DENGUE VACCINATION IMPACT: BEYOND EFFICACY

Isabelle Delrieu, PhD & Bradford D. Gessner, MD
Agence de Médecine Preventive
idelrieu@aamp.org & bguessner@aamp.org

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BURDEN CONCEPTS

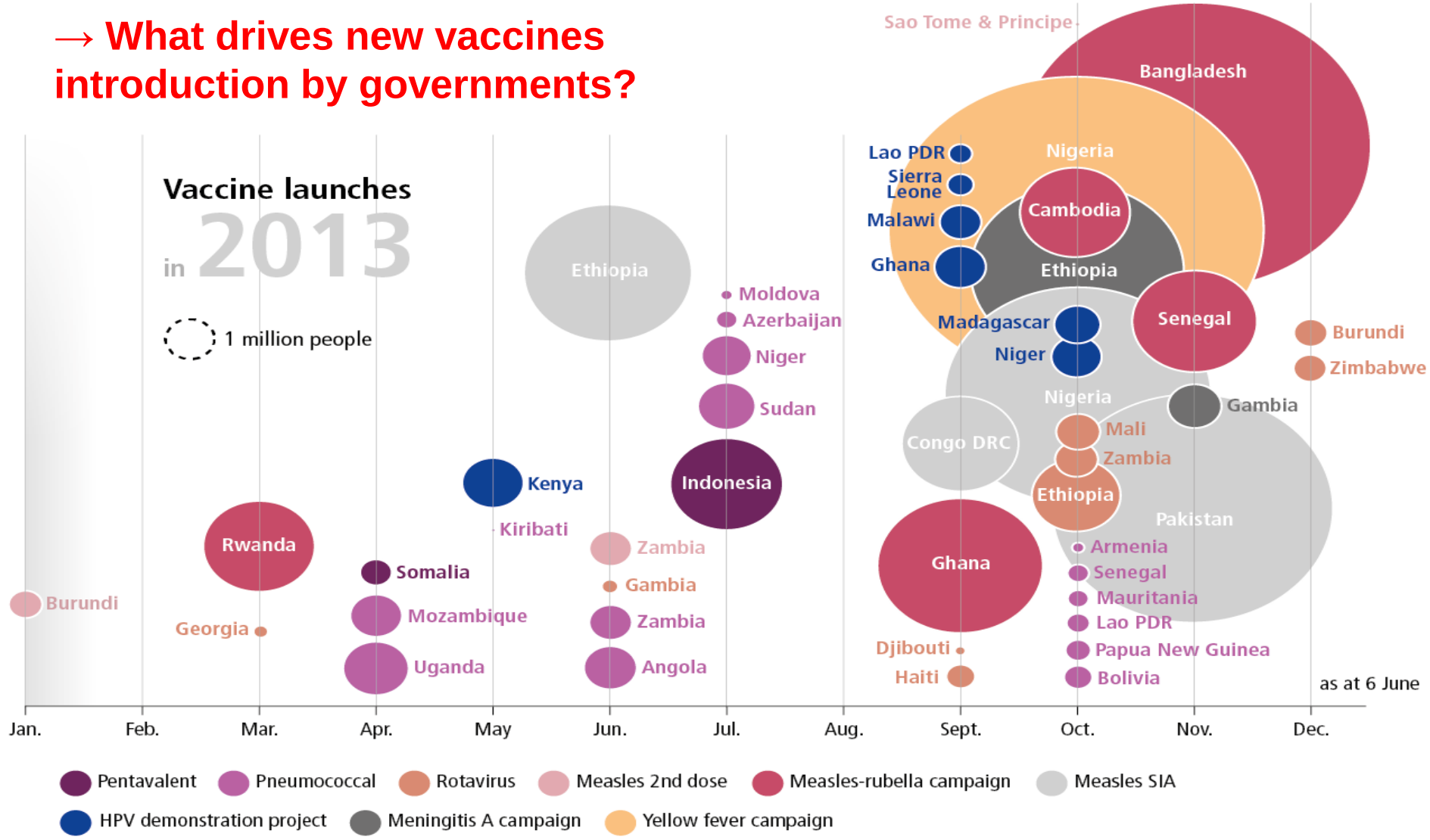
VE AND PH BURDEN MEASURES

DENGUE VACCINE

BEYOND BURDEN

Vaccine Launches 2013

→ **What drives new vaccines introduction by governments?**



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What influences government adoption of vaccines in developing countries? A policy process analysis

Syarifah Liza Munira[a,*], Scott A. Fritzen[b]

"**Disease burden** has been consistently mentioned by policymakers in countries to be the number one factor in setting priorities for vaccines to be introduced into immunization programs; the higher the burden, the more attractive a potential addition to the immunization regime of the country would be."

Burden measure limitations

- Poor diagnostics: non-bacteremic Hib/Sp, typhoid
- Causal etiology gone at time of presentation: flu/viral ARI pathogens precipitating bacterial ARI
- Pathogen present but not causal: flu
- Lack of testing, poor specimen transport systems: all etiologies
- Limited health care access: all etiologies

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VACCINE EFFICACY AND PUBLIC HEALTH

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Definition of measures

- Vaccine effectiveness/efficacy (VE)
  = 1 – (Incidence[vaccinated] ÷ Incidence[unvaccinated])

- Vaccine preventable disease incidence (VPDI)
  = Incidence[unvaccinated] – Incidence[vaccinated]
  = Incidence[unvaccinated] X VE

- Number needed to vaccinate (NNV)
  = 100,000/VPDI/length of follow-up for VPDI

- Number prevented (nationally) (estimated!)
  = VPDI * (birth cohort/100,000) * years of follow-up for VPDI

Feikin, Scott, Gessner. Use of vaccines as probes to define disease burden. Lancet 2014;383:1762-70

VPDI, NNV and Cases prevented; VPDI per 100,000 CYO

Lancet 2005;365:1139-46; Lancet 2005;365:43-52; Vaccine 2012;30 (suppl 1):A52-60

Syndrome	Etiology confirmed				Clinical outcome			
	VE	VPDI	NNV	Cases prev.	VE	VPDI	NNV	Cases prev.
Gambia PCV radiological pneumonia	70%	140	357	216	37%	1300	38	2002
Indonesia, Hib, hospitalized meningitis	86%	16	3125	1516	22%	160	313	15,155
Kenya rotavirus, acute gastroenteritis	84%	3300	15	101,244	34%	19,000	3	582,920

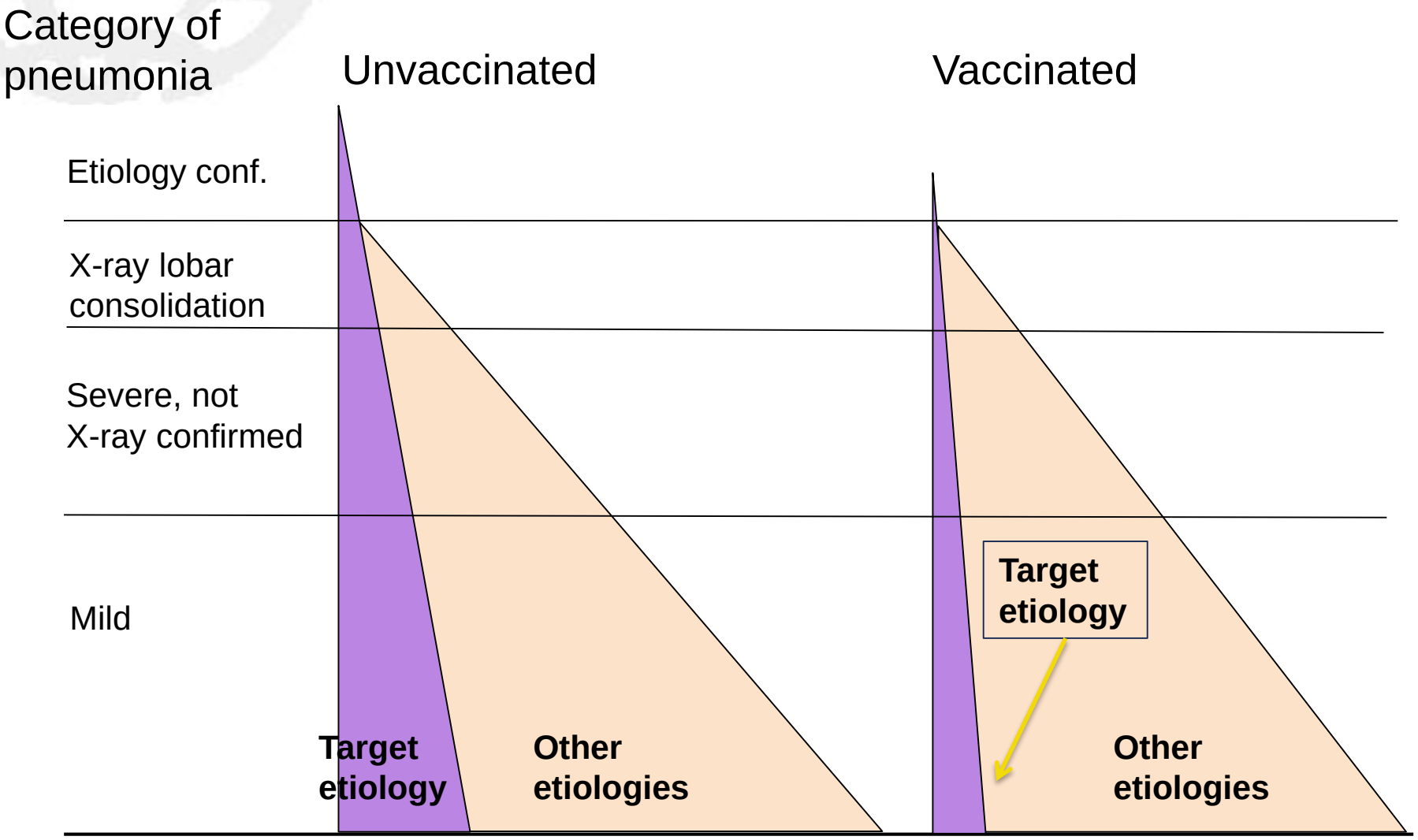
Measures useful outside of developing country settings: acute gastroenteritis (AGE)

Study	VE	VPDI	NNV	Cases prev.
Finland (Vaccine 2012;31:176-82)				
Confirmed inpatient AGE	80%	390	256	237
All cause inpatient AGE	54%	1070	93	651
Kenya (Vaccine 2012;30 Supp 1:A52-60)				
Confirmed severe	84%	3300	15	101,244
Community severe AGE	34%	19,000	3	582,920

Public health impact can be greater in settings where vaccine efficacy is lower: acute gastroenteritis (AGE)

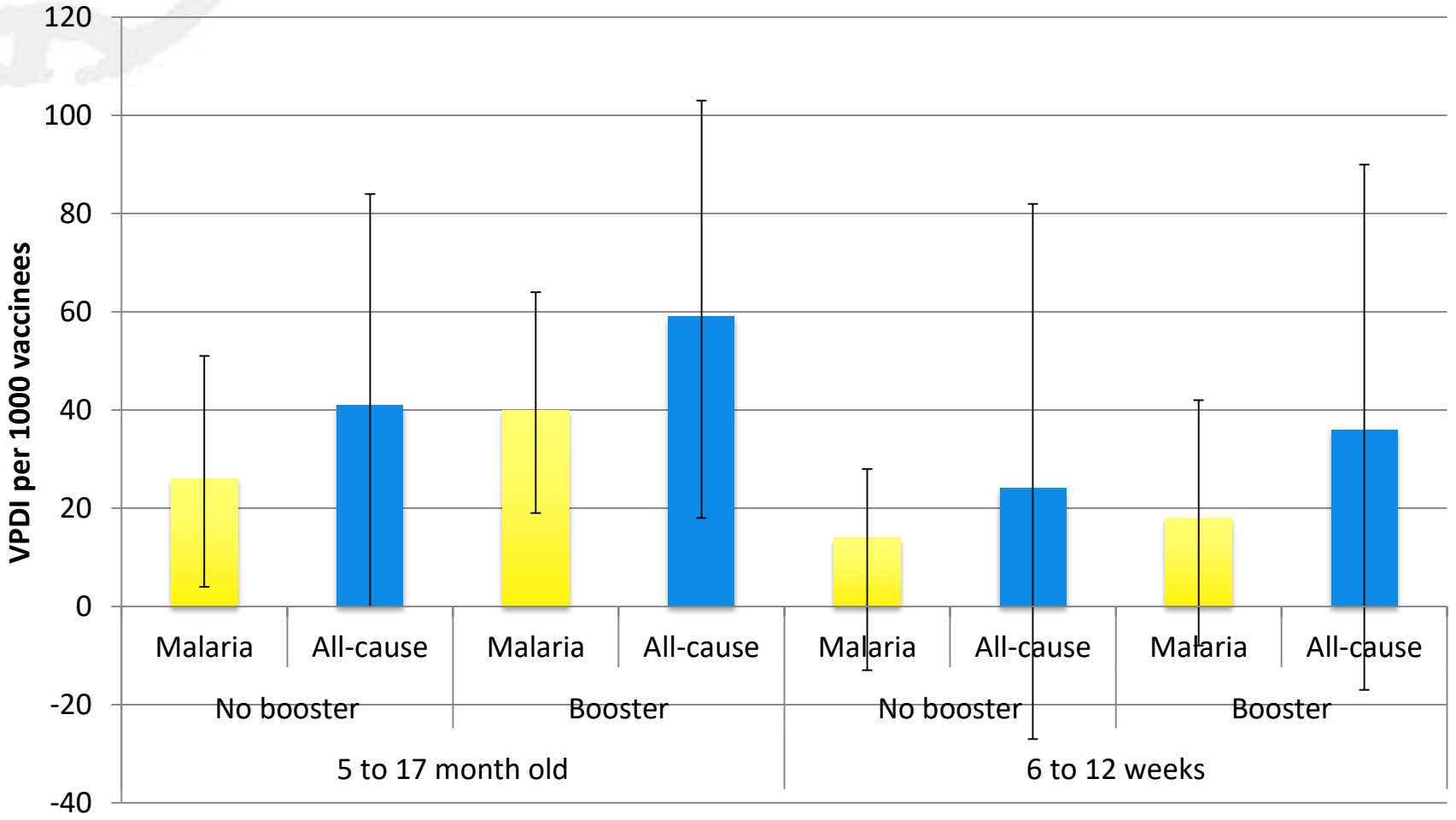
Study	VE	VPDI	NNV	Cases prev.
Severe rotavirus AGE (NEJM 2010;362:289-98)				
South Africa	77%	4200	24	46,284
Malawi	49%	6700	15	42,813
Severe rotavirus AGE (Lancet 2010;376:615-23)				
Vietnam	64%	2200	26	55,425
Bangladesh	43%	3500	16	192,950

Impact of vaccine against categories of pneumonia (Lancet 2014;383:1762-70)



RTS,S VPDI against malaria-specific and all-cause hospitalization

(Lancet 2015;386:31-45).



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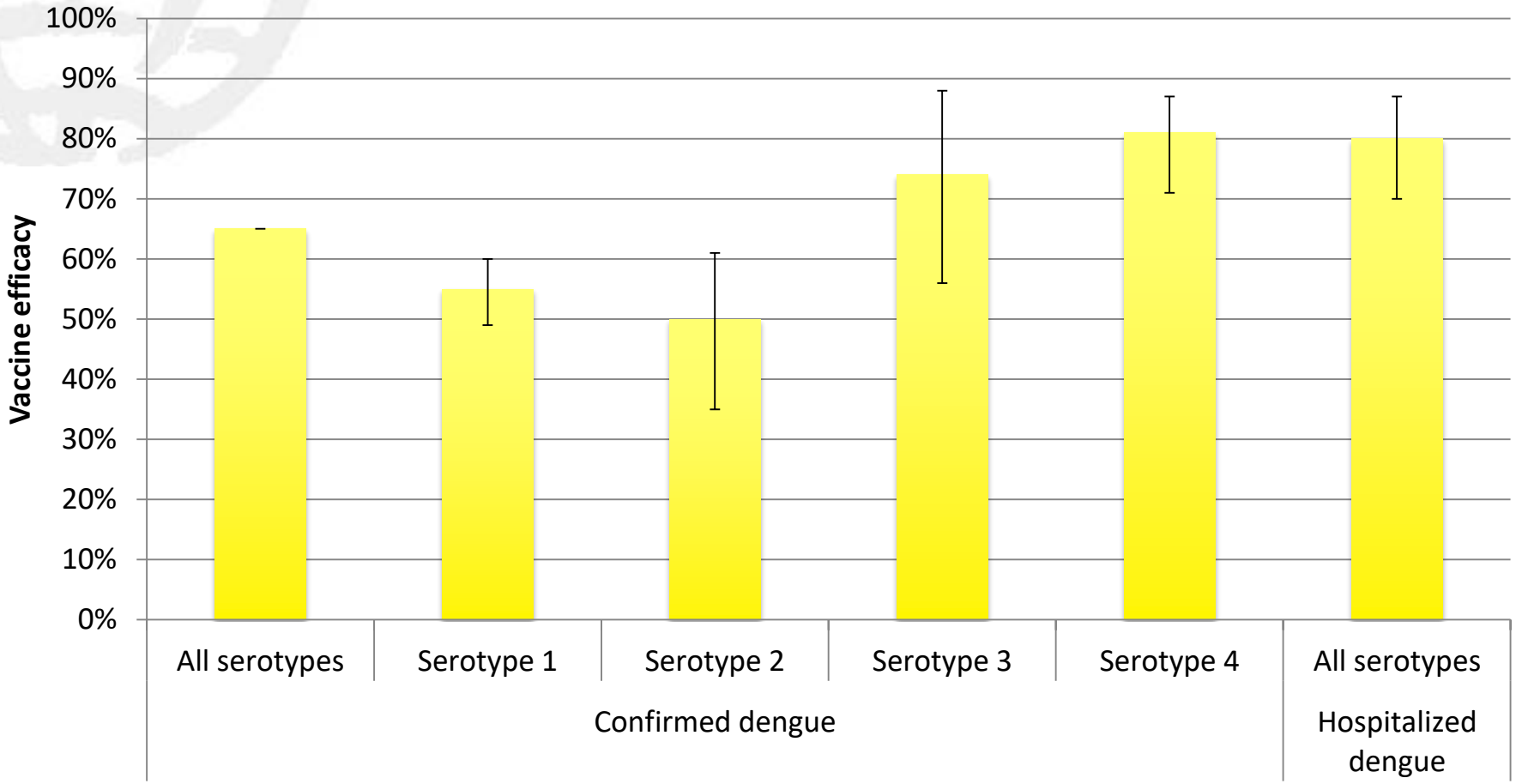
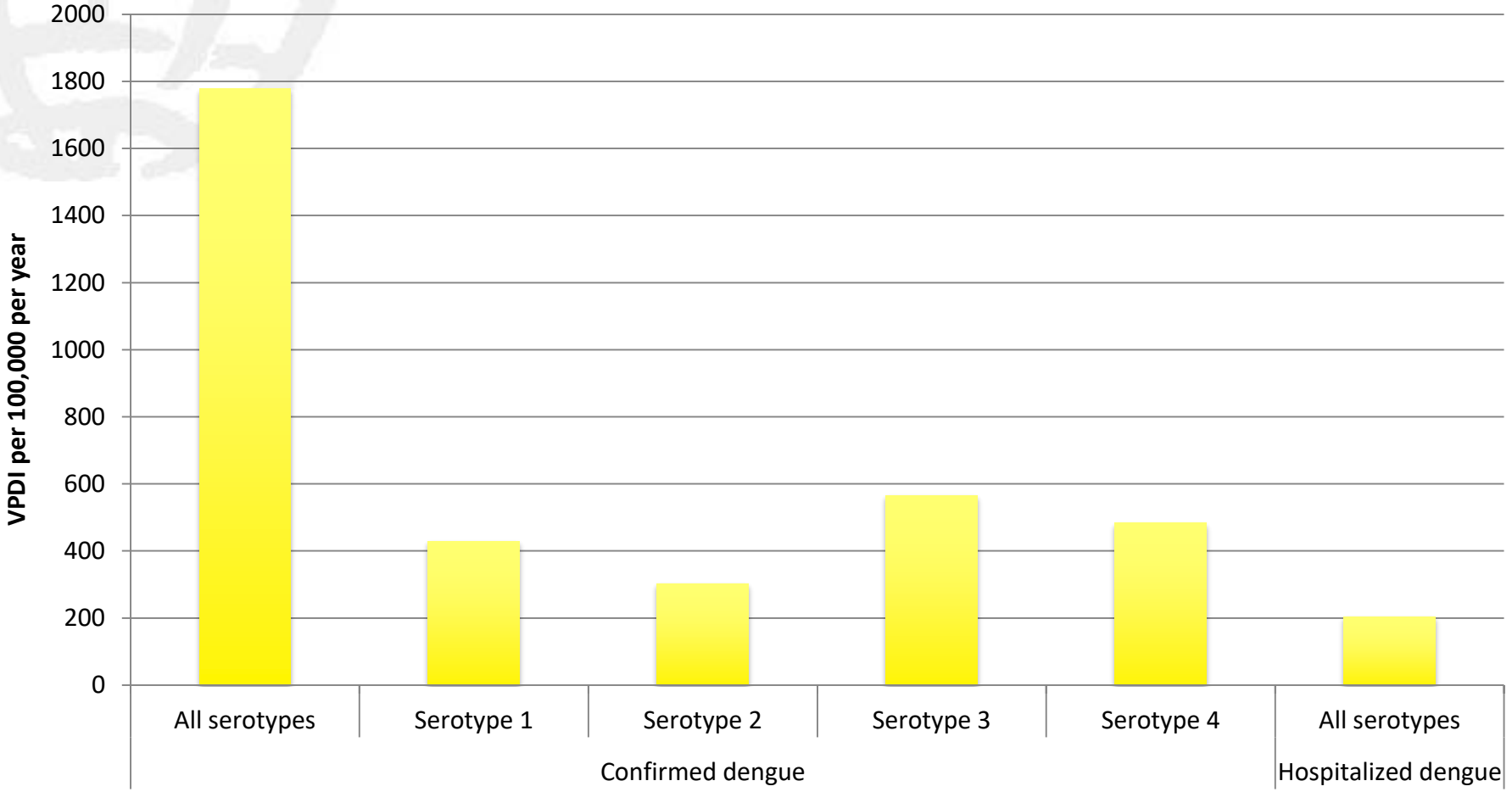
Vaccine efficacy against confirmed dengue in children 9-16 years of age in Latin America*



*All data based on 2 year VE estimates
NEJM 2015;373:1195-206 and NEJM 2015;372:113-23.

Vaccine preventable disease incidence for confirmed dengue in Latin America*



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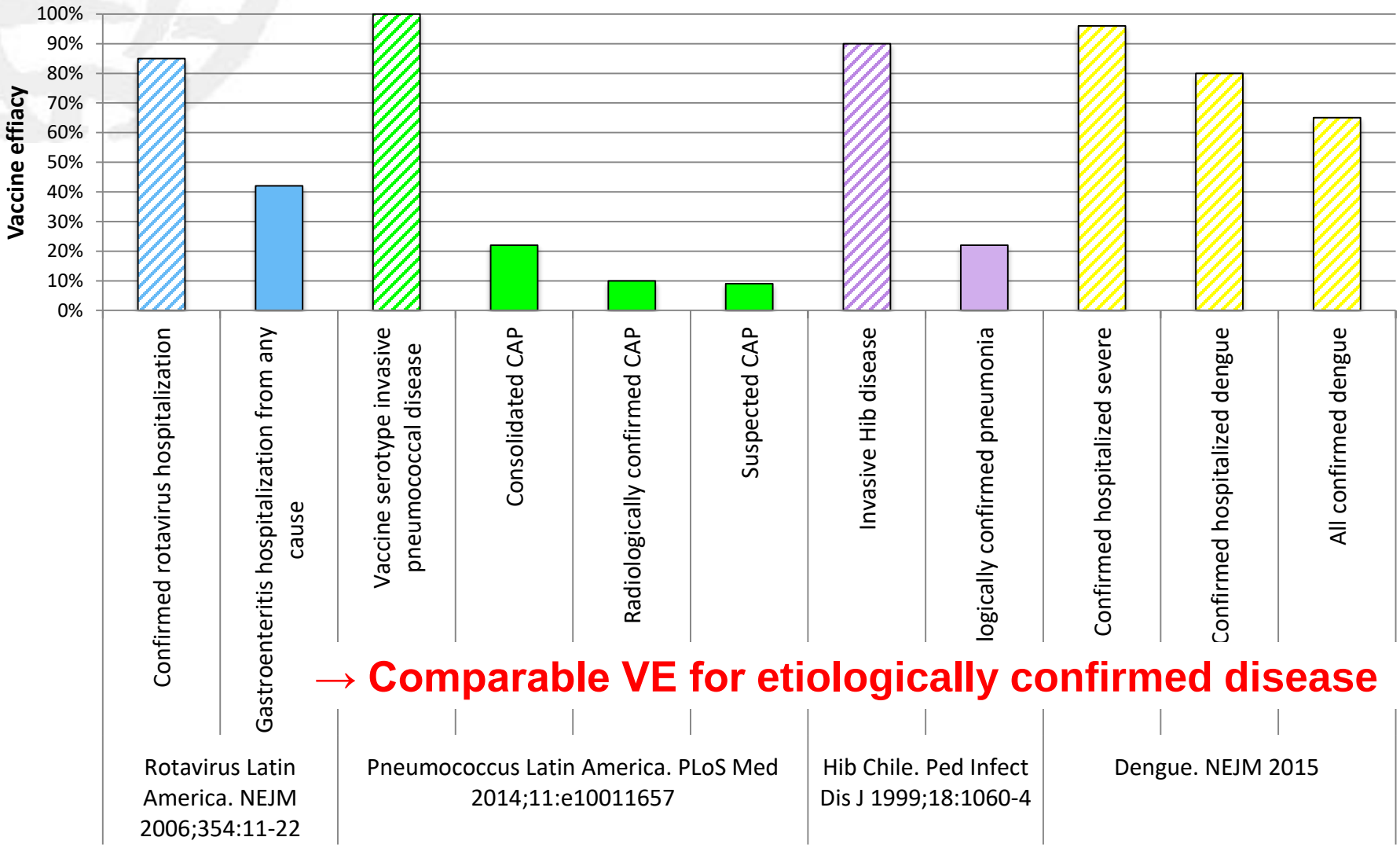
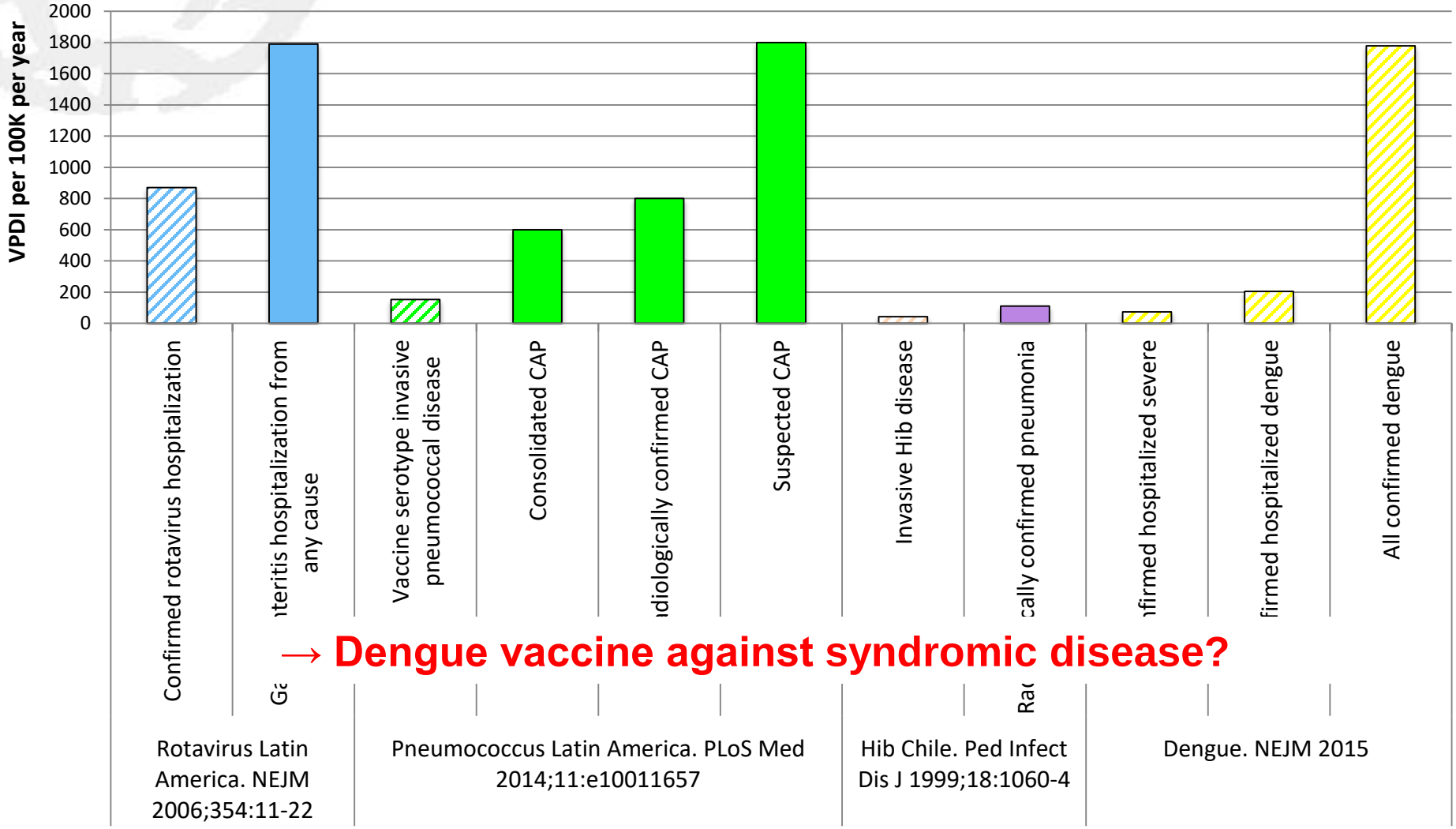
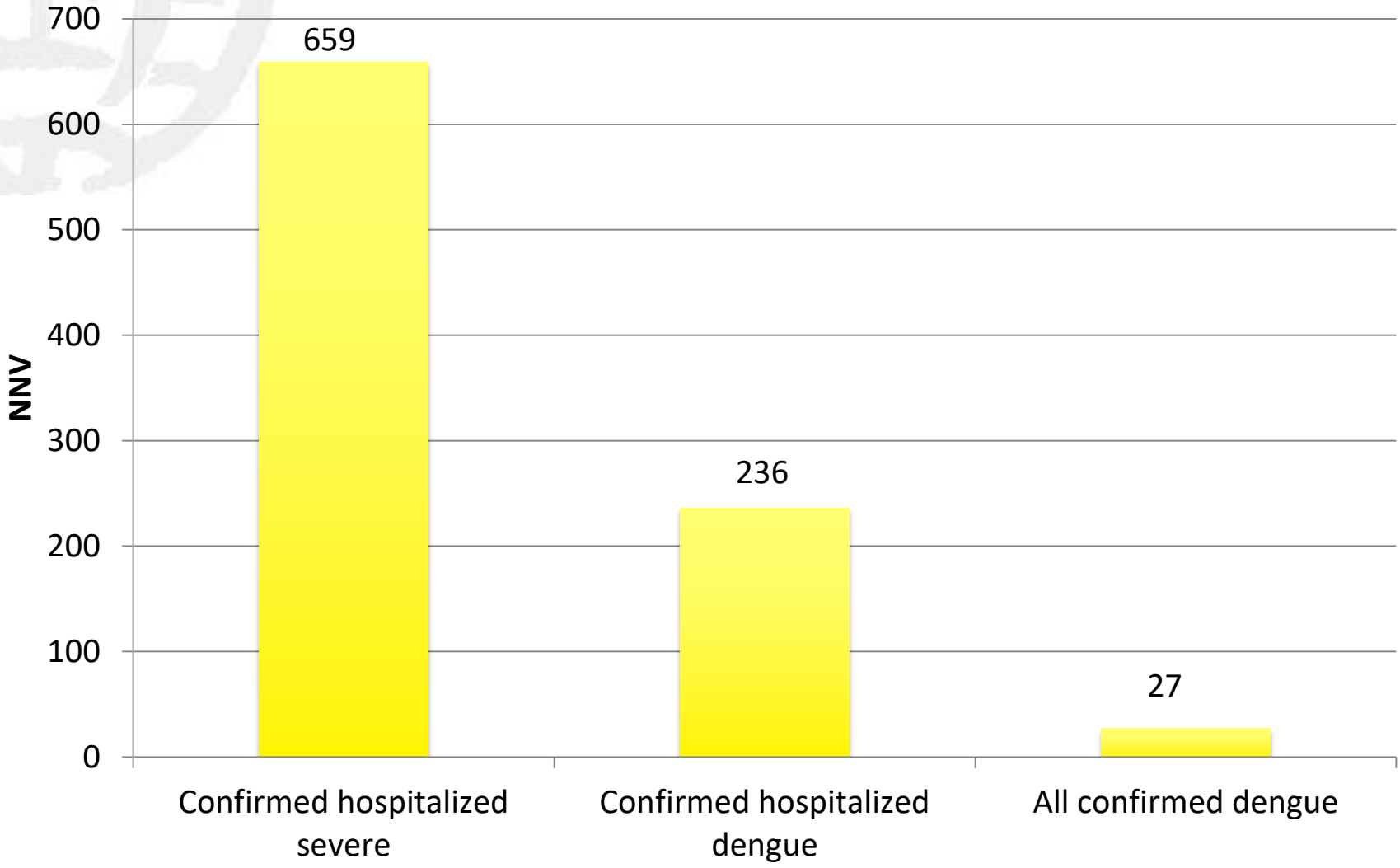
Vaccine efficacy for dengue compared to other vaccines studied and used in Latin America



Vaccine preventable disease incidence (VPDI) for dengue compared to other vaccines studied and used in Latin America



Number needed to vaccinate (NNV) to prevent cases of dengue



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Age distribution

	Sp	Hib	Rotavirus	Malaria	Dengue
<5 year disease	++++	++++	++++	++++	++/+++
<5 year severity/sequelae	++++	--	--	++++	+
5+ year disease	++/+++	+	--	++++	++++
5+ year severity/sequelae	+++	+	--	+	+

Sequelae/mortality

	Sp/Hib meningitis	Sp/Hib pneumonia	Rotavirus	Malaria	Dengue
Cognitive (MR, dev delay, learning disability, language)	++++	--	--	+++	--
Sensory (hearing, vision)	++++	--	--	--	--
Physical (CP, seizures)	++++	--	--	+++	+
Stunting	?	?	+	+++	--
Case fatality ratio	++++	+++	+	++	+

E.g., in US, big cost driver for Hib was long-term care and institutionalization for meningitis sequelae

Indirect/replacement/rebound effects

	Sp	Hib	Rotavirus	Malaria	Dengue
Indirect	+++	++++	++	--	?
Replacement	+++	+ (so far)	--	--	?
Rebound	-/+ (without booster)	+ (without booster in some settings)	--	+++ (depends on transmission)	?

Work in different directions:

- Indirect effects can greatly increase immunization efficiency and public health value
- Replacement can completely negate immunization efficiency
- Rebound shifts disease to older age; generally beneficial

Immunization program issues

	Sp	Hib	Rotavirus	Malaria	Dengue
Fits with current childhood schedule	+++	+++	+++	--	+
Duration of immunity (with booster)	+++	+++	Less relevant	-/+	??
Variable geographic distribution within affected countries	--	--	--	++	**+++**

Health system impact

	Sp	Hib	Rotavirus	Malaria	Dengue
Outbreak potential	+	--	--	+	+++
May overwhelm clinical resources	+	--	++	++	+++
Requires other intensive + expensive interventions	+	+	++	+++	+++
Increasing incidence in absence of vaccine	--	--	--	--	+++
Political dimension	+	+	+	+++	+++

Equity

	Sp	Hib	Rotavirus	Malaria	Dengue
Differences in infection by population	+	+	--	++	++
Differences in severe disease by population	+	+	++	++	+
Differences in mortality by population	++	++	+++	+++	+++

SUMMARY

- Safety and efficacy just the start of assessing public health value of vaccine
- Burden is the foundation of decision making
  - Incidence
  - VPDI
  - NNV
  - Cases prevented
  - Sequelae
  - Mortality
- Other key issues
  - Vaccine characteristics
  - Programmatic concerns
  - Health system impact
  - Equity
- All of these features contribute to models estimating public health value of vaccine
- Based on clinical trial data, dengue vaccine should have similar public health impact as other vaccines currently used in Latin American public health programs.

Obrigado

Gracias

Thank you

Merci

bgessner@aamp.org

Vaccine probe studies:

- 3 distinct insights into the epidemiology of vaccine-preventable diseases:

1. can estimate absolute burden of disease incidence that is preventable by a vaccine. The effect of a vaccine can be measured against different disease manifestations as well as health-system endpoints such as health-care visits or drug use.
2. can measure the contribution of a specific pathogen targeted by vaccination to a broad clinical syndrome.
3. Vaccines can be used to investigate the causal chain in disease pathogenesis. For example, if an infectious disease is hypothesised to cause a specific form of cancer, a trial of an effective vaccine against the infection could test the hypothesis

- epidemiological methods of vaccine probe studies do not differ from those of vaccine efficacy or effectiveness studies: RCT and non-randomised designs which measure disease incidence before and after vaccine introduction. The probe approach can be incorporated into the design of a vaccine efficacy study (eg, the Indonesian Hib vaccine study) or it can be applied retrospectively or prospectively to studies designed primarily to measure vaccine efficacy

- vaccine probe studies may add evidence to potential H impact of a vaccine with low VE by demonstrating impact against non specific syndromes (fever) or outcomes (hosp, AB use, visit)