



Dengue Vaccine Evidence to Recommendations Framework

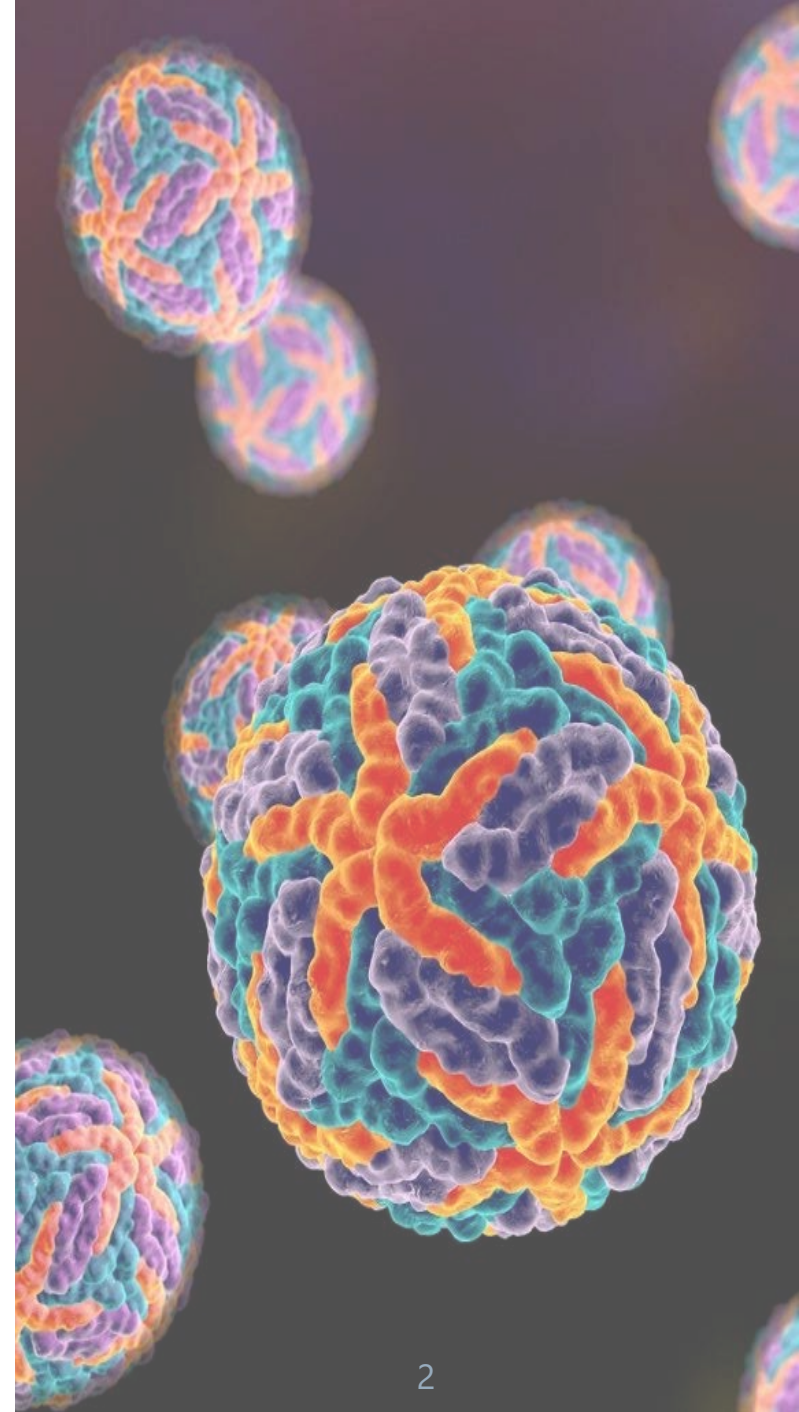
Gabriela Paz Bailey, MD, PhD, MSc

Dengue Branch, Division of Vector-Borne Diseases, CDC

ACIP, June 24, 2021

Dengue

- DENV-1, 2, 3, 4
 - Lifelong DENV type-specific immunity
 - Short-term cross-immunity
- Transmitted by the *Aedes* mosquitoes
- Most frequent arboviral disease globally



Dengvaxia timeline

2015

- Trial results showed increased risk of severe disease among 2-5 year-olds

2016

- WHO position paper: 9y and older in highly endemic areas

2017

- Additional testing showed increased risk of severe dengue and hospitalization among vaccinated seronegative children compared to controls
- WHO revised their recommendations vaccine should only be given to children with laboratory-confirmed evidence of a past infection.

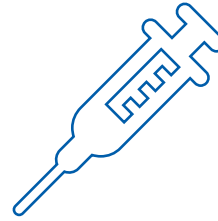
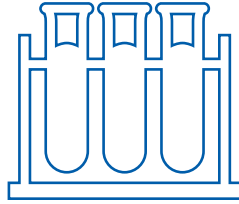
FDA Licensing of first dengue vaccine 2019



For use in U.S. children 9-16 years old with laboratory-confirmed previous dengue virus infection and living in an area where dengue is endemic.

Test performance guidance for pre-vaccination screening

■ 98% specific



■ 75% sensitive

■ 90% positive predictive value

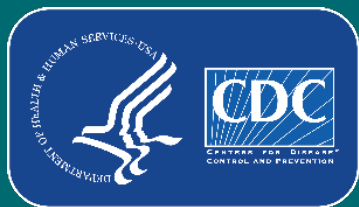
■ 75% negative predictive value

CDC evaluation of dengue virus IgG tests

Test	Sensitivity % (95% CI) DENV N=22	Specificity % (95% CI) NEG + ZIKV N=85
ELISA test 2	68 (45, 86)	97 (90, 99)
Rapid test 3a	82 (60, 95)	98 (92, 100)
Rapid test 3b	68 (45, 86)	98 (92, 100)

Dr. Freddy Medina, CDC, personal communication

Evidence to Recommendations Framework



Evidence to Recommendations (EtR) Framework

EtR Domain	Question
Public Health Problem	<ul style="list-style-type: none">• Is the problem (<i>Dengue</i>) of public health importance?
Benefits and Harms	<ul style="list-style-type: none">• How substantial are the desirable anticipated effects of the intervention (<i>dengue vaccine</i>)?• How substantial are the undesirable anticipated effects?• Do the desirable effects outweigh the undesirable effects?
Values	<ul style="list-style-type: none">• Does the target population feel the desirable effects are large relative to the undesirable effects?• Is there important variability in how patients value the outcomes?
Acceptability	<ul style="list-style-type: none">• Is the intervention acceptable to key stakeholders?
Feasibility	<ul style="list-style-type: none">• Is the intervention feasible to implement?
Resource Use	<ul style="list-style-type: none">• Is the intervention a reasonable and efficient allocation of resources?
Equity	<ul style="list-style-type: none">• What would be the impact of the intervention on health equity?

Policy Question

Question: Should 3-doses of Dengvaxia be administered routinely to persons 9-16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas?

Public Health Problem

Is dengue disease of public health importance?

- No Probably no Probably yes Yes Varies Don't know



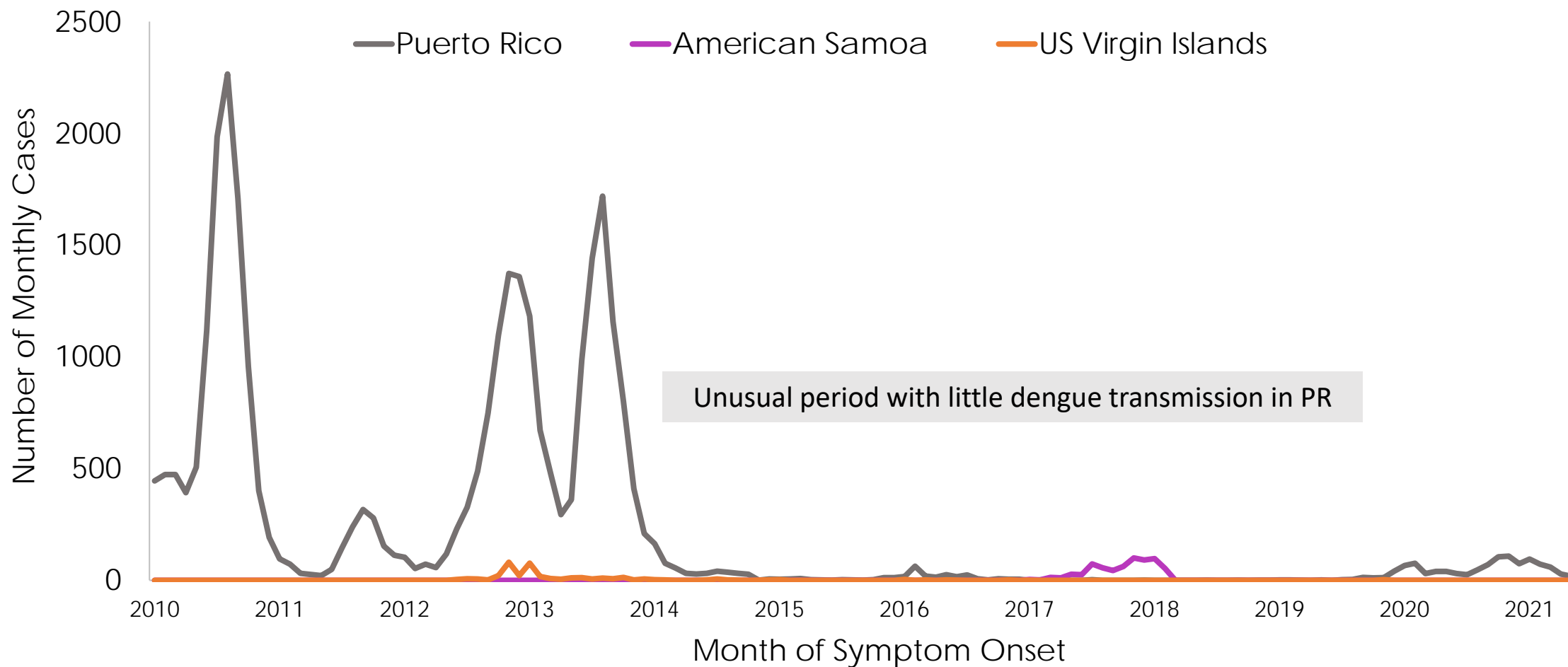
Dengue endemic areas in the United States

85% of the children to be vaccinated are in Puerto Rico

Territory/Associated State	Population 9-16 years (2019)	%
Puerto Rico	303,826	85%
US Virgin Islands	12,000	3%
American Samoa	10,100	3%
Federated States of Micronesia*	16,000	4%
Palau*	2,423	1%
Marshall Islands*	14,000	4%

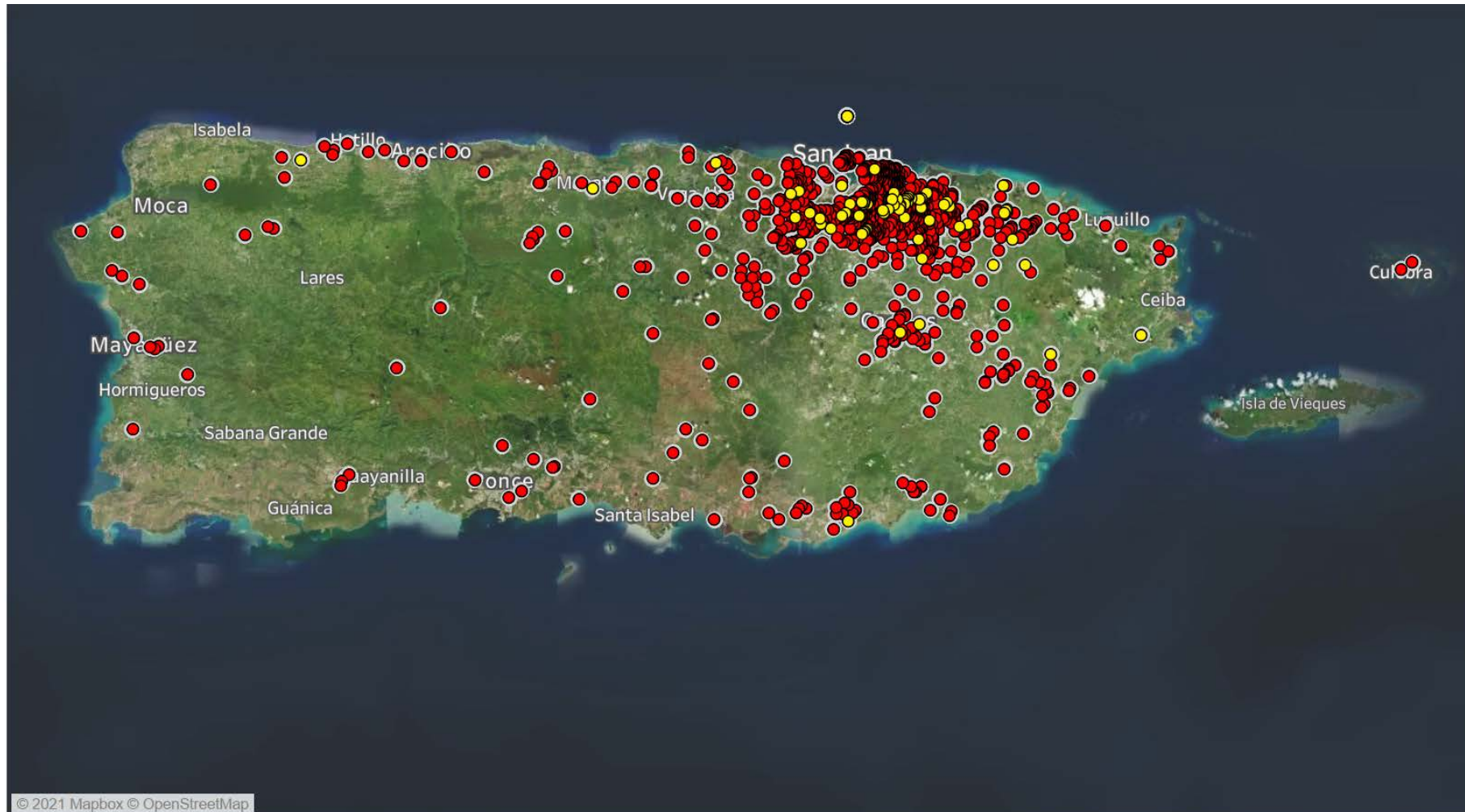
*Sovereign freely associated states

95% of dengue cases in U.S. territories occur in Puerto Rico



Source: Dengue cases in ArboNET, Jan 2010–May 2021. Case counts from 2020 and 2021 are preliminary and subject to change.

Dengue confirmed cases in Puerto Rico 2020-2021



Total cases Nov 2019-Jun 2021: 1,239

Legend ■ Apr/May/Jun 2021 ■ Earlier

Source: Dengue passive surveillance system, Jan 2020–May 2021. Case counts from 2020 and 2021 are preliminary and subject to change. Reproduced with permission from Jomil Torres.

Dengue seroprevalence in Puerto Rico

- Argüello et al: 10-18 years¹
 - 2007 (n=345): 50% (95% CI: 44–56)
- Sanofi Pasteur trial data: 9-16 years²
 - 2011 (n=152): 56% (95% CI: 47–64)
- COPA project³: 9-16 years, DENV PRNT>10
 - 2018 (n=414): 59% (95% CI: 54–63)

1. Argüello DF, et al. AJTMH. 2015 Mar 4;92(3):486-91.

2. L'Azou M, et al. TRSTMH. 2018 Apr 1;112(4):158-68.

3. Unpublished.

Public Health Problem:

Work Group Interpretation

Is dengue disease of public health importance?

- No Probably no Probably Yes Yes Varies Don't know



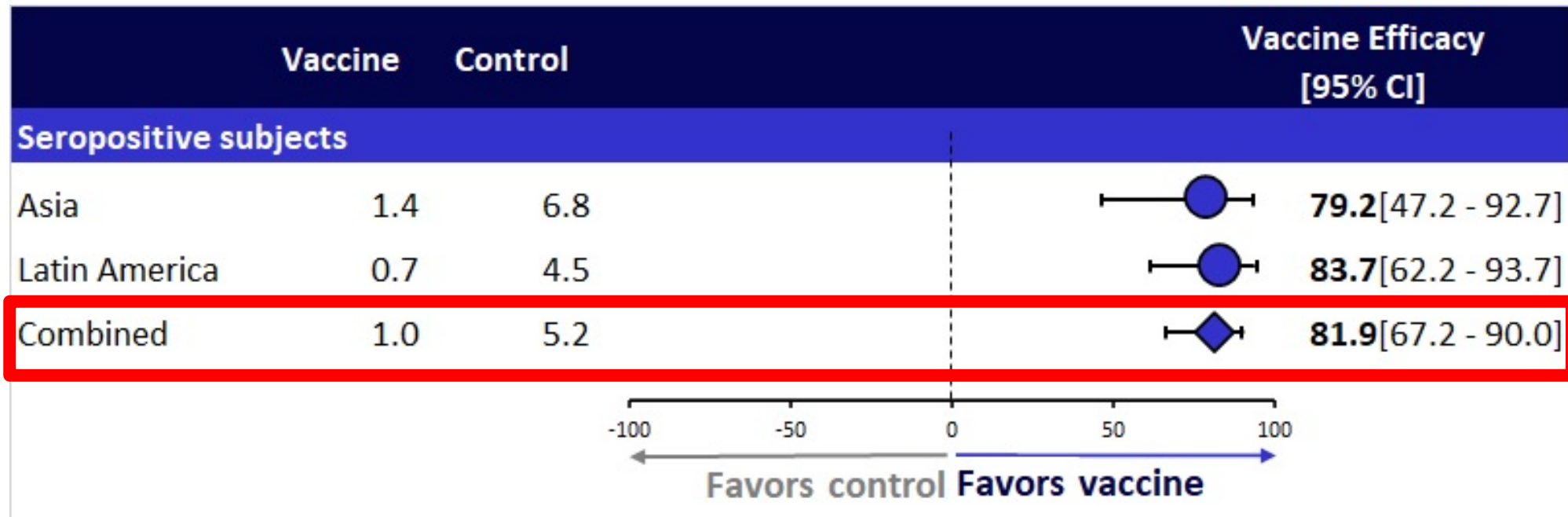
Benefits and Harms

How substantial are the desirable anticipated effects?

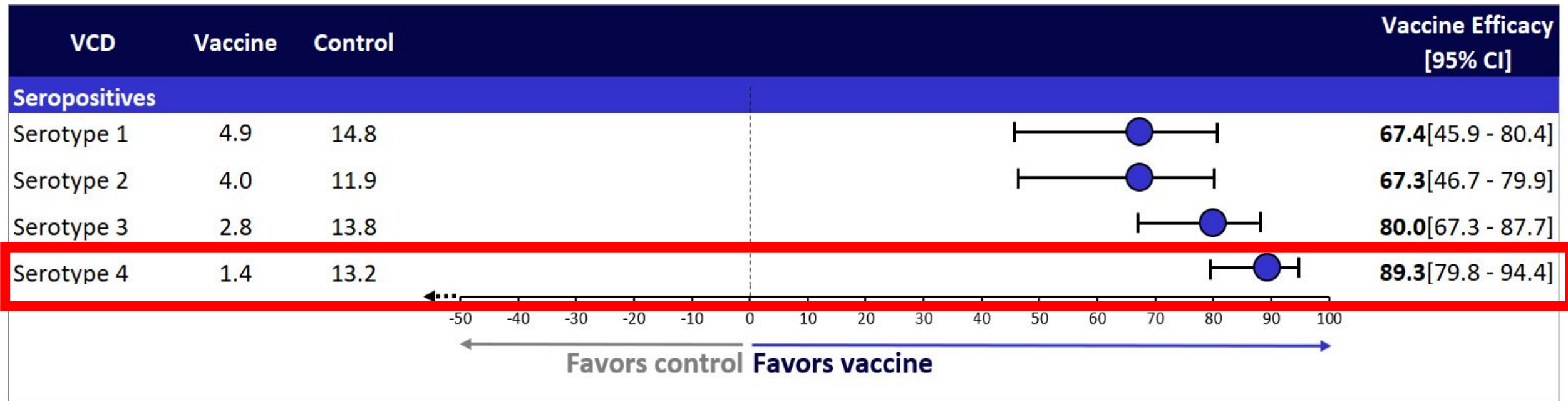
- Minimal
- Small
- Moderate
- Large
- Varies
- Don't know



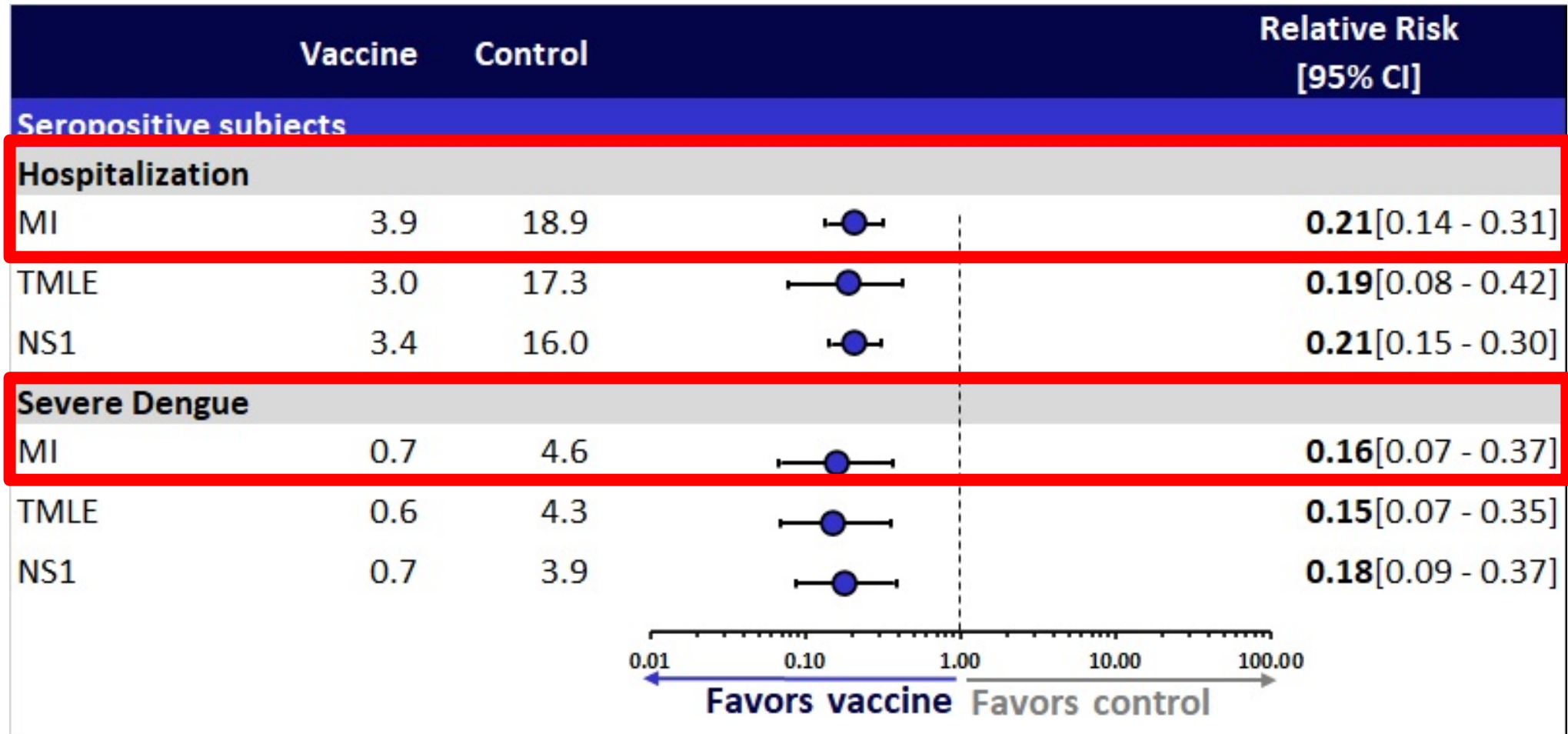
Efficacy virologically confirmed dengue (VCD) at 25 months, seropositive participants 9-16 years



Efficacy against VCD by serotype, seropositive participants 9-16 years

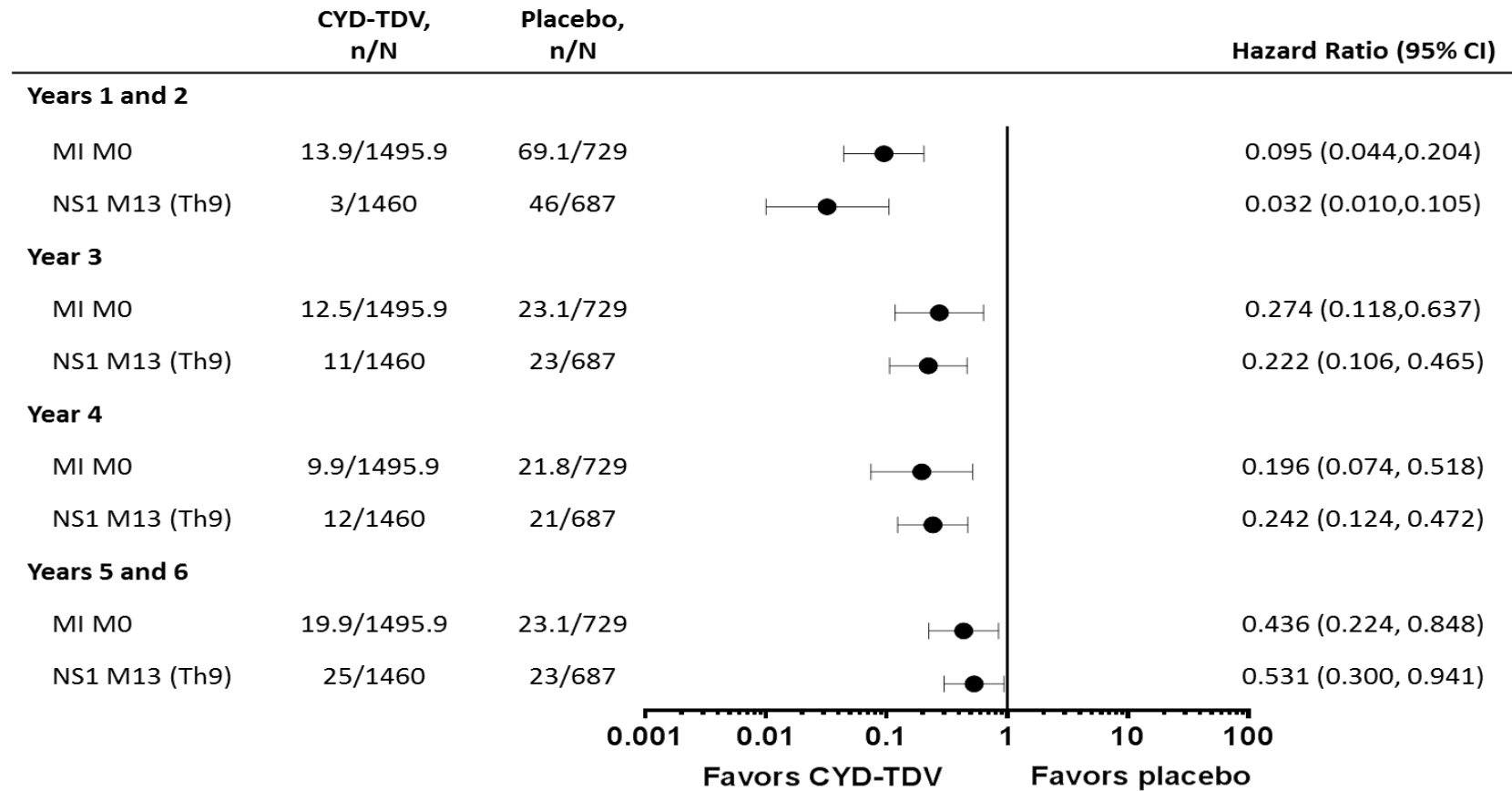


Efficacy against hospitalization and severe dengue at 60 months, seropositive participants 9-16 years





Risk of dengue hospitalization for each time period over 6-years, seropositive participants 9–16 year



How substantial are the desirable anticipated effects?

Minimal Small Moderate Large Varies Don't know

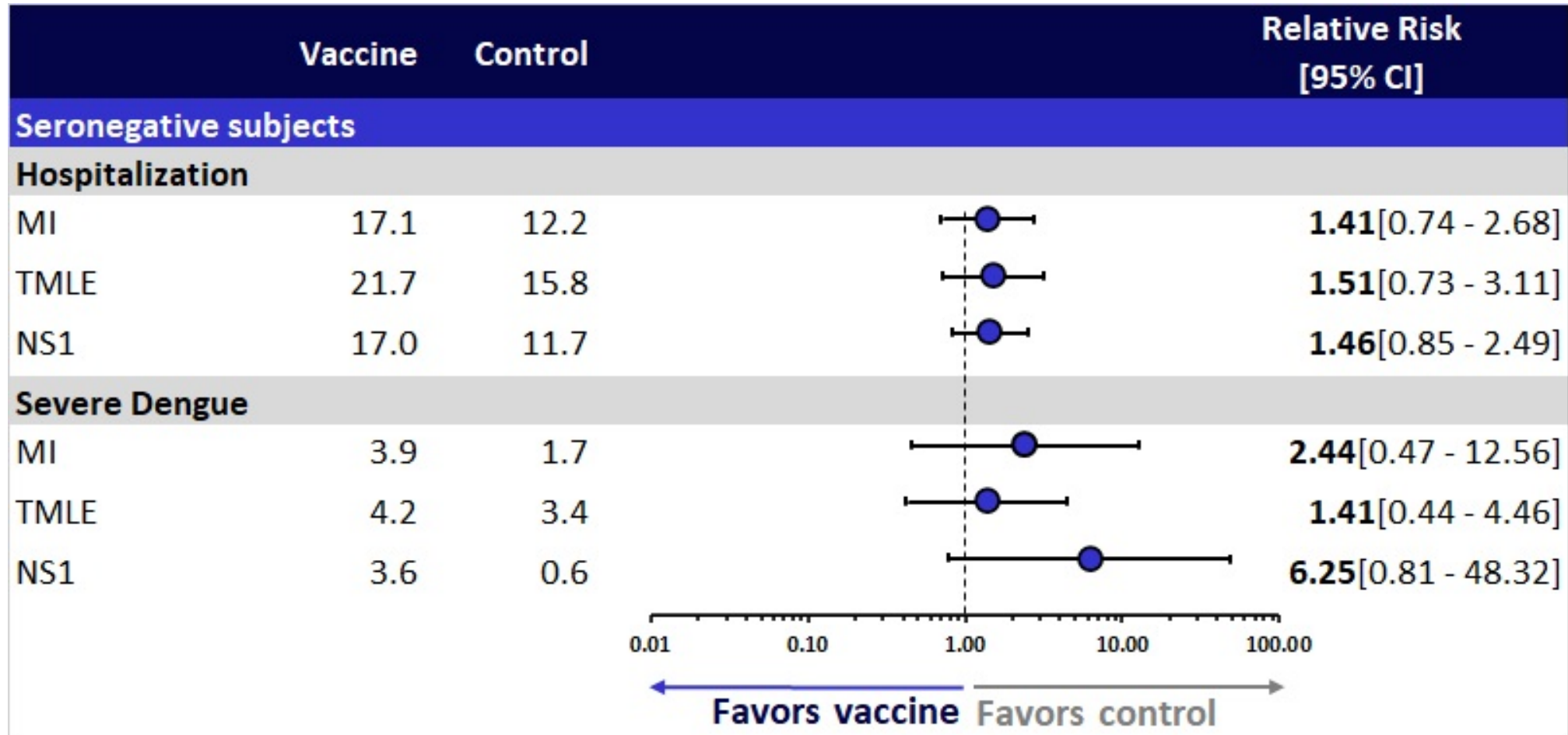


How substantial are the undesirable anticipated effects?

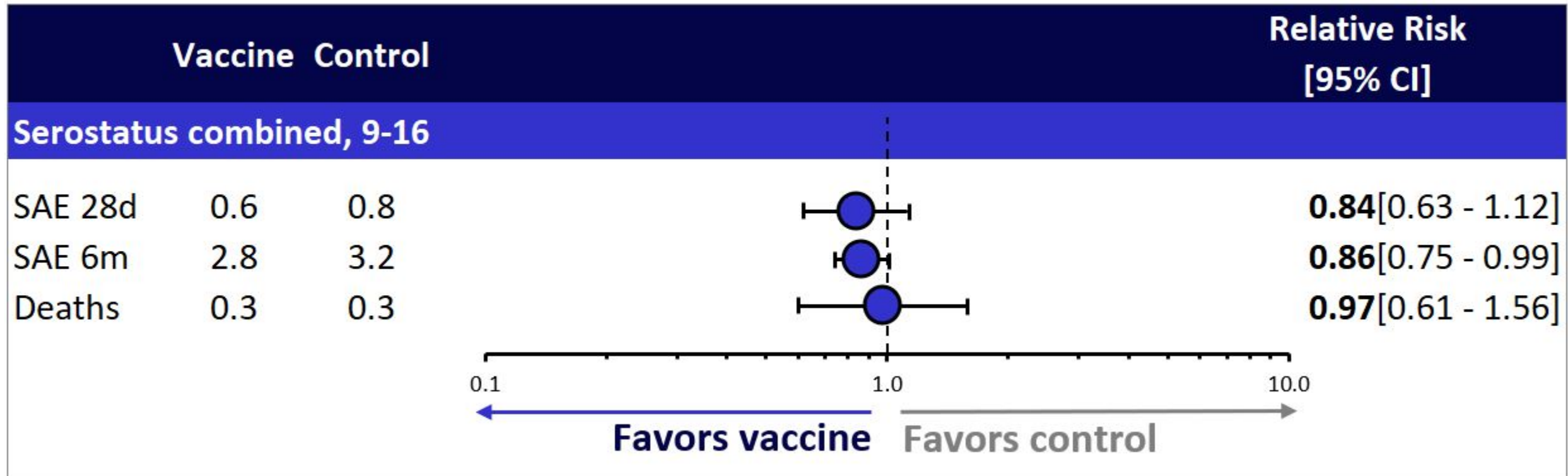
Minimal Small Moderate Large Varies Don't know



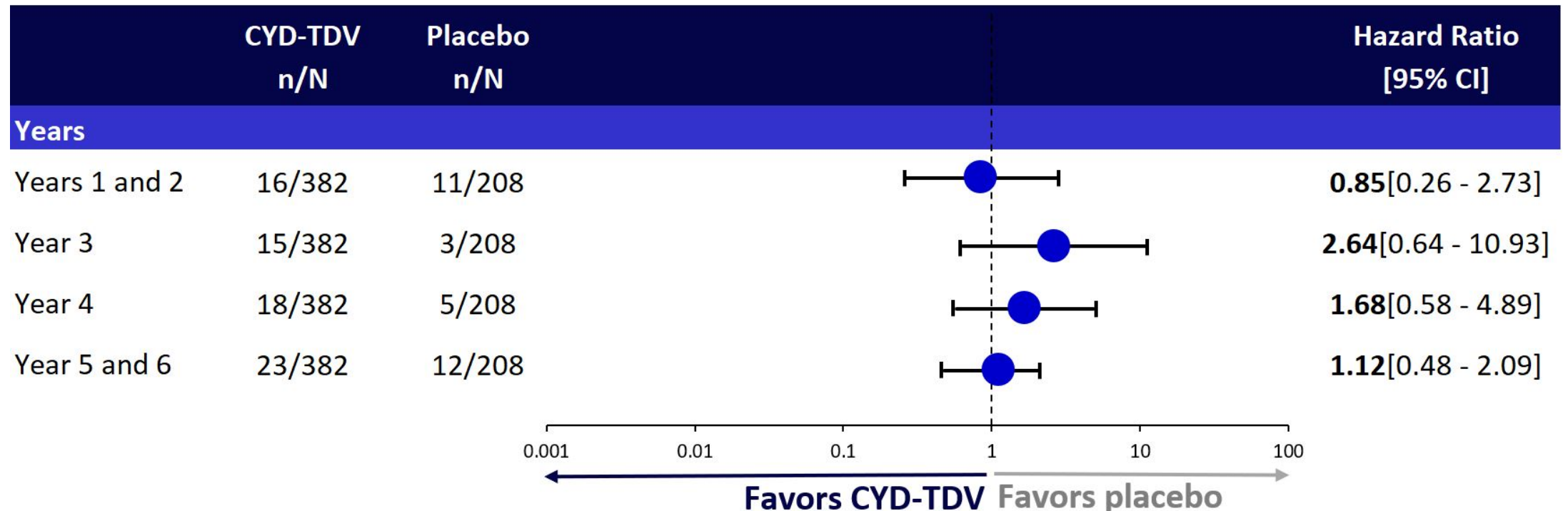
Risk of hospitalization and severe dengue at 60 months, seronegative participants 9-16 years



Severe adverse events and deaths among participants 9-16 years, serostatus combined



Risk of dengue hospitalization for each time period over 6 years, seronegative participants ages 9–16 years



Multiple imputation

Sanofi Pasteur, personal communication, March 15, 2021

How substantial are the undesirable anticipated effects?

- Minimal
- Small
- Moderate
- Large
- Varies
- Don't know



Do the desirable effects outweigh the undesirable effects?

- Favors intervention
- Favors comparison
- Favors both
- Favors neither
- Varies
- Don't know



Benefits and harms

- **Benefits of Dengvaxia**

- Efficacy against symptomatic virologically confirmed dengue (82%, CI: 67-90)
- Efficacy against dengue hospitalizations (79%, CI: 69-86)
- Efficacy against severe dengue (84%, CI: 63-93)

- **Harms of Dengvaxia**

- Increased risk of vaccine-induced hospitalization if a seronegative child is vaccinated after a false-positive laboratory test

Population impact of screen and vaccinate strategy

- Agent-based model of dengue transmission with humans and mosquitoes represented as agents
- Calibrated to simulate dengue transmission in Puerto Rico
- Compares pre-vaccination screening and subsequent vaccination of seropositive 9-year-olds to the status quo
- Model population followed for 10 years keeping track of dengue infections, hospitalizations and deaths
- Prevalence at age 9 years of age of 50% and 30%
- Population level benefits: symptomatic and hospitalized cases averted
- Risks: vaccine –induced hospitalizations among dengue-naïve individuals

Population-level impacts of the intervention in Puerto Rico

Total numbers of symptomatic and hospitalized cases as well as cases averted and additional hospitalizations among vaccinees.

Time frame modeled: 10 years

Strategy: testing and vaccinating cohorts of test-positive 9-year-old children in Puerto Rico annually

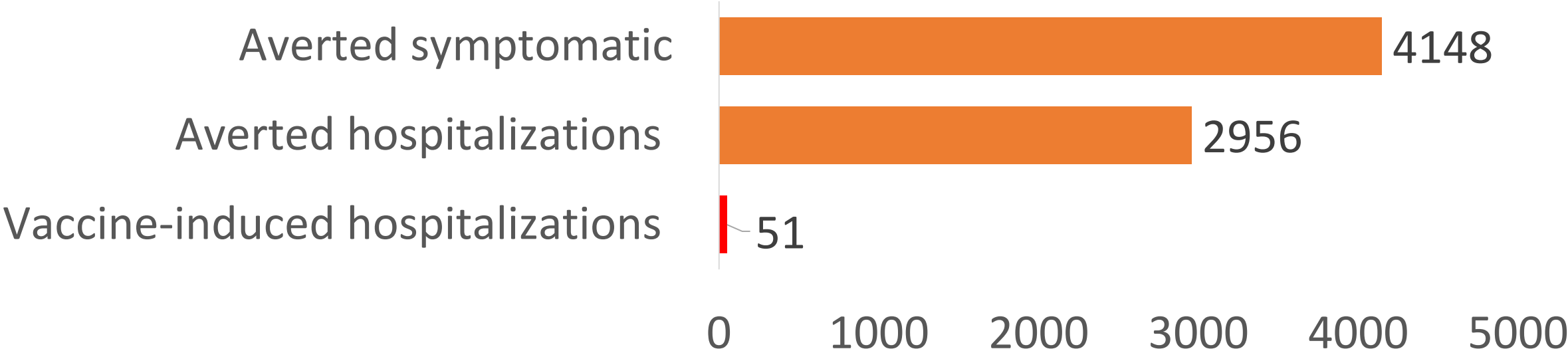
Test performance: sensitivity = 0.75 and specificity = 0.98.

	Baseline		Test and vaccinate strategy		Averted		Additional	Ratio
	Symptomatic	Hospitalizations	Tested	Vaccinated	Symptomatic	Hospitalizations	Hospitalizations	averted/additional
Prior exposure in 9-yr-olds								
30%	221751	51278	317823	61825	1551	1262	112	11/1
50%	260218	60663	317814	102884	4148	2956	51	57/1
60%	271711	63807	317809	125127	5538	4295	28	152/1

Benefits and harms of vaccination among a 10-year cohort of 9-year-old children 50% seroprevalence

Screening test 75% sensitive and 98% specific

50% seroprevalence



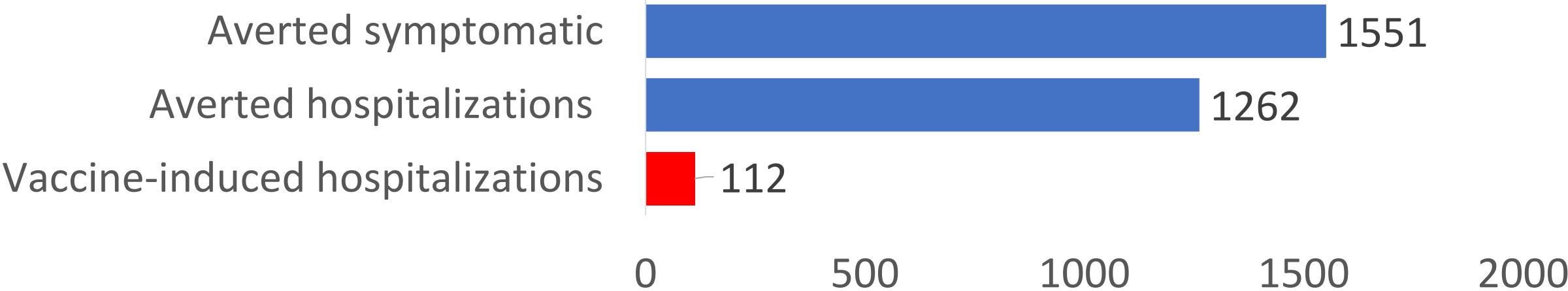
51 vaccine-induced hospitalizations in 102,884 vaccinees (completed series)

Espana G, Leidner A, Waterman S, Perkins A. Cost-effectiveness of Dengue Vaccination in Puerto Rico. <https://www.medrxiv.org/content/10.1101/2020.10.07.20208512v1>
Sensitivity and specificity modified by Espana G. for this presentation.

Benefits and harms of vaccination among a 10-year cohort of 9-year-old children 30% seroprevalence

Screening test 75% sensitive and 98% specific

30% seroprevalence



112 vaccine-induced hospitalizations in 61,825 vaccinees (completed series)

Espana G, Leidner A, Waterman S, Perkins A. Cost-effectiveness of Dengue Vaccination in Puerto Rico. <https://www.medrxiv.org/content/10.1101/2020.10.07.20208512v1>
Sensitivity and specificity modified by Espana G. for this presentation,

Summary of population benefits and harms of vaccination among a 10-year cohort of 9-year-old children

50% seroprevalence

- Risks
 - 51 vaccine-induced hospitalizations among seronegative children
- Benefits
 - 4148 fewer symptomatic cases
 - 2956 fewer hospitalizations

30% seroprevalence

- Risks
 - 112 vaccine-induced hospitalizations among seronegative children
- Benefits
 - 1551 fewer symptomatic cases
 - 1262 fewer hospitalizations

Interpretation benefits and harms

- Shows positive balance for benefits versus harms
- Balance of risk and benefits varies by seroprevalence

Do the desirable effects outweigh the undesirable effects?

Favors intervention

Favors comparison

Favors both

Favors neither

Varies

Don't know



What is the overall certainty of the evidence?

Effectiveness of the intervention

- 4 (very low)
- 3 (low)
- 2 (moderate)
- 1 (high)

Safety of the intervention

- 4 (very low)
- 3 (low)
- 2 (moderate)
- 1 (high)



Values

Does the target population feel that the desirable effects are large relative to undesirable effects?

- No Probably no Probably Yes Yes Varies Don't know



Is there important uncertainty about or variability in how much people value the main outcomes?

- Important uncertainty or variability
- Probably important uncertainty or variability
- Probably not important uncertainty or variability
- Not important uncertainty or variability
- No known undesirable outcomes



Acceptability

Is the intervention acceptable to key stakeholders?

- No Probably no Probably Yes Yes Varies Don't know



Feasibility

Is the intervention feasible to implement?

No Probably no Probably Yes Yes Varies Don't know



Feasibility assessment has focused in PR due to burden, lessons learned will help prepare

Territory/Associated State	Population 9-16 years (2019)	%	Vaccine providers	Laboratories
Puerto Rico	303,826	85%	505	450
US Virgin Islands	12,000	3%	11	8
American Samoa	10,100	3%	4	1
Federated States of Micronesia*	16,000	4%	2	2
Palau*	2,423	1%	4	1
Marshall Islands*	14,000	4%	2	2

*Sovereign freely associated states

USVI survey of healthcare facilities (n=11)

- 4/11 were aware there was an FDA approved vaccine
- 5/11 would recommend the vaccine if there was a test available for screening
- 7/11 need more information before recommending it

Pacific Islands

- Presentation on Dengvaxia to PIHOA
- Planning a survey of providers by University of Georgia
- Partnership to test left over samples of household-based surveys to determine dengue seroprevalence

Is the intervention feasible to implement?

- No Probably no Probably Yes Yes Varies Don't know



Resource Use

Is the intervention a reasonable and efficient allocation of resources?

- No Probably no Probably Yes Yes Varies Don't know



Cost-effectiveness analyses of Dengvaxia use in Puerto Rico 2019 Costs

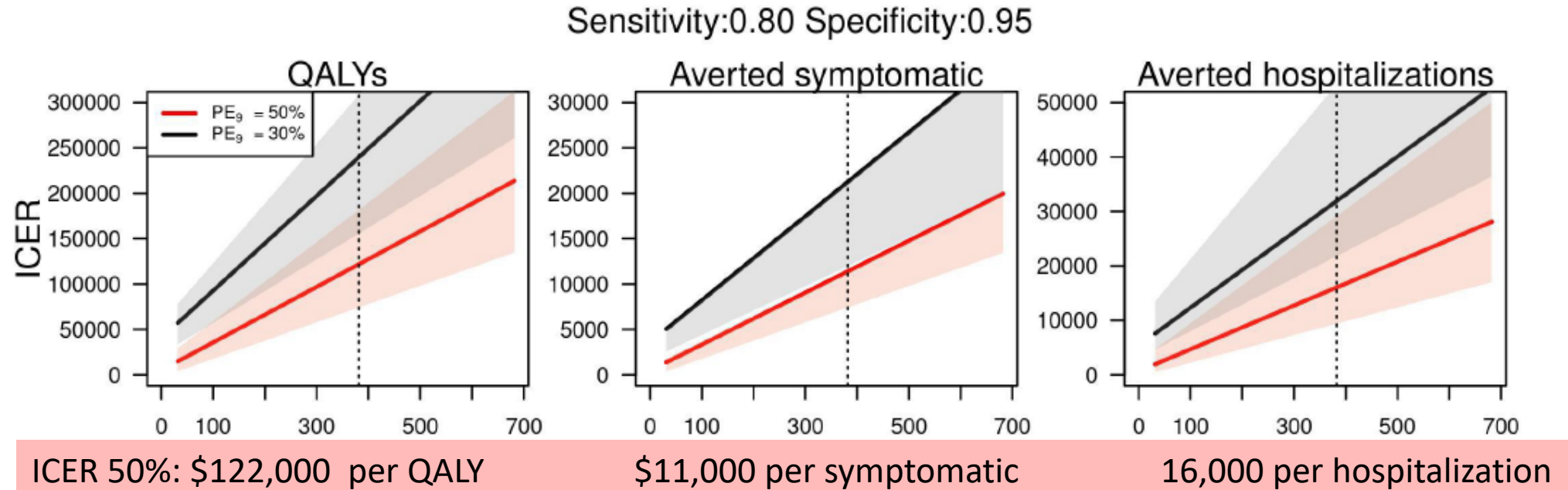


Figure 5. ICER of pre-vaccination screening strategy in Puerto Rico at different costs of vaccination (total cost for three doses per person), assuming a unit cost of serological screening of 30 USD. Dotted line represents the baseline assumption of vaccine cost (382 USD). All costs in 2019 USD.

- Espana G, Leidner A, Waterman S, Perkins A. Cost-effectiveness of Dengue Vaccination in Puerto Rico. <https://www.medrxiv.org/content/10.1101/2020.10.07.20208512v1>

Is the intervention a reasonable and efficient allocation of resources?

- No Probably no Probably Yes Yes Varies Don't know



Equity

What would be the impact on health equity?

- Reduced
- Probably reduced
- Probably no impact
- Probably increased
- Increased
- Varies
- Don't know



Balance of consequences

- Undesirable consequences *clearly outweigh* desirable consequences in most settings
- Undesirable consequences *probably outweigh* desirable consequences in most settings
- The balance between desirable and undesirable consequences is *closely balanced or uncertain*
- Desirable consequences *probably outweigh* undesirable consequences in most settings
- Desirable consequences *clearly outweigh* undesirable consequences in most settings
- There is insufficient evidence to determine the balance of consequences



Is there sufficient information to move forward with a recommendation?

Yes

No



Policy options for ACIP

- ACIP does not recommend the intervention (Intervention may be used within FDA licensed indications)
- ACIP recommends the intervention for individuals based on shared clinical decision-making
- ACIP recommends the intervention



Option 1: ACIP does not recommend

Cons

- A vaccine proven to protect persons with prior dengue infection will not be available to US citizens
- Puts off making difficult decision that may be needed for the next dengue vaccine approved by FDA

Pros

- Avoids a complicated implementation in the middle of COVID vaccinations programs

Option 2: Shared decision making

Cons

- Lower uptake
- Little progress in sorting out feasibility
- Coverage of test by insurance companies challenging
- May increase health inequities due to unequal health literacy
- Less buy-in for large scale education and communication

Pros

- Would lessen fears that the vaccine will become controversial and result in increased vaccine hesitancy

Option 3: Routine recommendation

Cons

- Public and media perception of the risks associated with the vaccine may increase vaccine hesitancy
- Potential public and provider perception that all hospitalizations among vaccinees related to vaccine

Pros

- Effective vaccine for seropositive children
- Greater coverage, reduction in hospitalizations
- Better buy-in from health department and immunization program to resolve challenges with feasibility
- Broader communication and media campaign
- Increase in health equity

Policy options for ACIP consideration

- ACIP does not recommend the intervention (Intervention may be used within FDA licensed indications)
- ACIP recommends the intervention for individuals based on shared clinical decision-making
- ACIP recommends the intervention



Draft Recommendation

- ACIP recommends 3-doses of Dengvaxia administered 6 months apart at month 0, 6, and 12, in persons 9-16 years of age with a laboratory confirmation of previous dengue infection and living in endemic areas.

ACIP Dengue Vaccines Workgroup

ACIP Members

Kathy Poehling (Co-chair)

Wilbur Chen (Co-Chair)

Beth Bell

Veronica McNally

CDC Lead

Gabriela Paz-Bailey

Ex Officio Members

Kaitlyn Morabito (NIH)

Ralph LeBlanc (FDA)

Kirk Prutzman (FDA)

Srihari Seshadri (DOD)

Liaison Representatives

Elizabeth Barnett (AAP)

Rob Schechter (AIM)

Consultants

Edwin Asturias

Robert Atmar

Alan Barrett

Anna Durbin

Ines Esquilin

Tony Marfin

Hal Margolis

Kristen Pierce

Anita Shet

Steve Waterman

CDC Contributors

Laura Adams

Josh Wong

Mimi Eckert

Rachel Eidex

Susan Hills

Terri Hyde

Mike McNeil

Jorge Munoz

Erin Staples

Cindy Weinbaum