IMPORTANCE OF VACCINE PREVENTABLE DISEASE INCIDENCE

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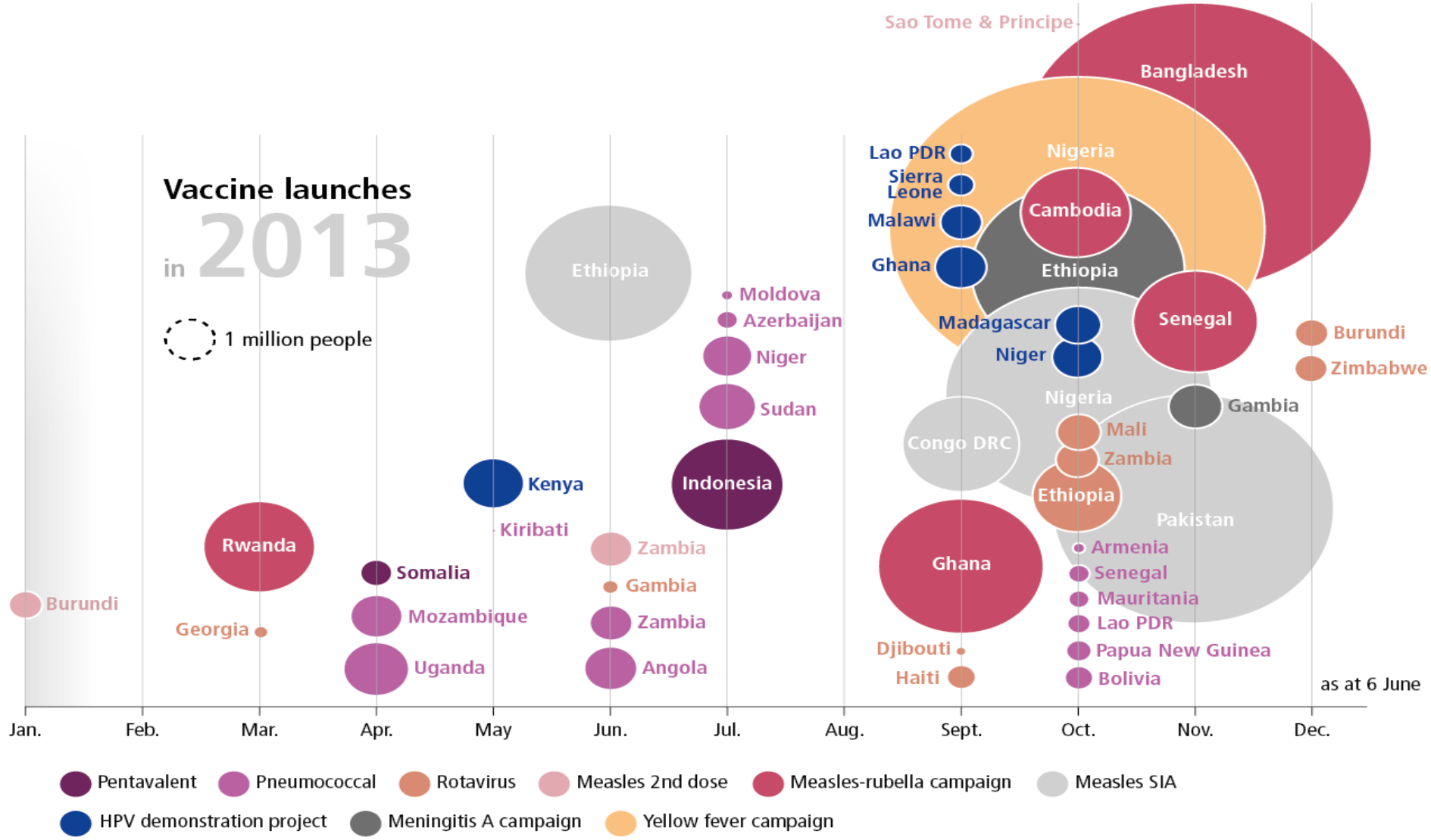
Vaccine Launches 2013



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

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"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."

Evaluation criteria and indicators for comparison across vaccines, Gavi Vaccine Investment Strategy

Category	VIS Criteria	Phase I Indicator
Health impact	Impact on child mortality	U5 future deaths averted, 2015 – 2030
		U5 future deaths averted per 100,000 vaccinated population
	Impact on overall mortality	Total future deaths averted, 2015 – 2030
		Total future deaths averted per 100,000 vaccinated population
	Impact on overall morbidity	Total future cases averted, 2015 - 2030
		Total future cases averted per 100,000 vaccinated population
		Long-term sequelae
Additional impact consid-erations	Epidemic potential	Epidemic potential of disease
	Global or regional public health priority	Presence of global / regional (UN) resolution on elimination or eradication
	Herd immunity	Herd immunity threshold
	Availability of alternative interventions	Current use of alternative interventions for effective disease control (prevention and treatment) and potential for scale up
	Socio-economic inequity	Disproportionate impact on poor
	Gender inequity	Disproportionate impact on one gender
	Disease of regional importance	Burden concentrated in a subset of GAVI countries within same region
Implemen-tation feasibility	Capacity and supplier base	Capacity to meet GAVI demand and # of manufacturers by 2020
	GAVI market shaping potential	GAVI demand as % of global demand
	Ease of supply chain integration	Packed volume (cm3) compared to benchmarks
	Ease of programmatic integration	Alignment with other vaccine schedules and significant change in health worker practices/behavior required
	Vaccine efficacy and safety	Vaccine efficacy (as defined by clinical endpoints) and safety (evidence of causal link with severe adverse events)
Cost and value for money	Vaccine procurement cost	Total procurement cost to GAVI and countries, 2015 – 2030
	In-country operational cost	Incremental in-country operational cost per vaccinated person
	Procurement cost per event averted	Procurement cost per death / case averted

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

Definition of measures

- Vaccine effectiveness/efficacy (VE)

  = 1 – (Incidence[vaccinated] ÷ Incidence[unvaccinated])

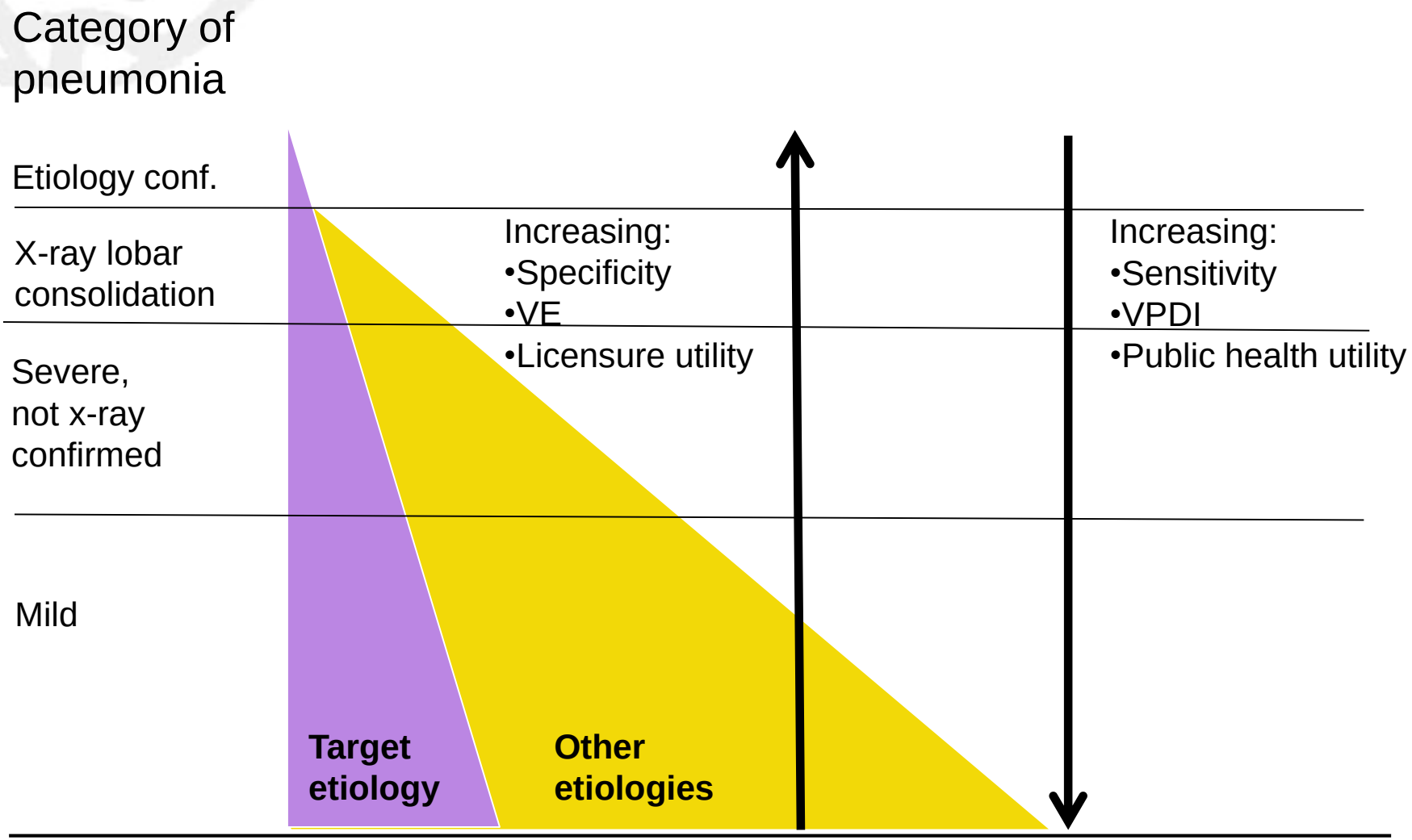
- Vaccine preventable disease incidence (VPDI)

  = Incidence[unvaccinated] – Incidence[vaccinated]

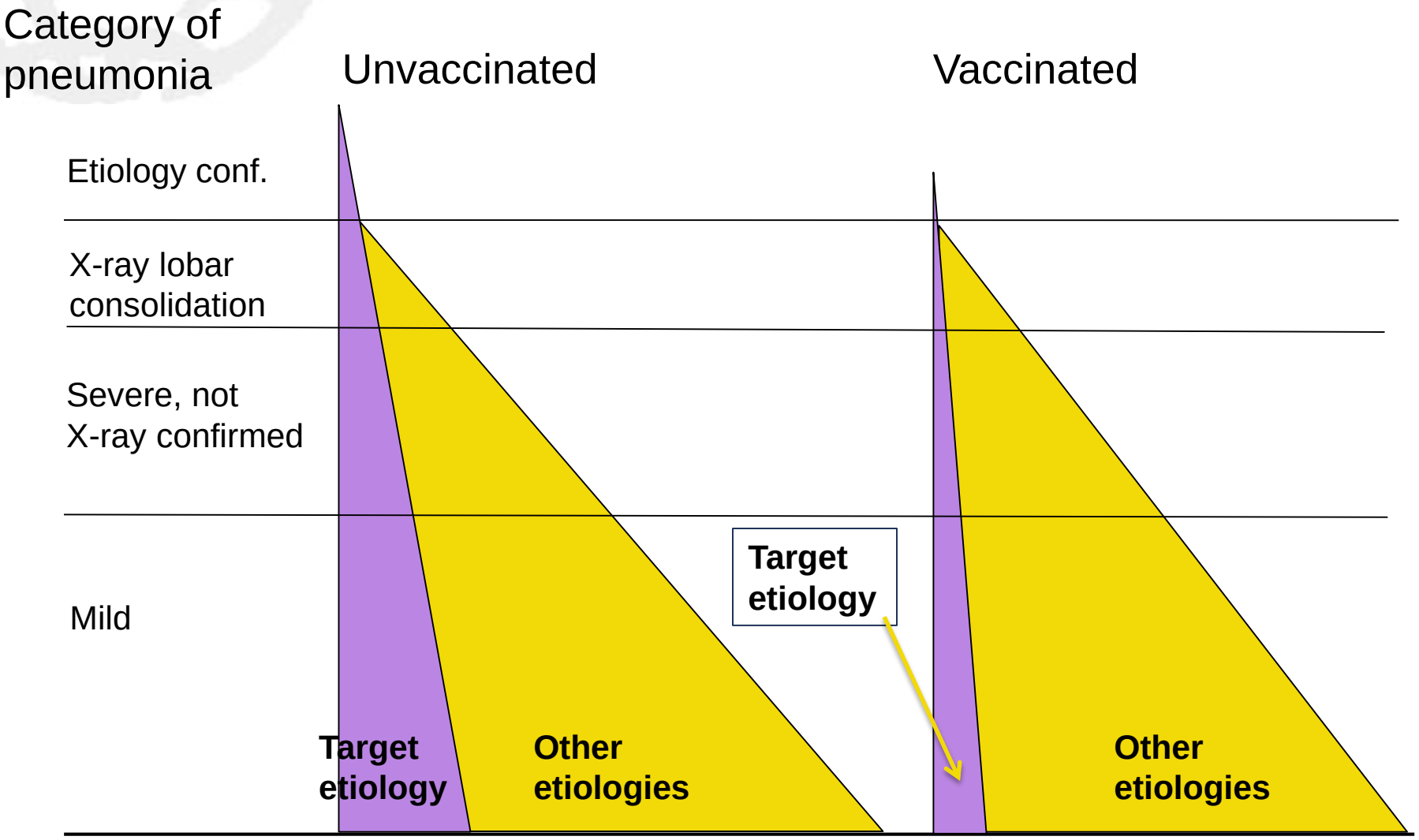
  = Incidence[unvaccinated] X VE

Feikin, Scott, Gessner. Use of vaccines as probes to define disease burden. Lancet 2015;383:1762-70

Contribution of hypothetical pathogen to pneumonia categories (Lancet 2014;383:1762-70)



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



Hypothetical example of results for a pathogen causing pneumonia

Pneumonia outcome	Incidence unvaccinated	Incidence vaccinated	VE	VPDI
	IU	IV	VE=1-(IV/IU)	VPDI=IU-IV
Etiologically confirmed	50	5	90%	45
X-ray conf. lobar infiltrate	200	128	36%	72
Any severe	800	620	23%	180
All clinical	5000	4550	9%	450

Examples of VPDI use; VPDI per 1000 CYO

	Syndrome	Etiology confirmed		Clinical outcome	
		VE	VPDI	VE	VPDI
Gambia, PCV	Radiological pneumonia	70%	1.4	37%	13
Indonesia, Hib	Hospitalized meningitis	86%	0.16	22%	1.6
Kenya, rotavirus	AGE (conf in hosp vs. all cause in comm)	84%	33	34%	190

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

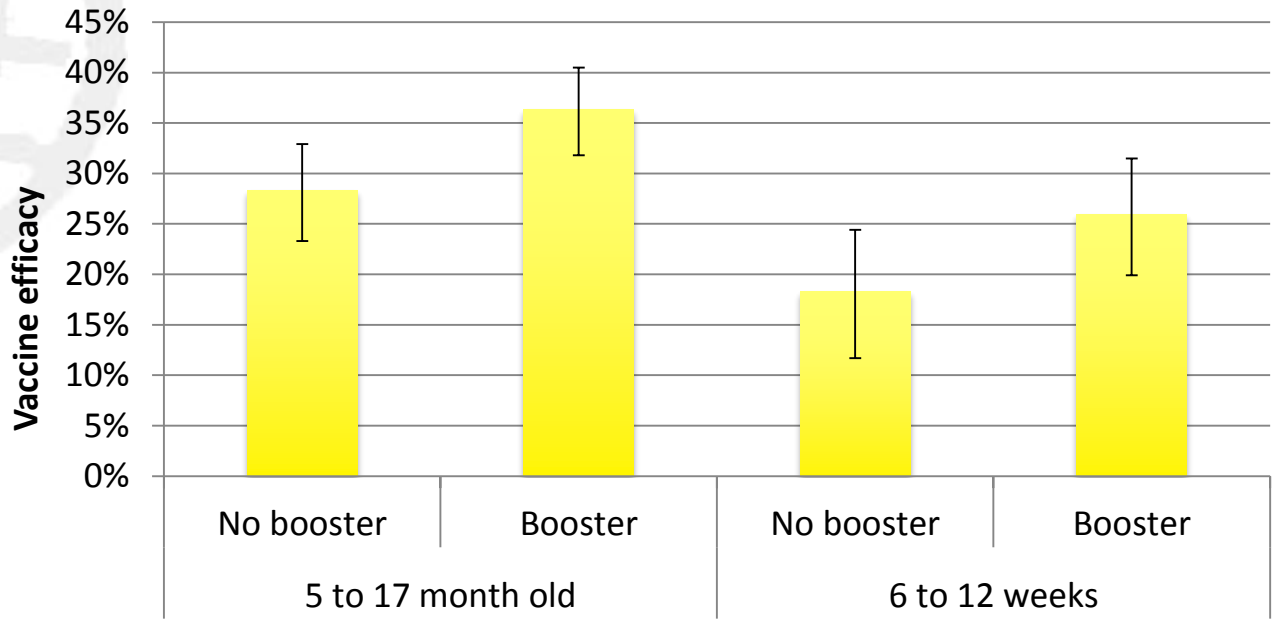
VPDI is useful outside of developing country settings

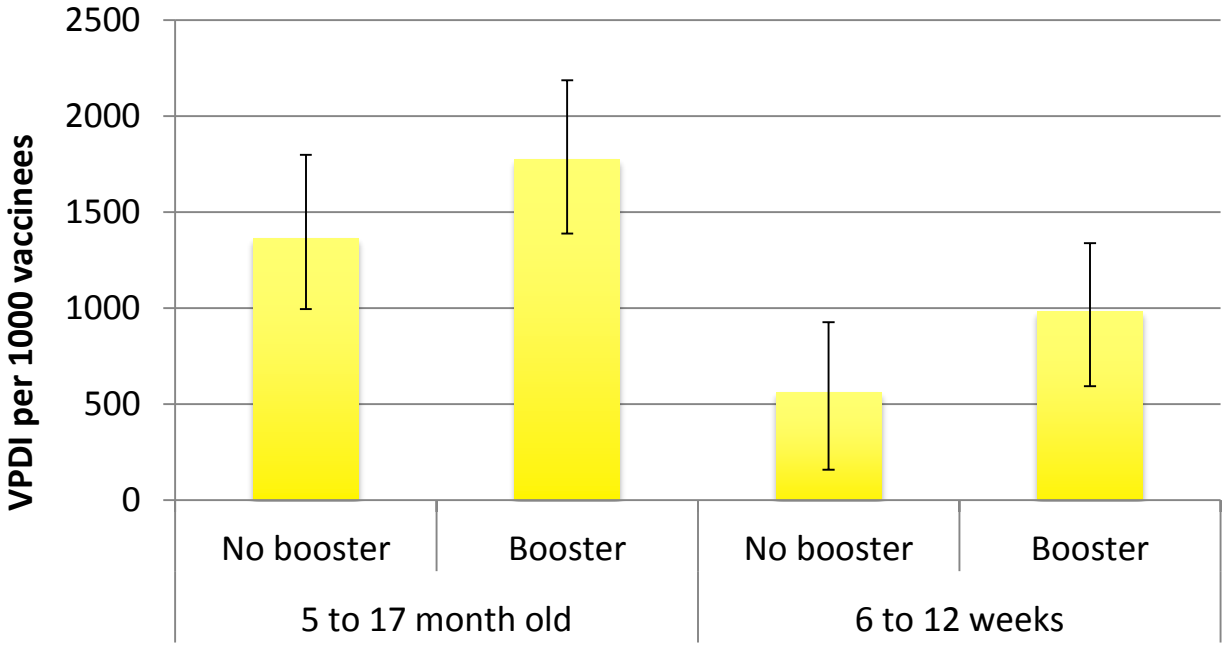
Study	VE	VPDI (per 1000 CYO)	Ref
Finland			Vaccine 2012;31:176-82
Confirmed inpatient AGE	80%	3.9	
All cause inpatient AGE	54%	10.7	
Kenya			Vaccine 2012;30 Supp 1:A52-60
Confirmed severe	84%	33	
Community severe AGE	34%	190	

Public health impact can be greater in settings where VE is lower

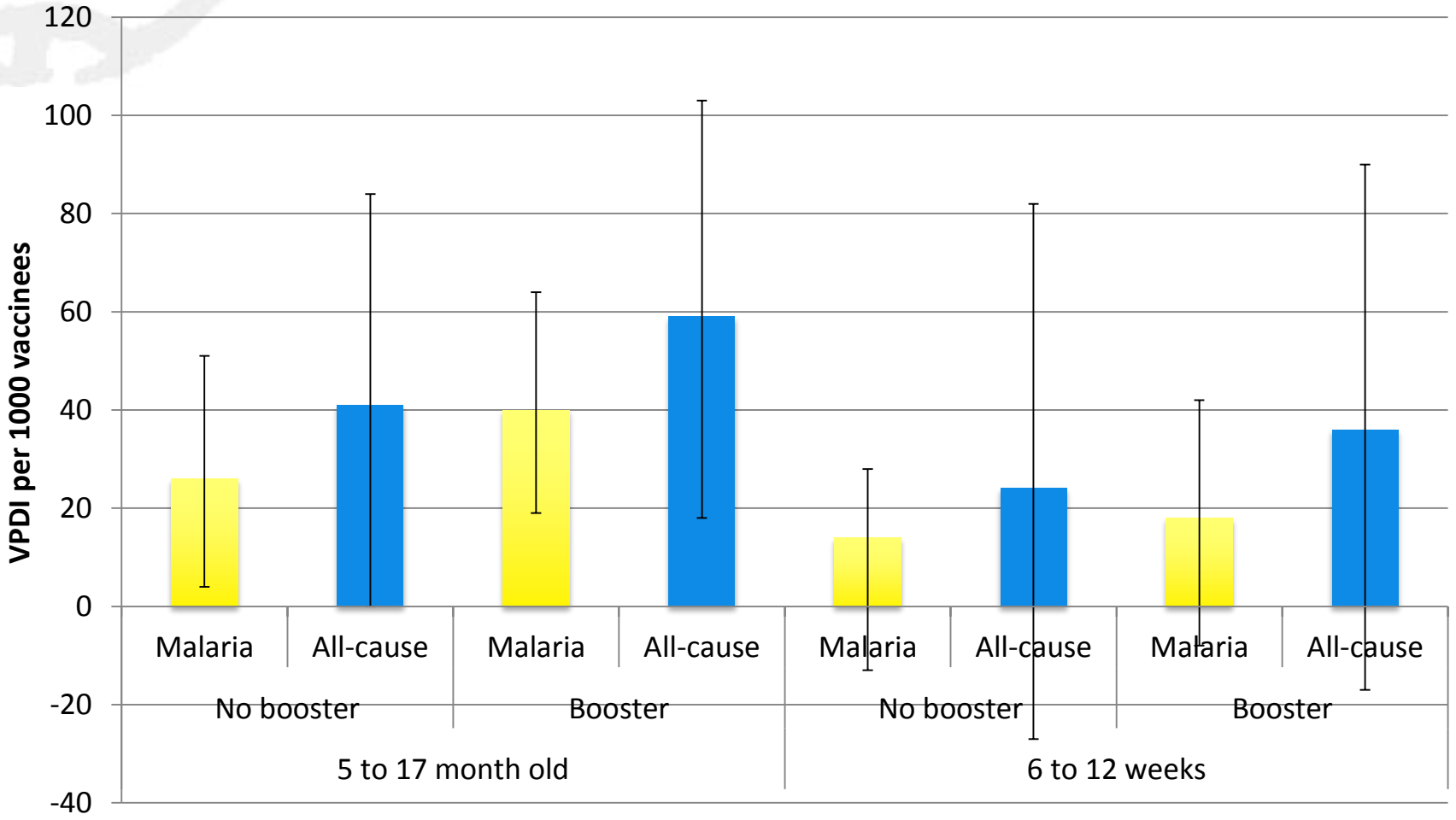
Study	VE	VPDI (per 1000 CYO)	Ref
Severe rota AGE			NEJM 2010;362:289-98
S. Africa	77%	42	
Malawi	49%	67	
Severe rota AGE			Lancet 2010;376:615-23
Vietnam	64%	22	
Bangladesh	43%	35	

RTS,S and clinical malaria (Lancet 2015 online)

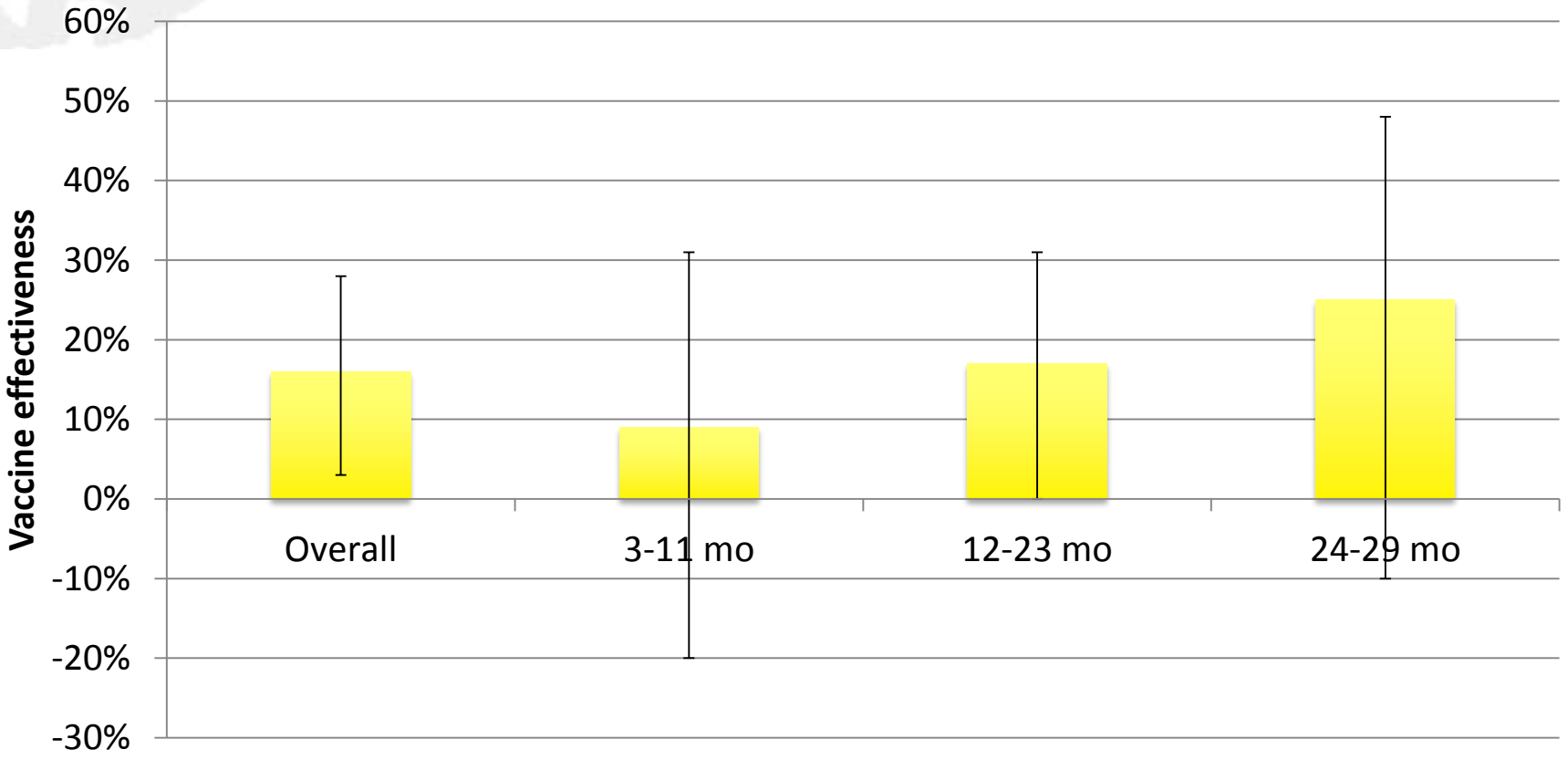




RTS,S VPDI against malaria-specific and all-cause hospitalization

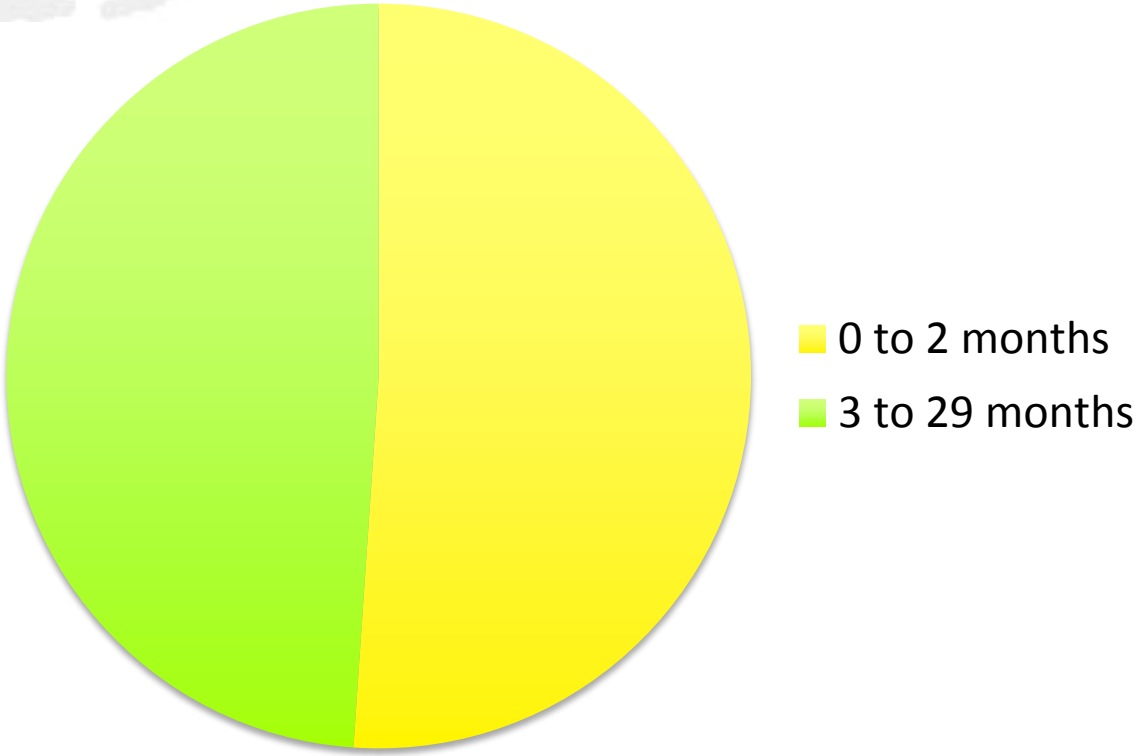


PCV-9 VE all cause mortality, The Gambia, by age group



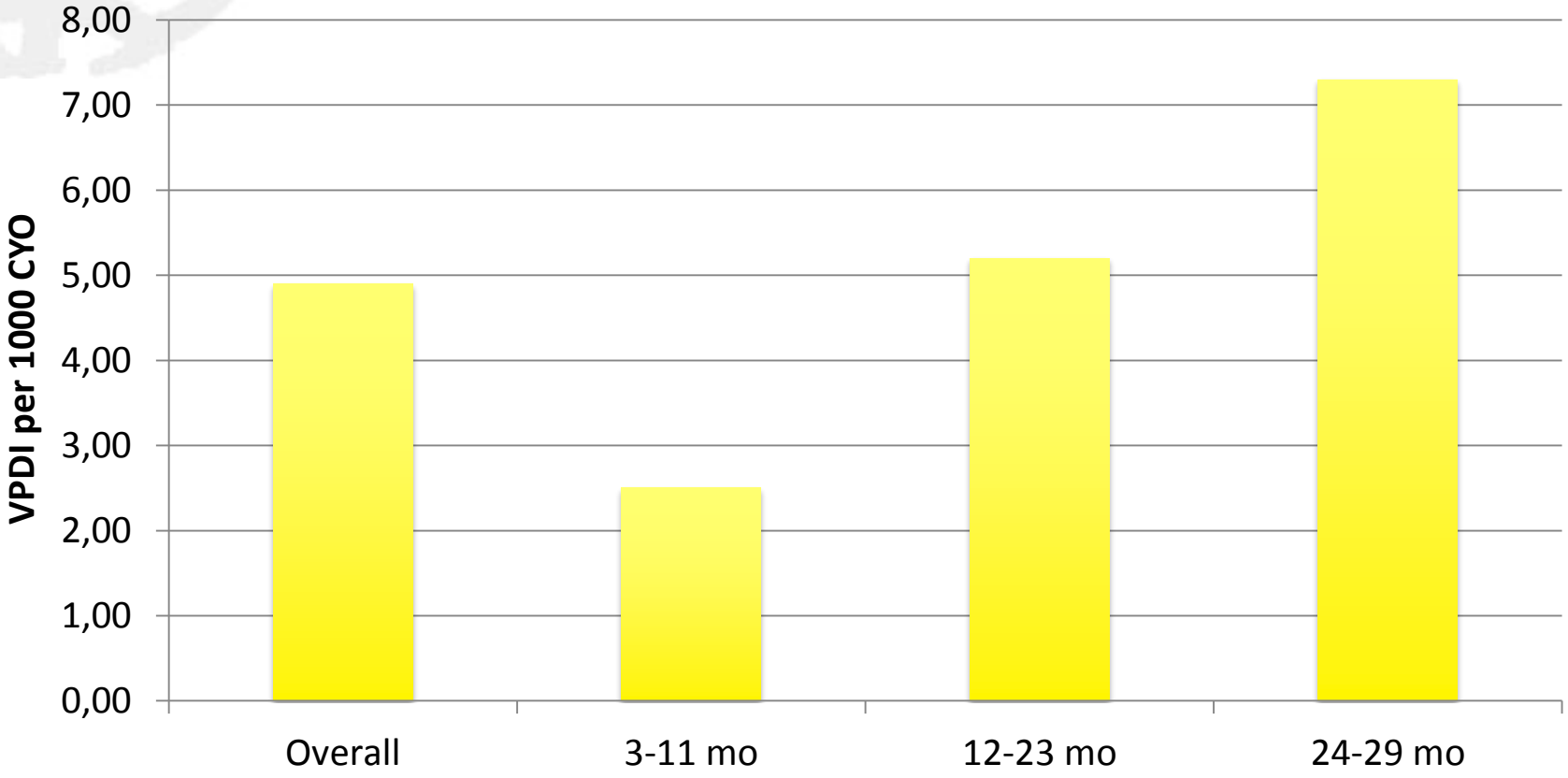
Lancet 2005;365:1139-46

Distribution of deaths by age, The Gambia 2002



- Age with >50% of deaths not included in study
- Likely VE in <30 month pop. = 8%

PCV-9 VPDI all cause mortality, The Gambia, by age group



Lancet 2005;365:1139-46

PCV and mortality: data points

- PCV9 reduced mortality among children age 3-29 months by 16% with wide confidence intervals
- This equated to a rate reduction of 5 per 1000 CYOs
- No data on PCV impact against mortality among children age <3 months who contribute ~50% of deaths; data suggest it may be minimal
- In other settings it is unknown whether one would approximate a reduction of 16%, a rate reduction of 5, or neither.
- Complicated by individually randomized study design; indirect protection from PCV9 suggests study may underestimate vaccine benefit.

Sequelae

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

Duration of immunity

	Sp/Hib	Malaria	Rotavirus	Cholera
Relatively long with booster	X			
Moderately long (based on existing data)				X
Short		X		
Less relevance (almost all disease at young age)			X	

Age distribution

		DISEASE	
		Age <5 yrs disease	All age disease
SEVERITY/SEQUELAE	Age <5 yrs	Rotavirus, Hib	Malaria
	All age		Pneumococcus, cholera

Indirect/replacement effects

	Indirect	No indirect
Replacement	Pneumococcus (indirect; replacement unclear)	
No replacement (yet)	Hib, rotavirus, cholera	Malaria

SUMMARY

- Burden is the foundation of decision making related to vaccines
- VE is useful as a licensing measure based on providing evidence a vaccine has biological effects
- VPDI a critical burden measure for vaccine preventable diseases → should be presented with VE to inform public health decisions in addition to regulatory decisions
- VPDI can in principle be used for any outcomes (cases, deaths, sequelae, DALYs)
- Interpretation can be subtle

QUESTIONS

- How can VPDI inform decision-making on newer vaccines such as dengue?
- What would be the utility of vaccine probe studies for typhoid conjugate, influenza, and other vaccines in the future?
- Should VPDI be considered by regulatory and licensing bodies in addition to VE?