



Dengue Vaccine

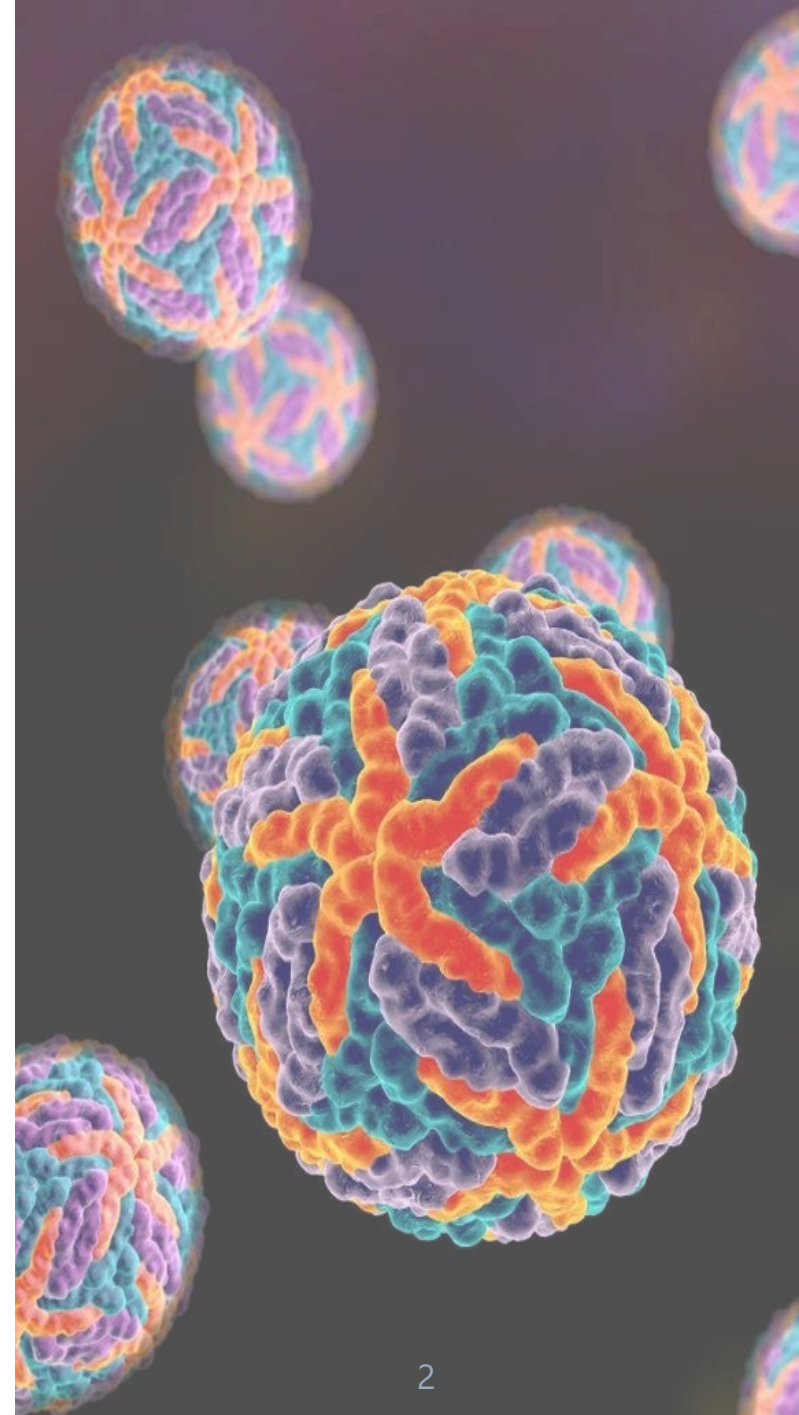
Evidence to recommendations framework

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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



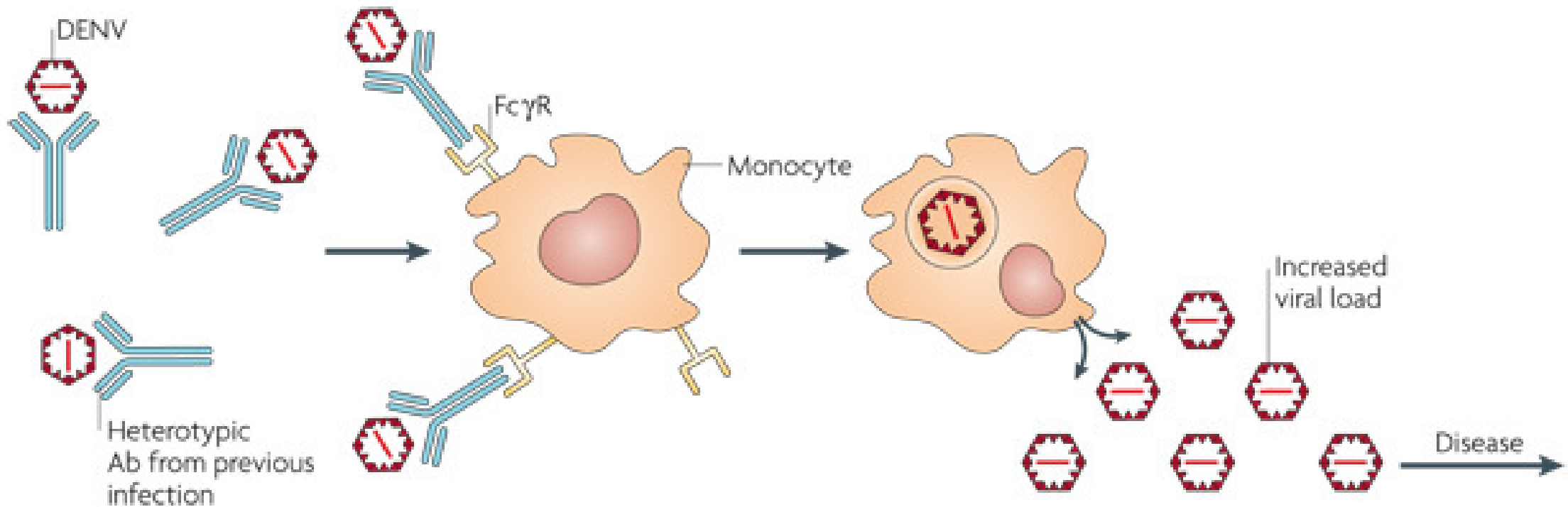
Dengue illness

- Dengue fever can range from asymptomatic or mild to severe
- Mortality can range from 0.2% (treated) to as high as 13% (untreated)
- Causes of death: unrecognized or prolonged shock, hemorrhage, fluid overload, nosocomial sepsis



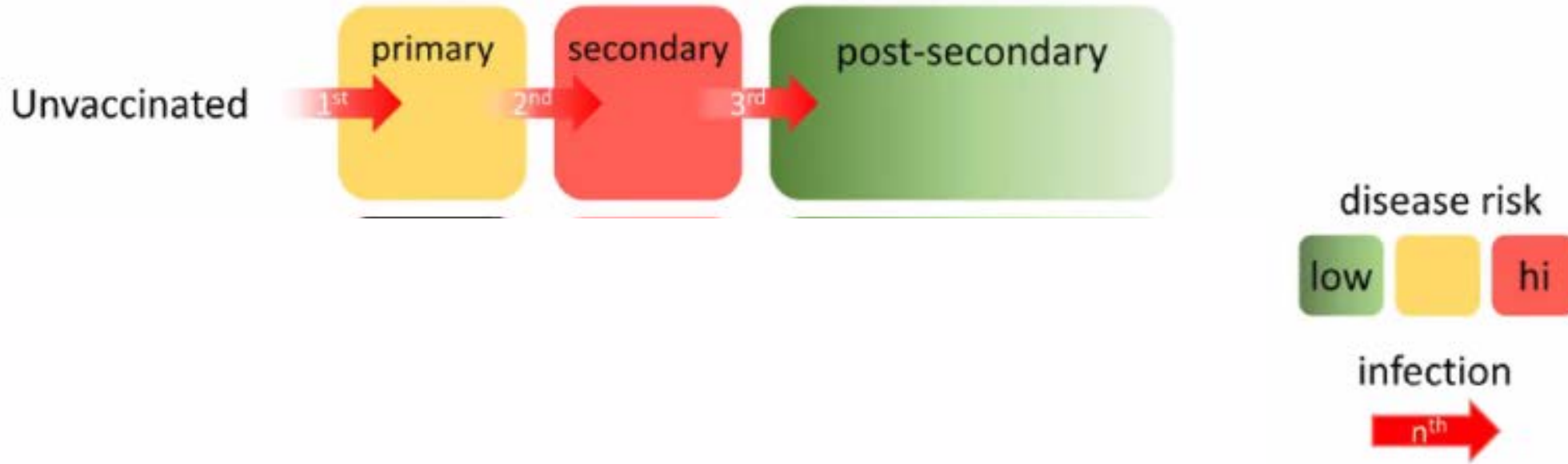
Hospital chapel converted to a dengue ward during dengue outbreak in Honduras in 2019.

Antibody-dependent enhancement (ADE) of dengue infection



Whitehead SS, Blaney JE, Durbin AP, Murphy BR. Prospects for a dengue virus vaccine. *Nat Rev Microbiol.* 2007;5(7):518-528. doi:[10.1038/nrmicro1690](https://doi.org/10.1038/nrmicro1690)

Secondary dengue infection is the riskiest for poor outcomes



Dengvaxia timeline

2015

- Trial results showed increased risk of severe disease among 2-5 year-olds
- Dengvaxia licensed in the Philippines for children >9 years old.

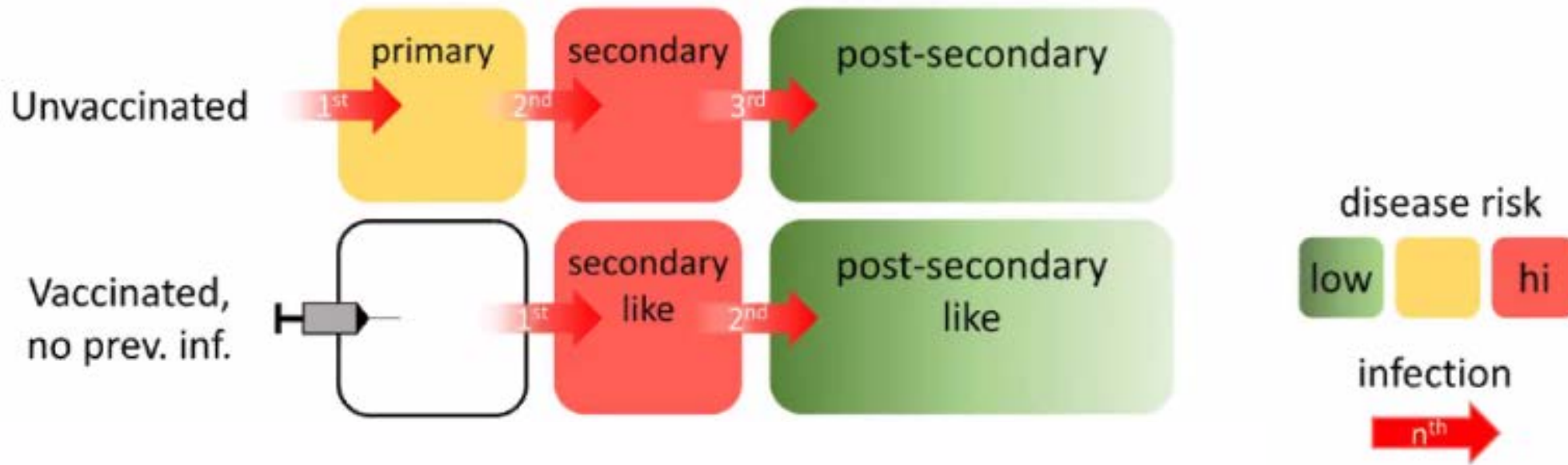
2016

- WHO position paper: 9y and older in highly endemic areas
- Philippines starts vaccinating 1 million children ages 9-10 years

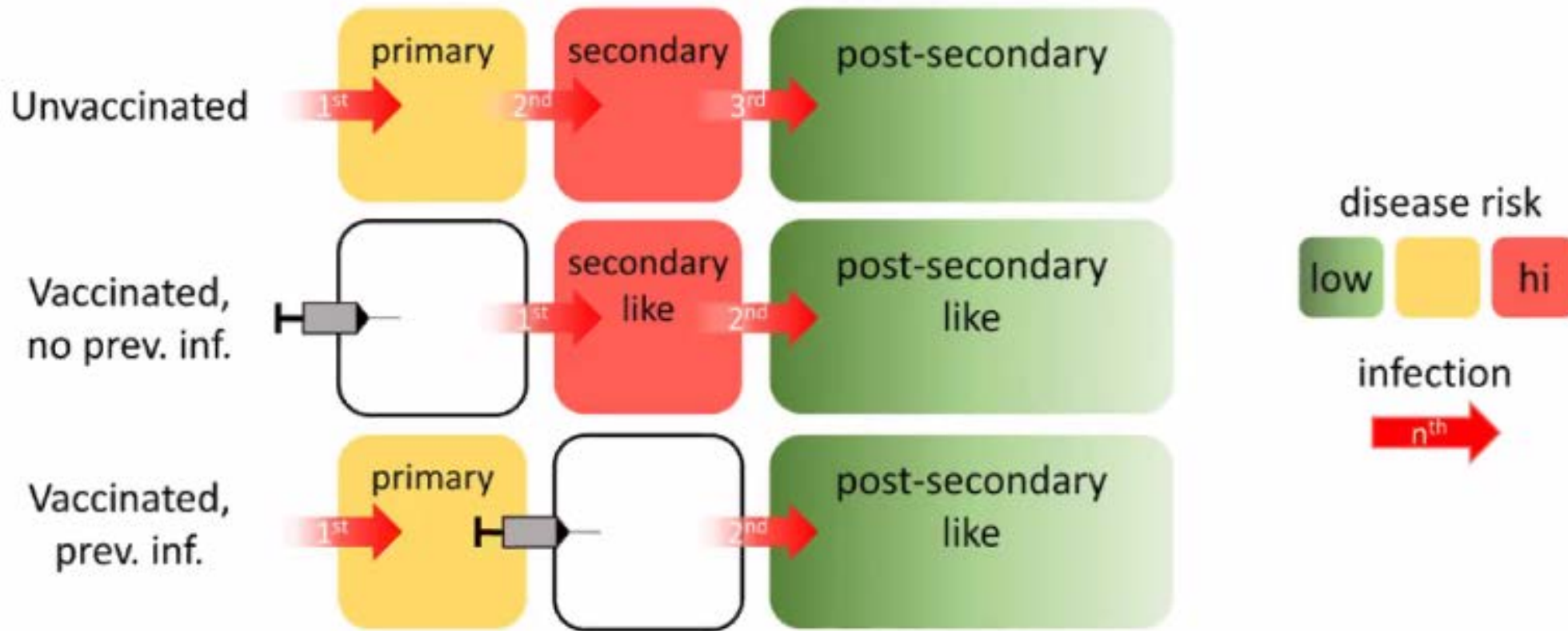
2017

- Additional testing showed increased risk of severe dengue and hospitalization among vaccinated seronegative children compared to controls

Secondary dengue infection is the riskiest for poor outcomes



Secondary dengue infection is the riskiest for poor outcomes



Flasche S, Jit M, Rodríguez-Barrquer I, 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. von Seidlein L, ed. *PLoS Med.* 2016;13(11):e1002181. doi:[10.1371/journal.pmed.1002181](https://doi.org/10.1371/journal.pmed.1002181)

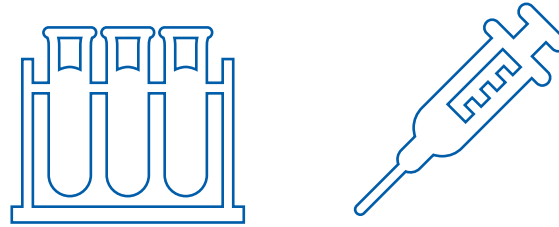
The Philippines experience: no screening before vaccination

- WHO revised their recommendations vaccine only be given to children with laboratory-confirmed past dengue
- Philippines had vaccinated almost 1 million children without testing
- The suspension of the program broke public trust in vaccines
- Hospitalized and severe dengue cases that occur following vaccination were a mixture of breakthrough cases from seropositive and cases from seronegative at vaccination
- Most dengue hospitalizations in the Philippines were due to breakthrough disease, baseline disease and a smaller percentage were vaccine-induced

FDA Licensing of first dengue vaccine 2019



Test performance guidance for pre-vaccination screening



- **98%** specific
- **75%** sensitive

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

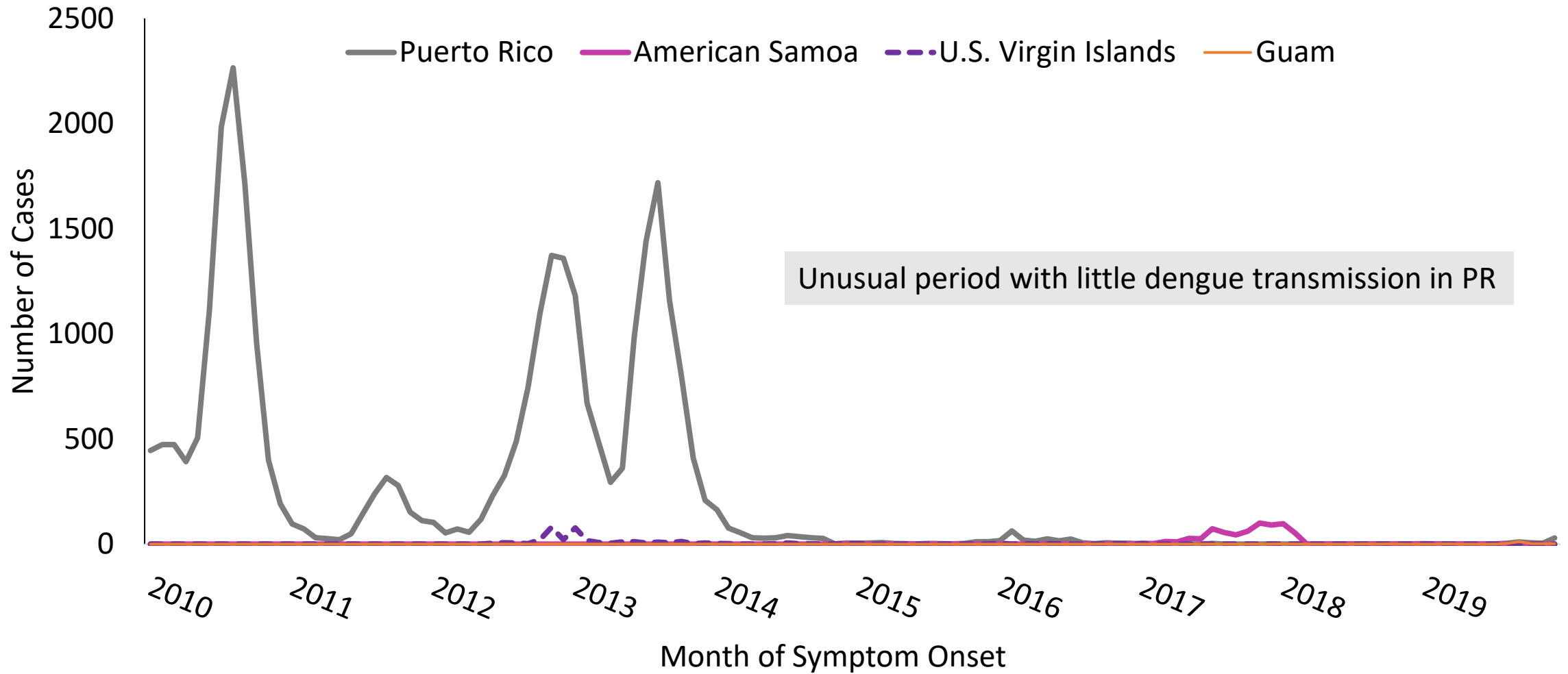


Dengue endemic areas in the United States

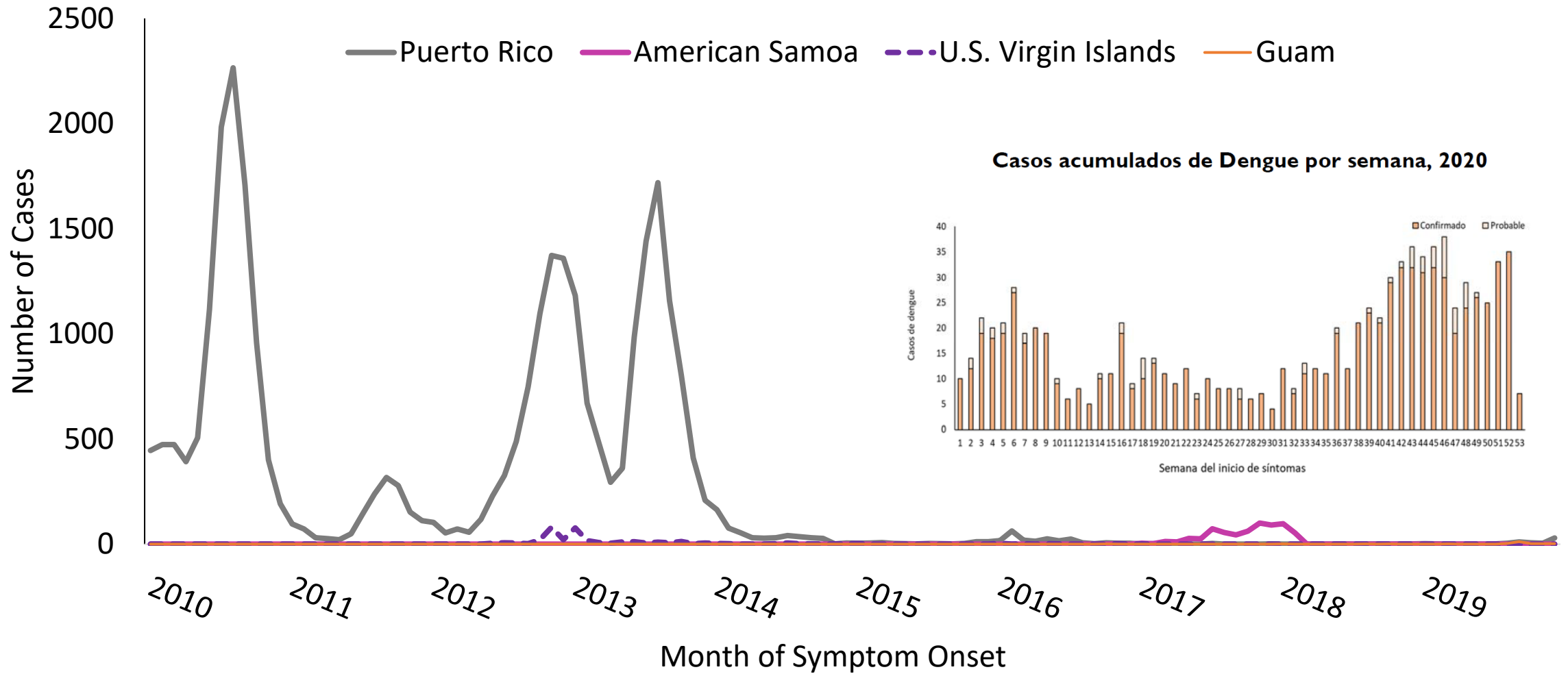
90% of the population at risk for locally-acquired dengue is in Puerto Rico

Country/Area	Level of dengue risk	Population
U.S. States	Sporadic/uncertain	
Territories and freely associated states		
American Samoa	Frequent/Continuous	55,465 (1%)
Puerto Rico	Frequent/Continuous	3,194,000 (90%)
US Virgin Islands	Frequent/Continuous	106,977 (3%)
Guam	Sporadic/uncertain	
Northern Mariana Islands	Sporadic/uncertain	
Micronesia		
Federated States of Micronesia	Frequent/Continuous	112,640 (3%)
Palau	Frequent/Continuous	17,907 (<1%)
Marshall Islands	Sporadic/uncertain	59,000 (2%)
Total population at risk		3,545,989

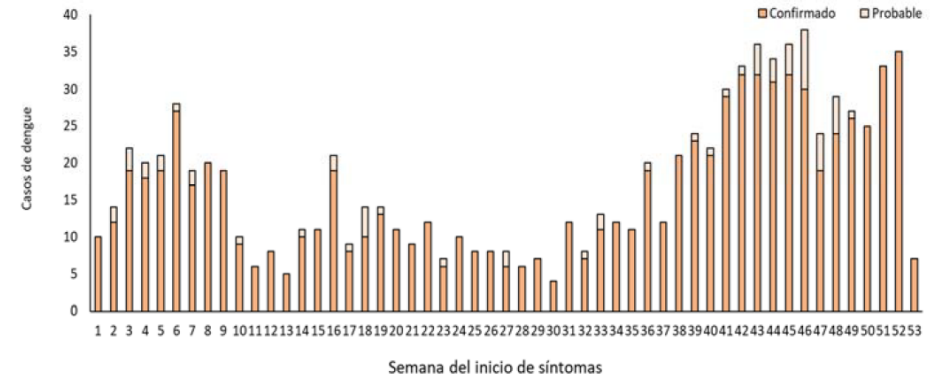
95% of dengue cases in U.S. territories occur in Puerto Rico



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

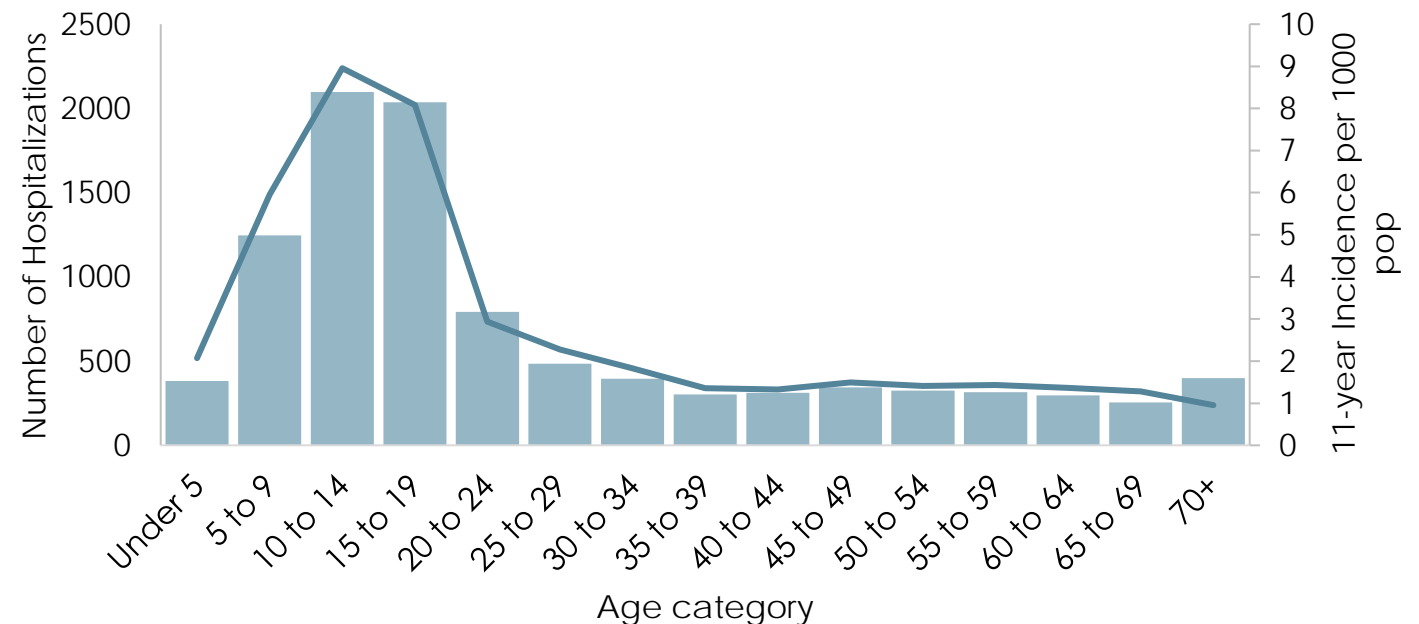
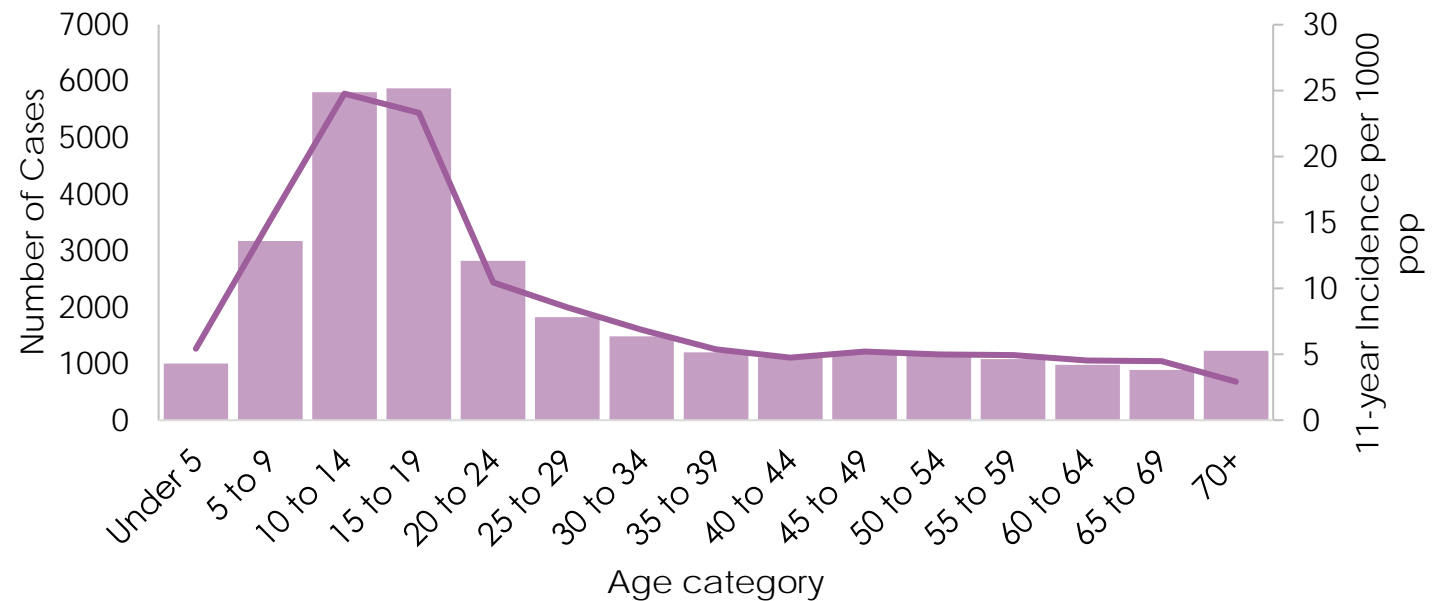


Casos acumulados de Dengue por semana, 2020



Dengue virus cases and hospitalizations by age, Puerto Rico, 2010–2020*

Highest incidence of cases and hospitalizations among children 10–19 years old

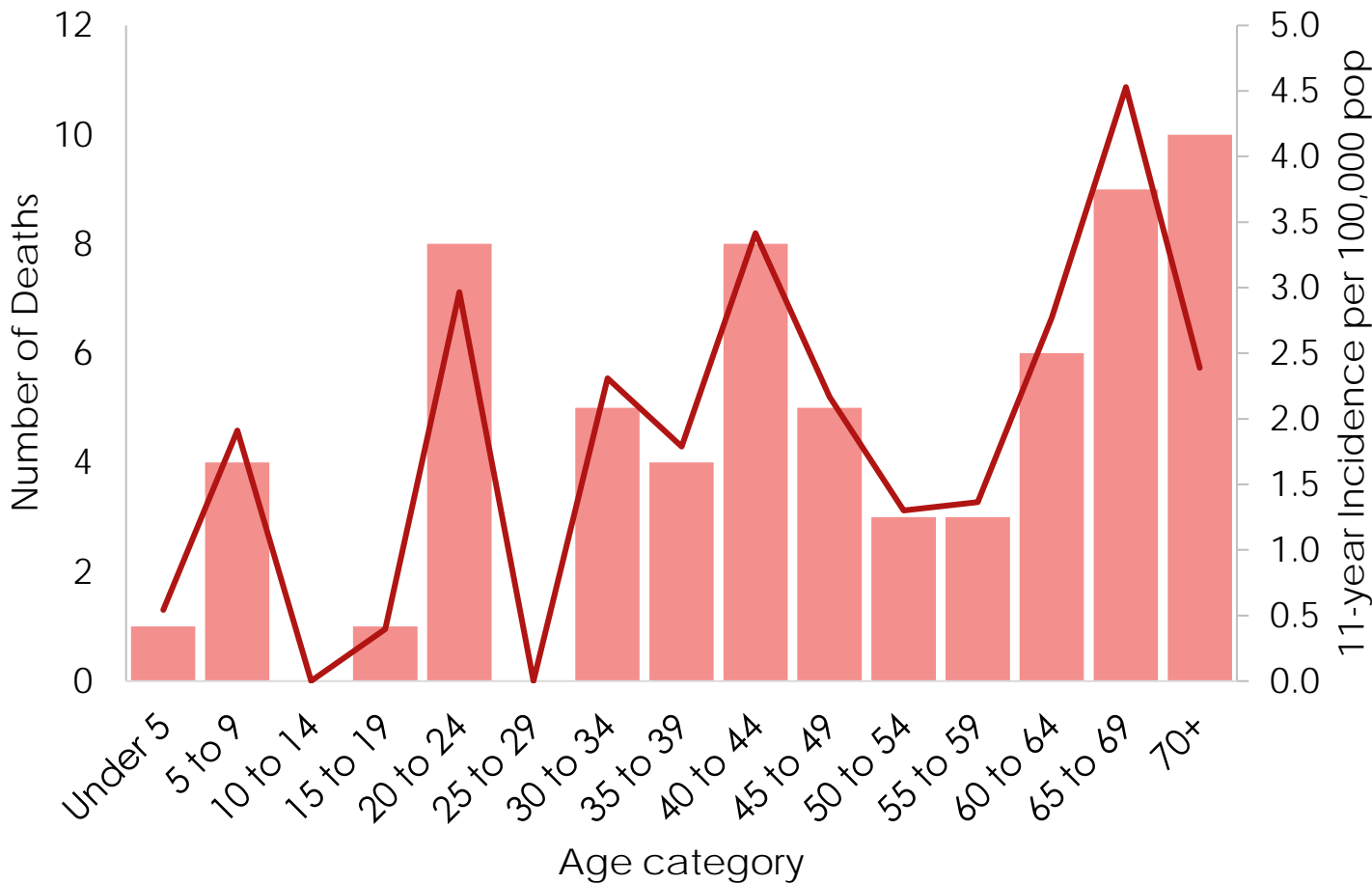


*Includes confirmed and probable cases reported to Arbonet, National Arbovirus Surveillance System.

2020 data is preliminary; accessed Feb 4, 2021

Dengue virus **deaths** by age, Puerto Rico, 2010–2020*

Most dengue deaths (88%; 61/69) occurred among adults ≥20 years old



*Includes confirmed and probable cases reported to Arbonet, National Arbovirus Surveillance System. 2020 data is preliminary; accessed Feb 4, 2021

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)
 - 50% seropositive at age 9 years

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



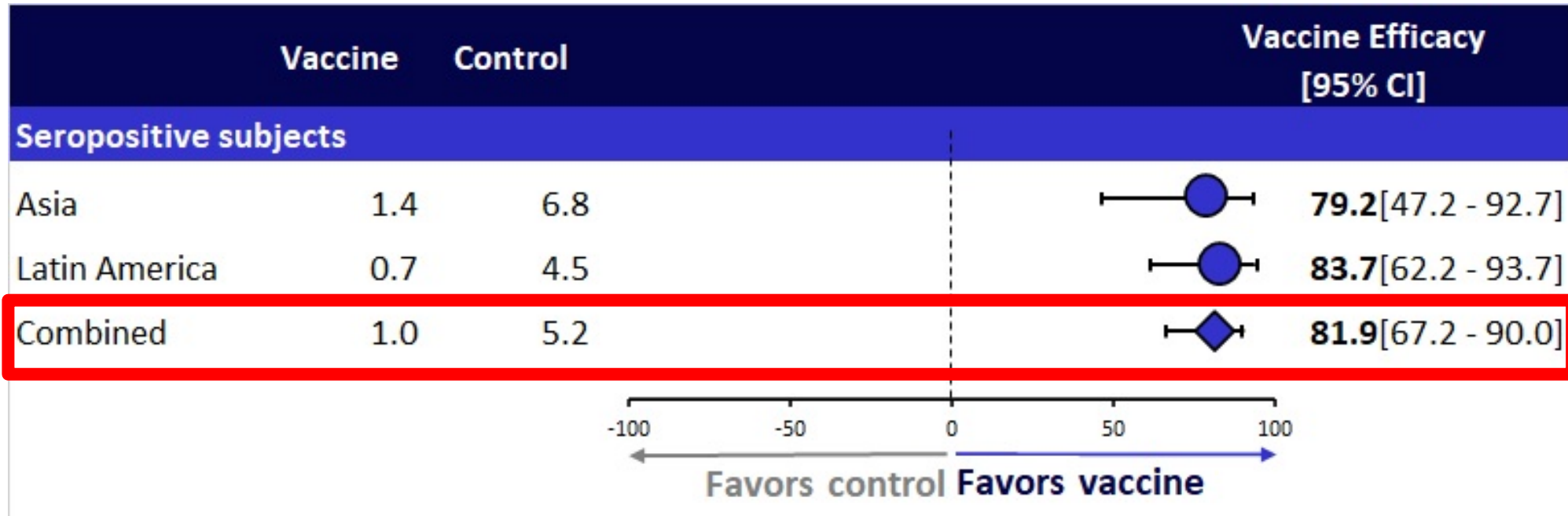
Benefits and Harms

How substantial are the desirable anticipated effects?

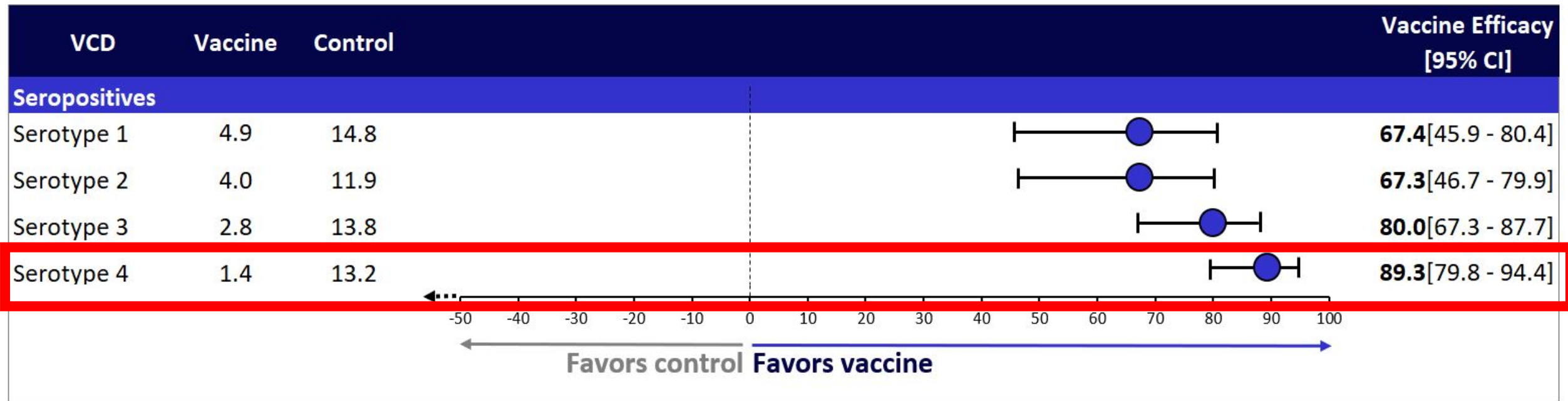
- Minimal
- Small
- Moderate
- Large
- Varies
- Don't know



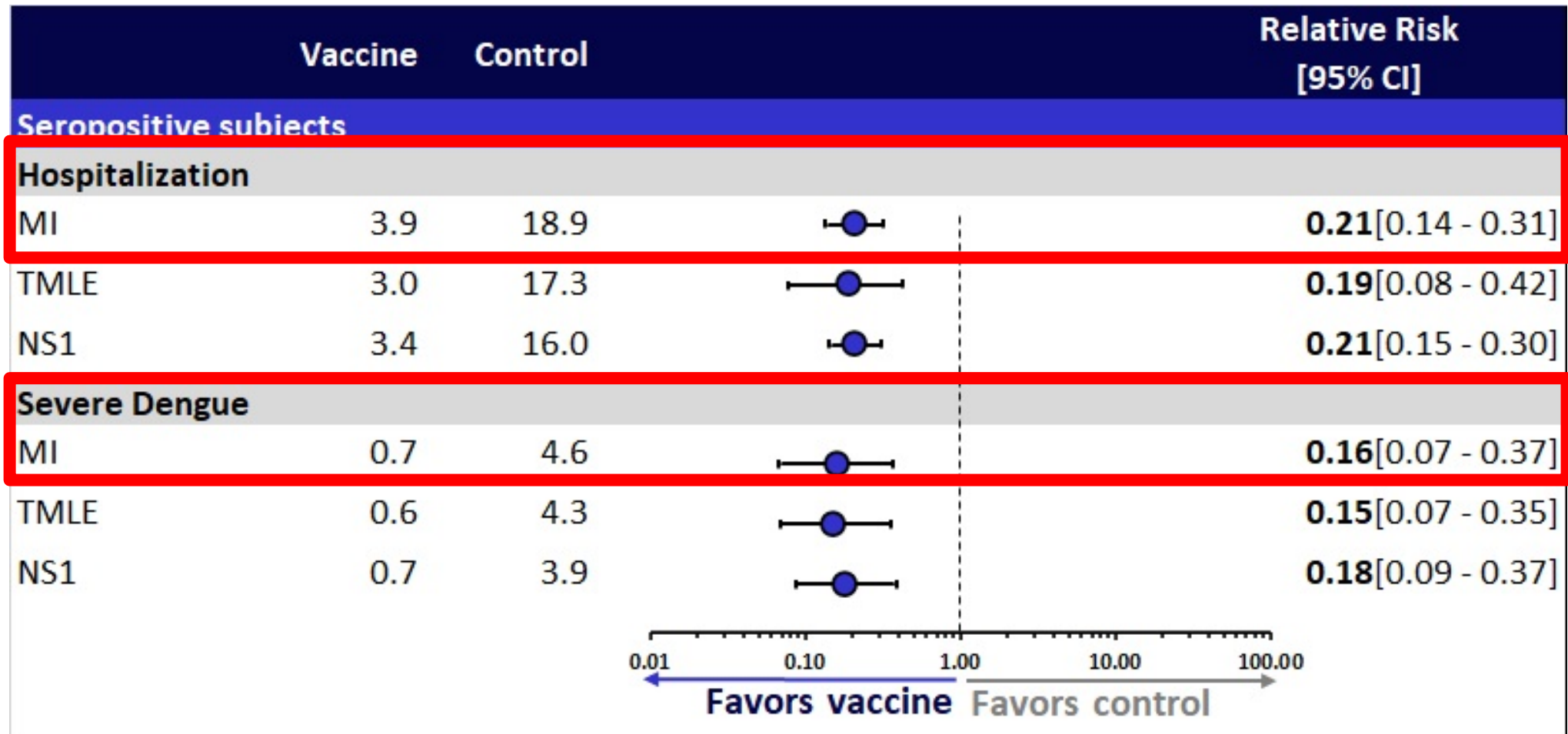
Efficacy against virologically confirmed dengue (VCD) seropositive participants 9-16 years



Efficacy against VCD among dengue seropositive participants 9-16 years



Efficacy against hospitalization and severe dengue seropositive participants 9-16 years



How substantial are the desirable anticipated effects?

Minimal Small Moderate Large Varies Don't know

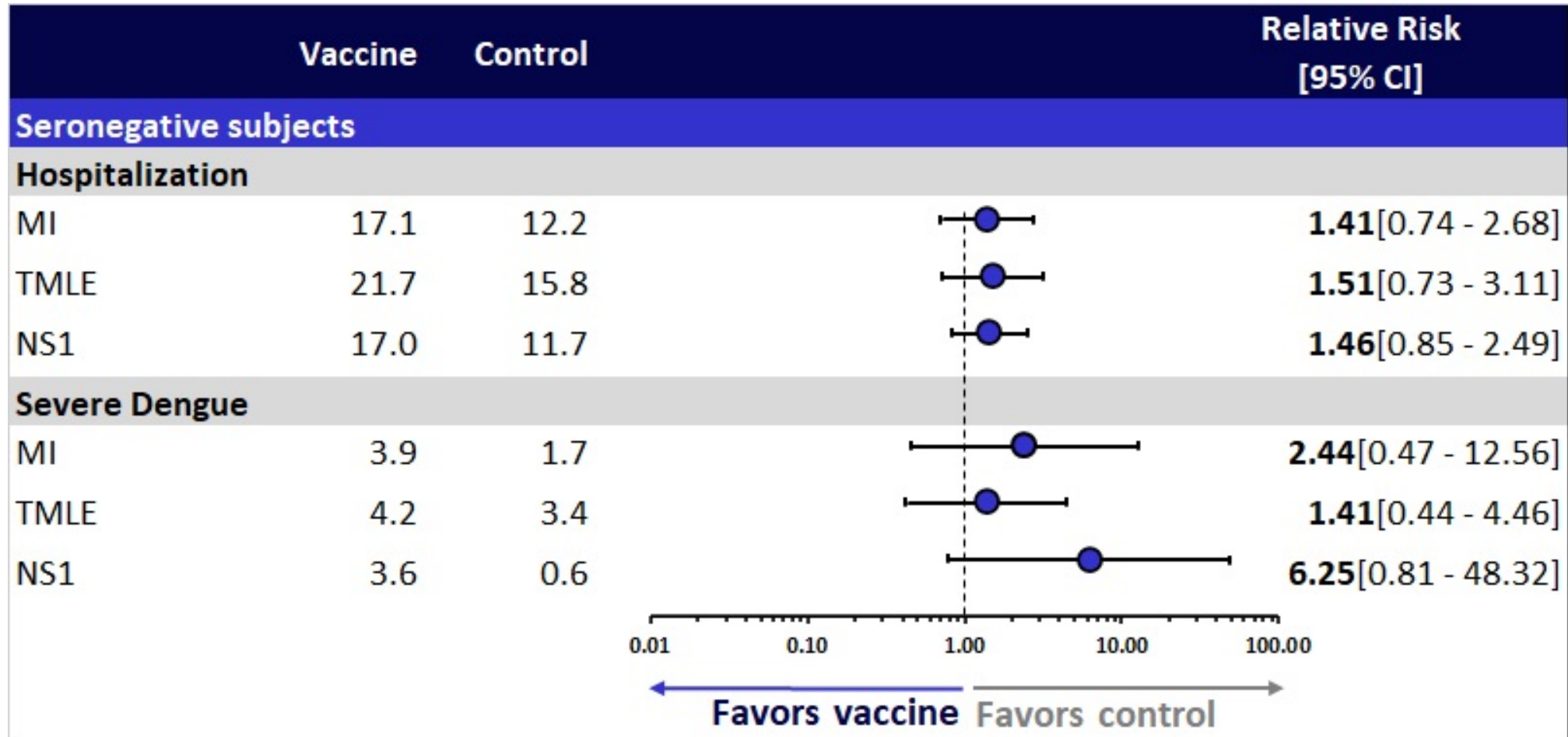


How substantial are the undesirable anticipated effects?

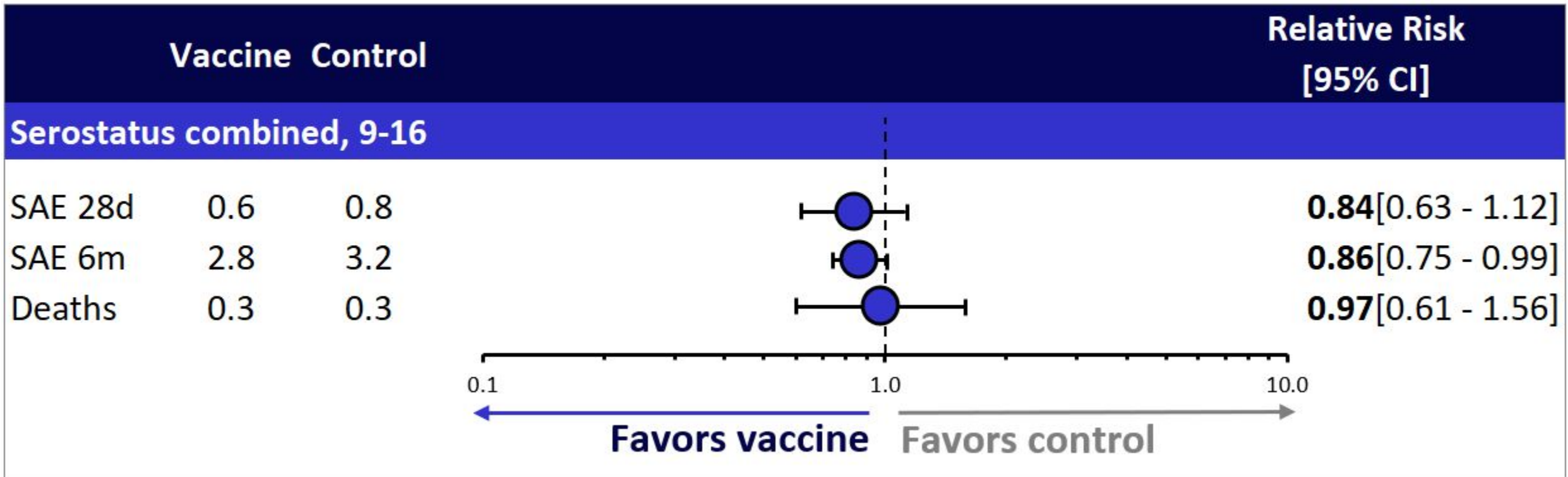
Minimal Small Moderate Large Varies Don't know



Risk of hospitalization and severe dengue when vaccinating a seronegative child 9-16 years



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



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

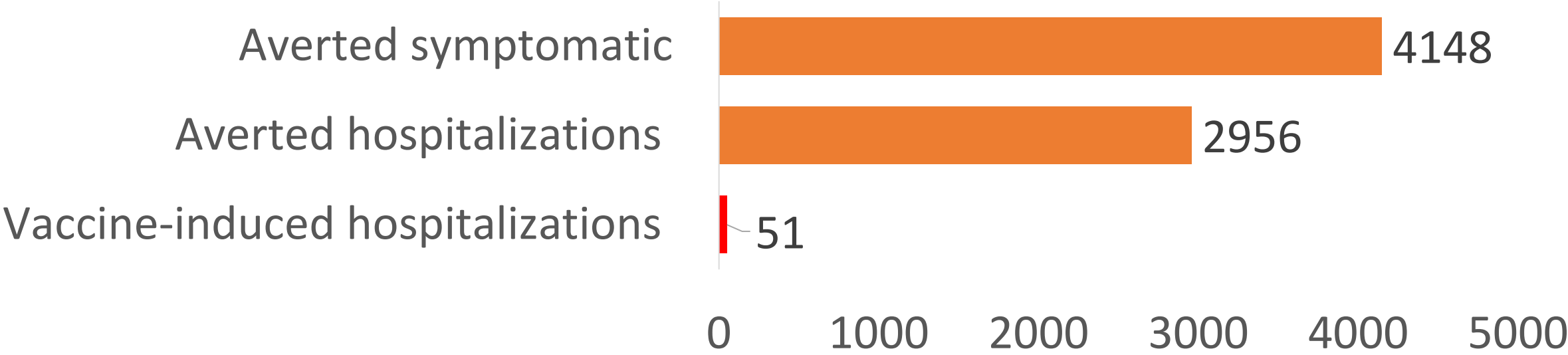
Test performance: sensitivity = 0.75 and specificity = 0.98.

	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



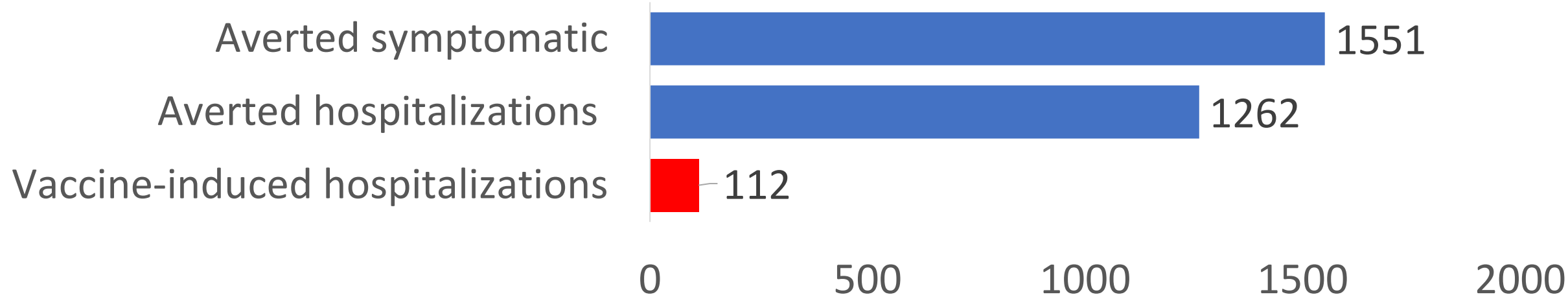
51 vaccine-induced hospitalizations in 102,884 vaccinees (completed series)

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



122 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)



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

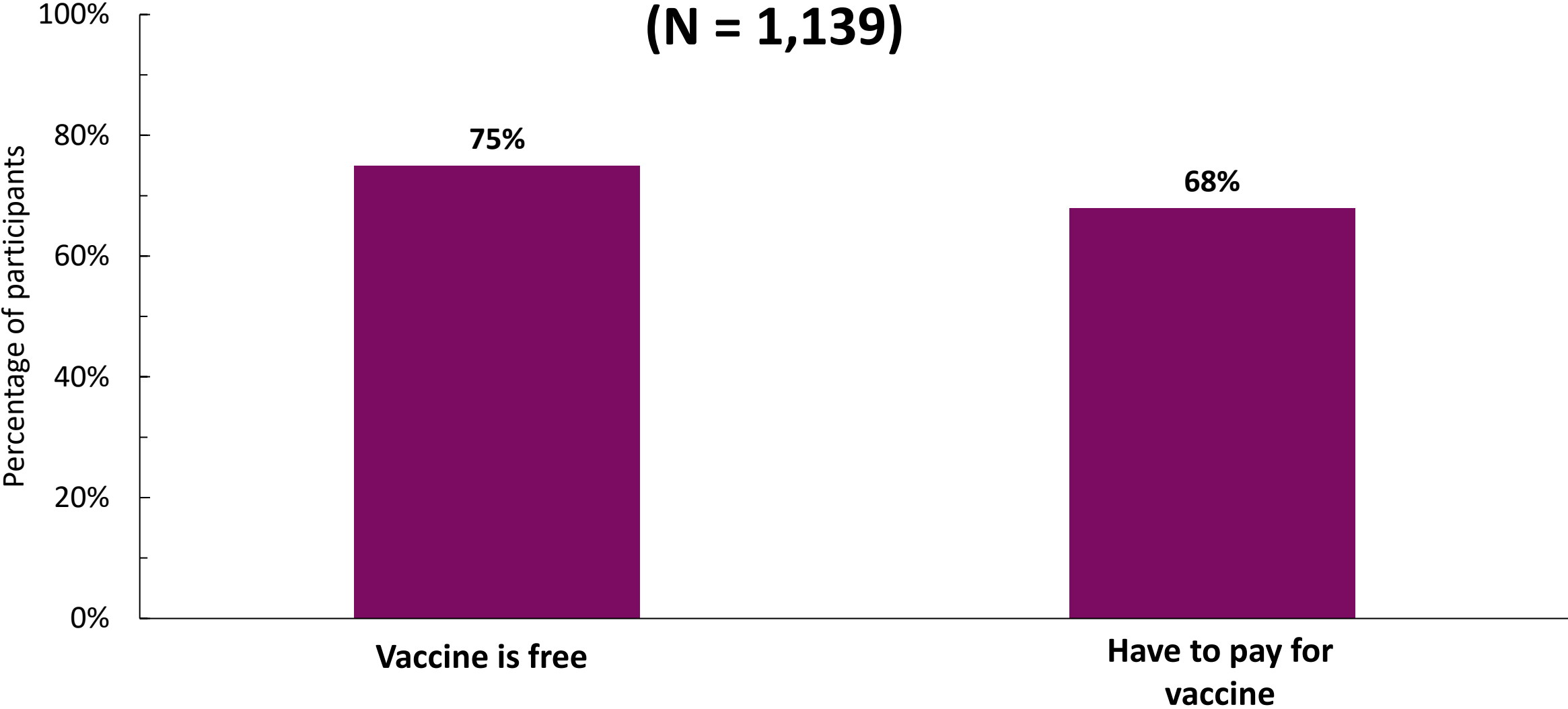
Does the target population feel that the desirable effects are large relative to undesirable effects?

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

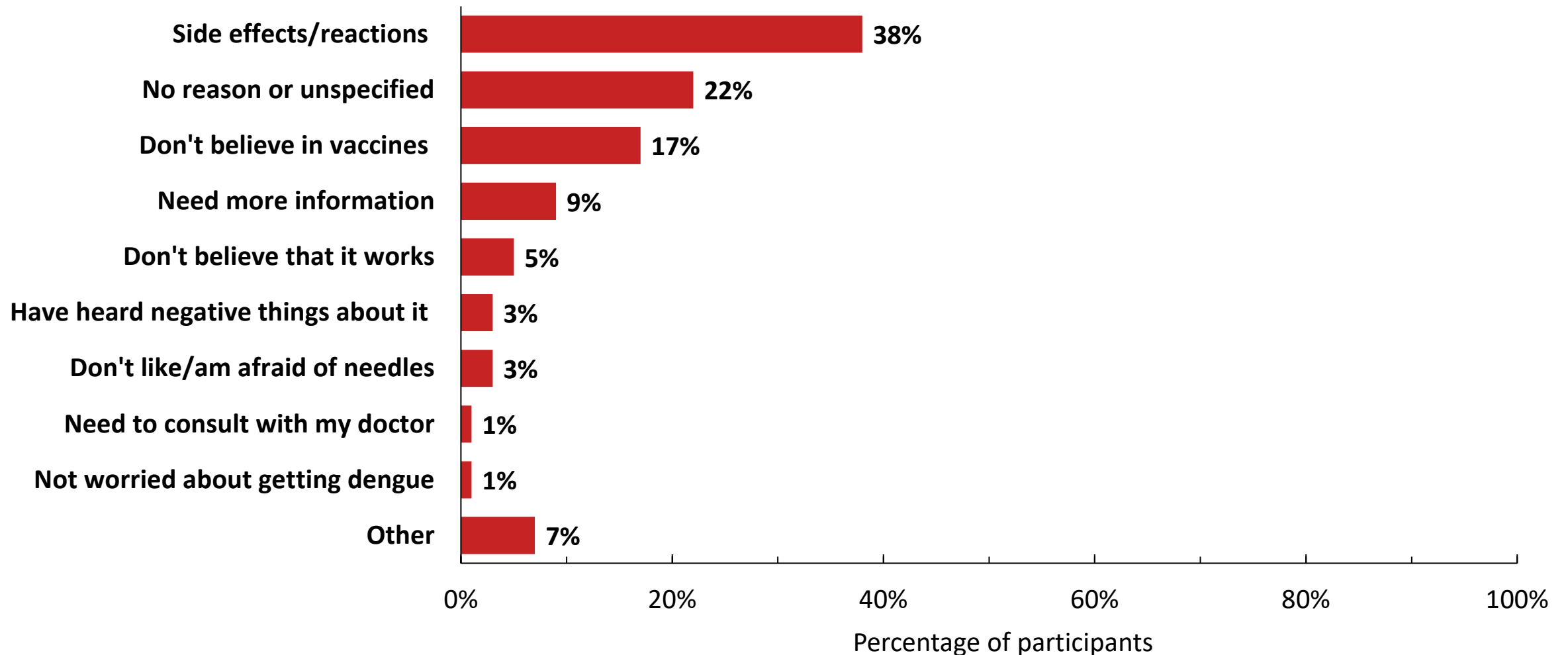


Interest in vaccinating children against dengue among adults, Ponce, Puerto Rico

(N = 1,139)



Reasons would not/unsure vaccinate, Ponce, PR (342 of 1139 participants)



*Includes participants who would not receive dengue vaccine for themselves and/or for their children where applicable.

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

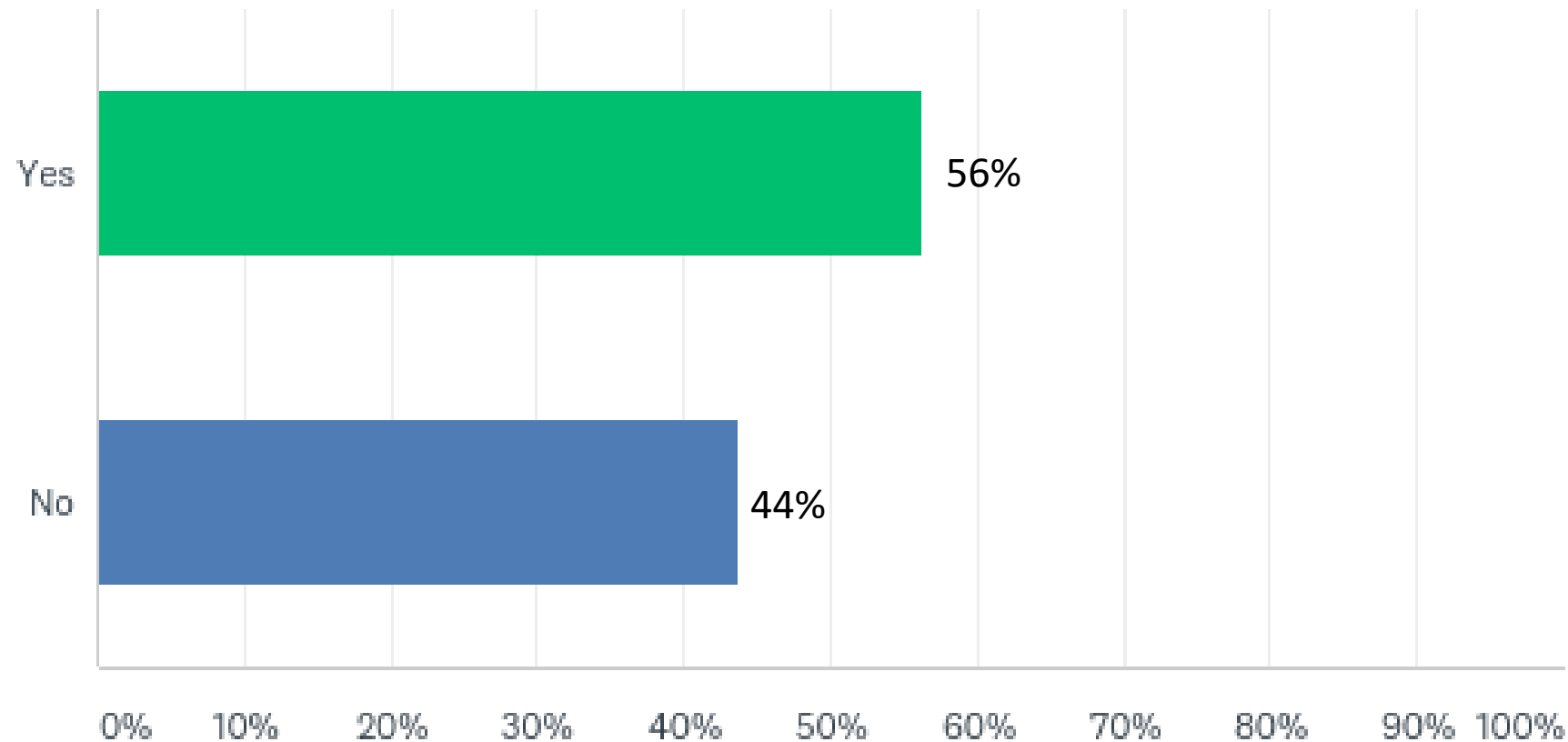
Is the intervention acceptable to key stakeholders?

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



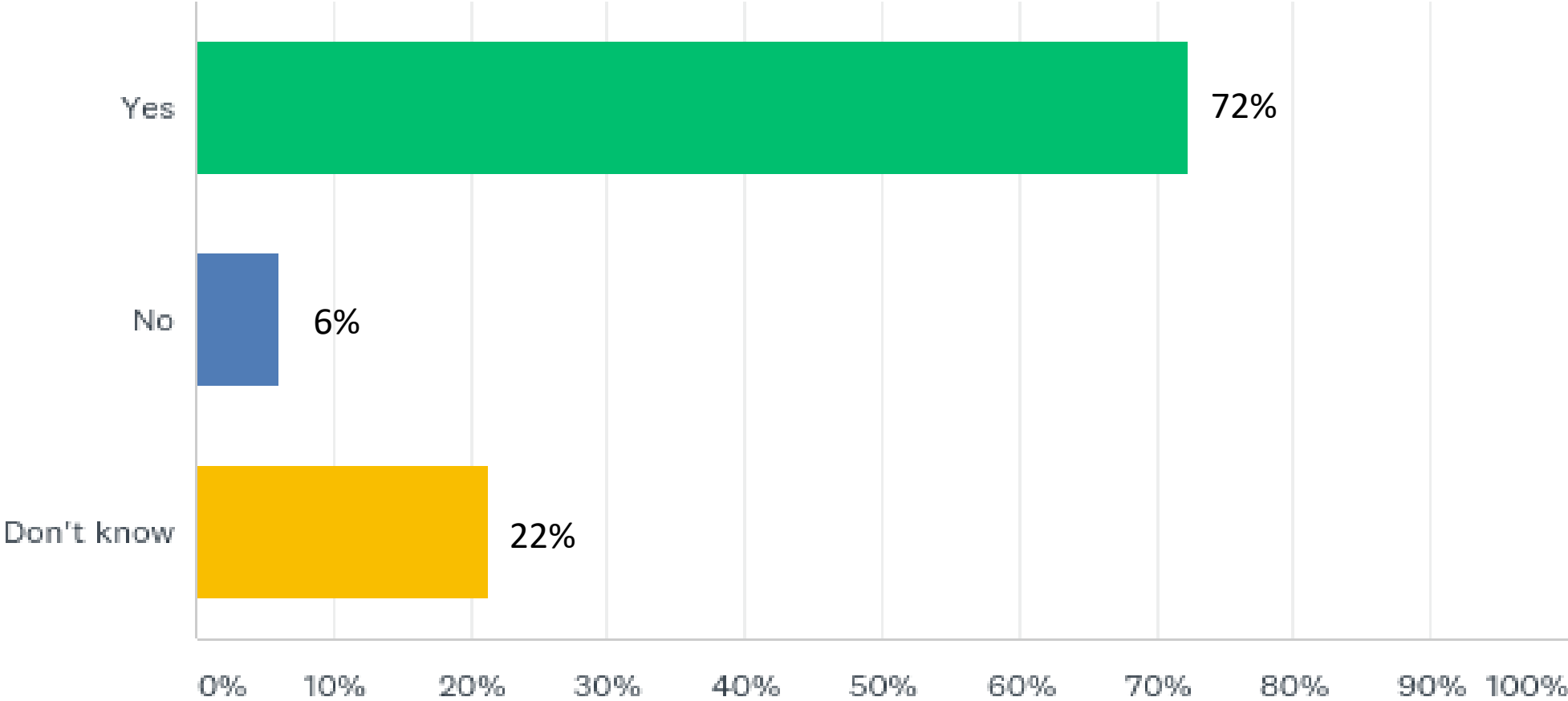
Survey to pediatricians in Puerto Rico, 2020

Do you know there is an FDA approved vaccine for dengue known as Dengvaxia? (n=109)



Survey to pediatricians in Puerto Rico, 2020

Assuming a laboratory test with acceptable specificity were available, would you recommend Dengvaxia to your pediatric patients? (n=109)



Is the intervention acceptable to key stakeholders?

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



Feasibility

Is the intervention feasible to implement?

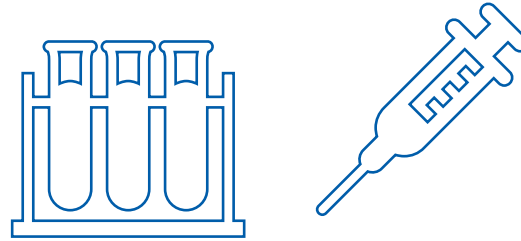
No Probably no Probably Yes Yes Varies Don't know



Dengvaxia feasibility considerations

- Three doses at 0, 6 and 12 months
- Education of providers and parents about Dengvaxia efficacy and safety
- Out of pocket expenses with multiple visits
- Screening before vaccination
 - There are tests available with acceptable performance
 - Implementation of point of care in Puerto Rico is challenging
 - None of the tests with adequate performance are FDA approved
 - Can be implemented under CLIA
 - Cost coverage of test by insurance and Medicaid
 - Extra visits

Test performance guidance for pre-vaccination screening



- Test should have sensitivity $\geq 75\%$ and a specificity of $\geq 98\%$
- The positive predictive value (PPV) should be $\geq 90\%$
- A negative predictive value of $\geq 75\%$ to minimize missing persons who would potentially benefit from the vaccine
- Sequential testing may be an option as more IgG tests are available to improve specificity $>98\%$

Provider counseling on risk/benefit for Dengvaxia

- **Risk of disease:** Dengue is common in Puerto Rico. The risk of getting dengue more than once while living on the islands is high, with most people getting dengue two or more times before adulthood. Second dengue infections can be more dangerous and require hospitalizations. However, any infection can be dangerous.
- **Benefit:** In children who have previously been infected with dengue, Dengvaxia **protects against illness or hospitalization** caused by dengue 8 out of 10 times.
 - Some people can still get dengue after vaccination. This is called a breakthrough infection.
- **Risk:** In children who have not already been infected with dengue, Dengvaxia **increases the risk of severe illness and hospitalization** if the child gets dengue after vaccination.
 - The risk is similar to what a child faces when living in an endemic area and being naturally exposed to dengue multiple times.
- **How do we reduce this risk:** To reduce the risk of vaccinating children who have never had dengue, a laboratory test for dengue is required. No test is 100% accurate.
 - There is a chance that 3 in 100 children who test positive might not have had dengue before (false positive test result).

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

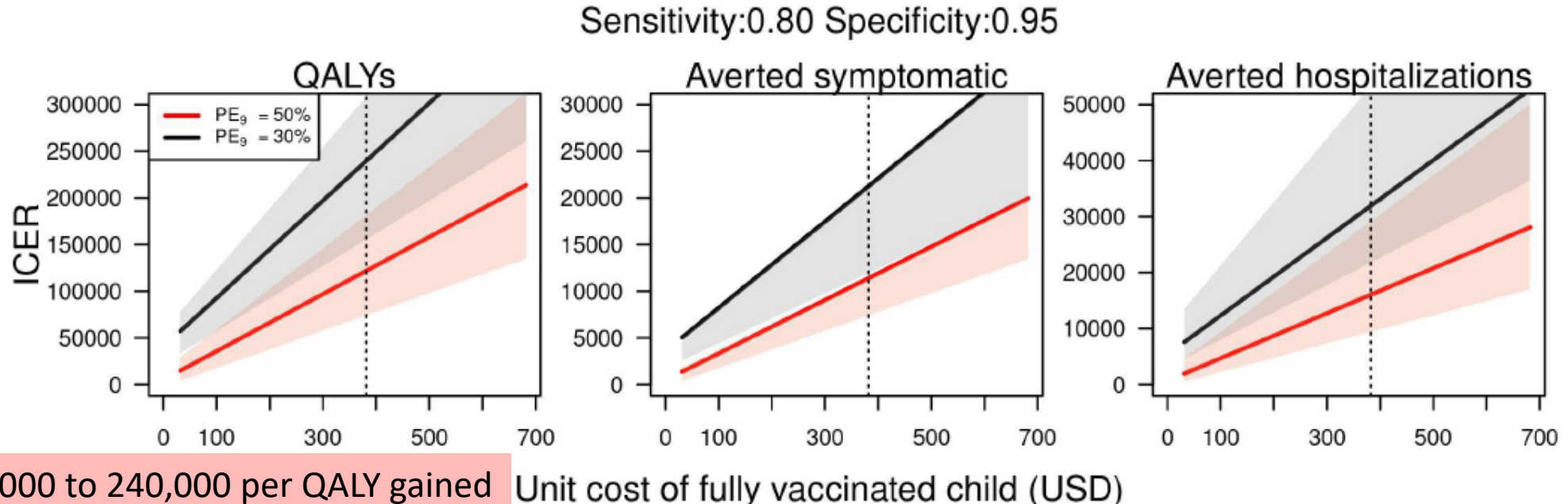


Figure 5. ICER of pre-vaccination screening strategy in Puerto Rico at different costs of vaccination (total cost for three doses per person), assuming a unit cost of serological screening of 30 USD. Dotted line represents the baseline assumption of vaccine cost (382 USD). All costs in 2019 USD.

- 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



Disparities between Puerto Ricans and other US citizens in healthcare

Puerto Rico has the lowest Medicaid and Medicare per capita annual spending

Mosquito-borne diseases

Natural disasters



Considerations to ensure that health inequities are reduced with Dengvaxia

Health insurance coverage for lab test

Diagnostic testing should be economical

- For the very poor, that cannot pay fees, public funds need to be available and accessible

Multiple visits to healthcare providers for diagnostic testing and vaccine eligibility may be a greater burden for low-income families because of transportation costs and missed days of work.

Strategies to reduce the number of visits are needed.

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



Questions?

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

Routine versus shared decision making

Attribute	Routine recommendation	Shared decision making
Reduction dengue transmission	Unlikely in the short term. Greater impact for DENV4.	No reduction in dengue transmission.
Reduction in disease burden	Of all dengue hospitalizations, 6% hospitalizations will be averted in a 10- year period (80% coverage and 50% seroprevalence at age 9y).	No measurable benefit in reducing hospitalizations.
Harms	For every 57 hospitalizations prevented 1 additional hospitalization would occur due to the vaccine.	Coverage will be low and among a selected group of patients so adverse events unlikely.

Routine versus shared decision making

Attribute	Routine recommendation	Shared decision making
Cost	Coverage of screening test and vaccine by insurance companies and VFC/Medicaid. Minimizes cost to families.	Coverage of vaccine, uncertain coverage of the test without documented medical indication by a provider. Possibly higher out of pocket expenses.
Implementation and feasibility	<p>Greater engagement from health department (HD) with territory wide policies, will lead to greater coverage.</p> <p>Greater push to solve information systems connectivity, testing and logistical challenges.</p> <p>HD could centralize testing at reference lab facilitating testing and result logistics with phased implementation.</p> <p>Removes some burden of testing/vaccination from providers.</p> <p>May lead to implementation of dengue vaccine programs in other countries with high dengue burden.</p>	<p>May allow for quicker, but limited use of the vaccine.</p> <p>Theoretically allows for more careful discussion between provider and parents.</p> <p>May lead to full recommendation later after vaccine gains are more acceptable.</p> <p>Places the burden on providers leading to delays and missed opportunities for testing/vaccination.</p> <p>This path may be a “dead end” for this vaccine and any other unbalanced dengue vaccines that still have benefit.</p>

Routine versus shared decision making

Attribute	Routine recommendation	Shared decision making
Health Equity	Would increase health equity.	Likely decreased health equity. Only empowered and informed patients or those served by informed pediatricians would have access to the vaccine. Administrative hurdles and costs will reduce access for families with low-medical literacy and economic means.
Education of providers and families	Educational materials for families and training of providers more readily available.	CDC efforts on educating providers and patients with less buy-in from HD.
Cost-effectiveness	Can be cost effective in most scenarios.	Will not be cost-effective.

Routine versus shared decision making

Attribute	Routine recommendation	Shared decision making
Communication and media	<p>Communication will fall to HD and CDC.</p> <p>Hospitalizations among vaccinees will be mainly due to vaccine breakthrough and a small percentage will be vaccine-induced. Clinicians and the public may attribute all hospitalizations to the vaccine. Communication campaign needs to explain the difference.</p> <p>Faulty implementation may lead to negative perception of dengue vaccines and vaccines in general, a particular concern during efforts to achieve high coverage for COVID vaccines.</p>	<p>Slow implementation and limited coverage would make public relations issues less likely.</p> <p>Vaccine safety concerns may vary by individual so that shared decision making would lessen fears that the vaccine will become controversial and a stimulus to vaccine hesitancy.</p>

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
- 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

- Perception all hospitalizations among vaccinees related to vaccine, but most hospitalizations related to vaccine breakthrough
- Media backlash could reduce coverage for other vaccines

Pros

- Useful vaccine for seropositives, sustainable vector control for *Aedes aegypti* is still years off in the U.S. while dengue outbreaks continue to occur
- 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 in persons 9-16 years of age with 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)

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Veronica McNally

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Gabriela Paz-Bailey

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Kaitlyn Morabito (NIH)

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