Expansion factors were calculated by dividing the adjusted Incidence Density or Rates captured during CYD14 / CYD 15 for each case definition by the Incidence Rates reported by the national passive surveillance systems at each geographical unit.**

Asia



319 virologically confirmed dengue cases:

- 92 cases (28.8%) were clinically diagnosed as dengue fever or DHF by investigators
- 227 were not, indicating that most symptomatic disease fails to satisfy existing case definitions.

Asia

Table 3. Expansion factors for VCD, cVCD, and CDD over the active phase of the CYD14 study.

Country	VCD [95% CI]	cVCD [95% CI]	CDD [95% CI]
Indonesia	11.5 [7.4, 17.3]	6.9 [3.8, 12.0]	9.4 [5.6, 15.1]
Malaysia	31.7 [17.0, 57.5]	10.4 [4.5, 28.6]	12.0 [5.7, 30.3]
Philippines	11.5 [9.1, 14.3]	0.7 [0.3, 1.5]	0.7 [0.3, 1.5]
Thailand	12.0 [8.6, 16.2]	8.6 [5.9, 12.2]	8.8 [6.1, 12.5]
Vietnam	5.5 [3.6, 8.3]	0.5 [0.2, 2.1]	1.7 [0.3, 4.7]

CI, confidence interval; VCD, virologically confirmed dengue CDD, cVCD, clinically diagnosed and virologically confirmed dengue; CDD, clinically diagnosed dengue.

Results emphasize the heterogeneity of dengue case definitions, surveillance systems and clinical practices, which challenge the generation of consistent burden estimates.

Americas

Comparison between the CYD15 study cohort (aged 9–18 years) and National Epidemiological Surveillance System data (for those aged 10–19 years) for the period June 2011 to April 2014.

	IR confirmed cases per 100 (95% CI)		Ratio of CYD15/ NESS _(Local sites)
	CYD15 study (control arm)	NESS _(Local sites)	
Brazil	3.5 (2.8–4.4)	0.180 (0.1797–0.1807)	19.4 (15.8–24.2)
Colombia	2.6 (2.2–3.0)	0.734 (0.7320–0.7361)	3.5 (3.0–4.0)
Mexico	2.5 (1.9–3.2)	0.297 (0.2957–0.2989)	8.4 (6.5–10.9)
Overall	2.9 (2.6–3.2)	0.286 (0.2857–0.2868)	10.0 (8.8–11.0)

The level of underreporting estimated at the local level in Brazil (19.4-fold), Colombia (3.5-fold), and Mexico (8.4-fold) in the present study may be considered the closest to the real-life situation in these countries.

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; [‡]Full 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.

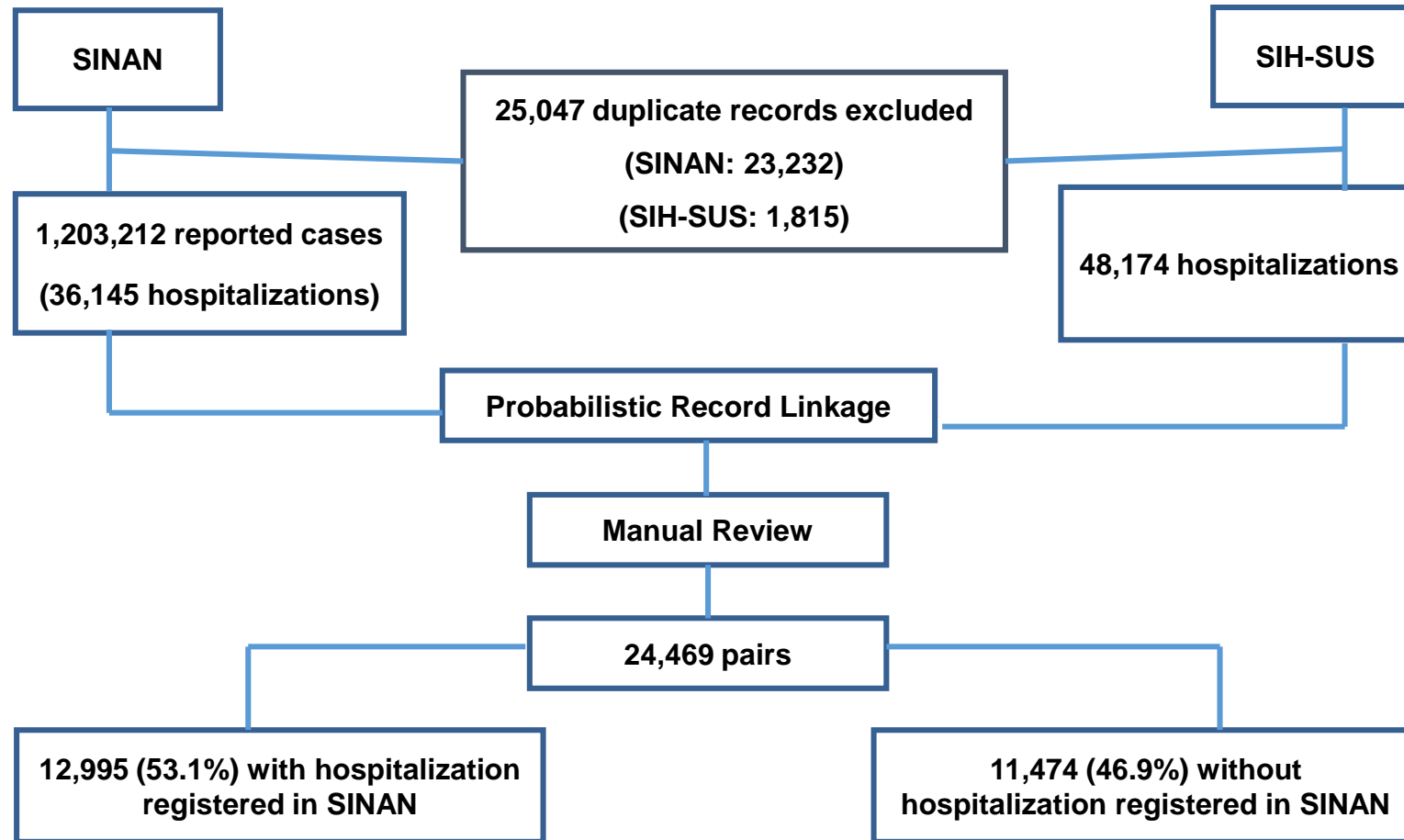
RESEARCH ARTICLE

Sensitivity of the Dengue Surveillance System in Brazil for Detecting Hospitalized Cases

Giovanini Evelim Coelho^{1,2}*, Priscila Leite Leal¹, Matheus de Paula Cerroni¹, Ana Cristina Rocha Simplicio¹, João Bosco Siqueira, Jr.²

- The need for accurate data is of paramount importance due to not only the increase of severe cases in the past decade and to monitor the impact of a vaccine as soon as it occurs.
- The evaluation of the sensitivity of surveillance system is a challenge (lack of a gold standard)
- Two very well structured and independent information systems with nationwide coverage were used to estimate the sensitivity of the surveillance system for detecting hospitalized cases.

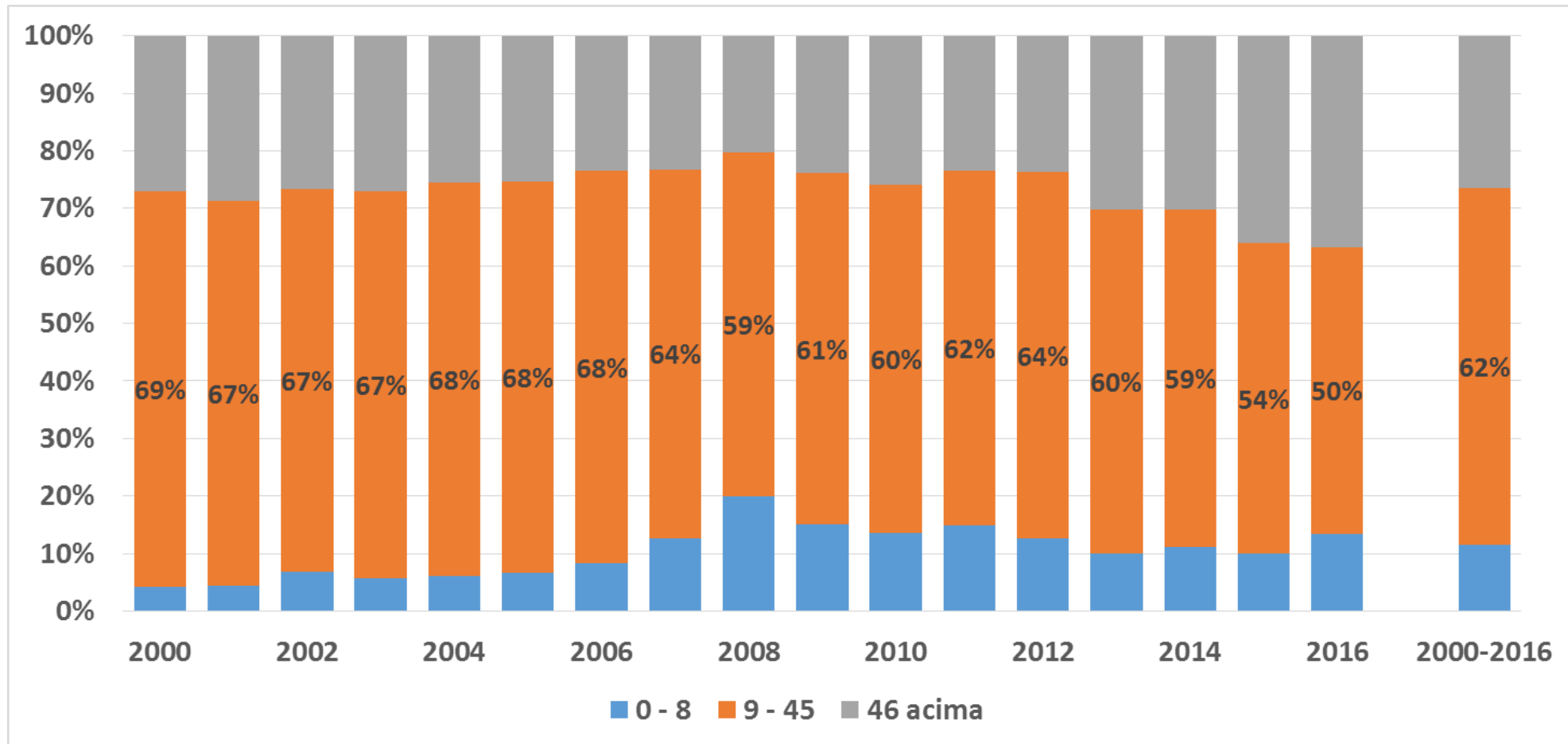
Probabilistic Record Linkage of hospitalized dengue from SINAN and SIH-SUS in ten municipalities of the study, 2008 – 2013



Number of cases hospitalized in SINAN, SIH-SUS and the sensitivity of the dengue surveillance system in detecting hospitalized cases in ten municipalities in Brazil, 2008 - 2013

Information Source	2008	2009	2010	2011	2012	2013	Total
	N	N	N	N	N	N	N
SINAN Hospitalization	11.108	788	6.514	9.094	3.758	3.494	34.756
SIH-SUS	18.251	3.455	8.202	10.050	4.836	3.380	48.174
Pairs SINAN and SIH-SUS	7.781	1.425	5.116	4.299	3.174	2.674	24.469
With hospitalization registered in SINAN (%)	3.462 (44.5)	287 (20.1)	3.055 (59.7)	2.942 (68.4)	1.832 (57.7)	1.417 (53.0)	12.995 (53.1)
Without hospitalization registered in SINAN (%)	4.319 (55.5)	1.138 (79.9)	2.061 (40.3)	1.357 (31.6)	1.342 (42.3)	1.257 (47.0)	11.474 (46.9)
Sensitivity method 1* % (IC95%)	19 (18.4-19.4)	8.3 (7.4-9.3)	37.2 (36.2-38.3)	29.3 (28.4-30.2)	37.9 (36.5-3.3)	41.9 (40.2-43.6)	27.0 (26.6-27.4)
Sensitivity Method 2† % (IC95%)	42.6 (41.9-43.3)	41.2 (39.6-42.9)	62.4 (61.3-63.4)	42.8 (41.8-43.7)	65.6 (64.3-66.9)	79.1 (77.7-80.5)	50.8 (50.3-51.2)
Total Estimated Hospitalizations‡	25,897	3,956	11,661	16,202	6,762	5,457	69,935

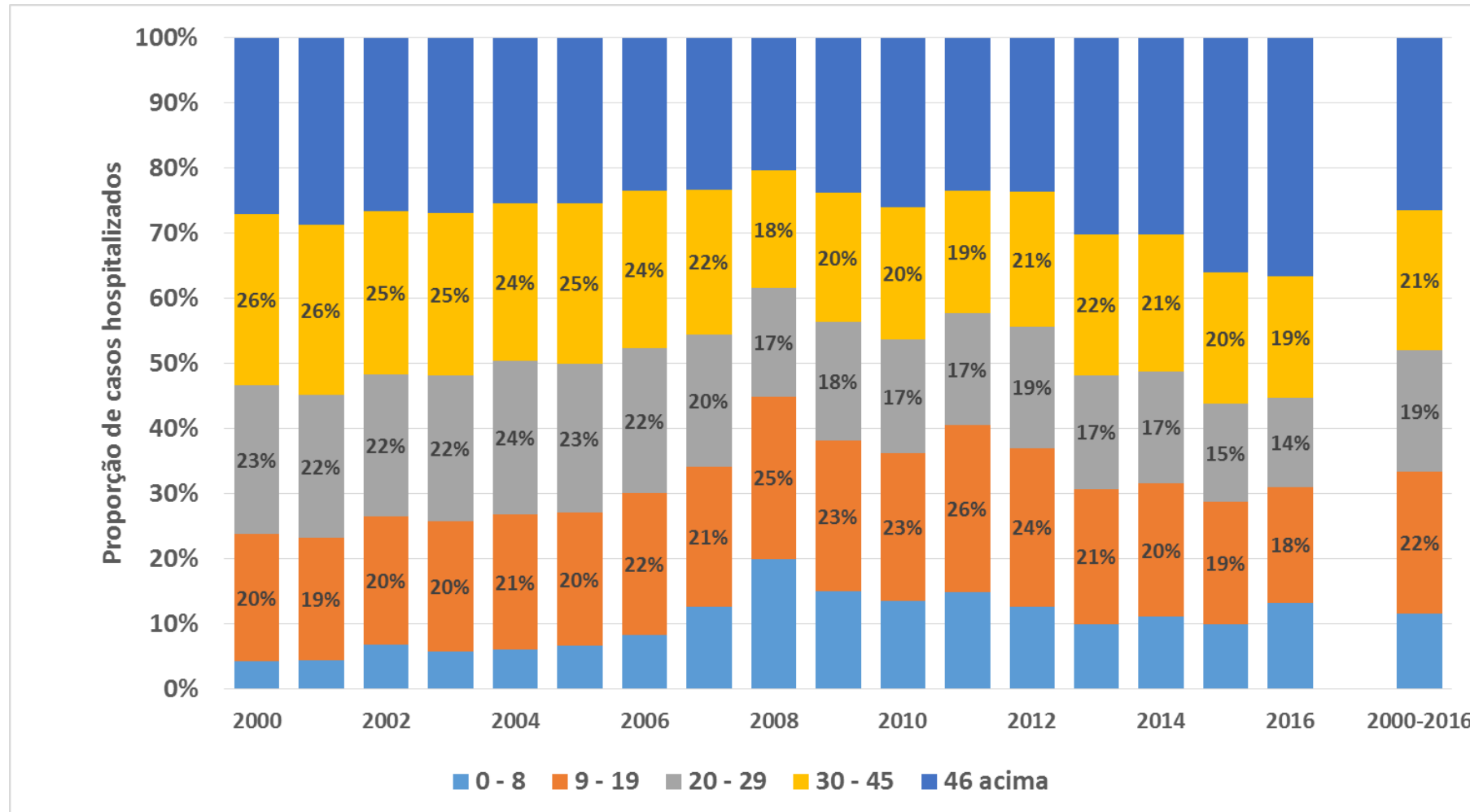
Proportion of Dengue Hospitalized Cases by Age Group, Brazil, 2000 – 2016*



*Preliminary data for 2016.

Source: SIH/SAS/MS

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Dengue Reported and Hospitalized cases in Brazil, 2006 - 2015

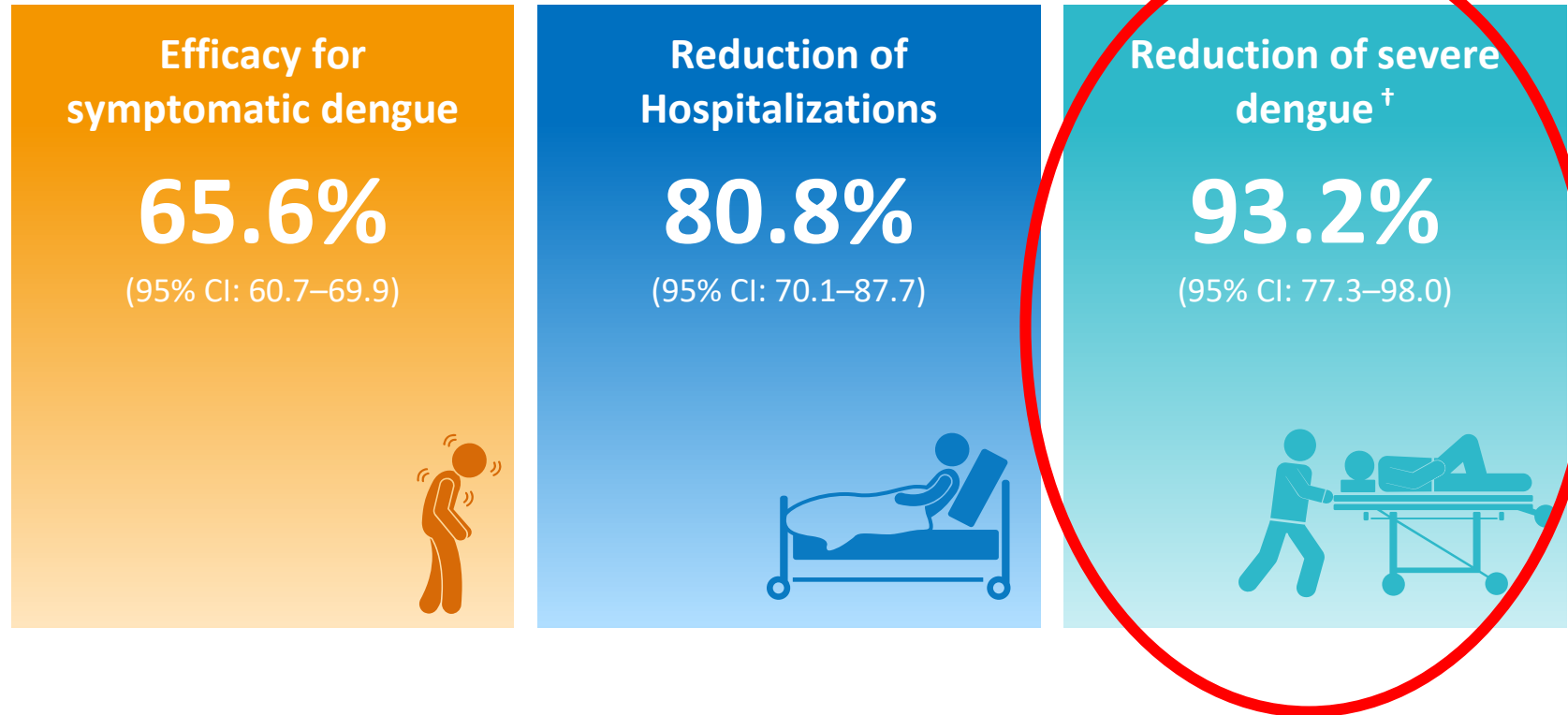
Dengue season	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Probables Cases (in thousands)	259,1	481,8	651	357,1	1025,7	771,4	588,3	1474,5	573,8	1579,8
Hospitalizations (in thousands)	31,5	51,2	77,2	50,7	91,9	83,3	54,2	64,5	36,8	65,6
Reported/Hospitalized	8,2	9,4	8,4	7,0	11,2	9,3	10,9	22,9	15,6	24,1

- Contingency plans in place after the 2010 epidemic

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

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ARTÍCULO ORIGINAL

Comportamiento de la mortalidad por dengue en Colombia entre 1985 y 2012

Pablo Chaparro-Narváez, Willian León-Quevedo, Carlos Andrés Castañeda-Orjuela

Observatorio Nacional de Salud, Instituto Nacional de Salud, Bogotá, D.C., Colombia

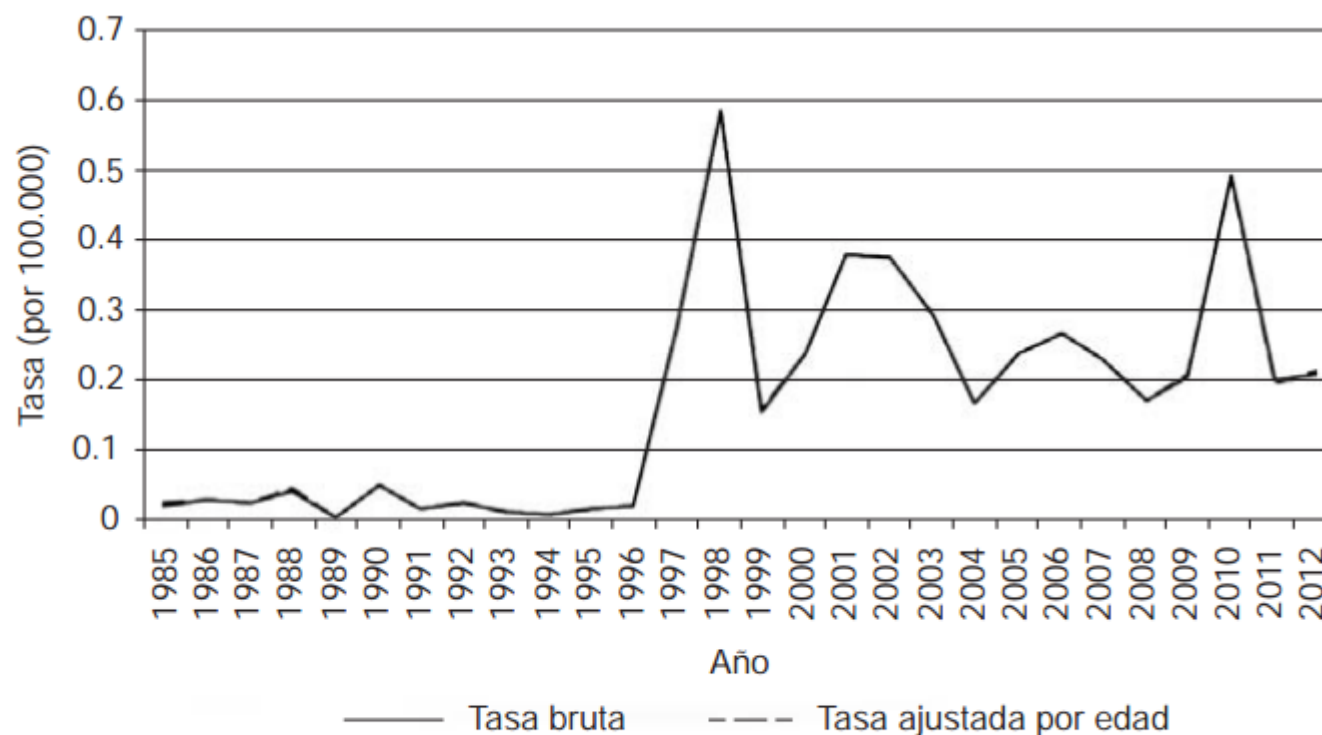


Figura 1. Tasas de mortalidad por dengue, Colombia, 1985-2012

Fuente: Estadísticas vitales, DANE

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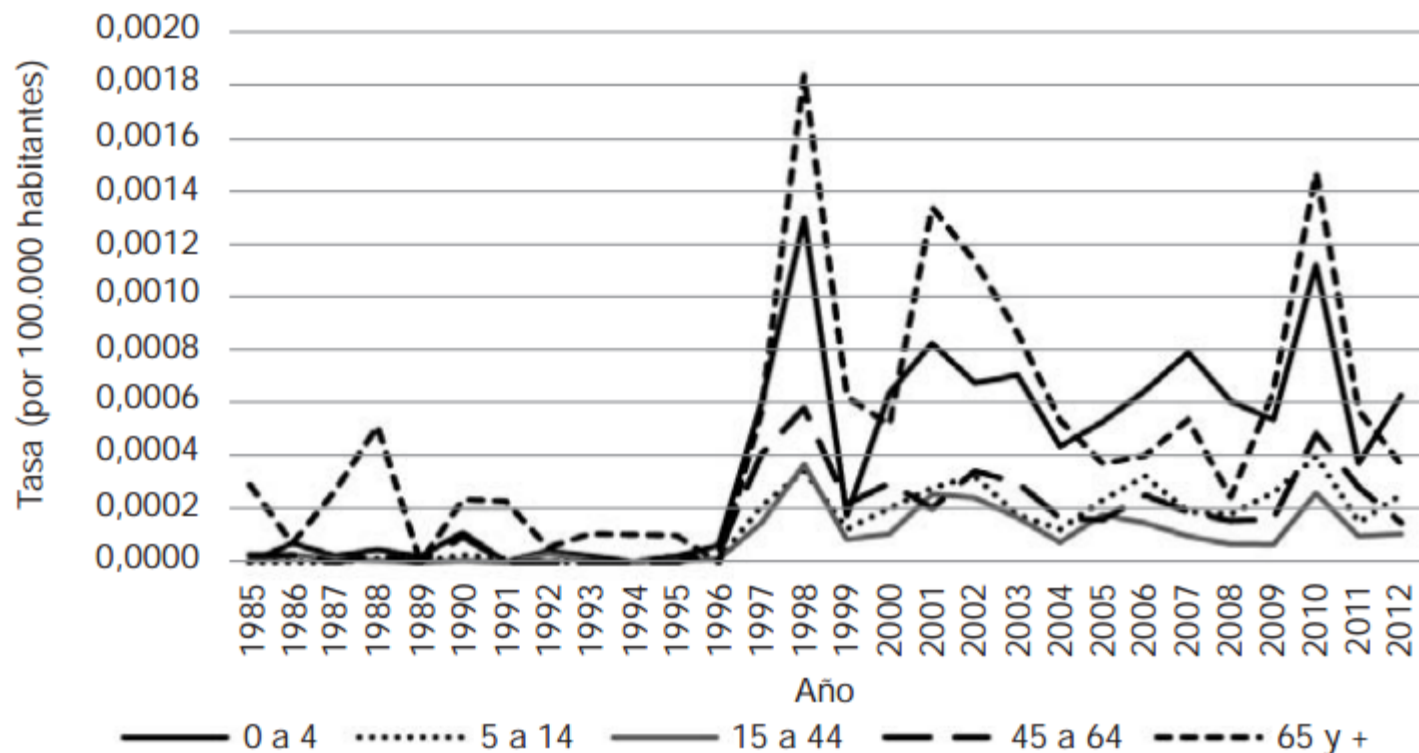
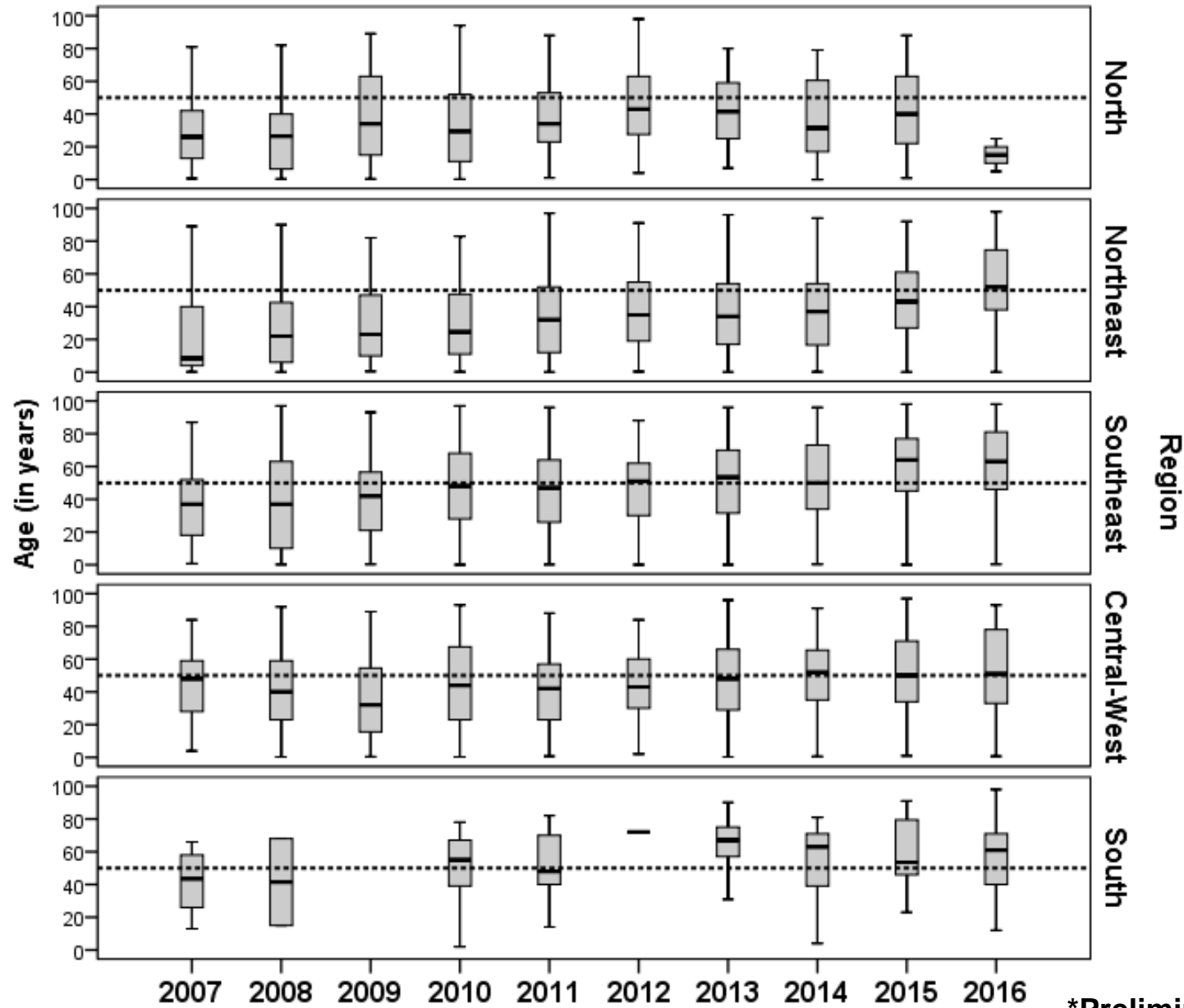


Figura 2. Tasas de mortalidad por dengue según grupo de edad, Colombia, 1985-2012

Fuente: Estadísticas vitales, DANE

Dengue deaths by Age and Region, Brazil, 2007 – 2016*



*Preliminary data. Source: Sinan/SVS

Postmortem Diagnosis of Dengue as an Epidemiological Surveillance Tool.

Cavalcanti LP¹, Braga DN², da Silva LM², Aguiar MG², Castiglioni M², Silva-Junior JU², Araújo FM², Pereira RA², Malta DL², Pompeu MM².

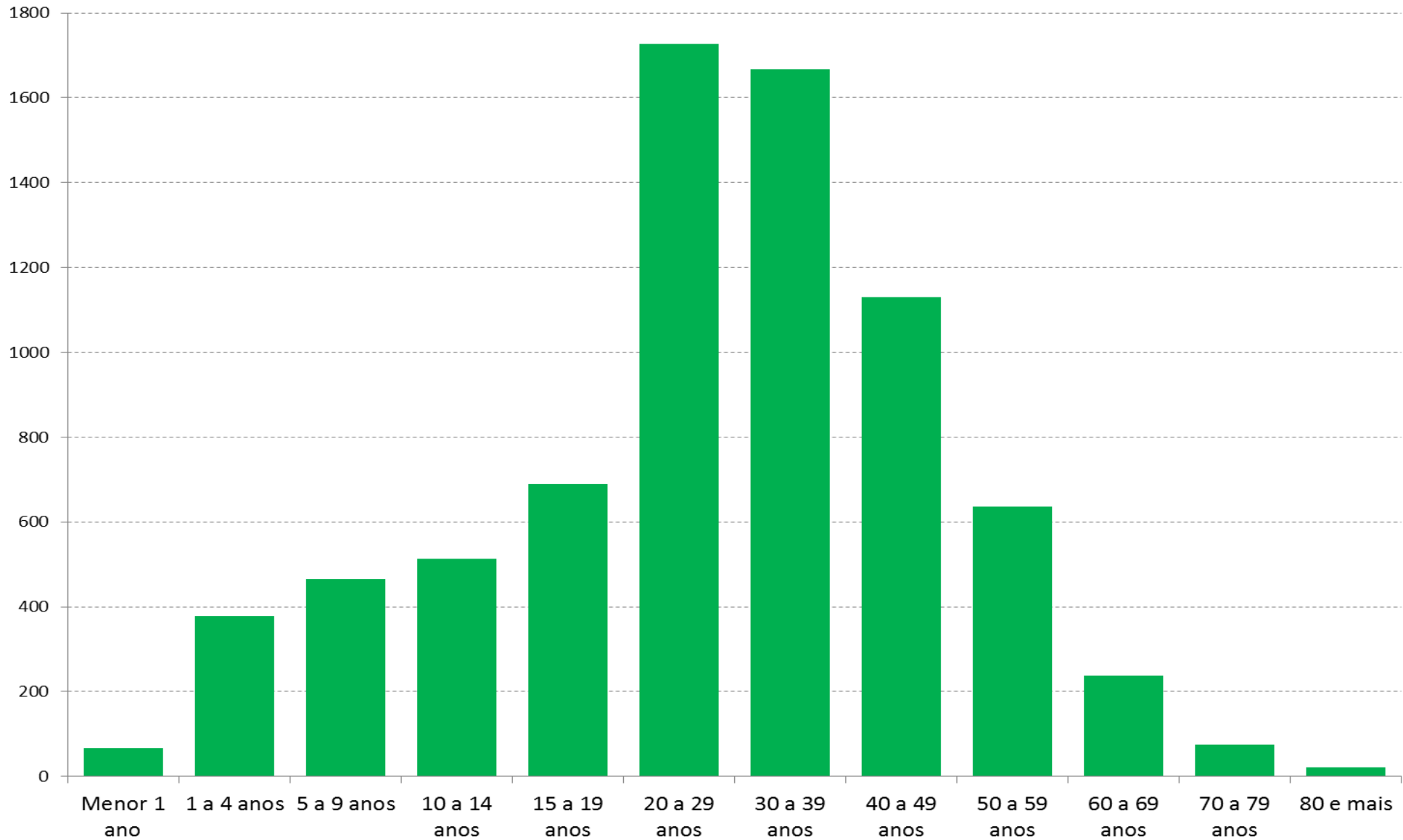
- **Impact of a protocol adopted by the Coroner's Office (CO) for the detection of unreported deaths from dengue**
- **Suspected dengue deaths referred to the CO and those referred with other diagnosis in which the pathologists suspected dengue as the cause of death.**
- **Biological material was collected for suspected dengue as the cause of death was dengue, between January 2011 and December 2012**
- **214 bodies autopsied: 134 (62.6%) tested positive for dengue - 90 deaths from dengue, which were not suspected during disease progression**
- **Combined effort of the surveillance and laboratory teams increased the detection of fatal dengue cases by 5-fold**

The Wizard of Oz...



Toto, I've got a feeling we're not in Kansas anymore



Age distribution of suspected cases by Zika virus in Brazil, 2015-2016





Case Report

Zika, Dengue and Chikungunya Co-Infection in a Pregnant Woman from Colombia

Wilmer E. Villamil-Gómez^{a, b, 1}, Alfonso J. Rodríguez-Morales^{a, c, 1}, Ana María Uribe-García^d, Edgardo González-Arismendy^d, Jaime E. Castellanos^e, , , Eliana P. Calvo^e, Melchor Álvarez-Mon^f, Didier Musso^g

- Weekly obstetric ultrasounds from 14.6 until 29 weeks of gestation were normal.
- Under follow-up and management according standard guidelines for management of ZIKV infected pregnant women

Some questions for the moment...

NATURE | NEWS



Brazil asks whether Zika acts alone to cause birth defects

Puzzling distribution of cases suggests Zika is not the only factor in reported microcephaly surge.

Declan Butler

25 July 2016

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IN DEVELOPING COUNTRIES

Emerging Problems in Infectious Diseases

Zika virus infection, associated microcephaly, and low yellow fever vaccination coverage in Brazil: is there any causal link?

Luciano Pamplona de Góes Cavalcanti¹, Pedro Luiz Tauil⁵, Carlos Henrique Alencar¹, Wanderson Oliveira², Mauro Martins Teixeira³, Jorg Heukelbach^{1,4}

[Trends Immunol.](#) 2016 Sep 2. pii: S1471-4906(16)30096-5. doi: 10.1016/j.it.2016.08.006. [Epub ahead of print]

Dengue Antibody and Zika: Friend or Foe?

[Durbin AP](#)¹.

Conclusions

- **Clinical trials of dengue vaccines allowed to estimate expansion factors**
- **Better evidence to estimate the burden of dengue**
- **Impact on hospitalizations and deaths needs careful evaluation – what is the “true” scenario**
- **Need to improve knowledge of potential interactions of Dengue infections and Zika outcomes**