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

Advisory Committee on Immunization Practices

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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.

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

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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

* When the clinical trial estimate was negative or confidence interval included negative values, a VE model input of zero was assumed.

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Geographic area	San Juan municipality (N=280,000)	Puerto Rico (N=3,256,028)

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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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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*								
	Takeda†								

* Point estimate with 95% confidence interval

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

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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

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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

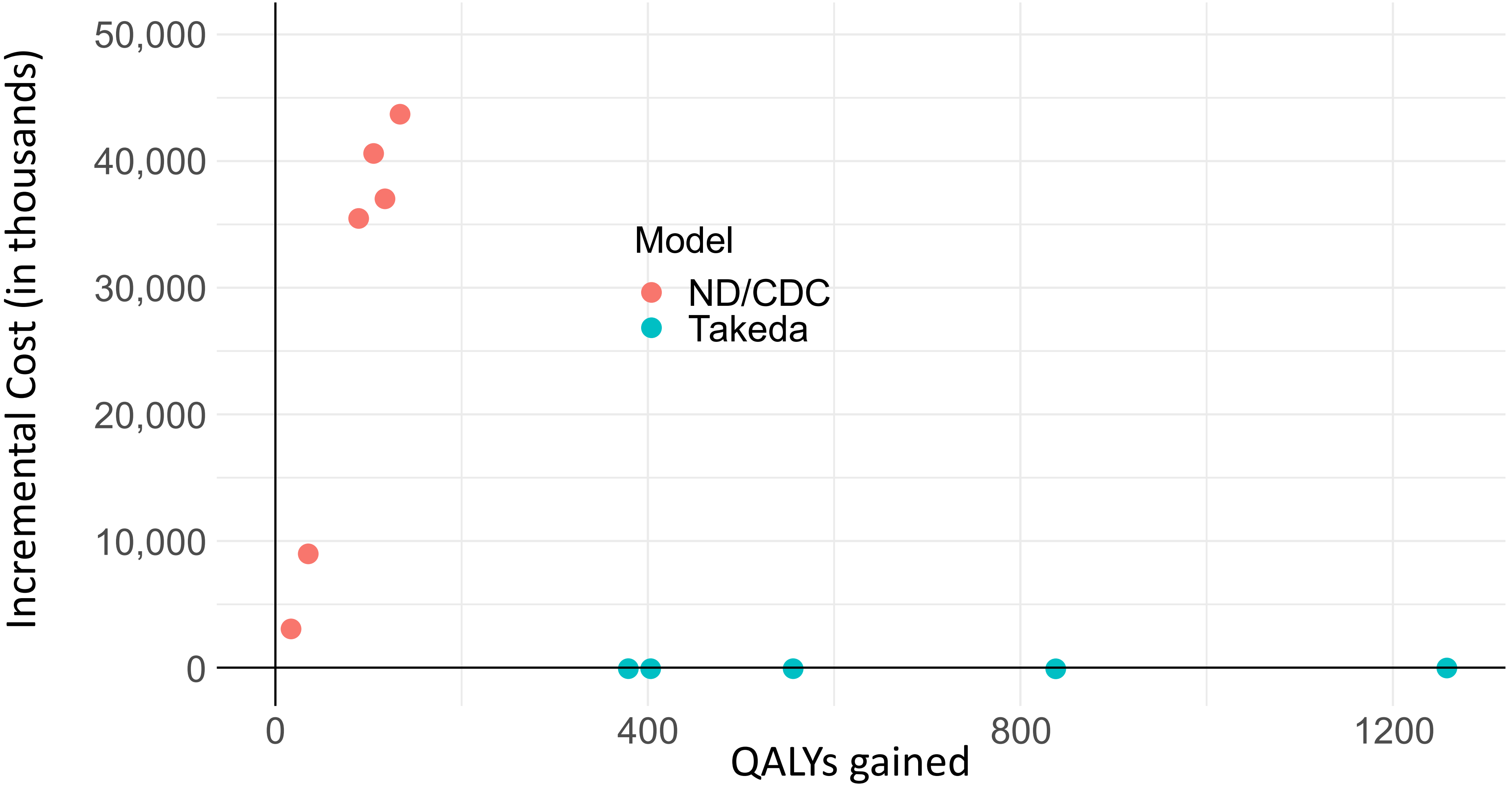
Takeda Model: Routine vaccination at age 8

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



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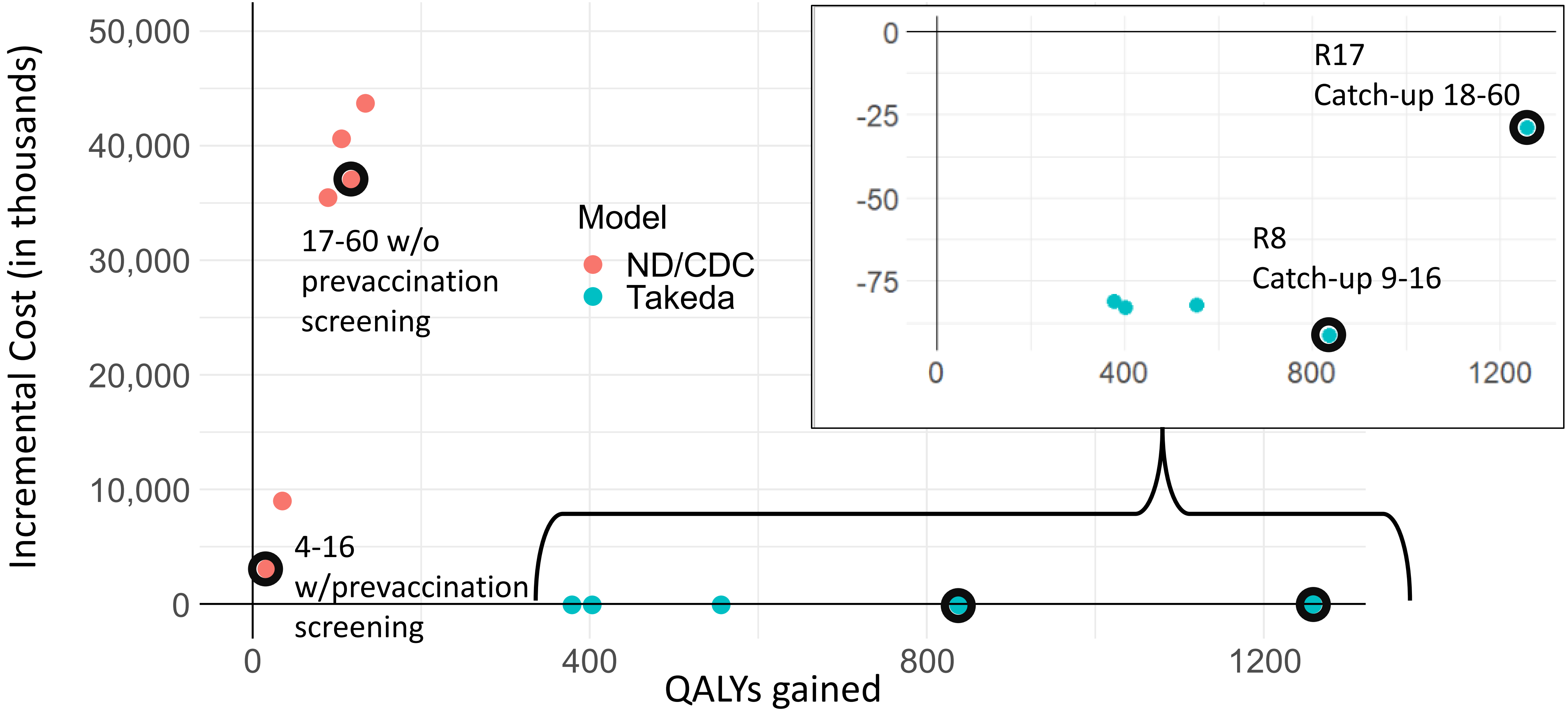

Limitations

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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