

Summary of two economic models for dengue vaccine TAK-003 use in Puerto Rico

Advisory Committee on Immunization Practices

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RajReni Kaul, PhD
CDC/NCIRD/ISD

The models summarized are currently undergoing the CDC economic review following the ACIP Guidance for Health Economics Studies, so results should be considered as preliminary.

The findings and conclusions in this presentation are those of the author(s) and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Acknowledgements

- This presentation summarizes work conducted by two modeling teams
 - Notre Dame team contracted by CDC (ND/CDC Model)
 - Guido España, Manar Alkuzweny, Alex Perkins
 - Takeda team (Takeda Model)
 - J. Shen, R. Hanley, I. Zerda, et al.
- CDC and ACIP contributors and reviewers
 - Dengue ACIP workgroup
 - Economists at CDC and colleagues (NCIRD/ISD)

Conflicts of Interest Statements

- RajReni Kaul: None.
- Notre Dame team:
 - Dr. Guido España and Dr. Alex Perkins have previously received research funding from GlaxoSmithKline to support unrelated research on dengue vaccine development.
 - Dr. Alex Perkins currently receives research funding and consulting fees from Emergent Biosciences to support unrelated research on chikungunya vaccine development.
- Takeda team:
 - Takeda is the developer and manufacturer of the TAK-003 vaccine.
 - Directly employed by Takeda or consultants employed by Putnam PHMR and contracted by Takeda

Terminology

Abbreviation	Full term/Meaning
ND/CDC	Notre Dame/CDC model
VE	Vaccine efficacy
DENV (e.g., DENV-3)	Dengue virus (e.g., serotype 3 dengue virus)
PICO	Policy question articulated as P opulation, I ntervention, C omparison, O utcomes
Case	Medically-attended case
Hosp	Hospitalization
Additional hospitalizations	Hospitalization induced by vaccine-enhanced disease
NNV	Number needed to vaccinate to avert an outcome (e.g., NNV hospitalization)
QALY	Quality-adjusted life-years

All values rounded to 3 significant figures.

Outline

- Recap of PICO questions
- Overview of models
- Comparison of results
- Exploring differences in assumptions
 - QALY values used, vaccine efficacy
- Summary of Takeda model results
 - Base case
 - Scenario analysis
- Model comparison summary and limitations
- Application to PICO questions

PICO Questions

- Should two doses of TAK-003 be administered routinely to **seropositive** persons aged 4 – 16 years living in dengue-endemic areas?
- Should two doses of TAK-003 be administered routinely to **seronegative** persons aged 4 – 16 years living in dengue-endemic areas?
- Should two doses of TAK-003 be administered routinely to **seropositive** persons aged 17 – 60 years living in dengue-endemic areas?
- Should two doses of TAK-003 be administered routinely to **seronegative** persons aged 17 – 60 years living in dengue-endemic areas?

General Model Design

Assumption/Model Characteristic	Notre Dame/CDC	Takeda
Model type	Stochastic individual-based model	Deterministic compartmental model
Prevaccination screening	Included	Not included
Vaccine implementation	Age range, varying coverage rate over time	Single age, a catch-up routine in year 1 possible, varying coverage rate over first four years then constant thereafter
Serotype specific VE point estimate	Point estimate estimated using multi-level Bayesian model	Point estimate estimated using traditional methods from clinical trial*
Serotype specific VE ranges	Each simulation used VE inputs sampled from the confidence interval around the point estimate	No range, only point estimate used
Geographic area	San Juan municipality (N=280,000)	Puerto Rico (N=3,256,028)
DENV caused deaths	Not included in QALYs	Included in QALYs

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Economic Model Preliminary Results by PICO

Age 4-16 years

Model	Scenario conditions			Number vaccinated	Net number averted with vaccination §			\$/QALY (ICER) §
	Geographic Area†	Age	Prevaccination screening		Cases	Hospitalizations	Deaths	
ND/CDC	San Juan Municipality	4-16	Yes	11,700	485 (1.2%)	182 (2.6%)	1 (2.9%)	182,000*
ND/CDC	San Juan Municipality	4-16	No	30,300	1,070 (2.5%)	192 (2.8%)	1 (2.9%)	255,000*
Takeda	Puerto Rico	8, catch-up 9-16	No	157,000	46,700 (12%)	9,150 (14 %)	5 (13%)	Cost-saving

†Modeled population size is 280,000 for the San Juan Municipality (ND/CDC model) and 3,256,028 for all of Puerto Rico (Takeda model).

§ When compared to no vaccination

*Death is not incorporated into QALYs gained in the ND/CDC model base case assumptions. If QALY gains from averted deaths were included, then the ICERs would change from \$182,000 to \$65,000 per QALY for the scenario with prevaccination screening and would change from \$255,000 to \$137,000 per QALY for the scenario without prevaccination screening.

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Economic Model Preliminary Results by PICO

Age 17-60 years

Model	Scenario conditions			Number vaccinated	Net number averted with vaccination §			\$ /QALY (ICER) §
	Geographic Area†	Age	Prevaccination screening		Cases	Hospitalizations	Deaths	
ND/CDC	San Juan Municipality	17-60	Yes	105,000	2,710 (6%)	724 (10%)	5 (11%)	397,000*
ND/CDC	San Juan Municipality	17-60	No	121,000	3,360 (8%)	928 (13%)	4 (14%)	315,000*
Takeda	Puerto Rico	17, catch-up 18-60	No	449,000	67,000 (17%)	13,100 (21%)	8 (21%)	Cost-saving

†Modeled population size is 280,000 for the San Juan Municipality (ND/CDC model) and 3,256,028 for all of Puerto Rico (Takeda model).

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Economic Model Preliminary Results by PICO

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Exploring Difference

Model Inputs : QALY loss from dengue episodes

Disease Outcome	Quality-adjusted days lost	
	ND/CDC	Takeda
Non-hospitalized dengue	11.2 [§]	5.5
Hospitalized dengue	12.8 [§]	6.8
Persistent dengue after non-hospitalized or hospitalized case	NA	4.9*
Dengue caused deaths	NA	Age-dependent

[§] QALY lost for dengue episodes includes persistent dengue in 34% of all cases.

* Model assumes 34% of dengue episodes aged 30 or older develop persistent symptoms.

Exploring Difference

Model Inputs : QALY loss from dengue episodes

Disease Outcome	Quality-adjusted days lost	
	ND/CDC	Takeda
Non-hospitalized dengue	11.2 [§]	6.1 [†]
Hospitalized dengue	12.8 [§]	7.2 [†]
Persistent dengue after non-hospitalized or hospitalized case	NA	-
Dengue caused deaths	NA	Age-dependent

When persistent dengue QALY loss is combined with acute phase QALY loss

[§] QALY lost for dengue episodes includes persistent dengue in 34% of all cases.

[†] Calculated as if 34% of cases ages 30 or older develop persistent symptoms.

Exploring Difference

Model Inputs : Vaccine Efficacy

Vaccine efficacy inputs by serostatus and by dengue serotype							
Seronegative at vaccination				Seropositive at vaccination			
DENV-1	DENV-2	DENV-3	DENV-4	DENV-1	DENV-2	DENV-3	DENV-4

Exploring Difference

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Non-hospitalized Symptomatic case	ND/CDC*								

* Point estimate with 95% confidence interval
† Average VE over 5 years post-vaccination. Includes vaccine waning.

Exploring Difference

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Non-hospitalized Symptomatic case	ND/CDC*								
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Hospitalized case	ND/CDC*								
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		DENV-1	DENV-2	DENV-3	DENV-4	DENV-1	DENV-2	DENV-3	DENV-4
Non-hospitalized symptomatic case	ND/CDC*	29.7% (6.7, 48.5)	96.3% (87.1, 100)	30.0% (7.8, 49.4)	-1.1% (-73.5, 64.4)	63.1% (52.7, 82.2)	85.2% (75.6, 94.4)	42.5% (26.4, 55.8)	60.2% (19.8, 89.6)
	Takeda†	30.8%	69.8%	0%#	0%#	46.7%	69.8%	42.6%	61.2%
Hospitalized case	ND/CDC*	84.6% (54.5, 98.7)	99.0% (95.6, 100)	-30.3% (-91.6, 25.6)	39.2% (-20.4, 81.0)	54.1% (13.3, 82.2)	99.5% (97.8, 100)	70.2% (45.6, 90.4)	68.1% (27.2, 86.2)
	Takeda	75.8%	98.5%	0%#	0%§	75.8%	98.5%	71.4%	100%

* Point estimate with 95% confidence interval

† Average VE over 5 years post-vaccination. Includes vaccine waning.

§ Due to lack of data

Value used because pivotal clinical trial estimate or confidence interval included negative values

Exploring Difference

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Exploring Difference

Impact of vaccine efficacy inputs on outcome

- What if the ND/CDC model uses the Takeda VE inputs in the scenario where 4–16-year-olds are vaccinated without screening?
 - Takeda’s VE inputs did not substantially impact the results of the ND/CDC model.

VE inputs	Number vaccinated	Net number averted with vaccination			Vaccination enhanced disease		NNV hosp.	QALYs gained*	\$/QALY (ICER)*
		Cases	Hosp.	Deaths	Additional cases	Additional hosp.			
ND/CDC†	30,300	1,070 (651-1,470)	192 (112-300)	1 (0.5 -1.5)	45 (35-52)	32 (29-37)	158 (101-270)	35	255,000
Takeda†	30,300	1,030 (699-1,300)	287 (197-425)	1 (0.9 - 2.1)	NA	NA	105 (71-153)	34	262,000

*QALY loss due to dengue caused death is not incorporated into ICER calculation.

†Range of model results due to stochasticity

Outline

- Recap of PICO questions
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Takeda Base Case Preliminary Results

Routine vaccination at age 8

Base case conditions

- Entire population of Puerto Rico
- 20-year time horizon
- Routine vaccination at age 8
- Vaccination rate increases from 0% at year 0 to 60% at year 4.
- Using slightly different QALY loss than previously presented*

Base Case

Number vaccinated	449,000
Averted cases	123,000 (15%)
Averted hospitalizations	25,000 (20%)
Averted deaths	15 (20%)
NNV hospitalization	17.6
QALYs gained	2,070
\$/QALY	Cost-saving
\$/hospitalization	Cost-saving

*Values reported in supplemental slides

Scenario Analysis

Takeda Model: Routine vaccination at age 8

Scenario				Number vaccinated	Number averted with vaccination			NNV hosp	QALYs gained	ICER (\$/QALY)
Time (years)	TAK-003 routine age	TAK-003 catchup age	TAK-003 coverage*		Cases	Hosp	Deaths			
10	8	None	22%	87,000	24,000 (6%)	4,510 (7%)	3 (8%)	19.3	402	Cost-saving
10	8	9-16	22%	157,000	47,000 (12%)	9,150 (14%)	5 (13%)	17.1	838	Cost-saving

*Used a fixed vaccine coverage parameter of 21.5% to approximate vaccination coverage that increases from 0% to 43% over 10 years.

Overall Cost-effectiveness

Preliminary results

Incremental Cost (in thousands)

QALYs gained

Overall Cost-effectiveness

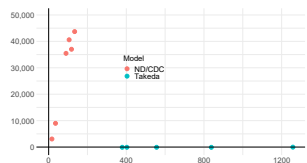
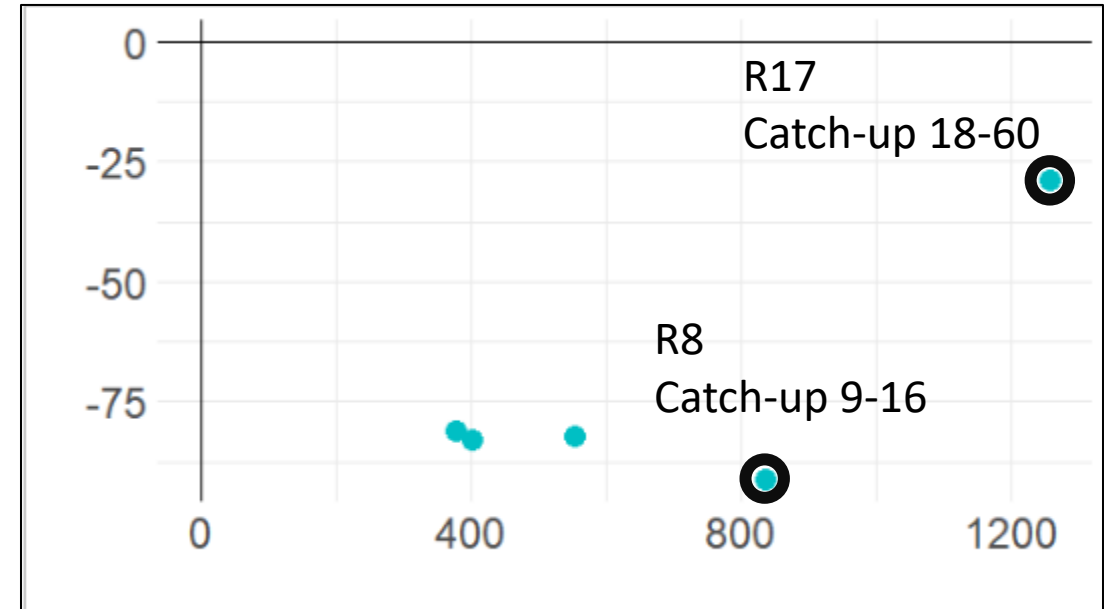
Preliminary results

Incremental Cost (in thousands)

17-60 w/o
prevaccination
screening

4-16
w/prevaccination
screening

QALYs gained



Limitations

The models summarized are currently undergoing the CDC economic review following the ACIP Guidance for Health Economics Studies, so results should be considered as preliminary.

- Parameter Uncertainty
 - Large confidence interval (>100%) for DENV-3 and DENV-4 VE estimates for those seronegative at vaccination.
- Given vaccine's range in serotype specific efficacy, actual outcome will be heavily influenced by the dominant circulating serotype.
- In the ND/CDC model, deaths were not part of the QALY calculation.
- Using Takeda's model, we cannot assess benefits and risks of pre-vaccination screening strategies vs strategies without pre-vaccination screening.

Models answering the PICO Questions

	Only seropositives (prescreening)	All individuals (no prescreening)
4–16 years Children/Adolescents	Answered by ND/CDC Model	Answered by ND/CDC Model & Takeda Model
17–60 years Adults	Answered by ND/CDC Model	Answered by ND/CDC Model & Takeda Model

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