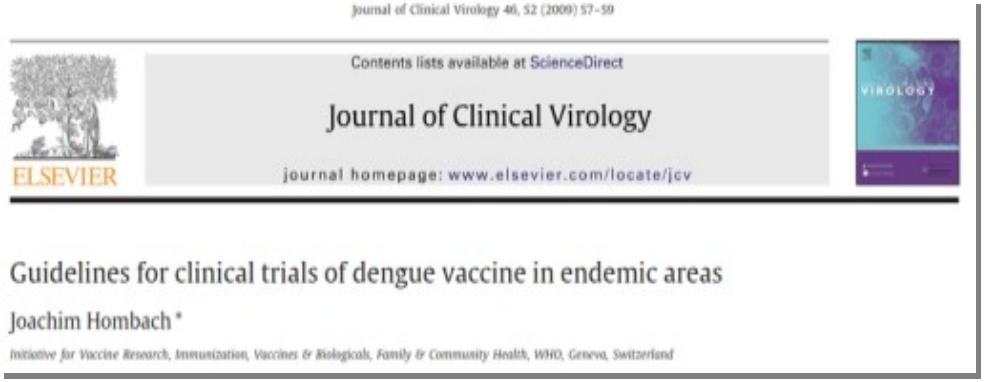
I Reunión de la Comisión Nacional de Inmunizaciones
Marzo 2018

Actualización de vacunas contra el dengue

Dra. Marina Pasinovich
DiCEI, MSAL

CoNaIn

Ministerio de Salud
Presidencia de la Nación


Journal of Clinical Virology 46, S2 (2009) S7–S9

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Guidelines for clinical trials of dengue vaccine in endemic areas

Joachim Hombach *

Initiative for Vaccine Research, Immunization, Vaccines & Biologicals, Family & Community Health, WHO, Geneva, Switzerland

Complejidad de la infección por dengue y dificultades en el diseño de la vacuna

1. Mayor riesgo de enfermedad grave por infección heterotípica secundaria. Generación de una vacuna tetravalente destinada a proporcionar protección a largo plazo contra todos los serotipos del virus.
2. Falta de un modelo adecuado de enfermedad animal
3. Incertidumbre en torno a los correlatos de protección
4. Anticuerpos subneutralizantes heterotípicos por infección previa que conllevan riesgo de infección severa con la segunda exposición (ADE)
5. Evaluación de la respuesta inmune en personas con o sin infecciones previas por flavivirus.
6. Seguridad de la vacuna

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Thisyakorn U. *Ther Adv Vaccines* 2014;2(1):3–9

Vacuna ideal contra el dengue

- vacunas monovalentes capaces de inducir protección homotípica, y posteriormente combinarlas en una formulación tetravalente.

- Inducción de una inmunidad protectora fuerte y equilibrada contra los cuatro serotipos DV para evitar el riesgo potencial de ADE después de la vacunación.

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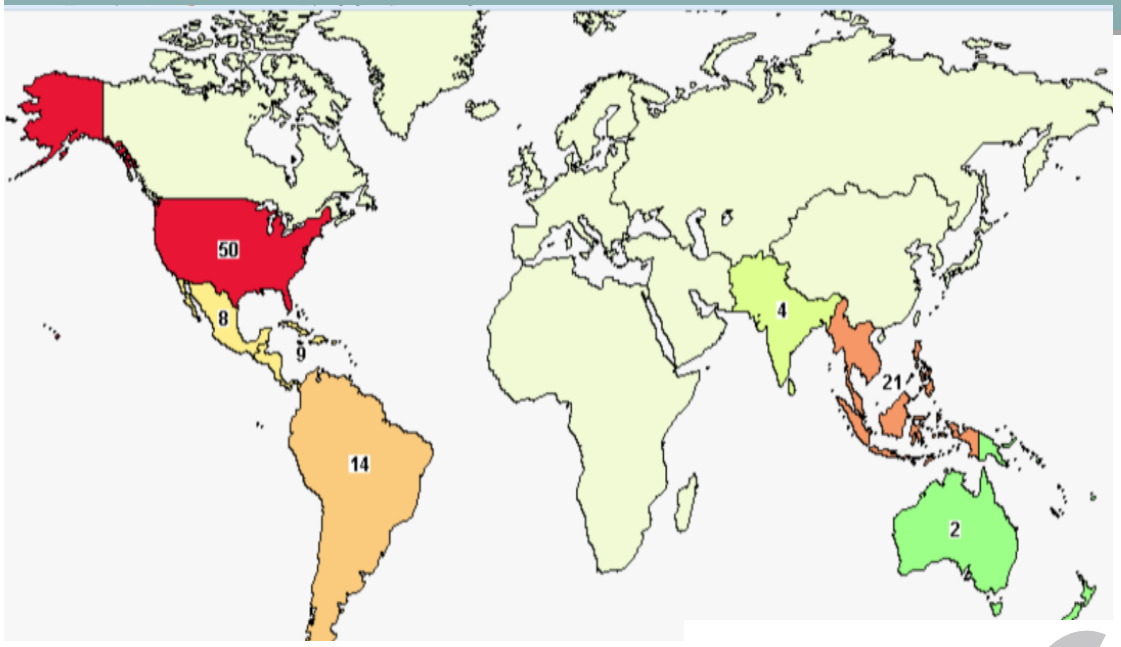
Angel RMd, Valle JR-d. PLoS Pathog 2013; 9(10): e1003551. doi:10.1371/journal.ppat.1003551

Vacunas contra el dengue en desarrollo



Region Name	Number of Studies	
World	96	
Central America [map]	9	
North America	58	
Mexico	8	[studies]
United States [map]	50	[studies]
Pacifica [map]	2	
South America [map]	14	
South Asia [map]	4	
Southeast Asia [map]	21	

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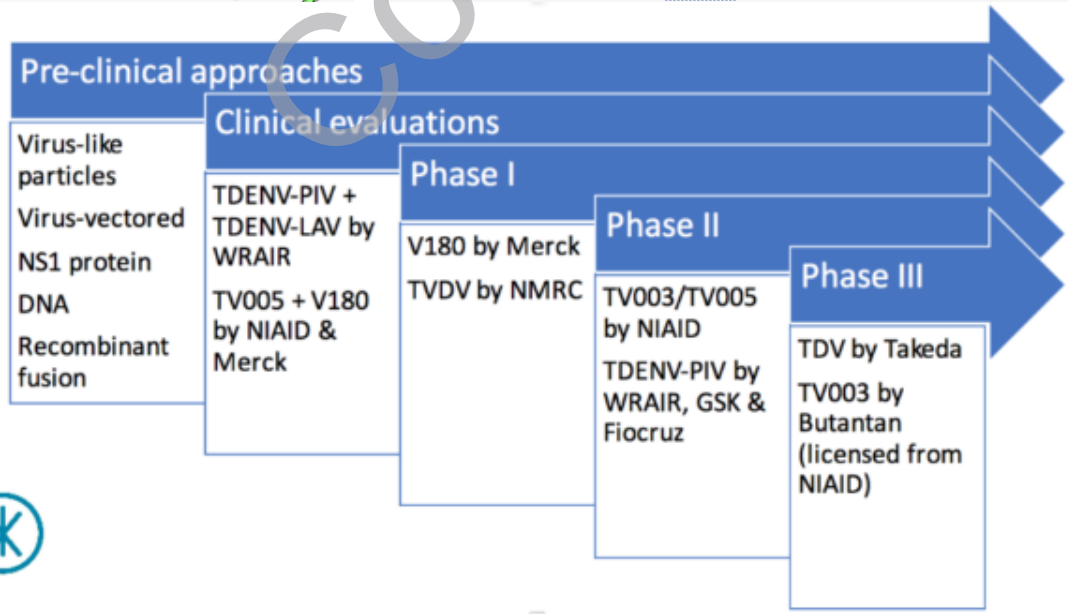

https://clinicaltrials.gov/ct2/results/map?cond=dengue+vaccine&map
=
Updated: Dec 18, 2017.

Vacuna CYD-TDV

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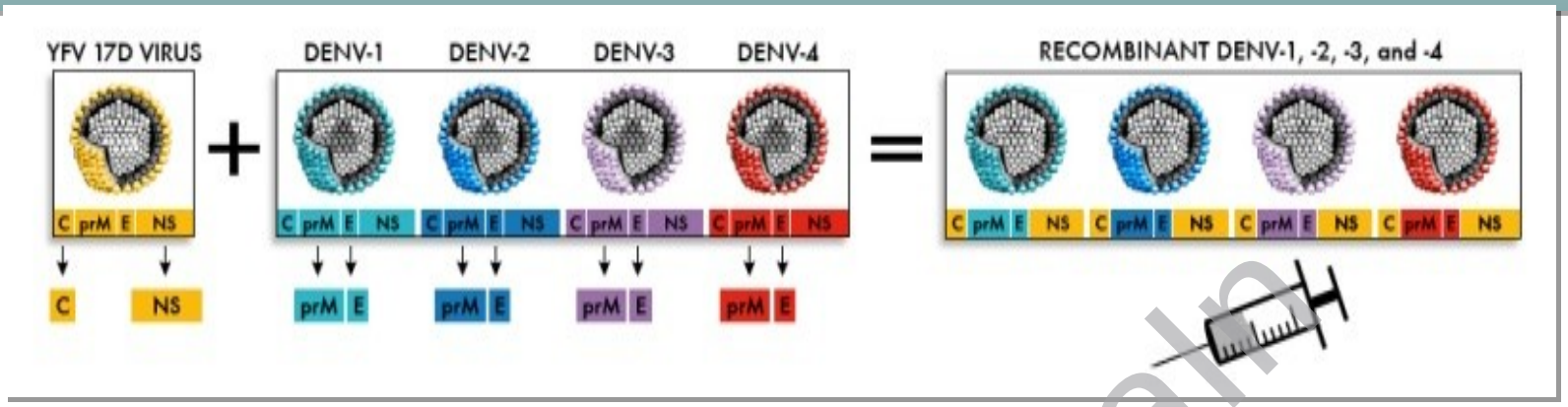
CYD TDV (Dengvaxia®)



- Sobre estructura de vacuna contra la fiebre amarilla 17D

- Reemplazo de los genes estructurales premembrana (preM) y de envoltura (E) por los de cada uno de los 4 serotipos de dengue (DENV-1-4)

- 3 dosis (administradas a 0, 6 y 12).

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CYD TDV (Dengvaxia®)

CYD14 Asia
NCT01373281
5 Countries, 11 Sites
2–14 years, 10, 275 volunteers

CYD15 Latin America
NCT01374516
5 Countries, 22 sites
9–16 years, 20,869 volunteers

ACTIVE PHASE
Active Surveillance/Detection of Dengue Cases
Including hospitalized dengue cases

HOSPITAL PHASE
Additional follow-up for safety of hospitalized dengue cases for 4 years after the end of the active phase

Per Protocol (PP)	13 mo – 25 mo	VE against symptomatic VCD, irrespective of disease severity or serotype, occurring >28 days post-dose 3
Intent to Treat (ITT)	25 mo	Efficacy, Immunogenicity and safety

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The NEW ENGLAND JOURNAL of MEDICINE

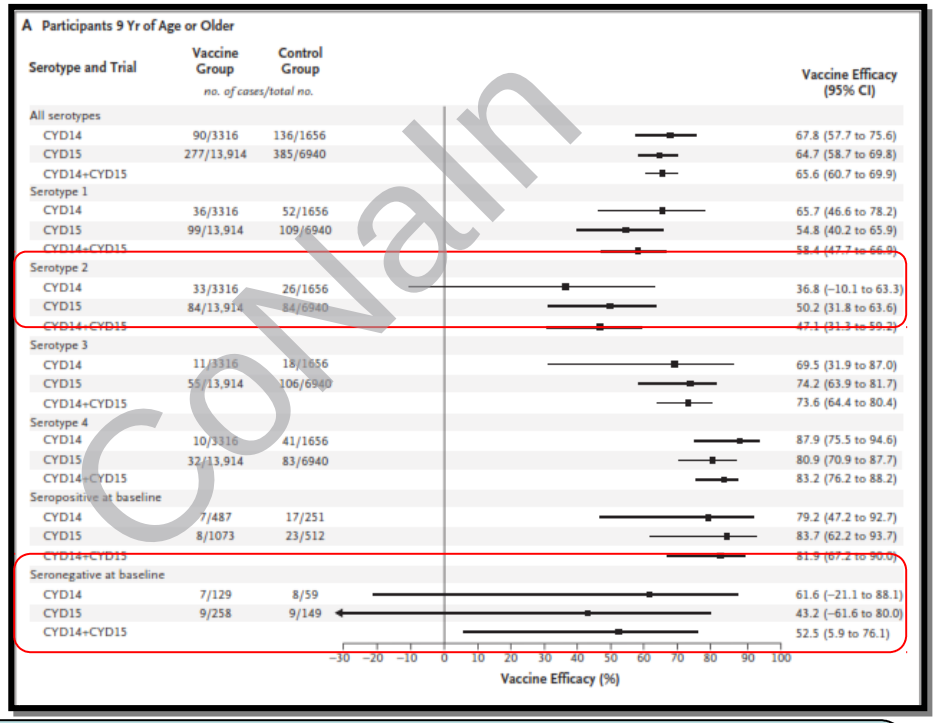
ESTABLISHED IN 1812 SEPTEMBER 24, 2015 VOL. 373 NO. 13

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

S.R. Hadinegoro, J.L. Arredondo-García, M.R. Capeding, C. Deseda, T. Chotpitayasunondh, R. Dietze, H.I. Hj Muhammad Ismail, H. Reynales, K. Limkittikul, D.M. Rivera-Medina, H.N. Tran, A. Bouckenooghe, D. Chansinghakul, M. Cortés, K. Fanouillere, R. Forrat, C. Frago, S. Gailhardou, N. Jackson, F. Noriega, E. Plennevaux, T.A. Wartel, B. Zambrano, and M. Saville, for the CYD-TDV Dengue Vaccine Working Group*

CYD14 y CYD15 (≥ 9 years)

Serotype/Seroprevalence	Vaccine Efficacy (CI 95%)
Overall	65.6 (60.7 – 69.9)
DENV-1	58.4 (47.7 – 66.9)
DENV-2	47.1 (31.3 – 59.2)
DENV-3	73.6 (64.4 – 80.4)
DENV-4	83.2 (76.2 – 88.2)
Seropositive at baseline	81.9 (67.2 – 90.0)
Seronegative at baseline	52.5 (5.9 – 76,1)



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2015 (CYD14 y CYD15): Reducción del riesgo de dengue sintomático para seronegativos 52,5% (IC 95% 5,9% a 71,1%)

Hadinegoro SR, et al. N Engl J Med 2015;373:1195-206.

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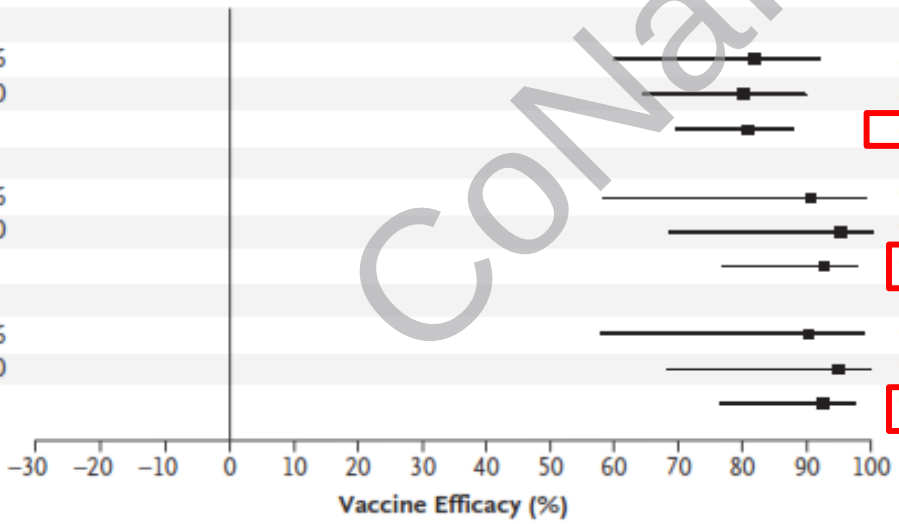
A Participants 9 Yr of Age or Older

Criteria and Trial	Vaccine Group	Control Group	Vaccine Efficacy (95% CI)
	no. of cases/total no.		
All severity hospitalized			
CYD14	10/3316	27/1656	81.6 (60.7 to 92.0)
CYD15	17/13,914	43/6940	80.3 (64.7 to 89.5)
CYD14+CYD15			80.8 (70.1 to 87.7)
Severe (IDMC) hospitalized			
CYD14	2/3316	11/1656	90.9 (58.4 to 99.0)
CYD15	1/13,914	11/6940	95.5 (68.8 to 99.9)
CYD14+CYD15			93.2 (77.3 to 98.0)
DHF (WHO 1997) hospitalized			
CYD14	2/3316	11/1656	90.9 (58.4 to 99.0)
CYD15	1/13,914	11/6940	95.5 (64.9 to 99.9)
CYD14+CYD15			92.9 (76.1 to 97.9)



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Hadinegoro SR, et al. N Engl J Med 2015;373:1195-206.

2016, 91, 349-364 No 30

World Health Organization

Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

29 JULY 2016, 91th YEAR / 29 JUILLET 2016, 91e 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 consider introduction of the dengue vaccine CYD-TDV only in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease.

In defining populations to be targeted for vaccination, prior infection with dengue virus of any serotype, as measured by seroprevalence, should be approximately 70% or greater in the age group targeted for vaccination in order to maximize public health impact and cost-effectiveness. Vaccination of populations with seroprevalence between 50% and 70% is acceptable but the impact of the vaccination programme may be lower. The vaccine is not recommended when seroprevalence is below 50% in the age group targeted for vaccination.

World Health Organization

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Immunization, Vaccines and Biologicals

Updated Questions and Answers related to the dengue vaccine Dengvaxia® and its use

Published 22 December 2017

This document takes into account new and unpublished data that were communicated by Sanofi Pasteur to WHO in November-December 2017.

WHO published the recommendations of the Strategic Advisory Group of Experts on Immunization (SAGE) on the use of Dengvaxia® on 27 May 2016 (1), and subsequently a WHO position paper on dengue vaccine on 29 July 2016 (2).

Following the disclosure to WHO of new data on Dengvaxia® by its manufacturer, Sanofi Pasteur, as described in more detail below, WHO has initiated a process engaging independent external experts to review the data in detail. This process is expected to lead to revised recommendations from SAGE in April 2018, and to an updated WHO position paper on dengue vaccine thereafter.

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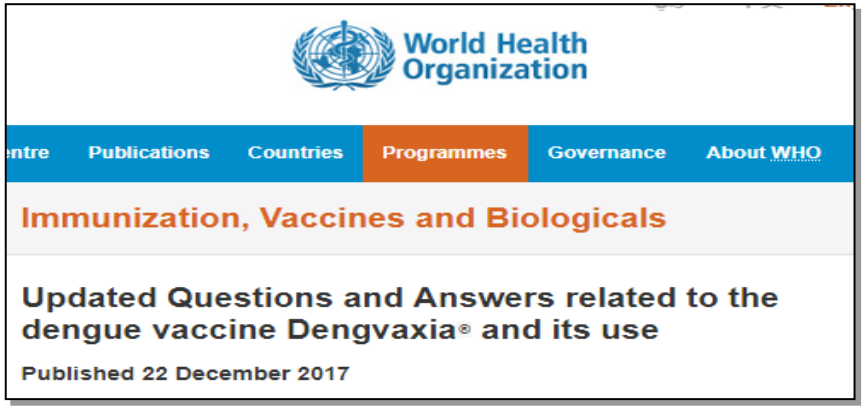

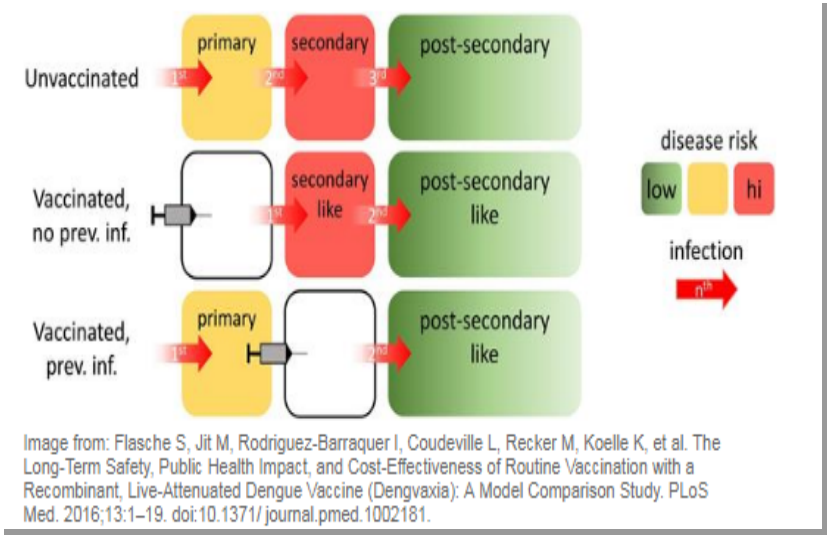

Image from: Flasche S, Jit M, Rodriguez-Barraquer I, Coudeville L, Recker M, Koelle K, et al. The Long-Term Safety, Public Health Impact, and Cost-Effectiveness of Routine Vaccination with a Recombinant, Live-Attenuated Dengue Vaccine (Dengvaxia): A Model Comparison Study. PLoS Med. 2016;13:1–19. doi:10.1371/ journal.pmed.1002181.

Información provista por el laboratorio Sanofi Pasteur en 2017 (5 años de observación)

- Método: Utilización de las muestras tomadas en el mes 13 del estudio (1 mes post 3era dosis) con evaluación de la presencia de Acs contra NS1 para inferir infección salvaje previa a la vacunación y determinar serostatus

- Resultados: Los pacientes vacunados seronegativos tuvieron mayor riesgo de dengue grave y hospitalización por dengue comparado con los no vacunados. Aunque ese riesgo observado a los 2 años declinó en el 3er año, persiste a los 5 años

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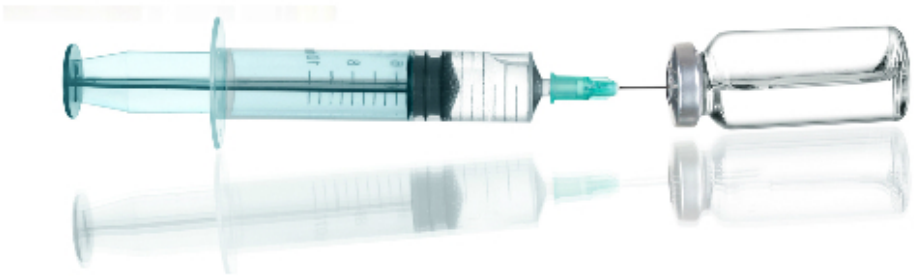
Essential medicines and health products

WHO advises Dengvaxia be used only in people previously infected with dengue



13 DECEMBER 2017 - Following a consultation of the Global Advisory Committee on Vaccine Safety, the World Health Organization (WHO) finds that the dengue vaccine CYD-TDV, sold under the brand name Dengvaxia, prevents disease in the majority of vaccine recipients but it should not be administered to people who have not previously been infected with dengue virus.

Dengvaxia no debe administrarse a personas que no hayan sido infectadas previamente con el virus del dengue debido al aumento en la incidencia de hospitalización y enfermedad grave en niños vacunados que nunca se infectaron con dengue.

CoNaIn

http://www.who.int/medicines/news/2017/WHO-advises-dengvaxia-used-only-in-people-previously-infected/en

Comunicado Sanofi 29/11/2017

"para las personas que no han sido infectadas previamente" por el virus del dengue, no se debe recomendar la vacunación "

(www.mediaroom.sanofi.com)

Los niños vacunados cuando eran seronegativos no estaban protegidos sino que estaban en riesgo de dengue grave y / u hospitalización durante las infecciones por dengue.

(www.cidrap.umn.edu/.../sanofi-restricts-dengue-vaccine-downplays-antibodyenhanc. ement.Dec 1, 2017)

Ministerio de Salud de Filipinas. Diciembre 2018

Conformación de un comité para investigar la muerte de los niños que habían recibido Dengvaxia

(www.philstar.com/headlines/2017/12/09/1766647/doh-forms-task-forcedengvaxia-dengue-vaccine)

(http://www.philstar.com/headlines/2018/01/12/1776969/dohconfirms-dengue-deaths-after-taking-dengvaxia)

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Human Vaccines & Immunotherapeutics

ISSN: 2164-5515 (Print) 2164-554X (Online) Journal homepage: http://www.tandfonline.com/loi/khvi20

Safety issues from a Phase 3 clinical trial of a live-attenuated chimeric yellow fever tetravalent dengue vaccine

Scott B. Halstead

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Scott B. Halstead (2018): Safety issues from a Phase 3 clinical trial of a live-attenuated chimeric yellow fever tetravalent dengue vaccine, Human Vaccines & Immunotherapeutics. DOI: 10.1080/21645515.2018.1445448

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vaccinated children, an observation consistent with their having received Dengvaxia when seronegative. Based upon published efficacy data and in compliance with initial published recommendations by the manufacturer and WHO the Philippine government undertook to vaccinate 800,000-plus 9 year-olds starting in April 2016. Eighteen months later, dengue hospitalizations and a deaths were reported among vaccinated children. The benefits of administering Dengvaxia predicted by the manufacturer, WHO and others derive from scoring dengue hospitalizations of vaccinated children as vaccine failures rather than as vaccine enhanced dengue disease. Recommended regimens for administration of Dengvaxia should have been structured to warn of and avoid serious adverse events. .

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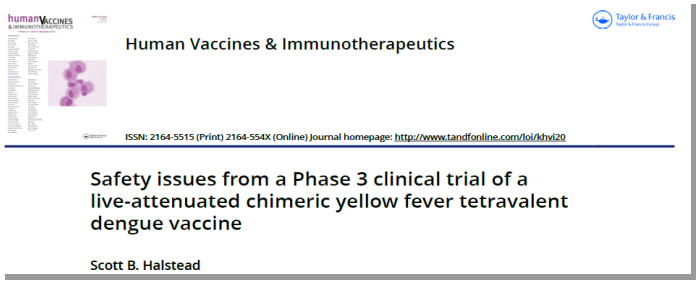

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Scott B. Halstead

- El documento del SAGE proporciona números de vacunados 9 - 11 años de edad.

- Estos datos se utilizaron para estimar el total de niños seronegativos de 9 a 11 años de edad.

- Se estimó que el 15.5% de los niños se exponen anualmente a la infección

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Human Vaccines & Immunotherapeutics

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The risk of dengue hospitalizations occurring in seronegative vaccinated 9 – 11 year-olds was higher than hospitalization risk for secondary DENV infections occurring in the open population, being observed approximately 3 times more frequently than the hospitalization rates of secondary DENV infection hospitalization rates from prospective and retrospective epidemiological studies.[16] The broadly reactive non-protective pan-DENV neutralizing antibodies raised by Dengvaxia are reminiscent of antibodies transferred from mothers with 2 or more lifetime dengue infections to their infants, first protective then enhancing.[17] Surprisingly, the hospitalization rate estimated for primary dengue infections in seronegative children receiving Dengvaxia is similar to estimated hospitalization rates during primary dengue infections for these infants.[16]

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Human Vaccines & Immunotherapeutics

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Safety issues from a Phase 3 clinical trial of a live-attenuated chimeric yellow fever tetravalent dengue vaccine

Scott B. Halstead

Tabla 1. Tasa de hospitalizaciones de seronegativos vacunados de 9-11 años de edad.
Niños con infección primaria por el virus del dengue

Country	Vaccinated	9 – 11 y.o.	% seronegative	No. seronegative	Ave. FOI
Indonesia	1870	430	.21	90	.2
Malaysia	1401	322	.35	113	.1
Philippines	3501	805	.18	145	.2
Thailand a	2666	613	.30	184	.15
Thailand b	1170	269	.22	59	.15
Vietnam	2333	537	.35	188	.18
Brazil	2370	782	.34	266	.1
Colombia	6497	2144	.10	214	.22
Honduras	1866	616	.15	92	.18
Mexico	2312	763	.44	336	.08
Puerto Rico	875	289	.46	133	.15
Totals		7570		1820	1.71/11=0.155

Cantidad de niños por país con infección por dengue promedio de los últimos 10 años

15,5% de exposición anual

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Coudeville Let al Estimation of parameters related to vaccine efficacy and dengue transmission from two large phase III studies. Vaccine 2016; 34 6417-25.

Human Vaccines & Immunotherapeutics

ISSN: 2164-5515 (Print) 2164-554X (Online) Journal homepage: http://www.tandfonline.com/loi/khvi20

Safety issues from a Phase 3 clinical trial of a live-attenuated chimeric yellow fever tetravalent dengue vaccine

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Tabla 2. Riesgo comparativo de hospitalización de niños vacunados de 9 a 11 años con una primera infección por dengue versus hospitalizaciones por infecciones secundarias de tipo salvaje.

From Table 1. Estimated seronegative/ vaccinated 9 – 11 year-olds (SAGE table 8)[15] 1820/7570	= 0.24
Seronegatives among actual vaccinated 9 – 11 year-olds [11-13] x % 8161 x 0.24	= 1959
DENV-infected vaccinated 9 – 11 year-olds - 4 years (1959 x 0.155 FOI x 4)*	= 1215
Observed hospitalizations, 9 – 11 year-olds, 4 years	= 77
Hospitalization rate, vaccinated seronegative 9 – 11 year-olds, (first dengue infections) 4 year total, 77/1215	= 6.3%
Hospitalization rate, secondary DENV infections From literature [16]	= 2 – 4%
Risk of dengue hospitalization in vaccinees vs controls (secondary DENV infections)	= ~3 fold greater risk

3 veces más riesgo de hospitalización para vacunados

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Journal of Clinical Epidemiology ■ (2017) ■

Journal of Clinical Epidemiology

COMMENTARY

Review of a licensed dengue vaccine: inappropriate subgroup analyses and selective reporting may cause harm in mass vaccination programs

Antonio L. Dans[a], Leonila F. Dans[a,*], Mary Ann D. Lansang[a], Maria Asuncion A. Silvestre[b], Gordon H. Guyatt[c]

[a]College of Medicine, University of the Philippines, Manila, 547 Pedro Gil Street, Ermita, Manila 1000, Philippines
[b]Asia-Pacific Center for Evidence-Based Healthcare, Mirasol Bldg, 854 Apacible St, Manila 1000, Philippines
[c]McMaster University, 1280 Main St W, Hamilton, ON L8S 4L8, Canada

Accepted 23 November 2017; Published online xxxx

Problemas en el análisis del CYD14 (Asia): RR de hospitalización por dengue

1. Presentación selectiva de datos
- < 9 años: RR: 8.5 (IC 95% 0,5-146,8)
- Todas las edades: RR: 5.5 (IC 95% 0,9-33)

2. Análisis e interpretación inapropiados:

A. RR según edad
- RR 2-5 años: 7,45 (IC 95% 1.15-313.8)
- RR 6-11 años: 0,63 (IC 95% 0,22-1,83)
- RR 12-14 años: 0,25 (IC 95% 0,02-1,74)

B. Corte a los 9 años
- <9 años: RR 1,58 (IC 95% 0,64-4,83)
- >9 años: RR 0,57 (IC 95% 0,18-1,86)

- El RR no está sujeto al grupo etario sino al serostatus
- Los IC no permiten excluir el riesgo en niños > de 5 años
- No puede usarse los 9 años como punto de corte

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Vacuna TDV (TAK-003)

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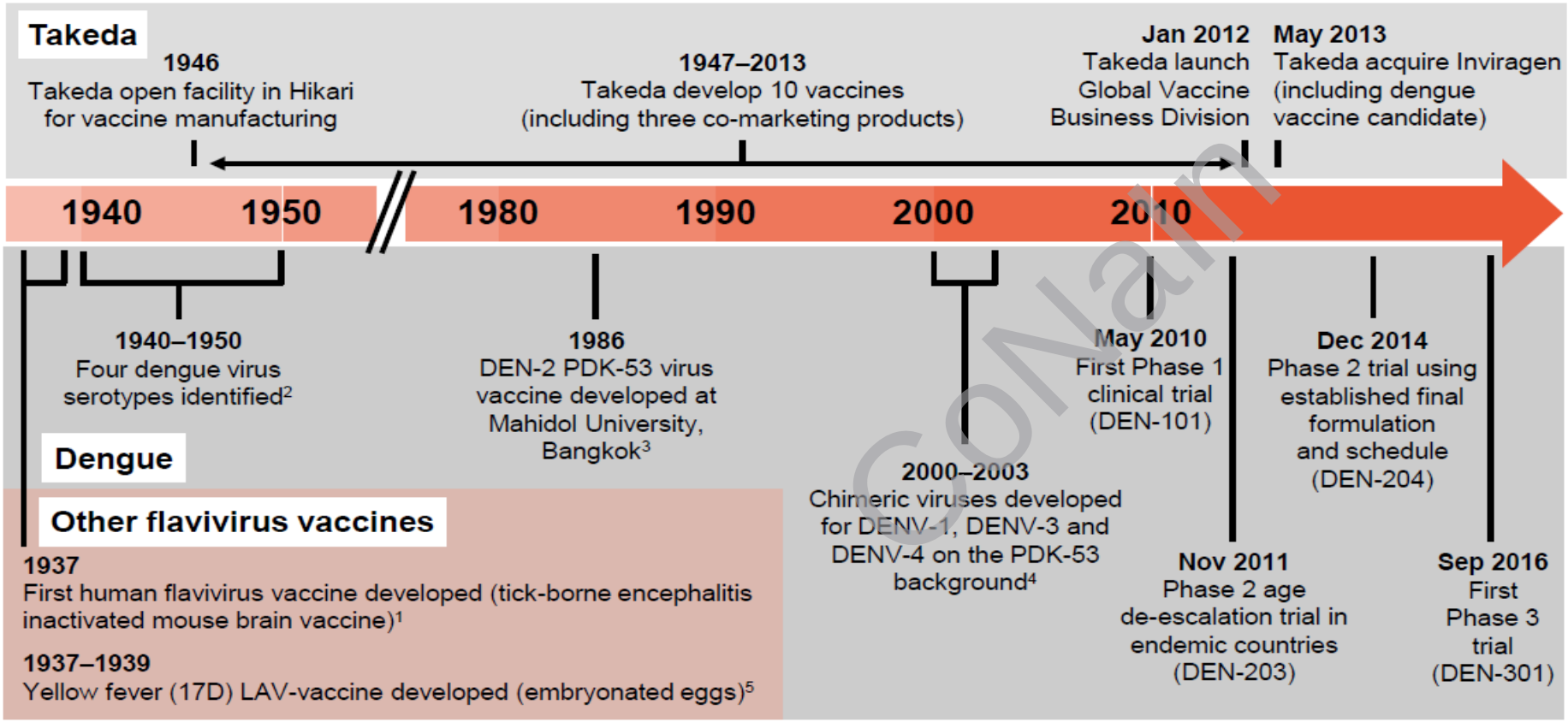
Vacuna laboratorio Takeda (TDV)



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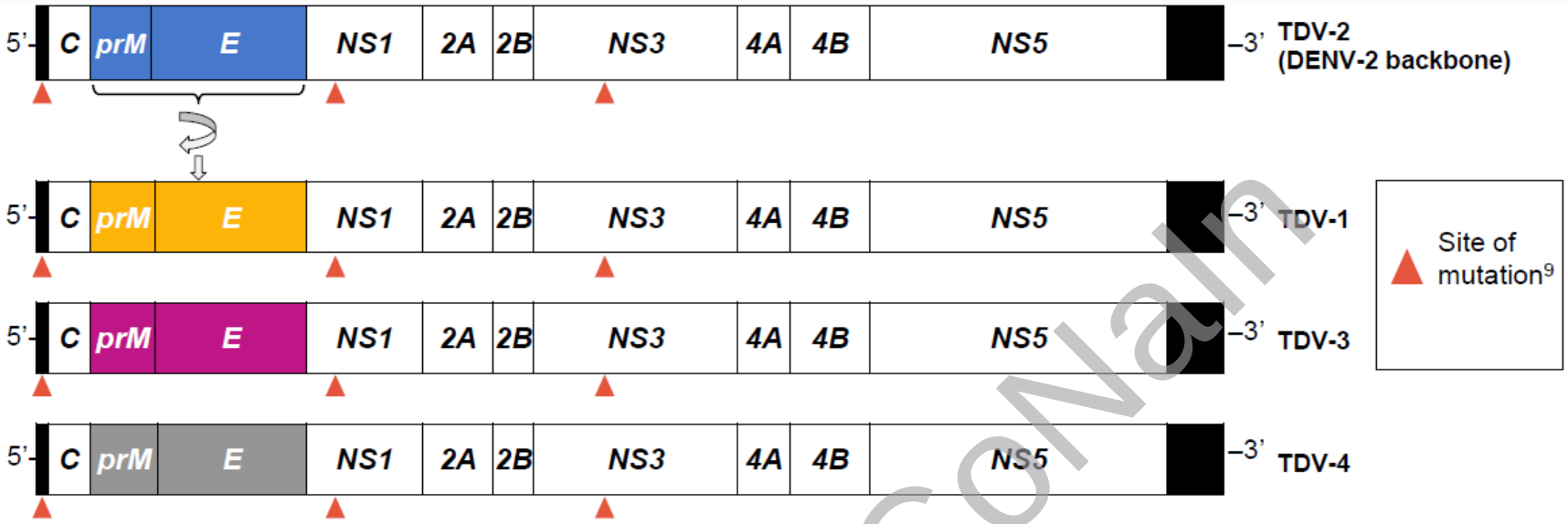
1. World Health Organization. Weekly epidemiological record. 2011;86:241–56
2. Messina, *et al. Trends Microbiol* 2014;22:138–46
3. Bhamarapravati, *et al. Bull World Health Organ* 1987;65:189–95
4. Huang, *et al. J Virol* 2003;77:11436–47
5. Frierson. *Yale J Biol Med* 2010;83:77–85

TDV : Vacuna recombinante basada en DENV2



DENV-2, dengue virus 2 C, capsid; E, envelope; NS, non-structural; prM, pre-membrane

Figure © Elsevier B.V., reproduced with permission.

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- Induces antibody responses to all four serotypes in dengue-naïve and dengue-exposed children and adults[2-6]
- TDV elicits multifunctional and cross-reactive T cell-mediated responses to dengue structural and non-structural proteins[7-8]

1, Osorio, *et al. Expert Rev Vaccines* 2016;15(4):497–508 | 2. George, *et al. J Infect Dis* 2015;212:1032–41 | 3. Osorio, *et al. Lancet Infect Dis* 2014;14(9):830–8 | 4. Rupp, *et al. Vaccine* 2015;33(46):6351–9 | 5. Sirivichayakul, *et al. J Infect Dis* 2016;213(10):1562–72 | 6. Sáez-Llorens , et al. Lancet Infect Dis 2017; **http://dx.doi.org/10.1016/S1473-3099(17)30166-4** |7. Ambuel, *et al. Front Immunol* 2014;5:263 | 8. Chu, *et al. J Infect Dis* 2015;212(10):1618–28| 9. Butrapet , et al., Journal of Virology 2000; 74 (7): 3011-3019

*In this presentation, DENV denotes wild type dengue virus

TDV: DEN-204 estudio de inmunogenicidad a 6 meses

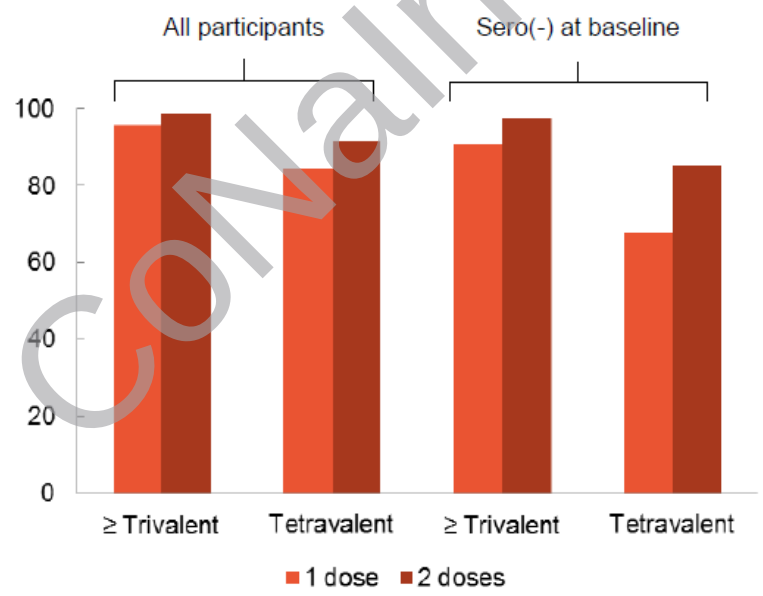
En todos los pacientes (sero + y sero-) se observaron altas tasas de seropositividad y GMT

A los 6 meses que eran seronegativos tuvieron:

- 67,5% de anticuerpos contra los 4 serotipos con 1 dosis
- 85% de seropositividad contra los 4 serotipos con 2 dosis

Los datos de inmunogenicidad a los 18 meses debían estar completos en Nov de 2017.

Multivalent seropositivity rates at Month 6 in all participants and those seronegative at baseline



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Takeaway: Test a two-dose regimen 3 months apart in the phase 3 efficacy trial to maximize vaccine take in participants who are seronegative at baseline

GMT, geometric mean titer

TDV : vacuna atenuada tetravalente

Immunogenicity and safety of one versus two doses of tetravalent dengue vaccine in healthy children aged 2–17 years in Asia and Latin America: 18-month interim data from a phase 2, randomised, placebo-controlled study

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Summary

Background Development of vaccines that are effective against all four dengue virus serotypes (DENV-1–4) in all age groups is important. Here, we present 18-month interim data from an ongoing study undertaken to assess the immunogenicity and safety of Takeda's tetravalent dengue vaccine (TDV) candidate over 48 months in children living in dengue-endemic countries.

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	Total (n=1794)	Group 1 (n=200)	Group 2 (n=398)	Group 3 (n=998)	Group 4 (n=198)
Febrile episodes evaluated (n)	861	102	199	451	109
Febrile participants evaluated (n)	531	61	115	283	72
Confirmed dengue cases (n)	30	4	3	14	9

All participants were monitored for episodes of febrile illness (defined as body temperature ≥38°C on two consecutive days) throughout the study. Within 5 days of the onset of fever or febrile illness suspected to be due to dengue infection, blood samples were collected and analysed for the presence of DENV by RT-PCR or ELISA. DENV=dengue virus.

Table 2: **Laboratory-confirmed cases of dengue (safety set)**

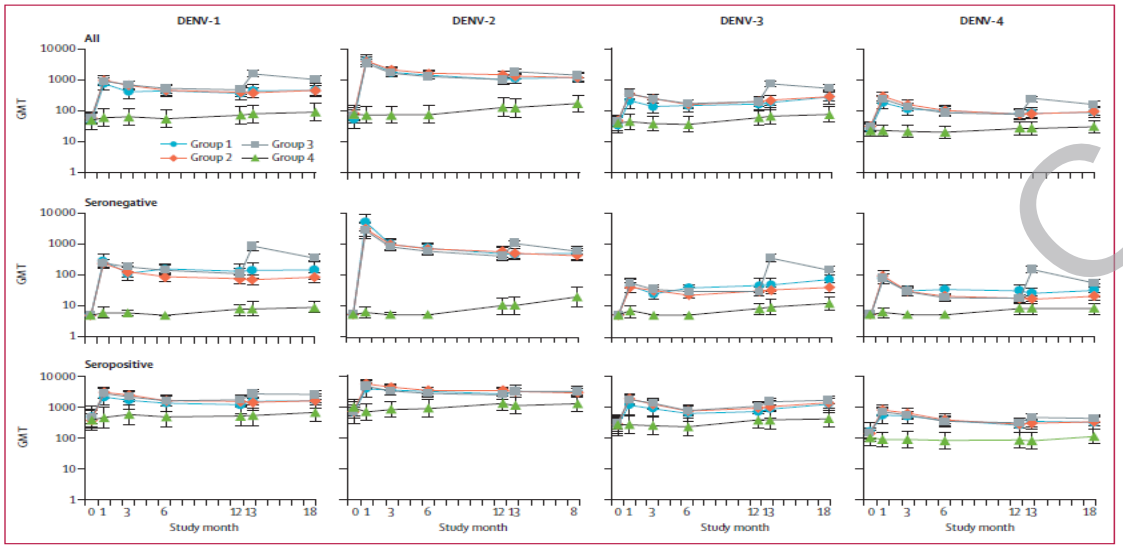
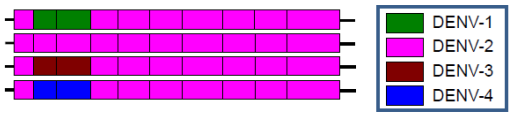


Figure 2: **Serotype-specific GMTs (per-protocol set)**
Upper plots are for all participants, middle plots are for those who were seronegative at baseline, and lower plots are for those who were seropositive at baseline. Datapoints are GMTs and error bars denote 95% CIs. DENV=dengue virus. GMT=geometric mean titre.

La vacuna TDV (TAK-003) fue bien tolerada e inmunogénica contra los 4 serotipos de dengue sin importar el estatus previo de infección. Estos datos soportan los estudios de eficacia fase 3 con 2 dosis separadas por 3 meses



CONAIN

TDV: Fase III

•Diseño: Doble ciego, randomizado, placebo-control para evaluación de eficacia, seguridad e inmunogenicidad de TDV subcutánea en niños de 4 a 16 años

•Objetivo: Evaluar la eficacia de 2 dosis de vacuna TDV en la prevención de dengue sintomático debido a cualquier serotipo de dengue en niños de 4 a 16 años

•20.100 sujetos de Brasil, Colombia, Rep Dominicana, Nicaragua, Panamá, Filipinas, Sri Lanka y Tailandia

CoNaIm

Vacuna laboratorio Takeda (TDV)

Fase III

- 400 enrolados de 12 a 17 años y 900 de 18 a 60 años (con vacuna FA)

- Eficacia:
  - GMT de Acs neutrolizantes para cada uno de los 4 serotipos a los 120 y 270 días en niños y 30, 90, 120 y 180 días para adultos
  - % de participantes seropositivos para cada uno de los 4 serotipos y para múltiples serotipos (2, 3 o 4) en niños y adultos

- Seguridad:
  - % de participantes con EA locales por severidad
  - % de participantes con atención médica por EA
  - % de participantes con EA severos

  - Sin resultados a la fecha

CoNaIn

Vacuna TV003/TV005

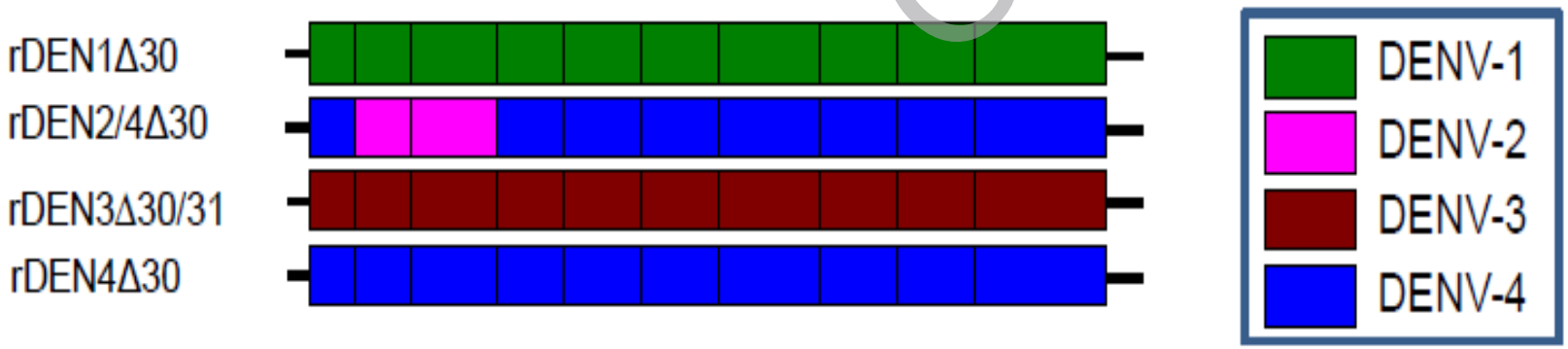
CoNaIn

Vacuna laboratorio NIH (TV003/TV005)

DISEÑO:

- VVA tetravalente en única dosis
- Atenuación primaria: deleción en 3´UTR
- Un componente de virus quimérico

CoNaIn



Vacuna laboratorio NIH (TV003/TV005)

Fase II Tailandia (TV005) y Brasil (Inst. Butantan) (TV003)

Una sola dosis de TV003 o TV005 induce seroconversión para los 4 serotipos de DENV en **74–92% (TV003) and 90% (TV005**) de los adultos seronegativos para flavivirus.

Con la segunda dosis administrada 6 a 12 meses después se alcanzaría **inmunidad casi-esterilizante**

CoNaIn

Vacuna laboratorio NIH-Buntantan (TV003)

Fase III: Febrero 2016 a Diciembre 2022. Brasil

- 16.944 enrolados
- Edad: 24 meses a 59 años
- Eficacia: incidencia de casos de dengue sintomático virológicamente confirmado
- Seguridad
- Sin resultados a la fecha

CoNaIn

CONCLUSIONES

- Nueva posición frente a vacuna CYD-TDV (información del laboratorio y posición de OMS-OPS)
- 8 estudios enrolando participantes actualmente
  - Fase III TDV (28/11/2018)
  - Fase III TDV + VFA (04/05/2019)
  - Fase III TV 003 (12/2022)
- Resultados pendiente

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Muchas gracias

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Ministerio de Salud
Presidencia de la Nación

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