

Presented at the Annual Conference of API WB Chapter on October 18, 2019

# Efficacy of Tetravalent Dengue Vaccine – Meta-analysis of Randomized Controlled Trials

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AGNIBHO MONDAL<sup>1</sup>, BISHAL GUPTA<sup>2</sup> AND RAMA PROSAD GOSWAMI<sup>1</sup>

1. DEPARTMENT OF TROPICAL MEDICINE

2. DEPARTMENT OF MICROBIOLOGY

SCHOOL OF TROPICAL MEDICINE, KOLKATA



# Background

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Dengue, the mosquito borne viral illness, is a serious health issue worldwide and can sometimes be life threatening as well.

Around 390 million people worldwide gets infected by dengue every year, among which 96 million people have clinical dengue (2013)

Around 3.9 billion people across 128 countries are at risk of dengue infections (2012)

The tetravalent dengue vaccine CYD-TDV has been licensed in 2015

This vaccine has been shown to be well-tolerated and immunogenic

CYD-TDV is currently approved in 20 countries

# About the vaccine

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CYD-TDV is a recombinant, live, attenuated, tetravalent dengue vaccine

Chimeric vaccine with yellow fever and dengue antigen

Each dose contains 0.5 ml of reconstituted vaccine

Total 3 doses

- At 0, 6 and 12 months
- Subcutaneous route

# The Question

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## **Can CYD-TDV actually prevent dengue?**

- In this meta-analysis we tried to analyze the efficacy data from multiple studies to answer the question.

# Literature search

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We searched the **PubMed** and **Cochrane** database for published papers on dengue vaccine

Keyword: “dengue AND vaccine AND randomized controlled trial [pt]”

PubMed and Cochrane database search yielded 74 and 80 results respectively

The authors independently filtered the search results

- First by title, then by abstract and lastly by full text
- Duplicate results were removed

Finally **7 studies** were included

- Comparing CYD-TDV with placebo for efficacy

# Outcome

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1. Virologically confirmed dengue
2. Hospitalization due to dengue

# Analysis

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Risk of Bias was analyzed by *RoB Tool version 2* created by Cochrane Collaboration

Analysis was carried out using **RevMan 5.3** software created by Cochrane Collaboration

*A random effects model* was used for analysis

Data for all age groups were combined together for the purpose of analysis

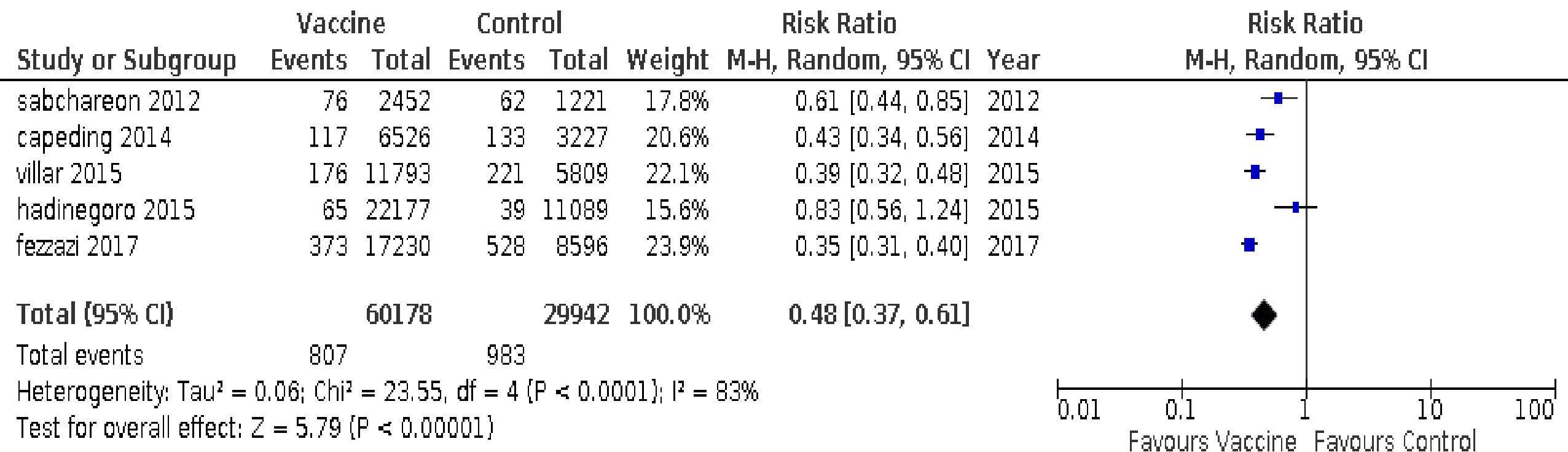
# Risk of Bias

Studies	Randomization Process	Deviation from intended intervention	Missing outcome data	Measurement of Outcome	Selection of reported result	Overall risk
<b>Arredondo-Garcia 2018</b>	Low risk	Some concerns	Low risk	Low risk	Some concerns	<b>Some concerns</b>
<b>Capeding 2014</b>	Low risk	Low risk	Low risk	Some concerns	Low risk	<b>Some concerns</b>
<b>Fezzazi 2017</b>	Some concerns	High risk	Low risk	High risk	Some concerns	<b>High risk</b>
<b>Gailhardou 2015</b>	Some concerns	High risk	High risk	High risk	Some concerns	<b>High risk</b>
<b>Hadinegoro 2015</b>	Low risk	Low risk	Low risk	Low risk	Some concerns	<b>Some concerns</b>
<b>Sabchareon 2012</b>	Low risk	High risk	Low risk	Low risk	Some concerns	<b>High risk</b>
<b>Villar 2015</b>	Low risk	Low risk	Low risk	Low risk	Some concerns	<b>Some concerns</b>



# Outcome analysis: Confirmed dengue

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# Outcome analysis: Confirmed dengue

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Total number of patients = 90120

- Total dengue among vaccine recipients = 807 / 60178
- Total dengue among placebo recipients = 983 / 29942

Risk ratio = 0.48

- Confidence interval = 0.37-0.61

Heterogeneity

- $I^2 = 83\%$

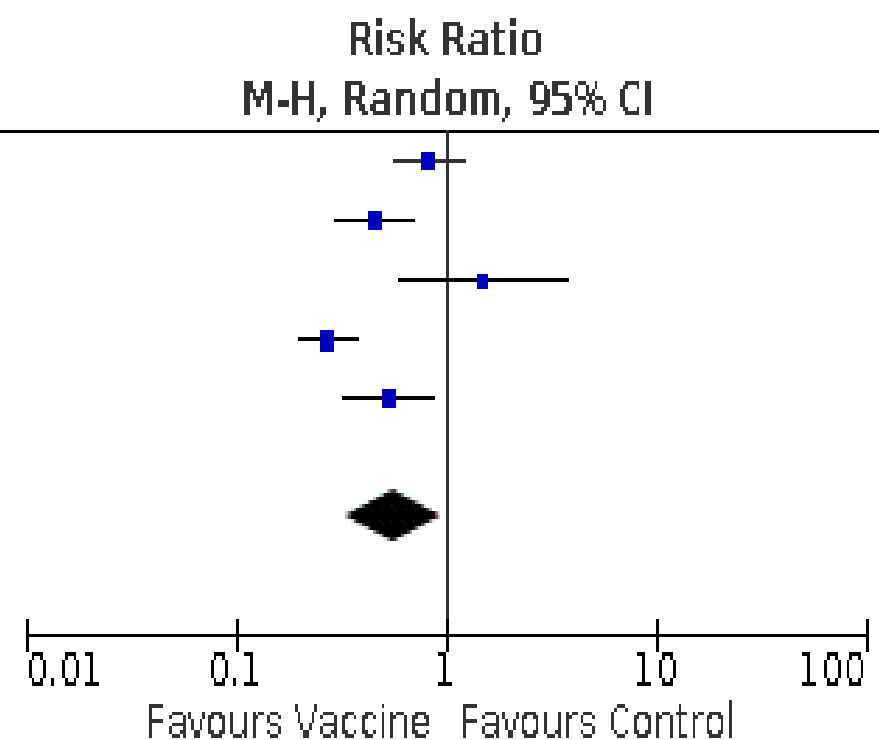
Overall effect

- $Z = 5.79$  ( $P < 0.00001$ )

# Outcome analysis: Hospitalization

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Study or Subgroup	Vaccine		Control		Weight	Risk Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI
arredondo-garcia2018	65	23429	39	11694	21.8%	0.83	[0.56, 1.24]
fezzazi 2017	26	564	70	695	21.2%	0.46	[0.30, 0.71]
gailhardou 2015	18	22177	6	11089	13.9%	1.50	[0.60, 3.78]
hadinegoro 2015	57	20762	104	10364	22.8%	0.27	[0.20, 0.38]
sabchareon 2012	32	2452	30	1221	20.3%	0.53	[0.32, 0.87]
<b>Total (95% CI)</b>		<b>69384</b>		<b>35063</b>	<b>100.0%</b>	<b>0.56</b>	<b>[0.34, 0.94]</b>
Total events	198		249				
Heterogeneity: $\tau^2 = 0.28$ ; $\chi^2 = 25.12$ , $df = 4$ ( $P < 0.0001$ ); $I^2 = 84\%$							
Test for overall effect: $Z = 2.18$ ( $P = 0.03$ )							



# Outcome analysis: Hospitalization due to dengue

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Total number of patients = 104447

- Total dengue among vaccine recipients = 198 / 69384
- Total dengue among placebo recipients = 249 / 35063

Risk ratio = 0.56

- Confidence interval = 0.34-0.94

Heterogeneity

- $I^2 = 84\%$

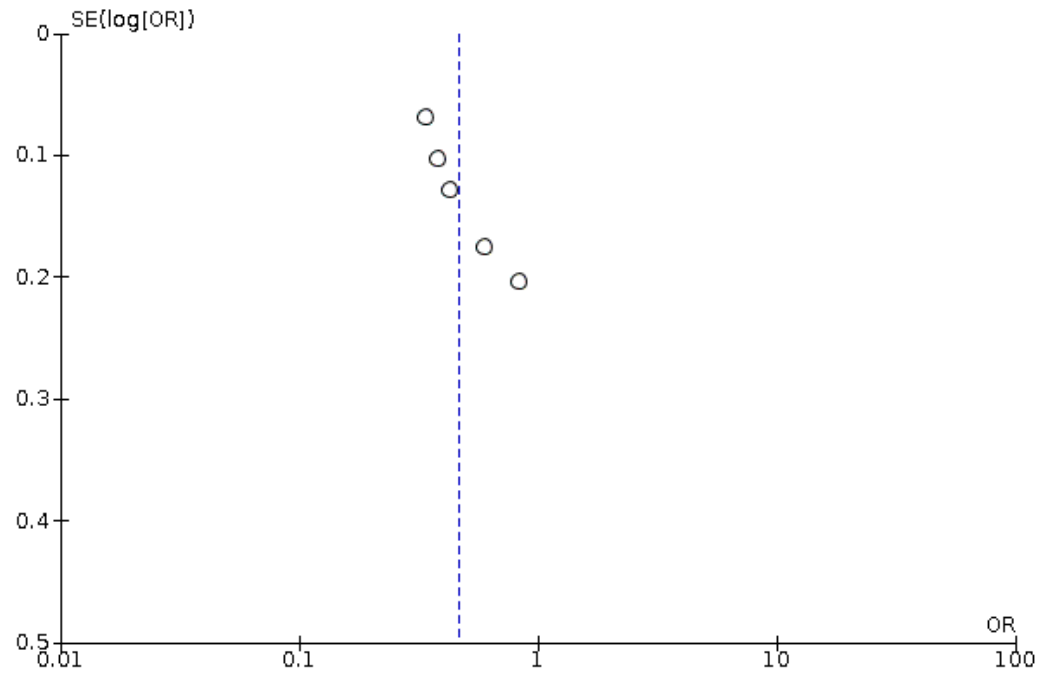
Overall effect

- $Z = 2.18$  ( $P=0.03$ )

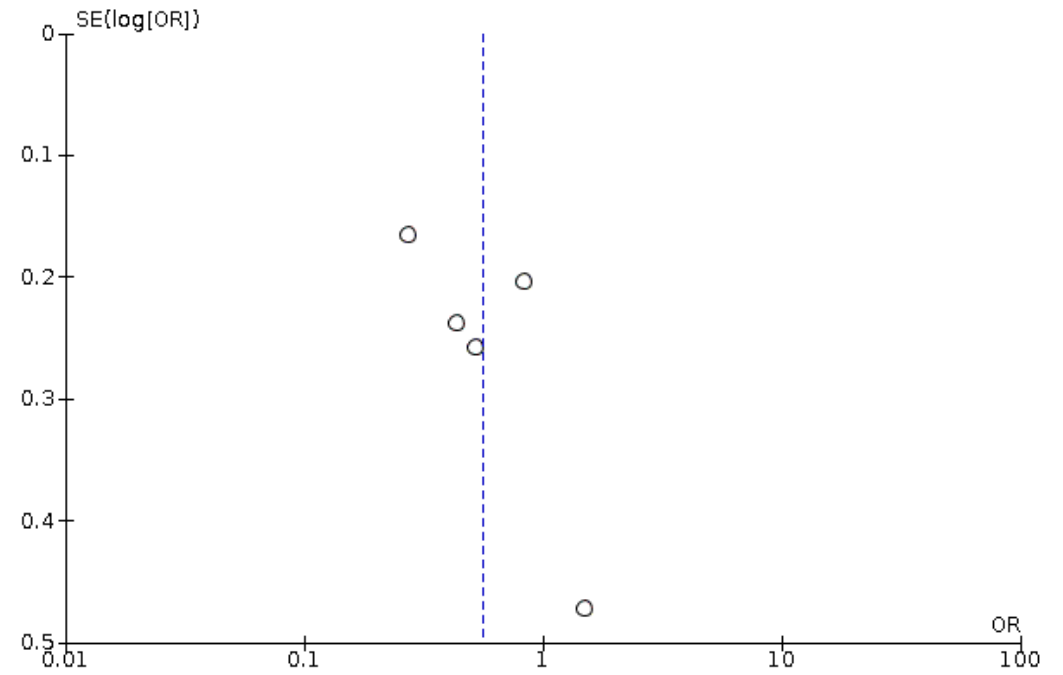
# Funnel plots

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CONFIRMED DENGUE



HOSPITALIZATION



# Summary

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CYD-TDV vaccine is efficacious in preventing dengue

- Risk ratio 0.48 (0.37-0.61) in favor of vaccine
- Calculated vaccine efficacy is **52%** (39%-63%)

It is also efficacious in preventing hospitalizations due to dengue

- Risk ratio 0.56 (0.34-0.94) in favor of vaccine

Both results were statistically significant ( $P < 0.05$ )



# Limitations

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High heterogeneity among the studies may be due to

- Different follow-up periods among studies

The funnel plots had some asymmetry

- There may be some publication bias

# Conclusion

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CYD-TDV vaccine is efficacious in preventing both dengue and hospitalizations related to dengue

CYD-TDV vaccine may be considered to reduce the burden of dengue in India

# References to included studies

- ✓ **Arredondo-García** JL, Hadinegoro SR, Reynales H, Chua MN, Rivera Medina DM, Chotpitayasunondh T, Tran NH, Deseda CC, Wirawan DN, Cortés Supelano M, Frago C, Langevin E, Coronel D, Laot T, Perroud AP, Sanchez L, Bonaparte M, Limkittikul K, Chansinghakul D, Gailhardou S, Noriega F, Wartel TA, Bouckenoghe A, Zambrano B; CYD-TDV Dengue Vaccine Study Group.. Four-year safety follow-up of the tetravalent dengue vaccine efficacy randomized controlled trials in Asia and Latin America.. *Clin Microbiol Infect.* 2018 Jul;24(7):755-763.
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- ✓ Hanna El **Fezzazi**, Marie Branchu, Gabriel Carrasquilla, Punnee Pitisuttithum, Ana Paula Perroud, Carina Frago and Laurent Coudeville. Resource Use and Costs of Dengue: Analysis of Data from Phase III Efficacy Studies of a Tetravalent Dengue Vaccine. *Am. J. Trop. Med. Hyg.* 2017;97(6):1898-1903.
- ✓ Sophia **Gailhardou**, Anna Skipetrova, Gustavo H. Dayan, John Jezorwski, Melanie Saville, Diane Van der Vliet, T. Anh Wartel. Safety Overview of a Recombinant Live-Attenuated Tetravalent Dengue Vaccine: Pooled Analysis of Data from 18 Clinical Trials. *PLOS Neglected Tropical Diseases* July 14, 2016;10(7).
- ✓ 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. Bouckenoghe, 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. Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease. *The New England Journal of Medicine* July 17, 2015.
- ✓ Arunee **Sabchareon**, Derek Wallace, Chukiat Sirivichayakul, Kriengsak Limkittikul, Pornthep Chanthavanich, Saravudh Suvannadabba, Vithaya Jiwariyavej, Wut Dulyachai, Krisana Pengsaa, T Anh Wartel, Annick Moureau, Melanie Saville, Alain Bouckenoghe, Simonetta Viviani, Nadia G Tornieporth, Jean Lang. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. *Lancet* September 11, 2012;380:1559-67.
- ✓ Luis **Villar**, M.D., Gustavo Horacio Dayan, M.D., José Luis Arredondo-García, M.D., Doris Maribel Rivera, M.D., Rivaldo Cunha, M.D., Carmen Deseda, M.D., Humberto Reynales, M.D., Maria Selma Costa, M.D., Javier Osvaldo Morales-Ramírez, M.D., Gabriel Carrasquilla, M.D., Luis Carlos Rey, M.D., Reynaldo Dietze, M.D., Kleber Luz, M.D., Enrique Rivas, M.D., Maria Consuelo Miranda Montoya, M.D., Margarita Cortés Supelano, M.D., Betzana Zambrano, M.D., Edith Langevin, M.Sc., Mark Boaz, Ph.D., Nadia Tornieporth, M.D., Melanie Saville, M.B., B.S., and Fernando Noriega, M.D., for the CYD15 Study Group. Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America. *The New England Journal of Medicine* November 3, 2014.

Thank You