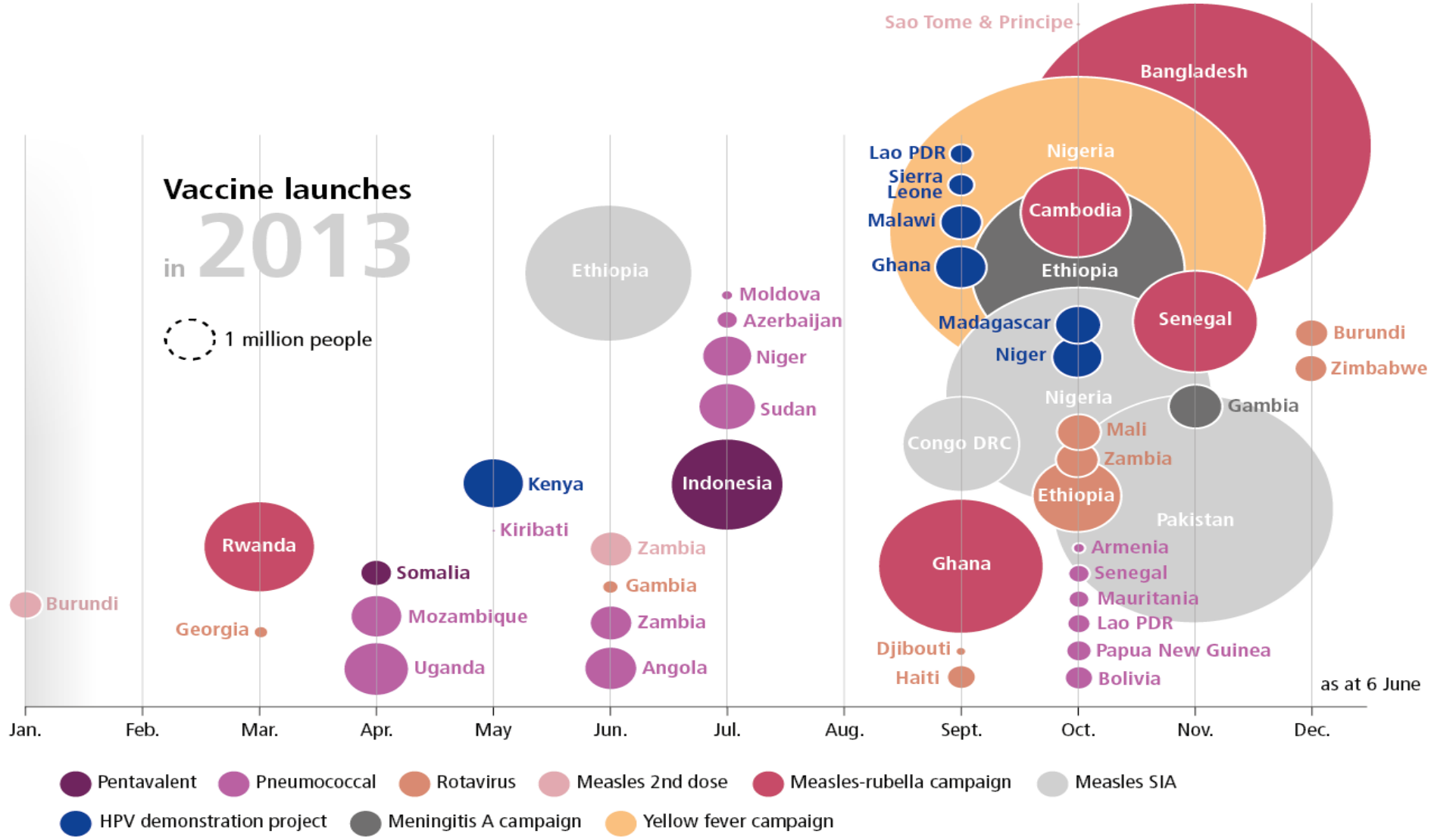
THE IMPORTANCE OF THE FULL PUBLIC HEALTH VALUE OF VACCINATION IN DECISIONS OF POLICY MAKERS: WHERE DO WE STAND AND WHERE SHOULD WE GO?

Brad Gessner, MD

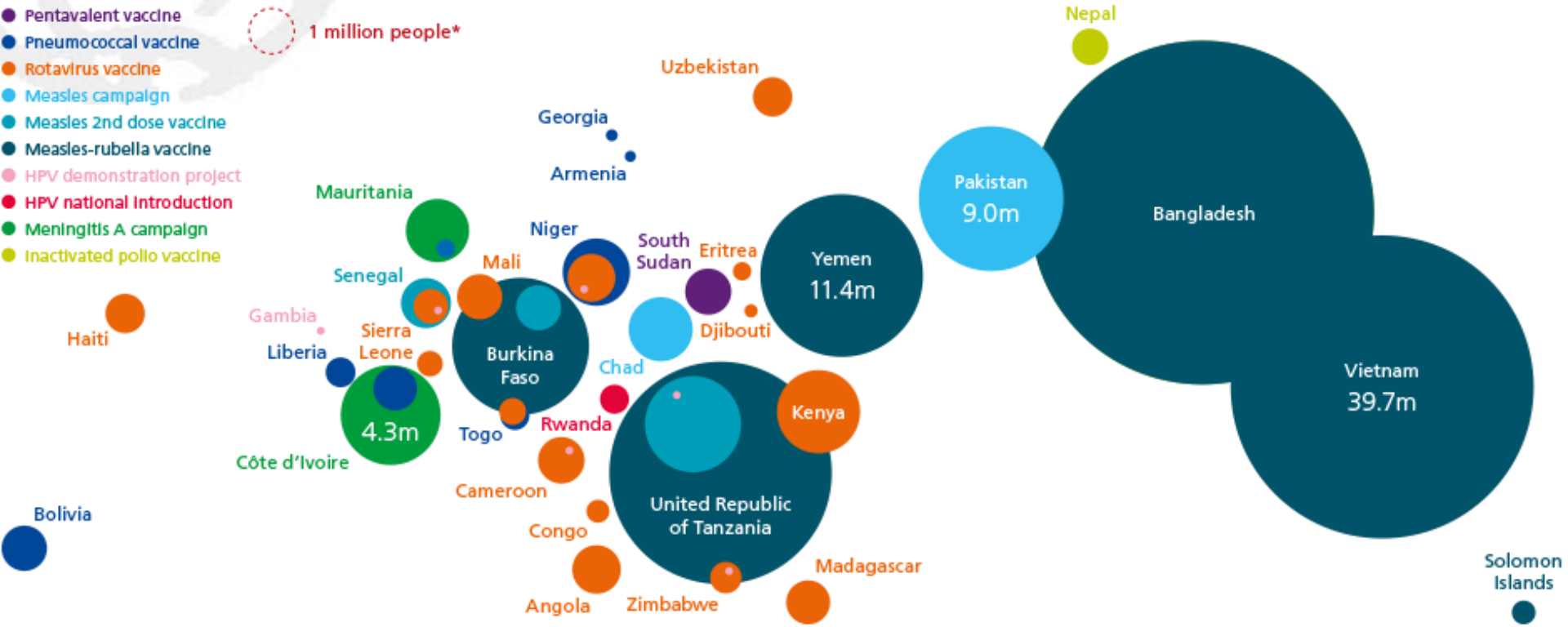
Agence de Médecine Preventive

DECISION MAKING

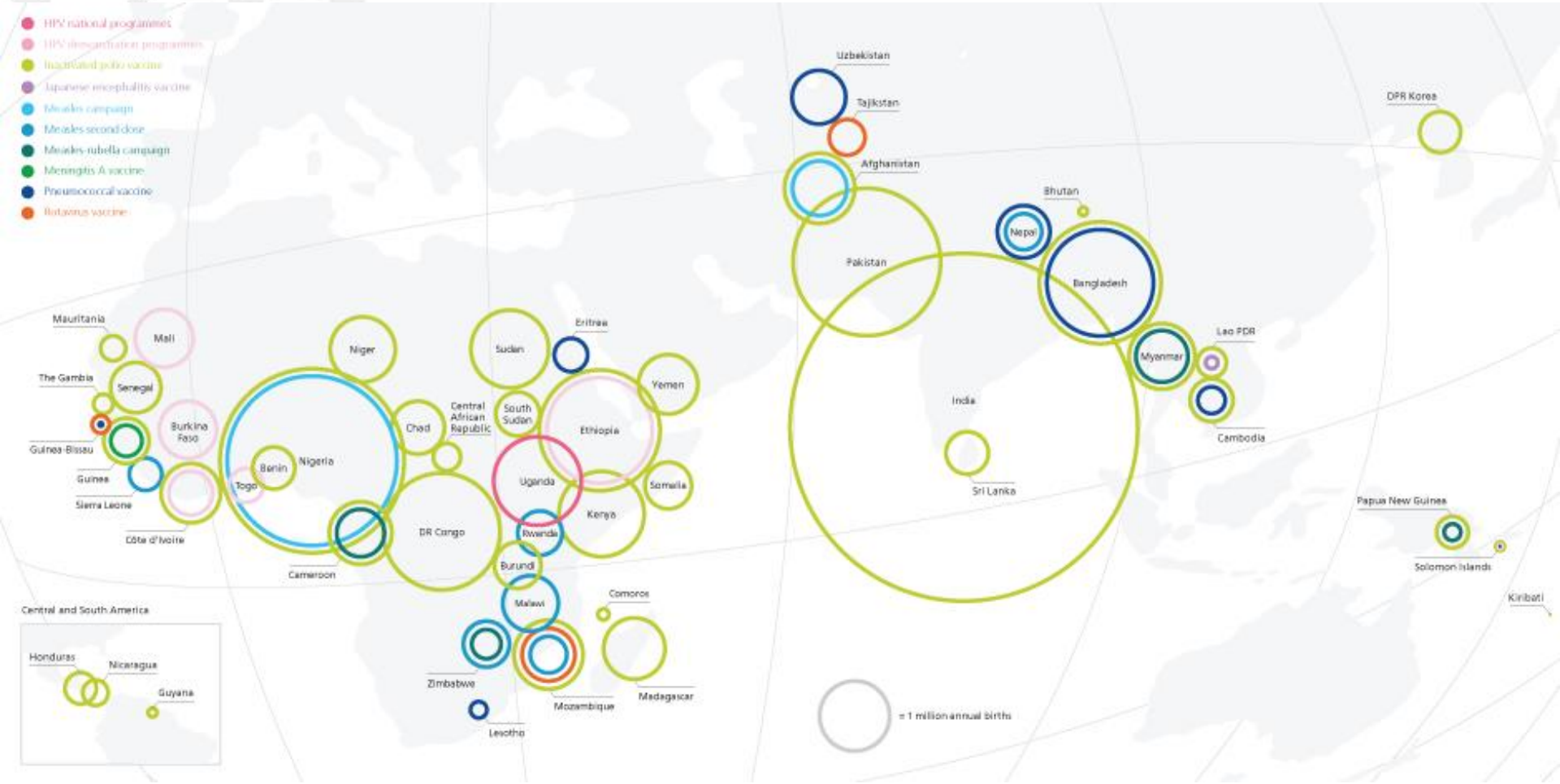
Vaccine Launches 2013



Vaccine Launches 2014



Vaccine Launches 2015



ELSEVIER

Social Science & Medicine 65 (2007) 1751–1764

SOCIAL SCIENCE & MEDICINE

www.elsevier.com/locate/socscimed

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."

Vaccine 28S (2010) A13–A17

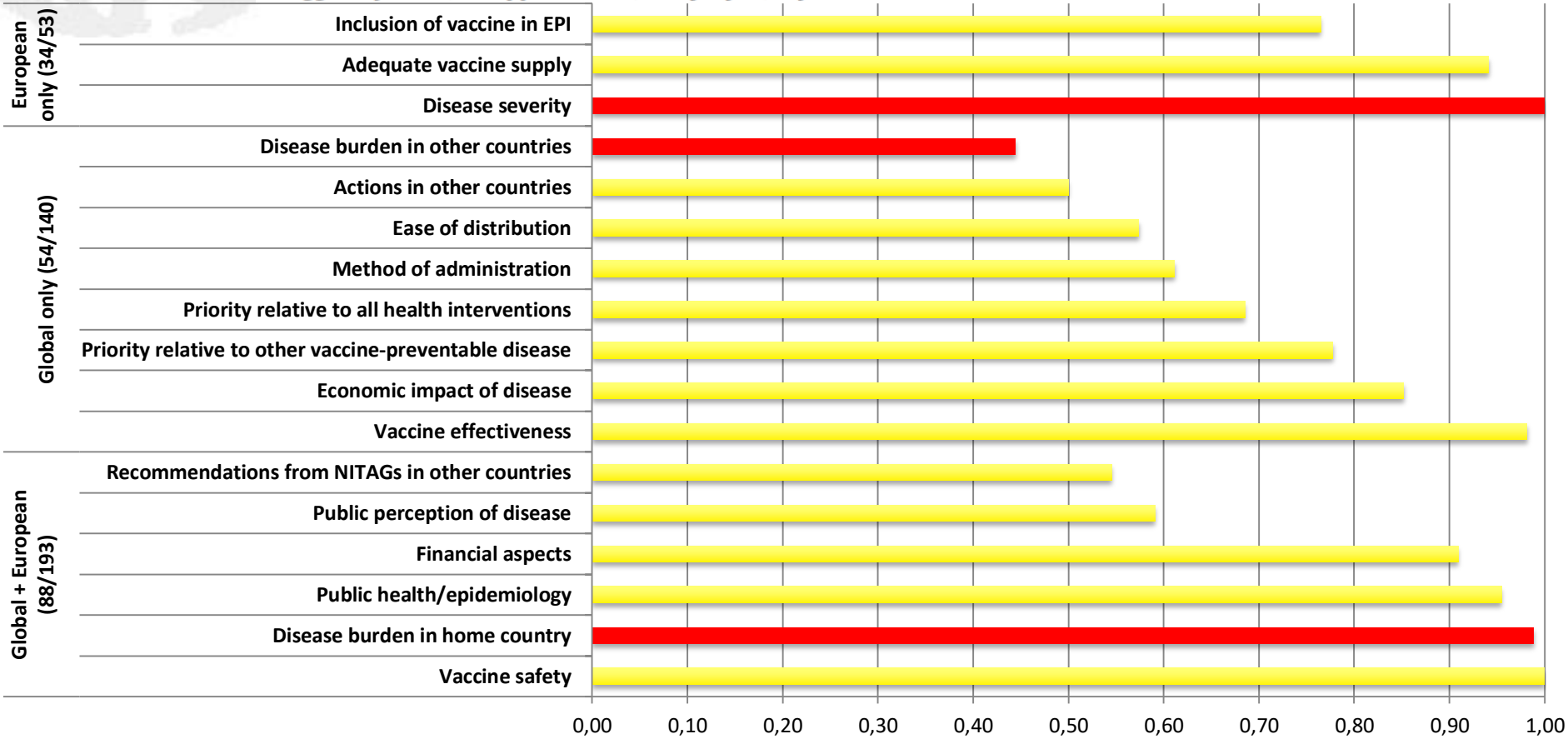
Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

A global look at national Immunization Technical Advisory Groups

Maggie Bryson[a,*], Philippe Duclos[b], Ann Jolly[a,c], Niyazi Cakmak[d]



EXPERT REVIEWS

Establishing global policy recommendations: the role of the Strategic Advisory Group of Experts on immunization

Expert Rev. Vaccines 10(2), 163–173 (2011)

In making its recommendations, SAGE takes into consideration issues such as disease epidemiology (disease burden including age specific mortality, morbidity, and societal impact; projections for future disease burden; specific risk groups; epidemic potential; disease occurrence over time; serogroup or serotype distribution for serogroup or serotype-specific vaccines; and changes in epidemiology over time), clinical characteristics (clinical management of disease; disease severity; primary/secondary/tertiary care implications; long-term complications of disease; and medical requirements)…

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

GLOBAL HEALTH

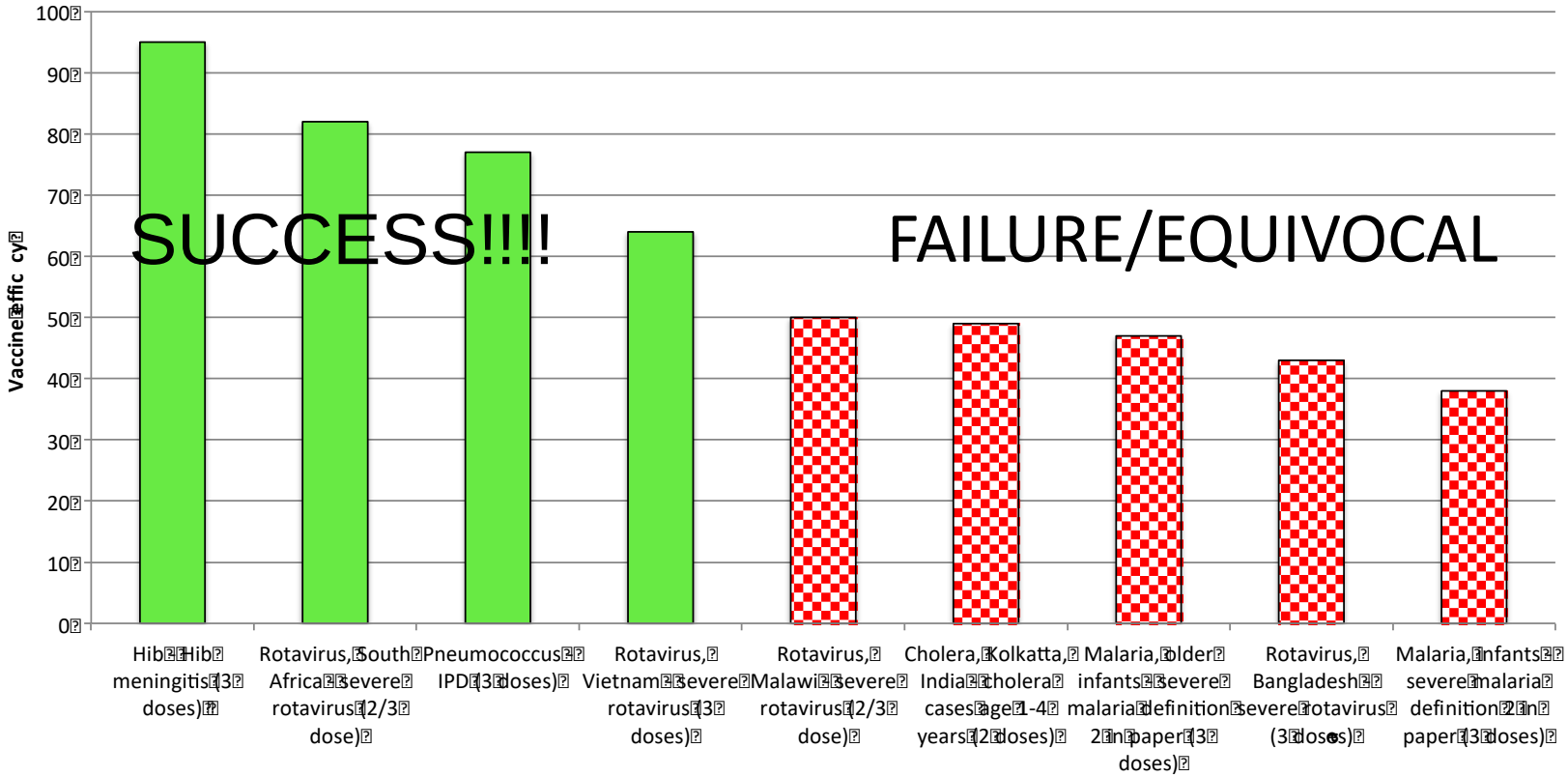
STRATEGY OVERVIEW

"Our starting point in deciding where to focus has been the disease burden in developing countries, as measured by disability-adjusted life years (DALYs) lost."

Decision making issues

- Low income countries
  - Many countries have introduced vaccines such as rotavirus, Hib, HepB, PCV, HPV, measles 2nd dose, IPV
  - Financing largely dependent on Gavi, with relatively small co-pays
  - Transition to full country financing will place strains on country health and NIP budgets
- Middle income countries
  - Already assume full cost of vaccines
  - May have only marginally more budgets than low income countries
- Anti-vaccine groups
- Complacency
- Valuing vaccines appropriately will be critical to sustaining programs
  - Traditional metrics like VE and safety not enough

PER PROTOCOL ANALYSIS OF VE



Vaccine 2014;32:3133-8

OUTCOME MEASURES

Between the idea and the reality...falls the shadow

- **Field issues**
  - Lack of referral
  - Lack of transportation
  - Economic barriers
- **Investigator issues**
  - Outcome not suspected
  - Staff not at work 24/7
  - Lack of diagnostic equipment
- **Laboratory issues**
  - Transportation (delay or loss)
  - Improperly trained staff
  - Variable test specificity/sensitivity
  - Insufficient blood volume
  - Pre-treatment with antibiotics
- **Epidemiological issues**
  - Imperfect entry criteria case definition sensitivity/specificity
  - Organism might be part of causal chain and not present
  - Organism might be present and not part of causal chain
  - Imperfect understanding of outcomes associated with infection (e.g., measles and malnutrition)

The above may vary by age group, risk group (HIV, marginalized, etc.), geography; often will impact most those most at risk of typhoid.

DEFINITIONS

VACCINE PREVENTABLE DISEASE INCIDENCE (VPDI)

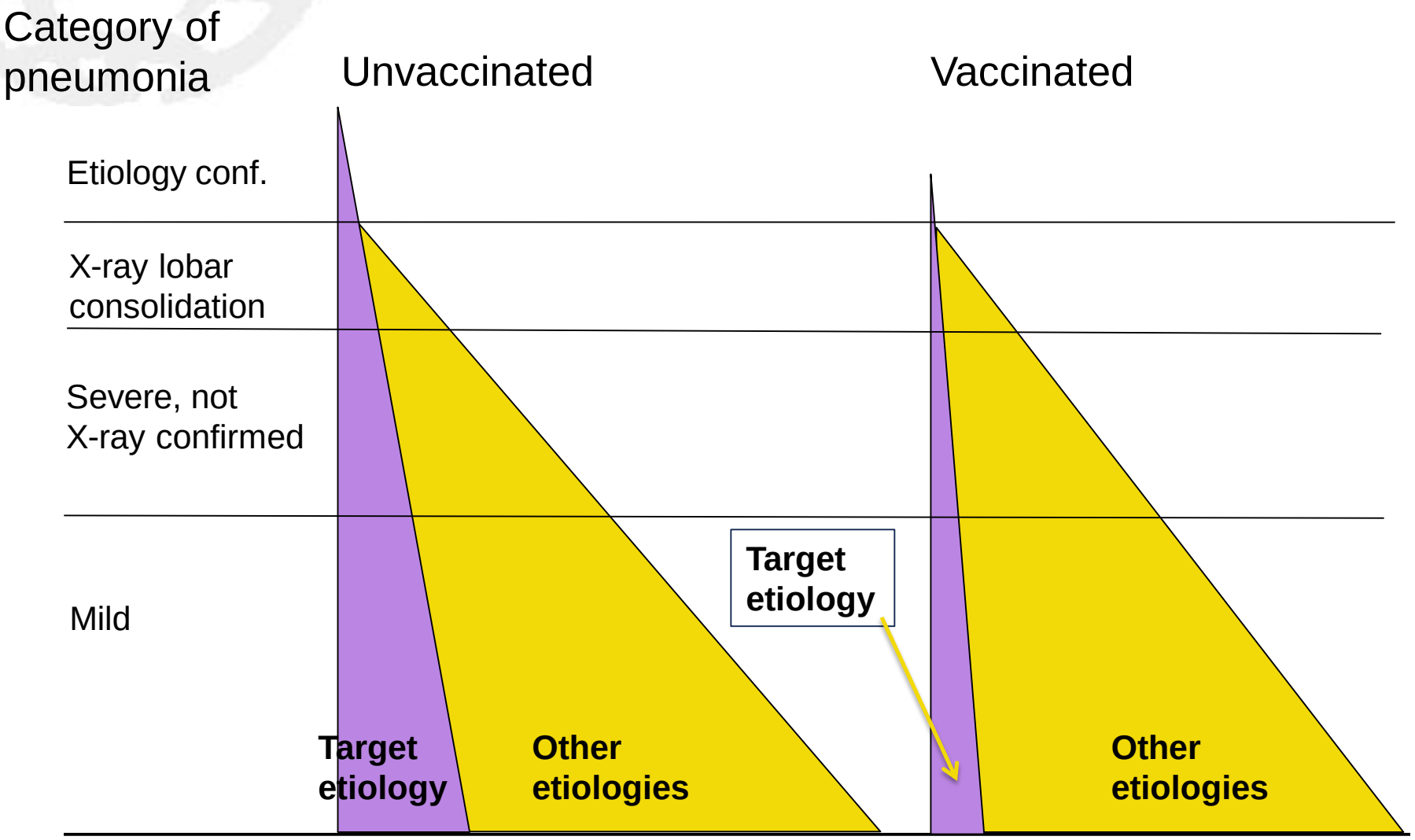
- Same as vaccine attributable risk,
- = Incidence [unvaccinated] – Incidence [vaccinated]
- = Incidence [unvaccinated] x VE
- ***= number of cases averted per unit of vaccinated people per year***

NUMBER NEEDED TO VACCINATE (NNV)

- The number of people that must be vaccinated to prevent one outcome
- Not a rate so incorporates length of trial (or duration of immunity)
- If VPDI is reported as cases prevented per 100,000 vaccinated persons per year, NNV = 100,000/VPDI/length of study

Impact of vaccine against confirmed and clinically defined pneumonia

(Lancet 2014;383:1762-70)



Examples of etiologically confirmed vs. clinical outcomes; VPDI per 1000 CYO

Study	Syndrome	Etiology confirmed			Clinical outcome		
		VE	VPDI	NNV	VE	VPDI	NNV
Gambia, PCV	Radiological pneumonia	70%	1.4	357	37%	13	38
Indonesia, Hib	Hospitalized meningitis	86%	0.16	3125	22%	1.6	313
Kenya, rotavirus	AGE (conf in hosp vs. all cause in comm)	84%	33	15	34%	190	3

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

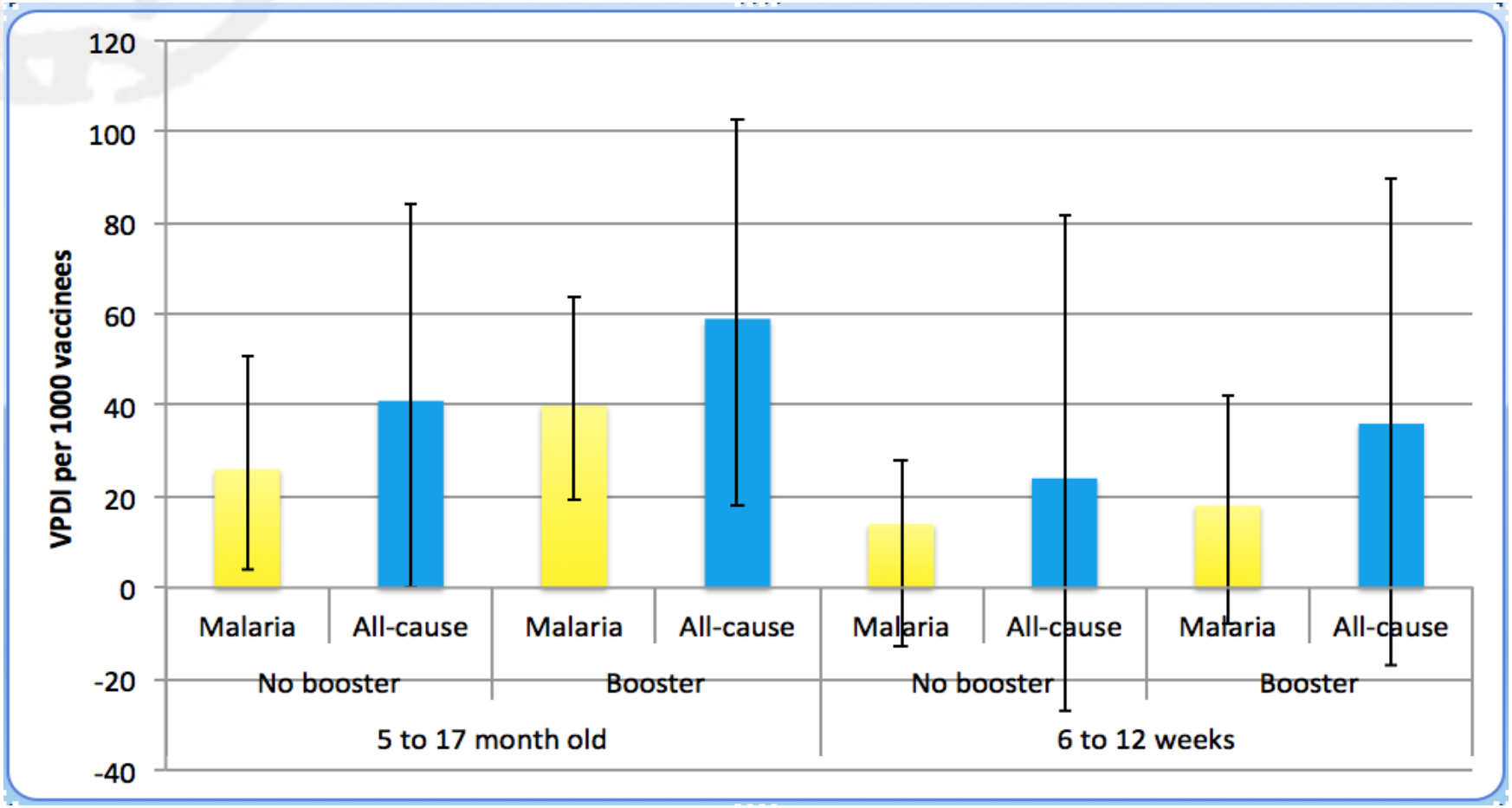
Clinical outcomes show greater VPDI outside of developing country settings

Study	VE	VPDI (per 1000 CYO)
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

Clinical outcomes can be particularly helpful where burden higher/VE lower

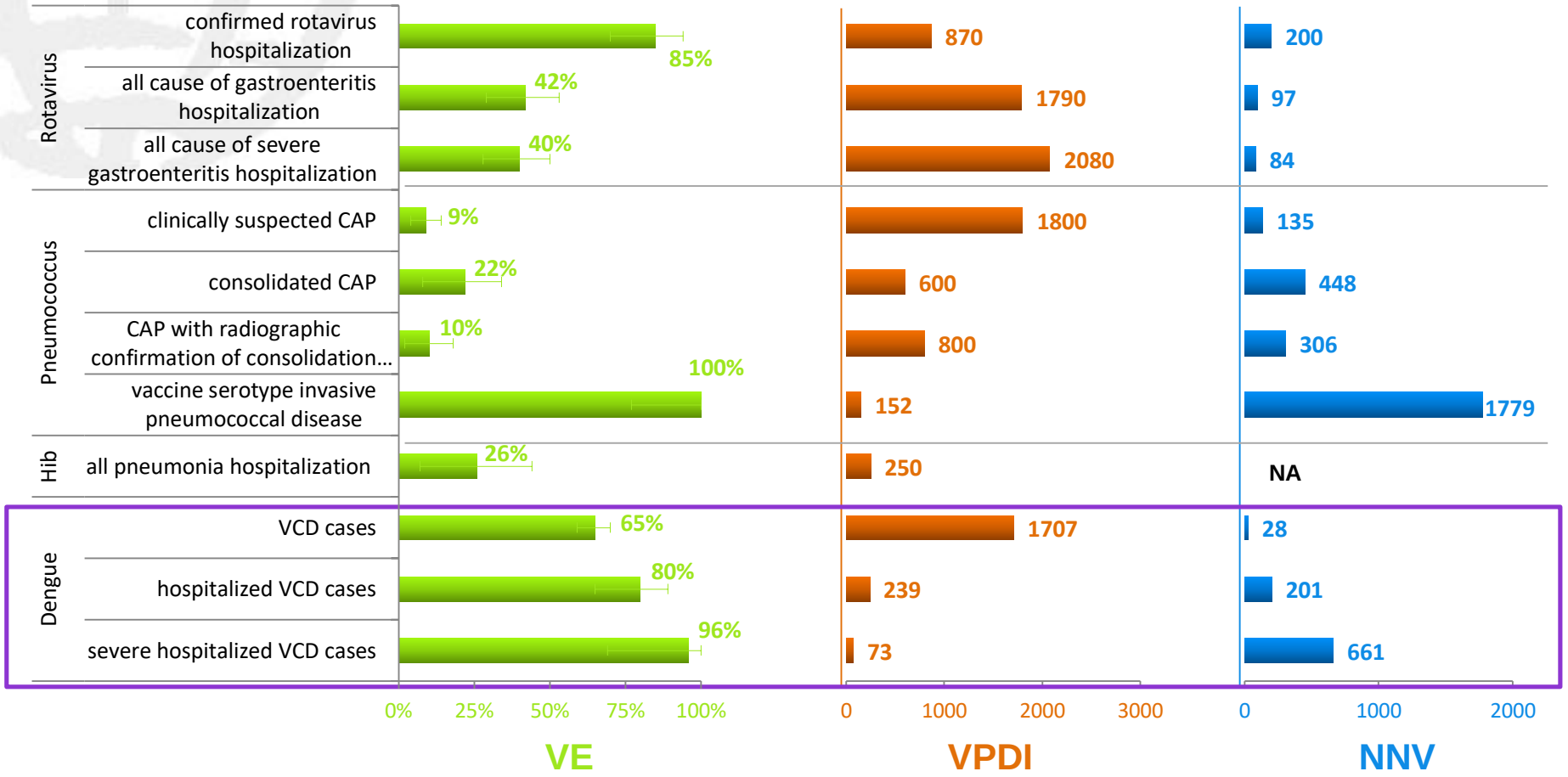
Outcome/study	VE	VPDI (per 1000 CYO)	NNV
Severe rota AGE (NEJM 2010;362:289-98)			
S. Africa	77%	42	24
Malawi	49%	67	15
Severe rota AGE (Lancet 2010;376:615-23)			
Vietnam	64%	22	33
Bangladesh	43%	35	21

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



CYD TDV dengue vaccine compared to other vaccines

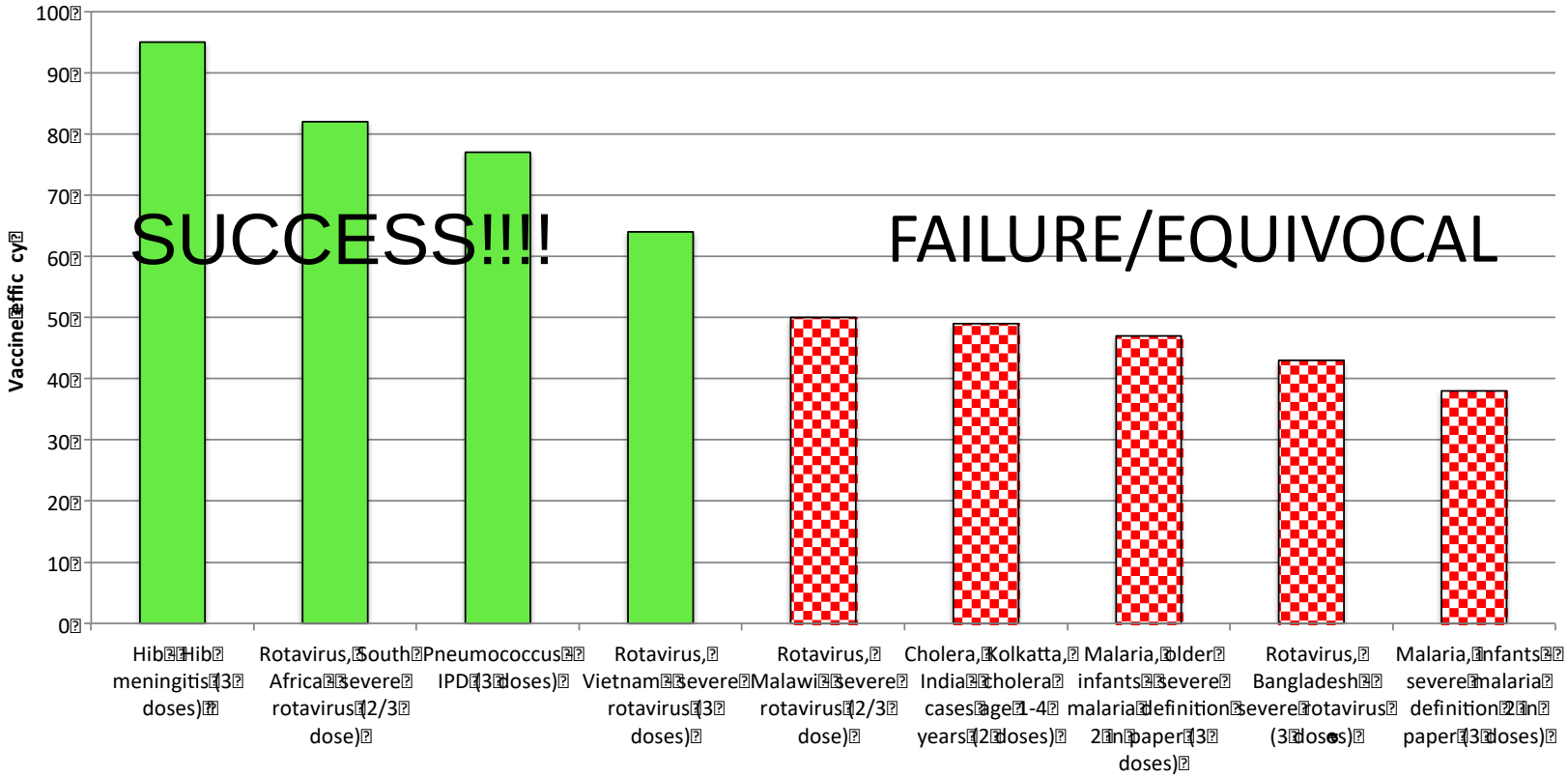
Latin America



In Latin America, while severe disease VPDI was relatively low, the VPDI for all hospitalized dengue was approximately equal to the sum of invasive Hib disease and severe pneumonia

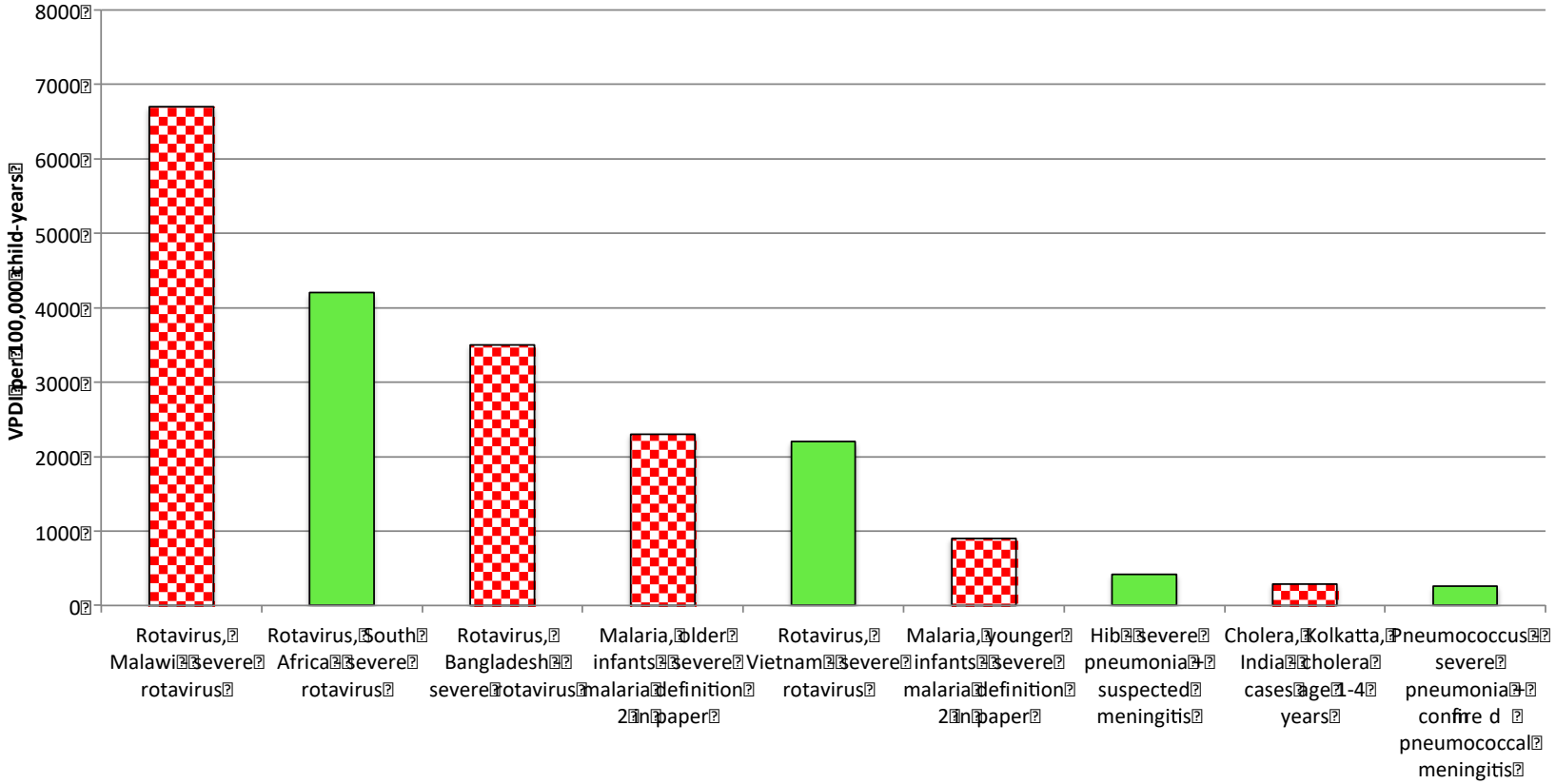
CAP: consolidated community acquired pneumonia; NA: not available

PER PROTOCOL ANALYSIS OF VE



Vaccine 2014;32:3133-8

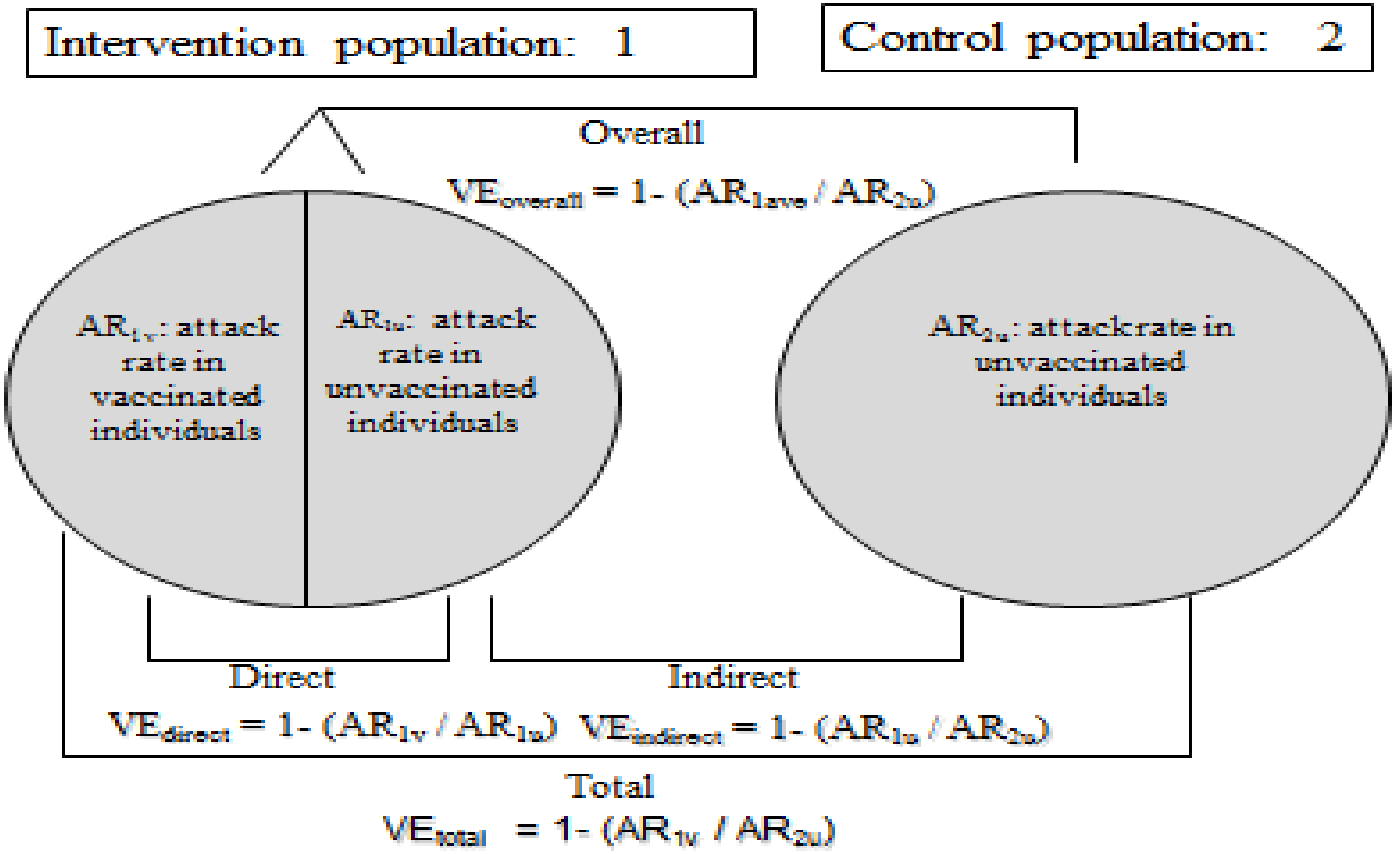
PER PROTOCOL ANALYSIS OF VPDI



Vaccine 2014;32:3133-8

INDIVIDUAL VERSUS CLUSTER RANDOMIZATION

Schematic of Effectiveness Analyses



Longini IM Jr, Nizam A, Ali M, Yunus M, Shenvi N, et al. (2007) Controlling Endemic Cholera with Oral Vaccines. PLoS Med 4(11): e336. doi:10.1371/journal.pmed.0040336
http://journals.plos.org/plosmedicine/article?id=info:doi/10.1371/journal.pmed.0040336

Limitations of licensing trials, particularly iRCT

- Indirect effects can't be measured in target age group
- Usually insufficient power for rare outcomes such as mortality
- Usually insufficient duration for some outcomes such as asthma/wheezing for RSV; neurologic sequelae for MCV, Hib conjugate, PCV
- iRCTs may be difficult to implement during outbreaks (cholera, Ebola, dengue).
- Focus on etiologically defined disease, which may greatly underestimate all disease
- VPDI and NNV may be underestimated by an iRCT

Hypothetical example of impact of IRT design on Hib vaccine VE and VPDI

Pre-study	Meningitis	No meningitis
Vaccine	100	99,900
Non-vaccine	100	99,900

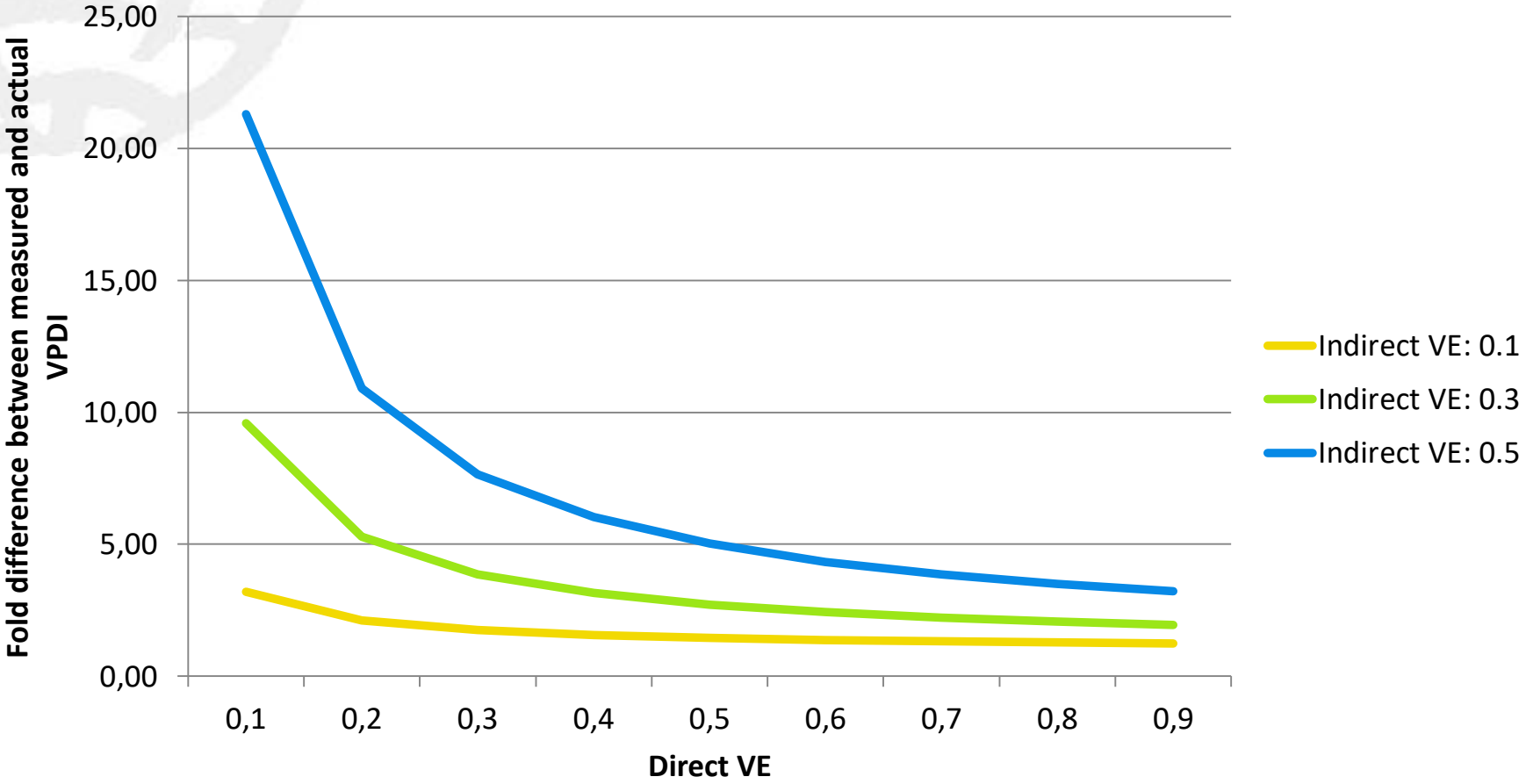
Study; no indirect	Meningitis	No meningitis
Vaccine	20	99,980
Non-vaccine	100	99,900

VE = 80%; VPDI = 80/100k/yr

Study; +indirect	Meningitis	No meningitis
Vaccine	10	99,990
Non-vaccine	50	99,950

Measured: VE = 80%; VPDI = 40/100k/yr
Actual: VE = 80%; VPDI = 140/100k/yr

Fold difference between actual and measured vaccine preventable disease incidence (VPDI) for different direct and indirect vaccine efficacies (VE)



OTHER CONCERNS FOR VALUING VACCINES APPROPRIATELY

Severity

	Sp/Hib meningitis	Sp/Hib pneumonia	Malaria	Rotavirus	Cholera	Dengue	HPV
Mortality	++++	++	+++	+	++	+	+++
Hospitalization	++++	+++	+++	++	+++	++	+
Outpatient disease	--	+	++++	++++	+	++++	--

Sequelae

	Sp/Hib meningitis	Sp/Hib pneumonia	Malaria	Rotavirus	Cholera	Dengue	HPV
Cognitive (MR, DD, LD, language)	++++	--	+++	--	--	--	--
Mental health	++++	--	?	--	--	--	++++
Sensory (hearing, vision)	++++	--	--	--	--	--	--
Physical (CP, seizures)	++++	--	+++	--	--	--	--
Stunting	?	?	+++	+	+	?	--

Duration of immunity

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

Age distribution

	Age <5 yrs disease	All age disease
Age <5 yrs severity/sequelae	Rotavirus, Hib	Malaria, dengue
All age severity/sequelae		Pneumococcus, cholera

HPV only post sexual activity initiation

Indirect/replacement effects

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

Outbreaks and politics

	Sp/Hib	Malaria	Rotavirus	Cholera	Dengue	HPV
Massive outbreaks	--	--	--	++/++++	++/++++	--
Disruption of health system	--	--	--	++/++++	++/++++	--
Politically sensitive	--	+++	--	++++	+++	--
Impact on tourism	--	+++	--	++++	+++	--

Gessner et al. BMC Infectious Diseases 2010, 10:22
http://www.biomedcentral.com/1471-2334/10/22

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

African meningitis belt pneumococcal disease epidemiology indicates a need for an effective serotype 1 containing vaccine, including for older children and adults

Bradford D Gessner[1*], Judith E Mueller[1], Seydou Yaro[2]

Abstract

Background: Pneumococcal conjugate vaccine strategies in GAVI-eligible countries are focusing on infant immunization but this strategy may not be optimal in all settings. We aimed to collect all available population based data on pneumococcal meningitis throughout life in the African meningitis belt and then to model overall meningitis risk to help inform vaccine policy.

Methods: After a systematic review of literature published from 1970 through the present, we found robust population-based *Streptococcus pneumoniae* (Sp) meningitis data across age strata for four African meningitis belt countries that included 35 surveillance years spanning from 1970 to 2005. Using these data we modeled disease risk for a hypothetical cohort of 100,000 persons followed throughout life.

Results: Similar to meningococcal meningitis, laboratory-confirmed pneumococcal meningitis was seasonal, occurring primarily in the dry season. The mean annual Sp meningitis incidence rates were 98, 7.8 to 14, and 5.8 to 12 per 100,000 among persons <1, 1 through 19, and 20 to 99 years of age, respectively, which (in the absence of major epidemics) were higher than meningococcal meningitis incidences for persons less than 1 and over 20 years of age. Mean Sp meningitis case fatality ratios (CFR) among hospitalized patients ranged from 36-66% depending on the age group, with CFR exceeding 60% for all age groups beyond 40 years; depending on the age group, Sp meningitis mortality incidences were 2 to 12-fold greater than those for meningococcal meningitis. The lifetime risks of pneumococcal meningitis disease and death were 0.6% (1 in 170) and 0.3% (1 in 304), respectively. The incidences of these outcomes were highest among children age <1 year. However, the cumulative risk was highest among persons age 5 to 59 years who experienced 59% of pneumococcal meningitis outcomes. After age 5 years and depending on the country, 59-79% of meningitis cases were caused by serotype 1.

Conclusions: In the African meningitis belt, Sp is as important a cause of meningitis as *Neisseria meningitidis*, particularly among older children and working age adults. The meningitis belt population needs an effective serotype 1 containing vaccine and policy discussions should consider vaccine use outside of early childhood.

Equity/ethics

	Sp/Hib	Malaria	Rotavirus	Cholera	Dengue	HPV
Occurrence higher in disadvantaged between countries	--	++++	--	++++	++	--
Occurrence higher in disadvantaged within countries	--	++	--	+++	++	--
Severity higher in disadvantaged	+	+++	+++	++	+	+++
Mortality higher in disadvantaged	+++	++++	++++	+++	+	+++

JUST THE FACTS, MA'AM

(SGT. JOE FRIDAY, DRAGNET, 1951-59)

I'm sorry, Jeannie, your answer was correct, but Kevin shouted his incorrect answer over yours, so he gets the points."

One thing that has been interesting this entire campaign season to watch, is that people that say facts are facts—they're not really facts. Everybody has a way—it's kind of like looking at ratings, or looking at a glass of half-full water. Everybody has a way of interpreting them to be the truth, or not truth. There's no such thing, unfortunately, anymore as facts.
Scottie Nell Hughes, News Director, Tea Party News Network

In the final three months of the US presidential campaign, the top-performing fake election news stories on Facebook generated more engagement than the top stories from major news outlets such as the *New York Times*, *Washington Post*, *Huffington Post*, NBC News, and others.
Craig Silverman, Buzzfeed Founding Editor

Even the coverage of fake news is "fake."
David Harsanyi, The Federalist

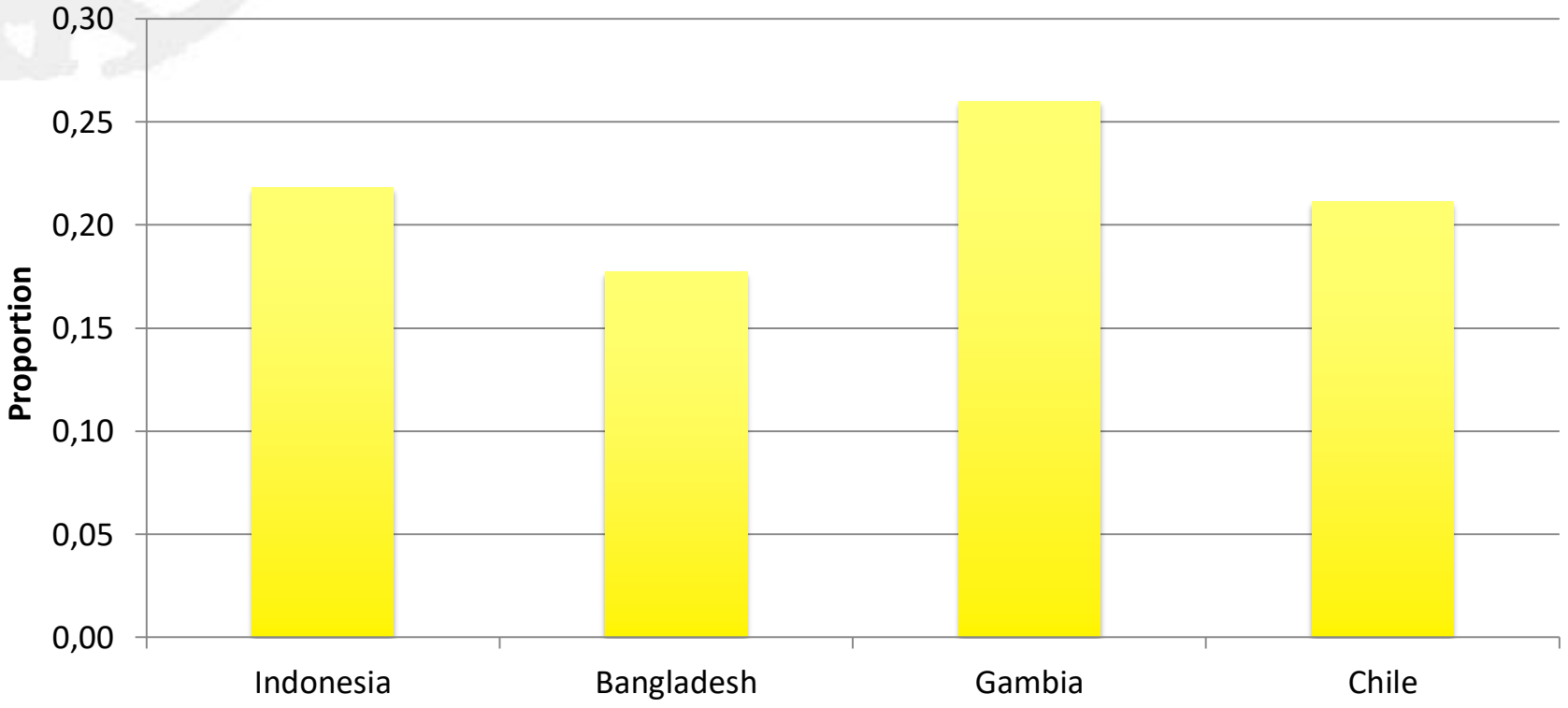
We do not want to be arbiters of truth ourselves.
Mark Zuckerberg, Facebook Founder

Truth doesn't need arbiters, it needs defenders…Today's fake news is limited only by the imaginations of its inventors and the number of shares it can garner on Facebook or Twitter.
Jim Rutenberg, New York Times

Hib vaccine impact on pneumonia: talking points

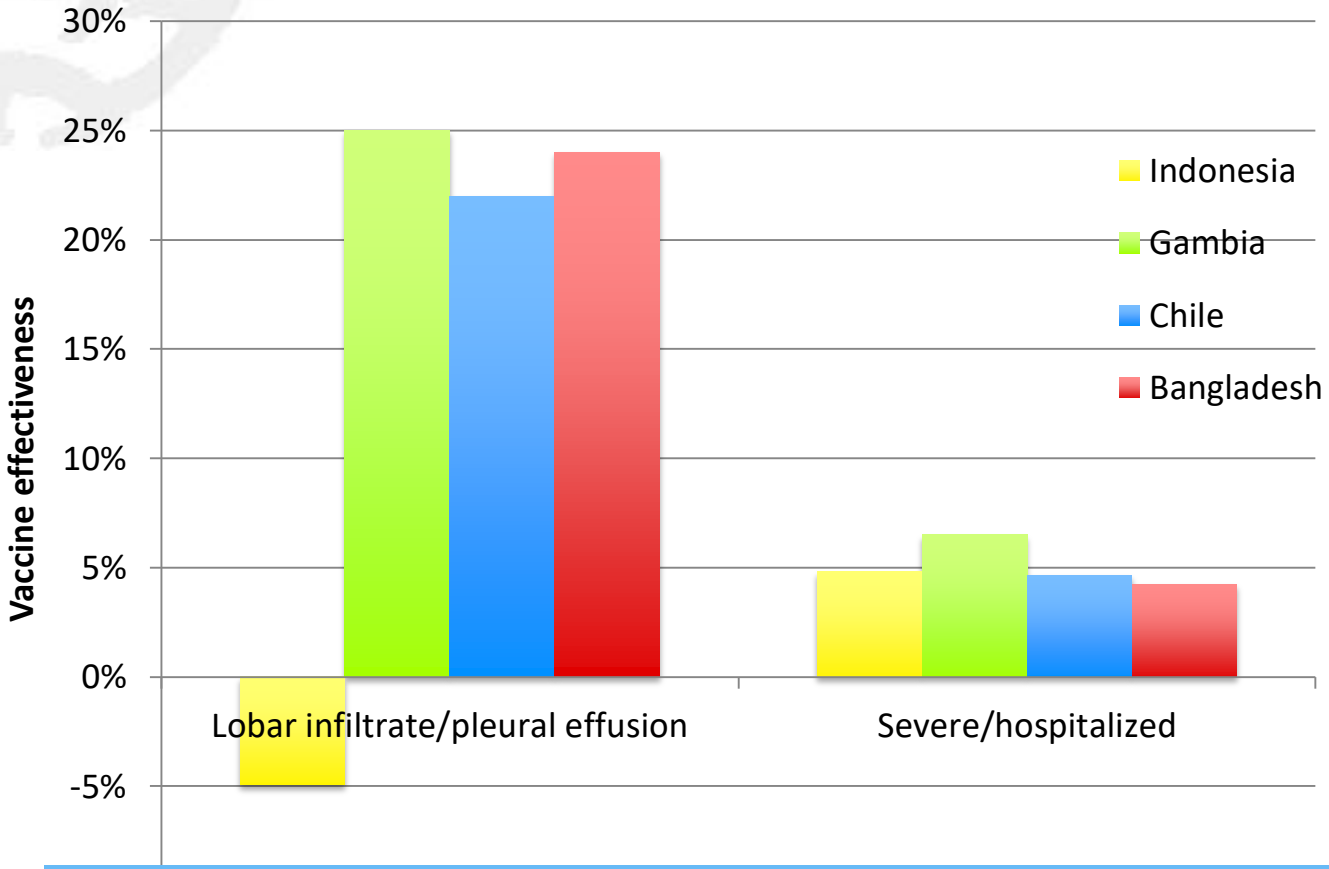
- “Pneumococcal and Hib conjugate vaccines reduced pneumonia by approximately 26% and 18%, respectively, in clinical trials when given as infant immunization”: Bull WHO 2012;90:289-94
- “Hib is estimated to cause over 20% of life-threatening childhood pneumonia”: Hum Vaccines 2011;7:1158-60.
- “In most pre-vaccine studies Hib caused approximately 20% of severe pneumonia”: The Hib Initiative, Hib Fact Sheet.

Proportion of severe/hospitalized pneumonia with lobar infiltrate/pleural effusion



Lancet 2005;365:43-52; PIDJ 2007;26:565-71; Lancet 1997;349:1191-7; PIDJ 1999;18:1060-4

VE against pneumonia with lobar infiltrate/pleural effusion and severe/hospitalized pneumonia



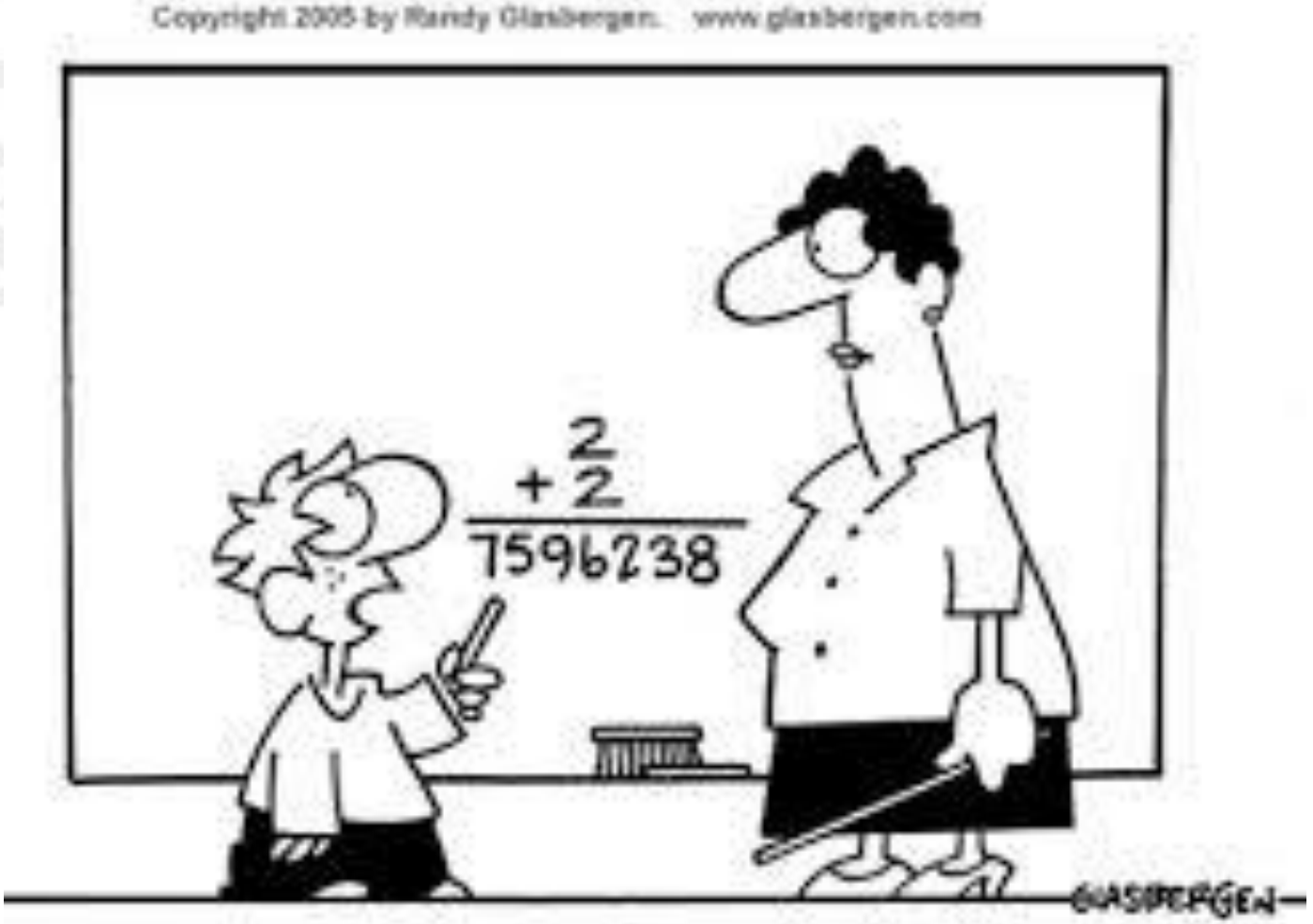
EVEN 5% MAY BE OVERESTIMATION
--STUDIES LIMITED TO AGE 6 WEEKS – 2 YEARS
--HIB LESS COMMON DURING NEONATAL PERIOD

Hib vaccine impact on pneumonia: data points

- Hib vaccine reduces severe/hospitalized pneumonia by approximately 5%
- In some but not all settings this reduction occurs primarily for pneumonia with lobar consolidation/pleural effusion on CXR, a category that constitutes about 20% of all severe/hospitalized pneumonias.

CONCLUSIONS

- Vaccines can and likely do have large effects beyond preventing etiology-confirmed disease in individuals
- Effects often poorly captured
- Areas for improvement:
  - Additional outcome measures
  - Different trial designs
  - Inclusion of clinically defined outcomes
  - Measurement and inclusion of societal benefits
- Many of these topics could be incorporated into licensing trials
- Good data are not good enough
  - Vaccine community must care about fully assessing a vaccine's value
  - Vaccine community should accurately communicate this value
  - Solutions should be found to overcoming misinformation and pre-existing biases



"In an increasingly complex world, sometimes old questions require new answers."