New Vaccine Introduction Decision Making:

Principles, Practices, and Realities

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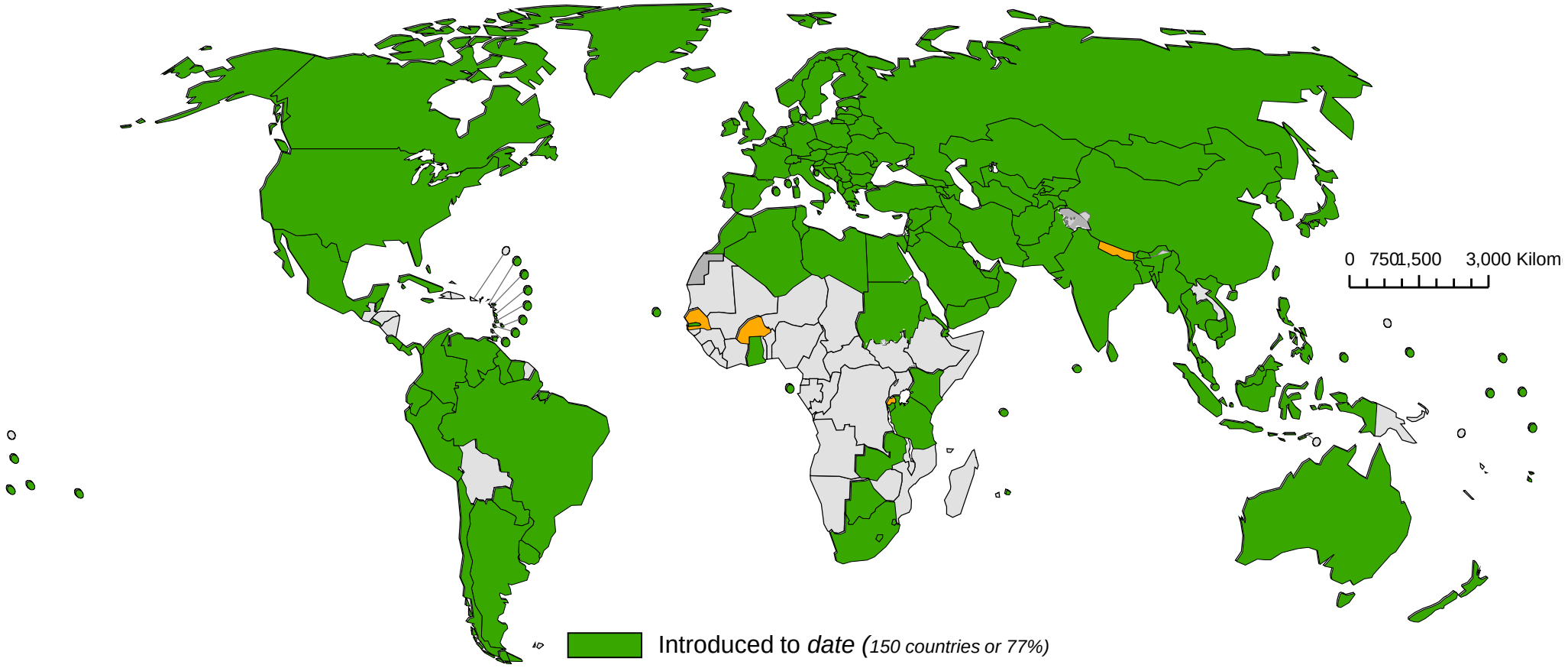
New Vaccine Introduction Decision Making: Objectives of Presentation

- To review and discuss the decision making process for introducing a new vaccine into the routine immunization program or publicly funded health insurance program
- To understand some of the challenges and issues around new vaccine introduction decision making
- To provide some examples of these challenges/issues from around the Globe, with a focus on Indonesia
- To review the status of new vaccine introductions globally (and regionally) to provide some perspective on where we currently are and what has been accomplished

Countries using Measles Second Dose vaccine to date; and planned introductions



Data Source: WHO/IVB Database, as at 29 September 2014

Map production: Immunization Vaccines and Biologicals, (IVB), World Health Organization

Date of slide: 29 September 2014

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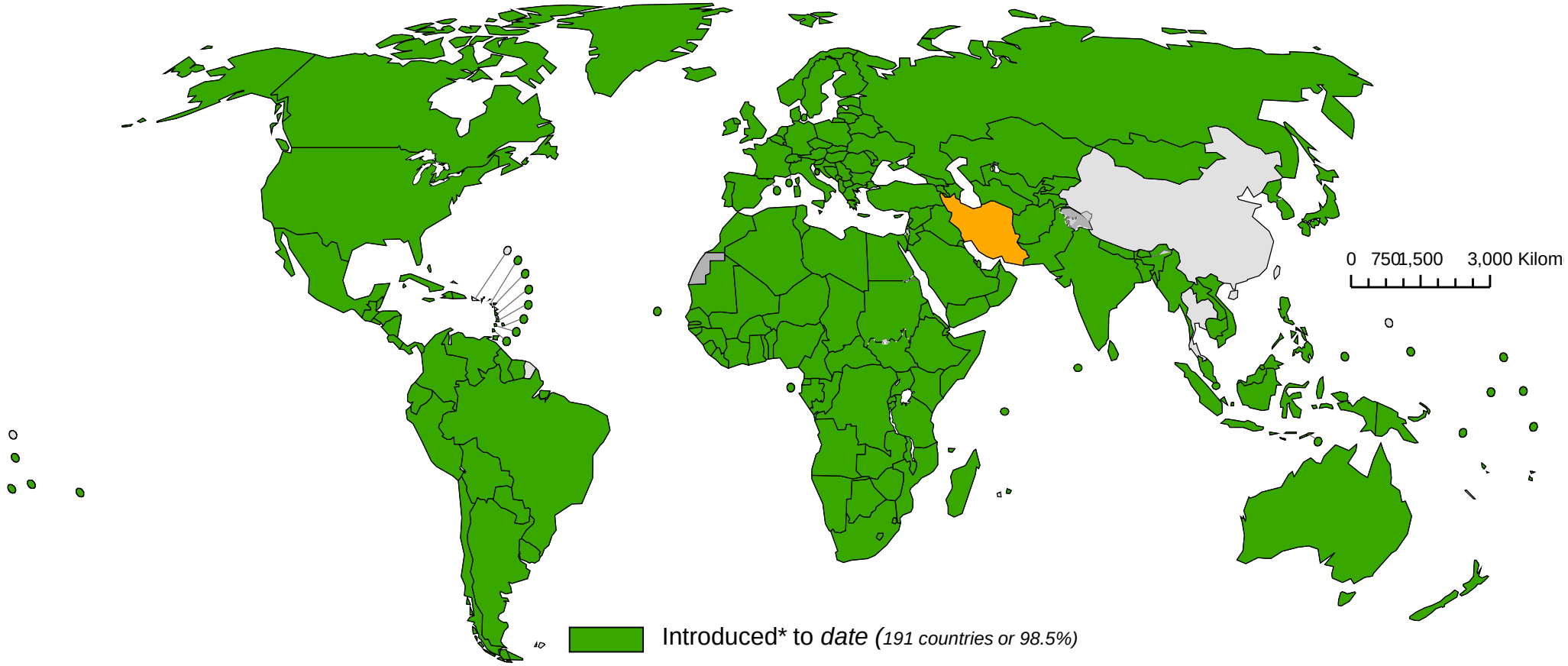
Countries with Hib vaccine in the national immunization programme; and planned introductions



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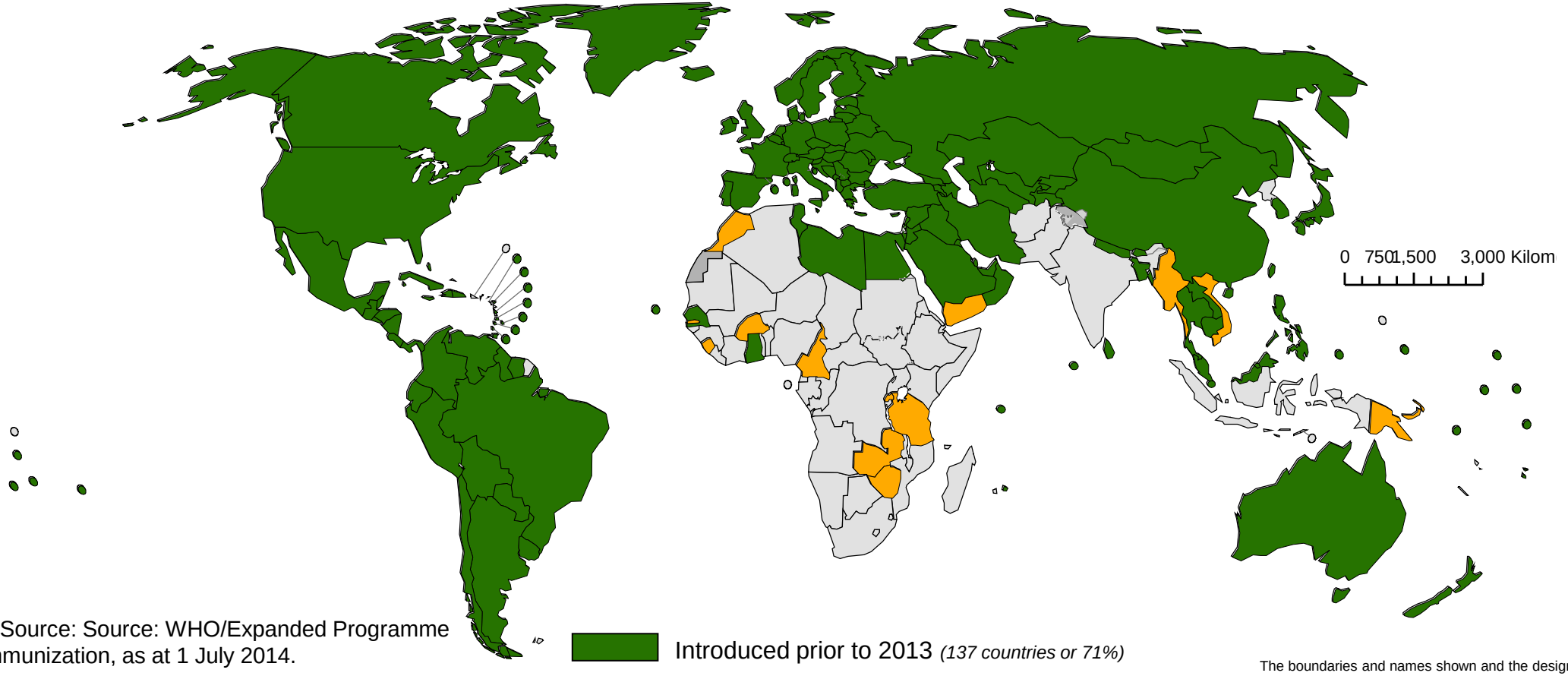
Distribution of countries using rubella vaccine in their routine immunization schedule in 2013 and countries planning introduction during 2014-2015



Data Source: Source: WHO/Expanded Programme on Immunization, as at 1 July 2014.

194 WHO Member States

Map production: Immunization Vaccines and Biologicals, (IVB), World Health Organization

Date of slide: 04 July 2014

- Introduced prior to 2013 *(137 countries or 71%)*
- Introduction planned 2014-2015 *(13 countries or 7%)*
- Rubella vaccine not in the routine schedule or planned before 2015 or data not available *(44 countries or 23%)*
- Not applicable

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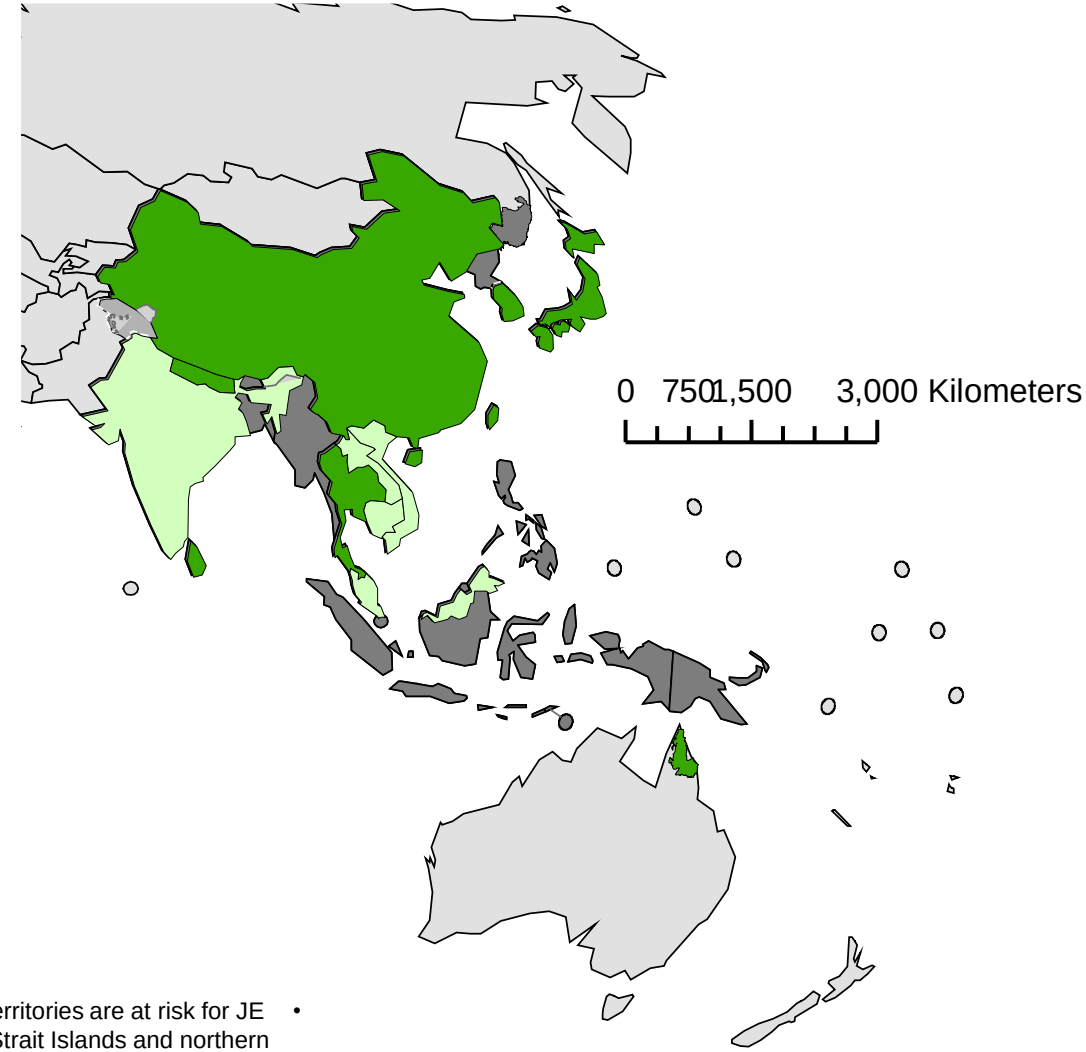
Countries and Territories using JE vaccine to date

- At risk countries/areas but not introduced *(11 countries or 48%)*
- Introduced to *date* *(7 countries/territories or 30%)*
- Introduced in parts of the country *(5 countries or 22%)*
- Not applicable



Data Source: WHO/IVB Database, as at 29 September 2014 and International travel Health Database (http://www.who.int/wer/2013/wer8834.pdf?ua=1)

Map production: Immunization Vaccines and Biologicals, (IVB), World Health Organization

Date of slide: 29 September 2014

- WHO considers that 23 countries/Territories are at risk for JE
- Risk Areas in Australia are: Torres Strait Islands and northern Cape York

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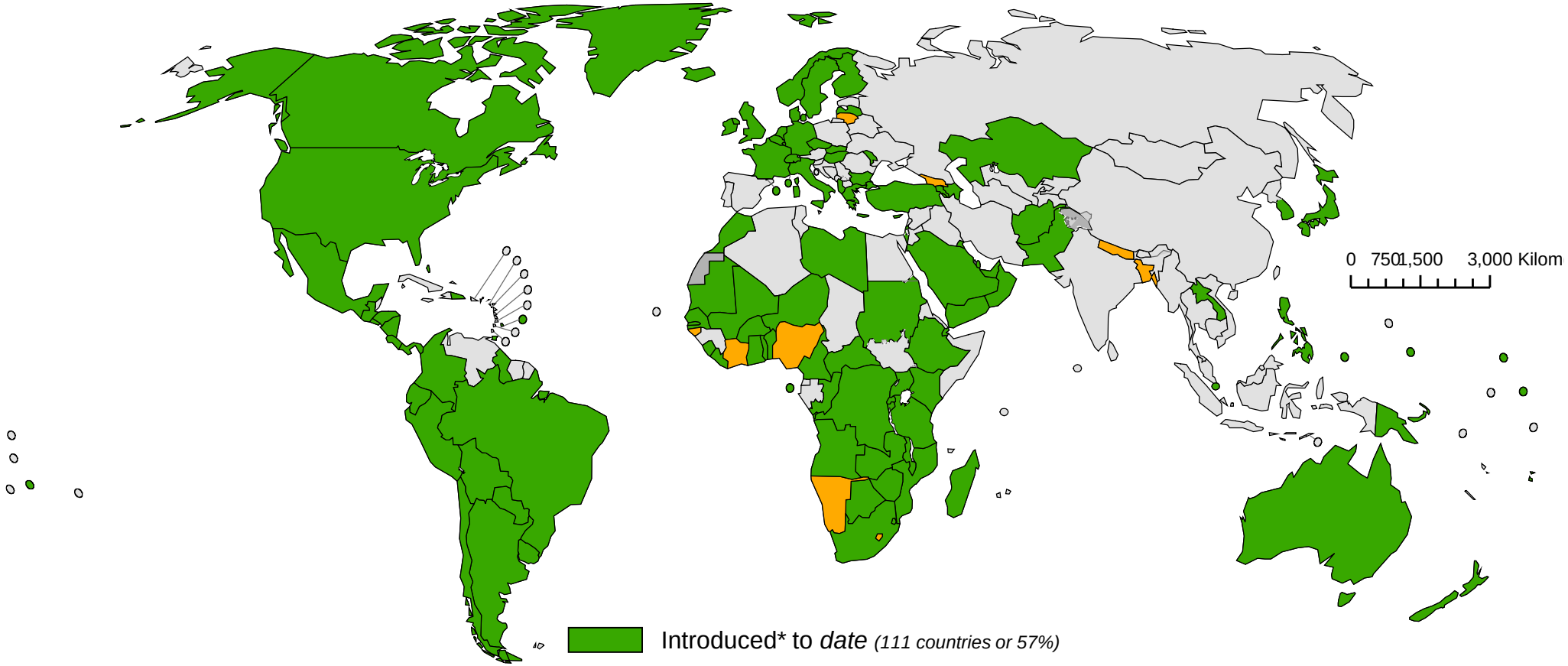
Countries with Pneumococcal Conjugate vaccine in the national immunization programme; and planned introductions in 2014



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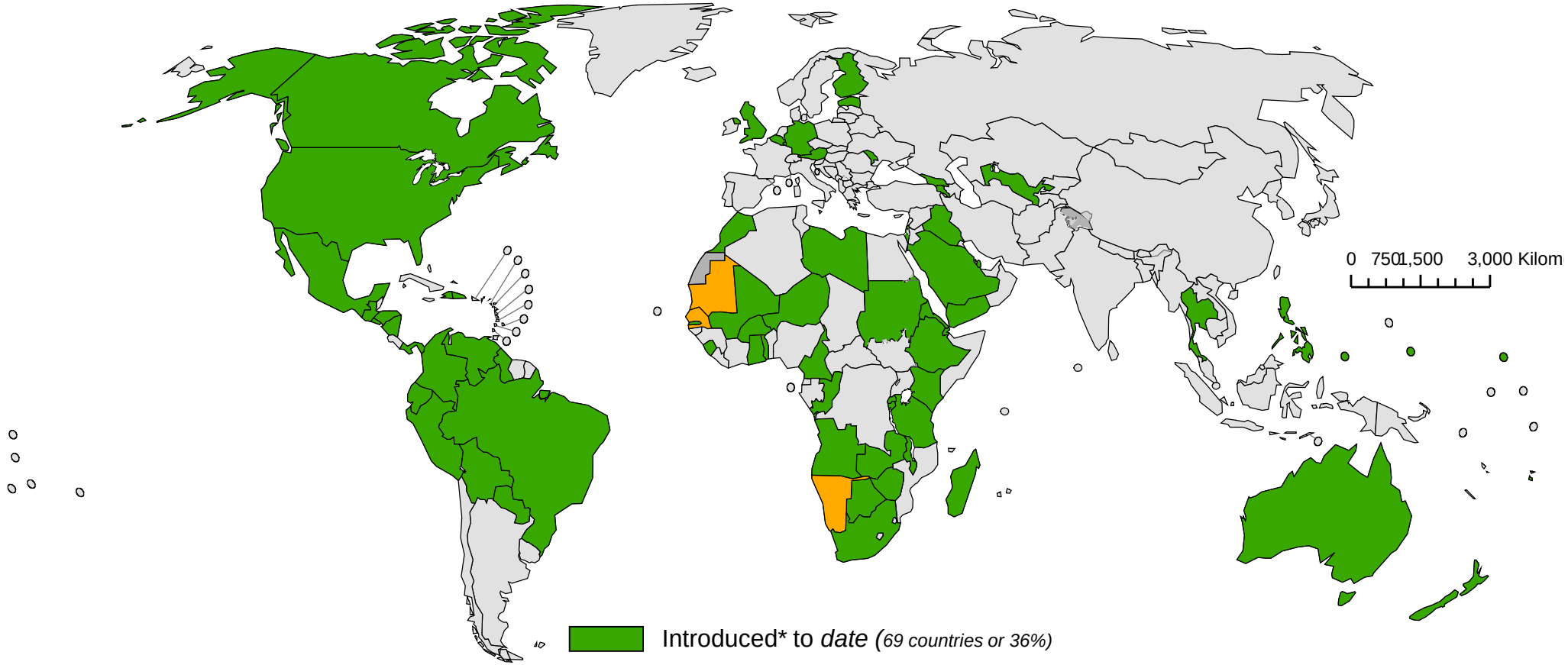
Countries with Rotavirus vaccine in the national immunization programme; and planned introductions for 2014



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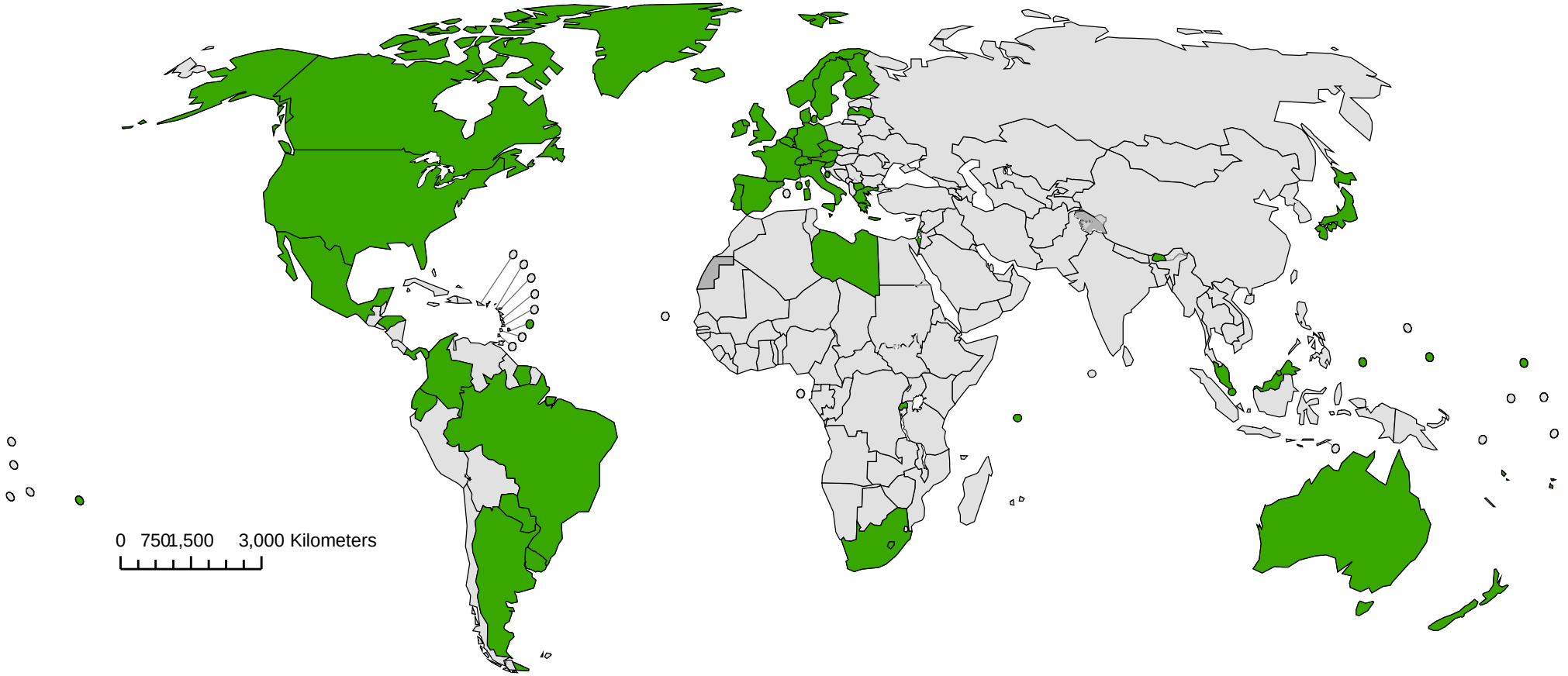
Countries with HPV vaccine in the national immunization programme



Introduced* to *date* (*57 countries or 29%)*

Not Available, Not Introduced /No Plans *(137 countries or 71%)*

Not applicable

Data Source: WHO/IVB Database, as at 29 September 2014

Map production: Immunization Vaccines and Biologicals, (IVB), World Health Organization

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New Vaccine Introduction Scenarios

- Scenario A: all new and efficacious vaccines are introduced on the market in a given country and are covered by the government or private insurance schemes or covered under basic public health services…as long as there is some evidence of vaccine cost effectiveness in some segments of the population

- Scenario B: no new vaccines are introduced in the public sector in a given country unless an outside donor is willing to pay for it for many years to come…since the government does not have the funds nor historical experience to introduce new vaccines on their own.

- Scenario C: Some but not all new vaccines are introduced in a given country in the public sector with or without some donor support …based on perceived need and/or vaccine cost effectiveness

New Vaccine Introduction Decision Making:
Criteria based on baseline pre-vaccine situation

"Burden of Disease"

- Incidence of the Disease among sub-groups of the population (age groups, regions, ethnic groups, etc.)
- Mortality associated with the Disease
- Long term Disability
- Other evidence of Patient Morbidity (hospitalization, absenteeism)
- Family Burden (missed days of work due to caregiving)

Invasive pneumococcal disease as an endpoint

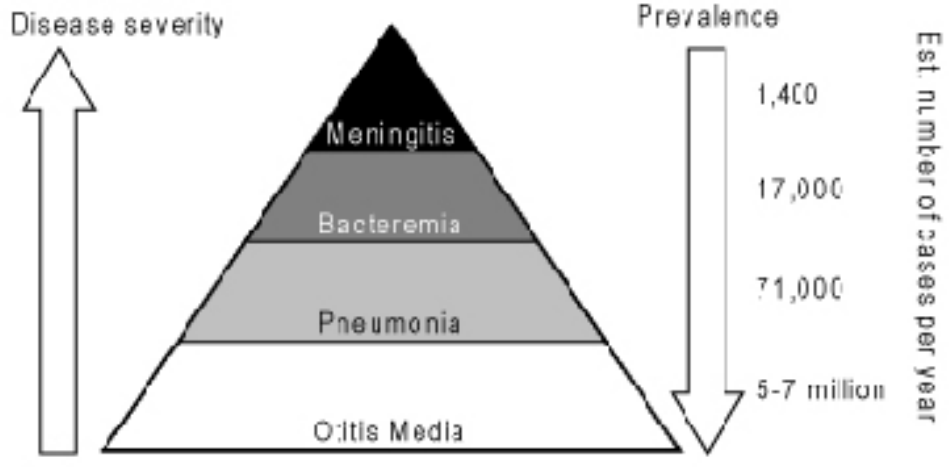
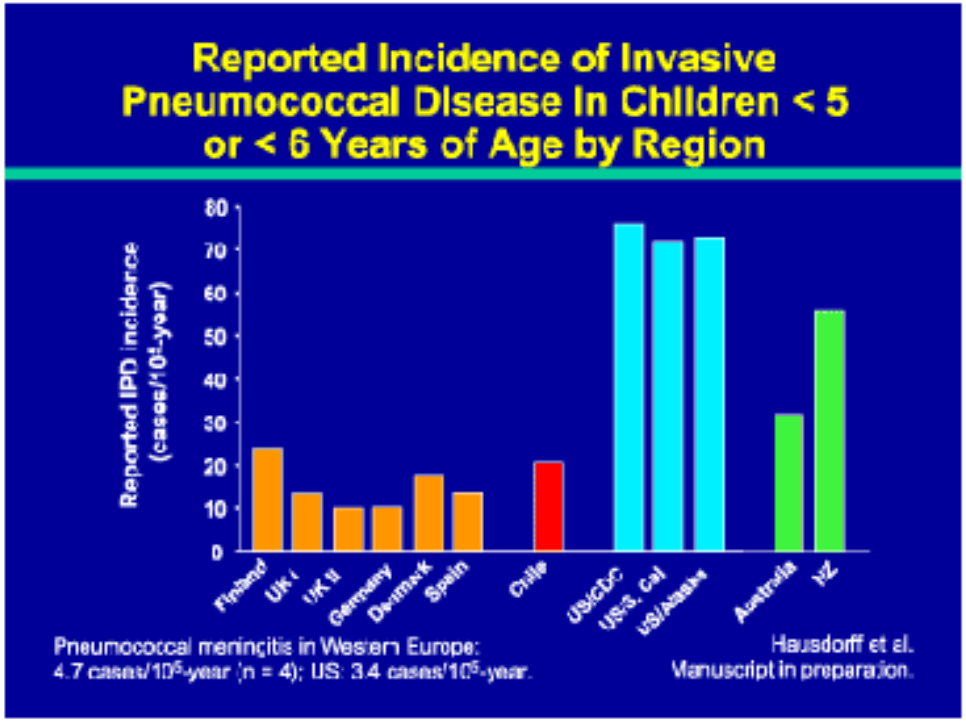
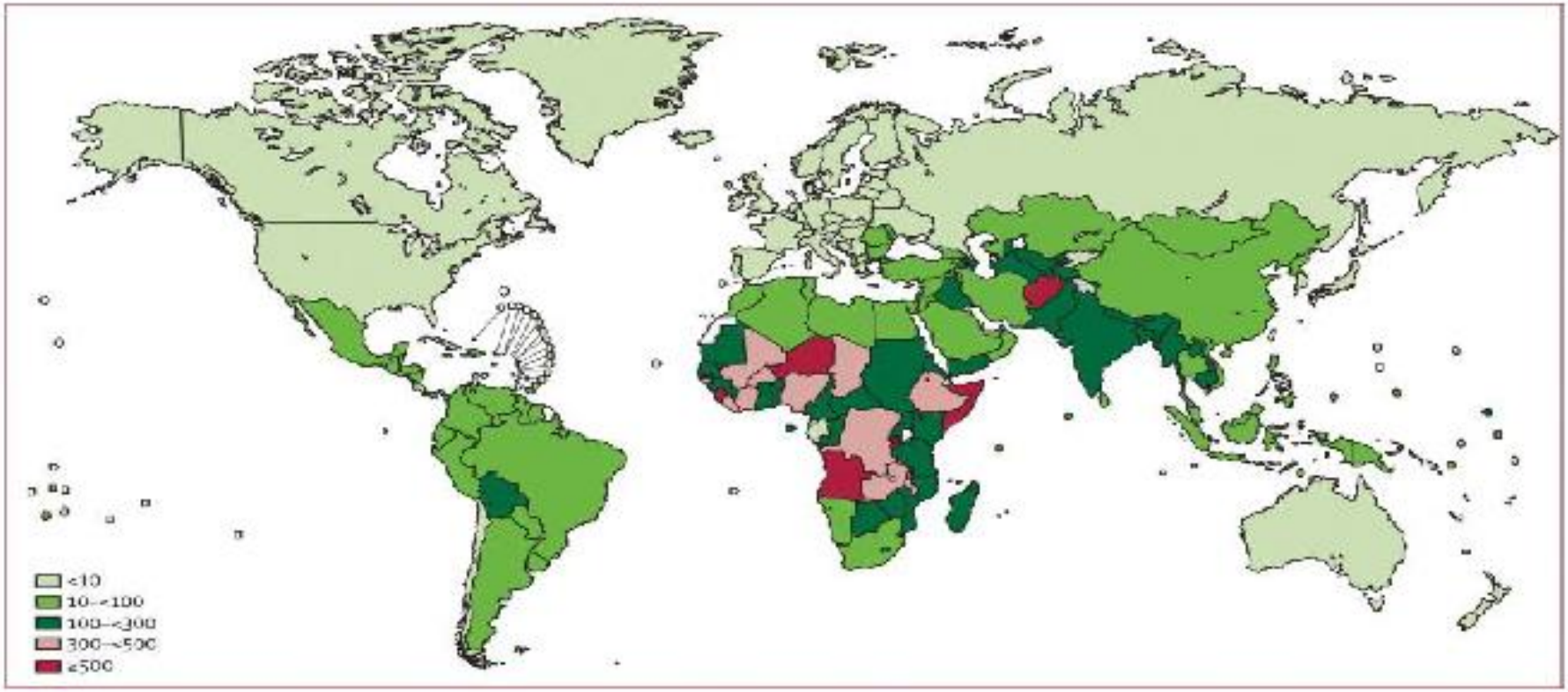


Figure 1. *S. pneumoniae* pathogen with significant disease burden in children in the United States. From Edwards, KM., Pneumococcal Infections: Therapeutic Strategies and Pitfalls. In The Pneumococcus. (2004) ASM Press, Washington, D.C.



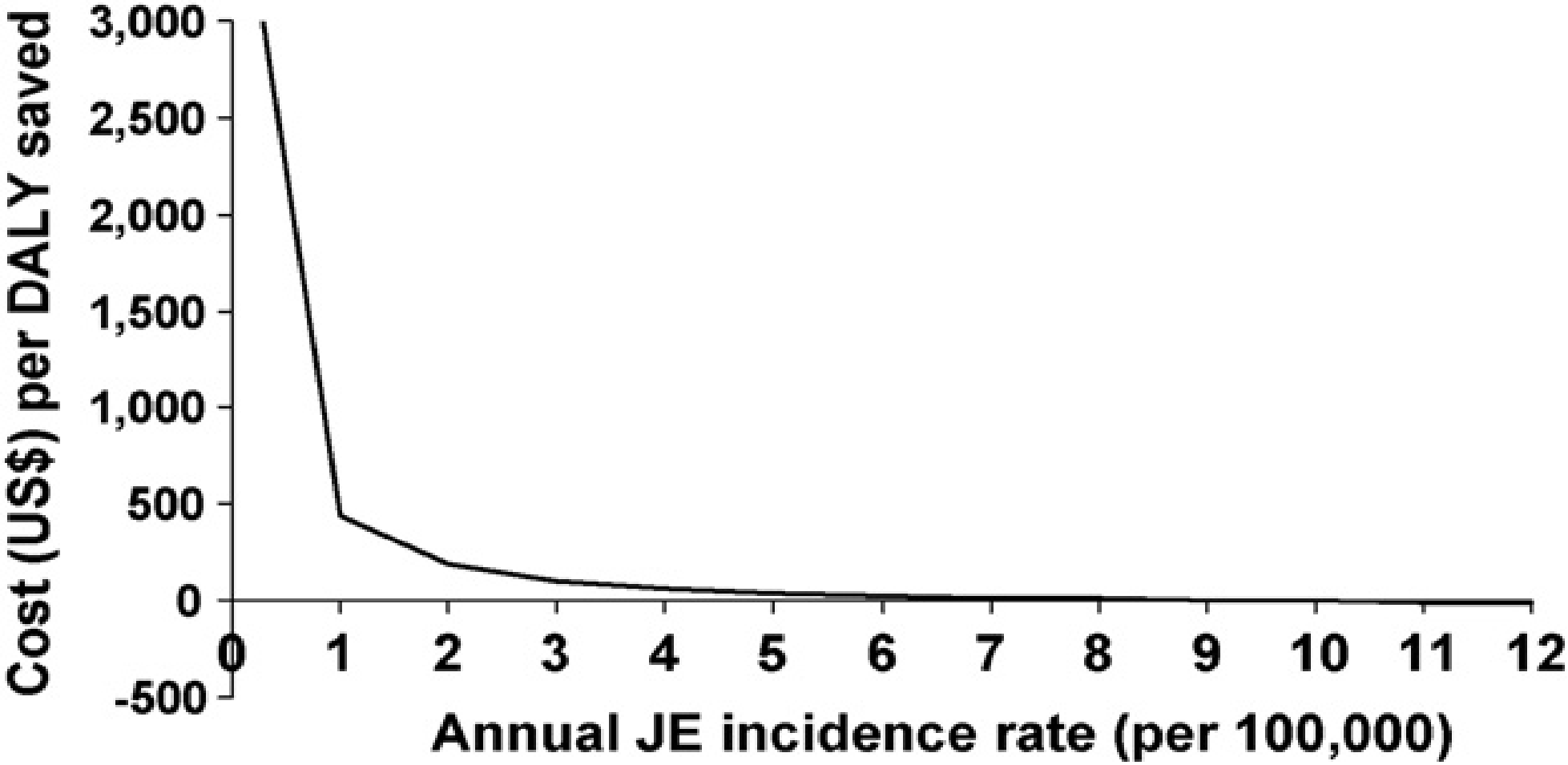
- IPD rare
- Problem compounded when evaluating serotype specific response
- Requires large costly studies

Pneumococcal deaths in children aged 1–59 months per 100 000 children younger than 5 years (HIV-negative pneumococcal deaths only).



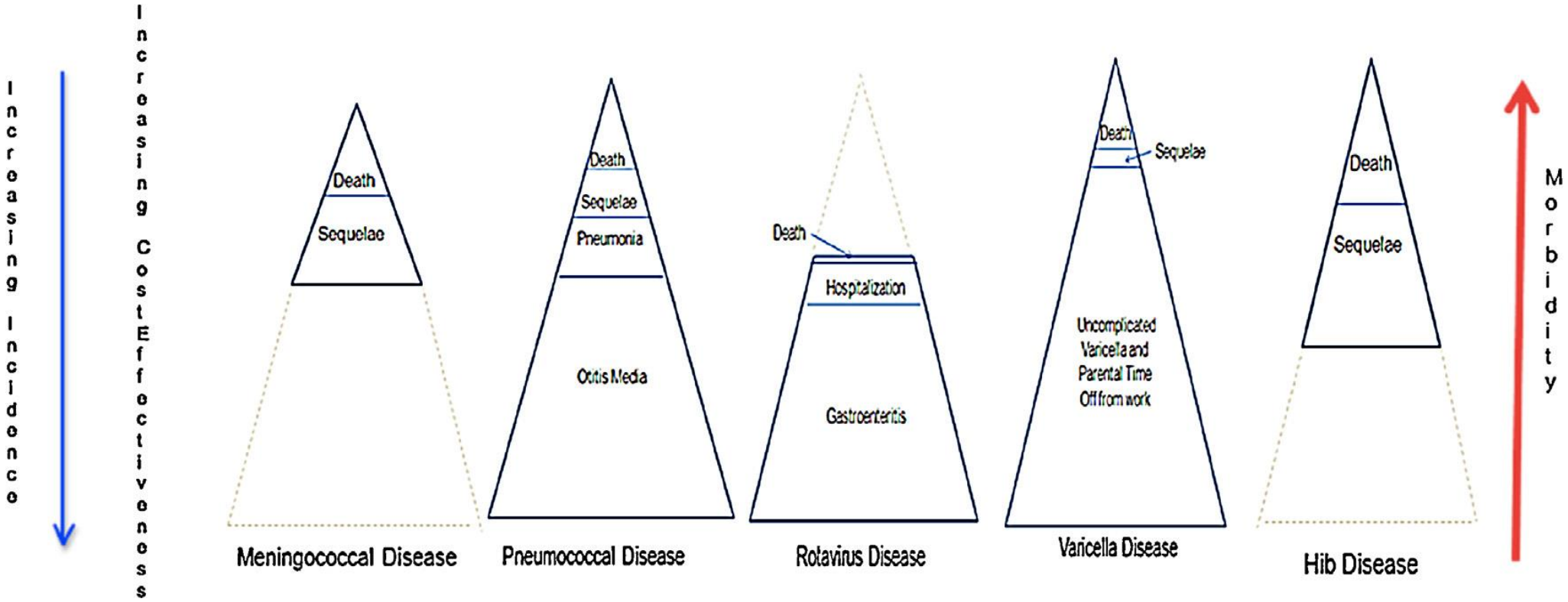
The Lancet Volume 374, Issue 9693 2009 893 - 902

Bali JE Model of DALY saved based on different JE incidence rates



W. Liu et al. / Vaccine 26 (2008) 4456–4460

Comparative disease burden for five vaccine preventable diseases: Annual Events Pre-Vaccine Introduction in US Children and Adolescents



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Estimating "Disease Burden" Practical Considerations

- Most laboratory-based disease surveillance systems underestimate true disease burden by a large margin
- However, some "syndromic surveillance" systems overestimate disease burden since the diagnosis is non-specific
- Conducting "burden of disease" studies in all countries and in each region of large countries is impractical
- What to measure (disease incidence, hospitalizations, deaths, other outcomes) is often difficult to decide

Estimated Measles Case per year in Indonesia

- Risk from 9 months to 6 years (school entry)
  - First dose measles coverage: 82%
  - First dose vaccine effectiveness: 85%
  - Therefore, % of 12 month old infants protected: 70%
  - 30% of 12 month to 6 year old not protected from measles

- 2nd dose measles given in school: coverage 90% of all 6 year olds ….
  - of 30% unprotected, 90% will get the 2nd dose in school and 95% of these will be protected…so **95.4% protected from 6 years to 15 years assuming immunity does not wane**

- What does this mean:
  - Birth cohort 4.8 million…so 1.44 million new children unprotected each year…and stay that way until age 6. If 10% of these unprotected children get measles before age 6, that is **144.000 cases of measles each year under age 6. If 50% get measles before 6, there would be >700,000 cases per year in children 6 years or less.**
  - Measles Campaigns can reduce this number because a 2nd dose is given before school entry
  - Introduction of a 2nd measles dose at 18 months or 24 months will also lower the number of measles cases. The higher the 2nd dose coverage, the more impact it will have

ANALYSIS of Case Based Measles Surveillance Indonesia, 2008-2013

YEAR	Total Susp Cases	Susp cases per 100,000	Total CBMS Cases	% susp Cases Lab tested	Cases			
					Measles	Estimated Total Measles Cases	Negative	Non-Measles Non-Rubella Rate
2008	25,000	10	395	1.6%	1	63	219	0.09
2009	20,000	8	2289	11%	247	2158	1001	0.40
2010	19,111	7.6	3101	16%	668	4117	1673	0.67
2011	23,282	9.3	4694	20%	1175	5828	1711	0.68
2012	**18,798**	**7.5**	**3558**	**19%**	**429**	**2267**	**1561**	**0.62**
2013	**11,288**	**4.5**	**2913**	**26%**	**677**	**2623**	**1293**	**0.52**

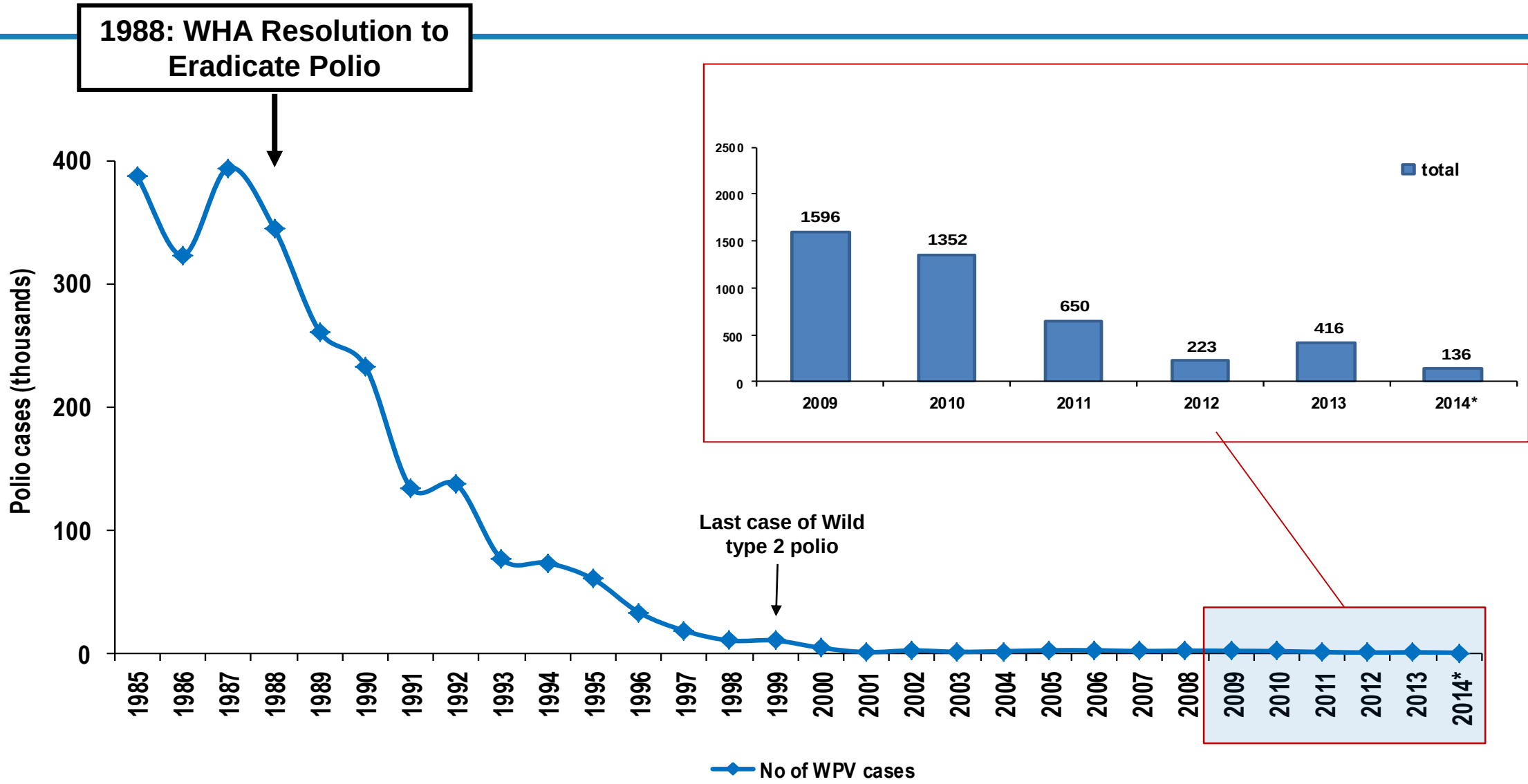
Estimating Burden of Disease using Official Hospital Discharge Data

- Typhoid Fever one of 27 notifiable diseases in Indonesia:
- Using Hospital Discharge data collected by the Bali Province Health Office
  - 1711 reported admissions in all hospitals in Bali in 2013 (public and private) who were widal positive (single test)
  - An additional 2242 reported outpatient cases in hospital OPDs in Bali in 2013 who were widal positive (single test)
  - Total Population of Bali: 4.1 million
  - Overall incidence of widal positive clinical cases in hospital settings in Bali: 105 cases per 100,000 population
- In comparison, there were 11,500 Dengue cases diagnosed in Bali Hospitals with an overall hospitalization rate of 287 per 100,000 population.
- What does this tell us? Can we use this data to estimate the burden of disease and compare various vaccine-preventable diseases?

New Vaccine Introductions Decision Making: Factoring in vaccine efficacy and effectiveness

- Many fantastically beneficial vaccines have modest vaccine efficacy
  - OPV in south Asia (requires 5+ doses to reach 95% efficacy)
  - Influenza vaccine (25-70% efficacy against all flu strains)
  - Typhoid vaccine (approximately 60% efficacy)
  - Rotavirus vaccine
  - Pneumococcal Conjugate Vaccine (since many serotypes not in the vaccine)
  - Pertussis vaccine (both whole cell and acellular)
  - Measles vaccine (efficacy 85% at 9 months of age)
  - Dengue (overall efficacy 56% but reduced Dengue hospitalizations 67% and DHF 81%)

Wild Polio Cases, 1985-2014*



*Source: WHO/Polio database, data as of 18 Aug 2014

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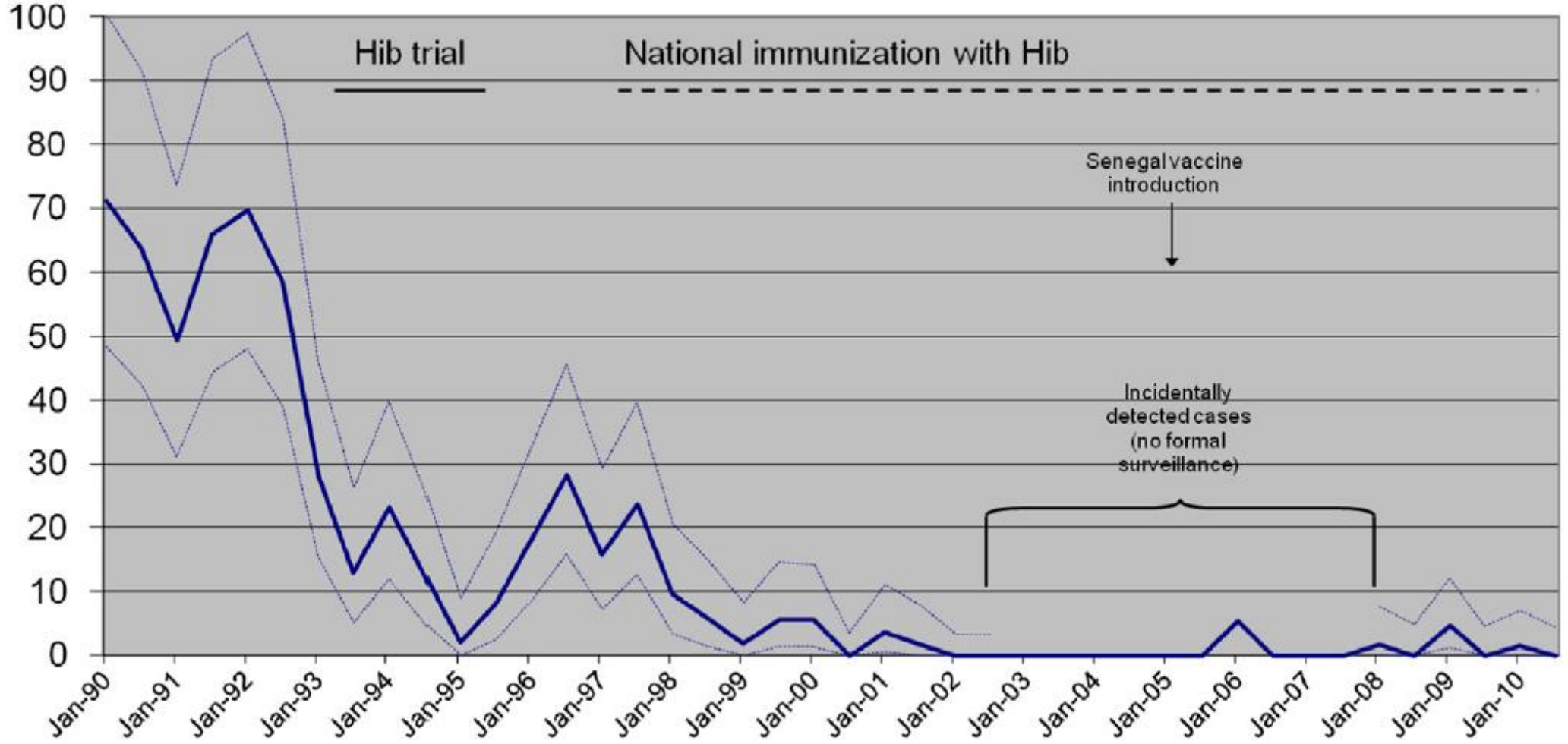
Impact of new vaccines: Hib meningitis in The Gambia



Oluwalana et al J Pediatr 2013;163:S4-7

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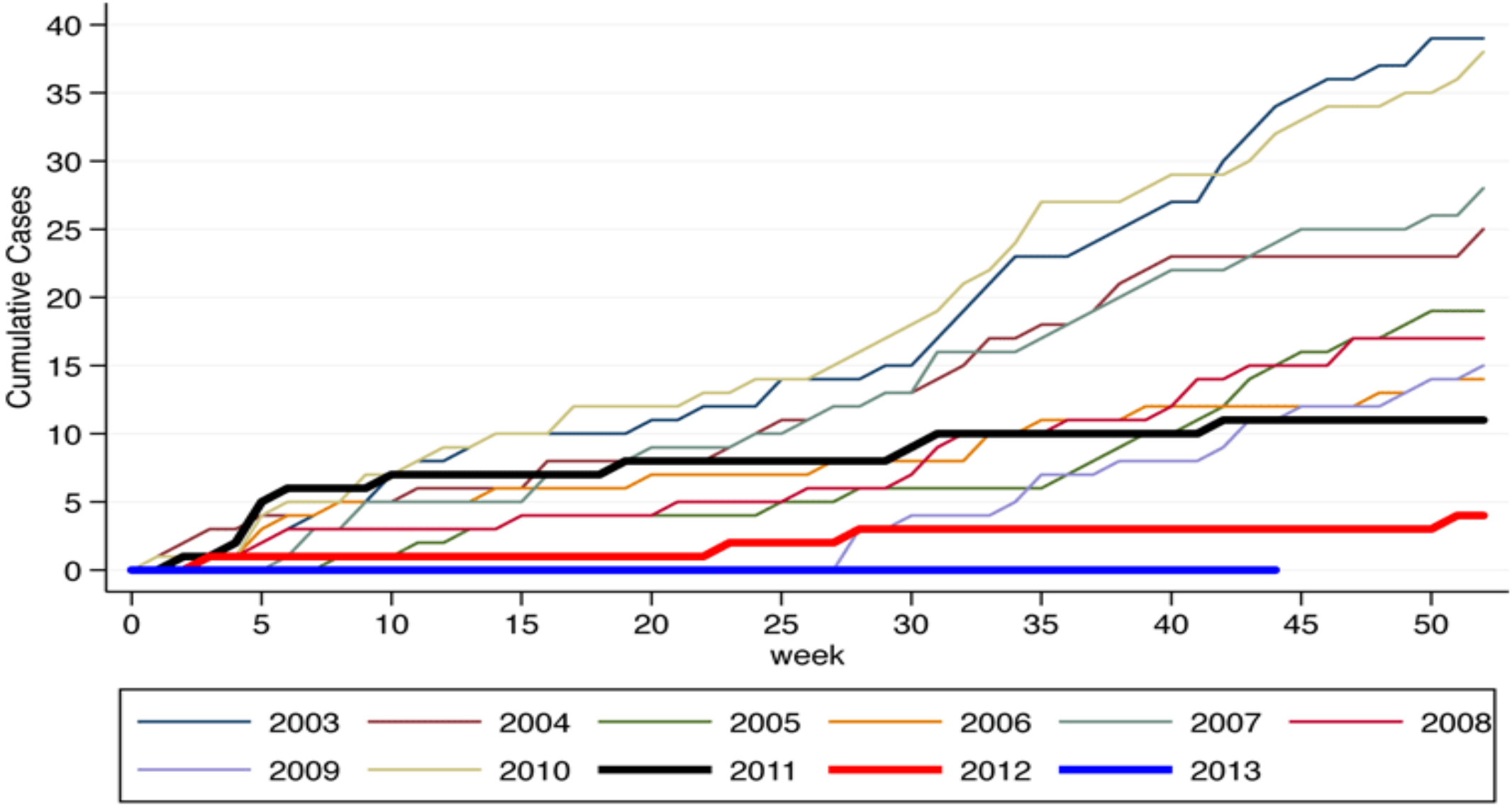
WHO Global Pneumococcal Recommendations

The WHO Recommendations were based in part on the following:

- US Experience after Pneumococcal Vaccine Introduction (PCV-7) given only to infants/children <2 yrs of age
  - 84% reduction in invasive pneumococcal disease among infants (<1 year of age)
  - 75% reduction in invasive pneumococcal disease among children <5 years
  - 52% reduction in invasive pneumococcal disease among adults 20-49 years
  - 27% reduction in invasive pneumococcal disease among adults >60 years
  - Reduction in Populations not receiving the vaccine (i.e., adults) due to "herd effect"
  - 25-30% reduction in radiologically-confirmed pneumonia among children

Cumulative weekly IPD admissions to KDH

PCV10 serotypes among KHDSS residents <5 years of age



Source: http://www.kemri-wellcome.org/index.php/en/studies_inner/75

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Impact of RV on diarrhoea mortality in Mexico and Brazil

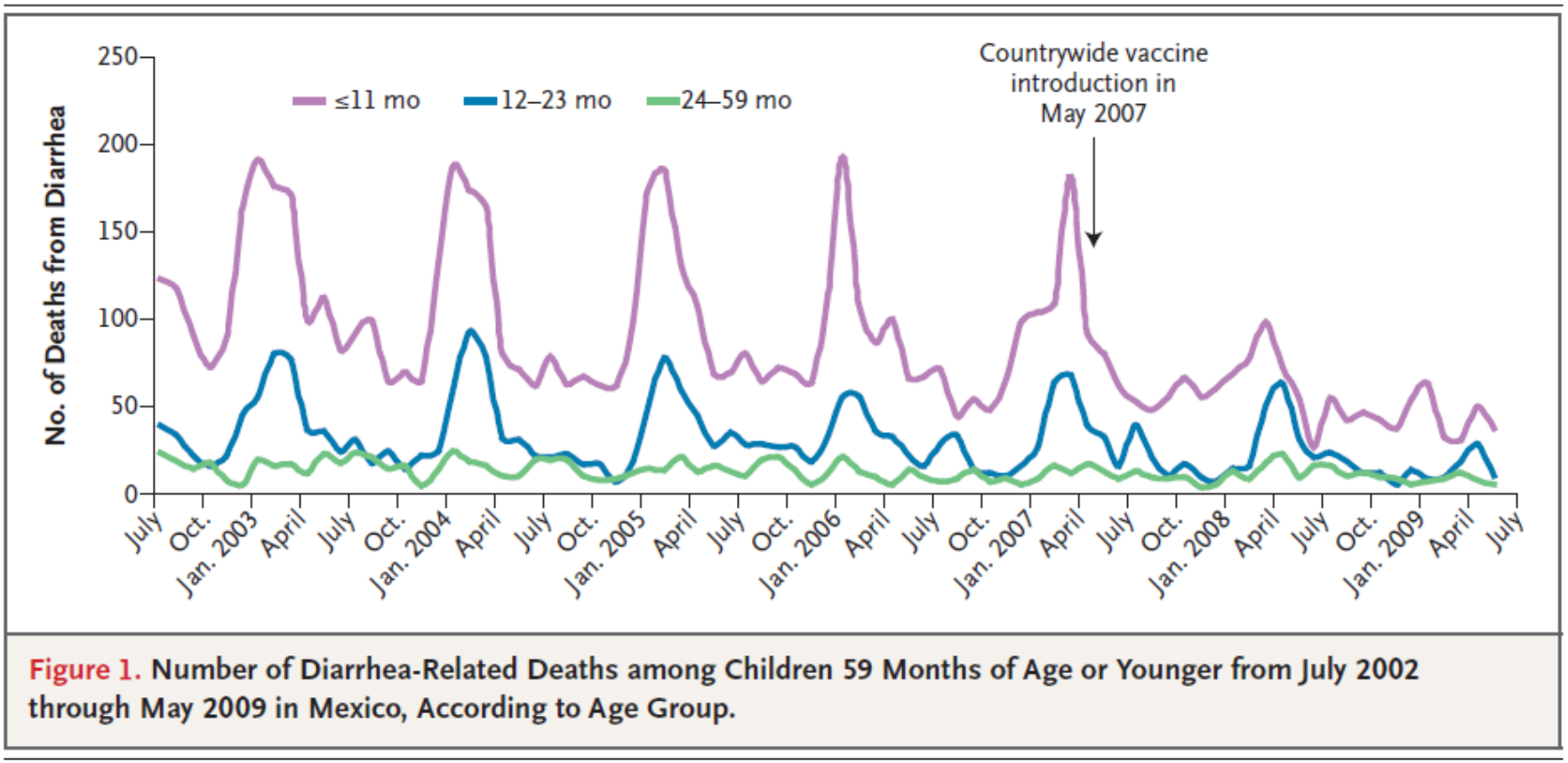

Figure 1. Number of Diarrhea-Related Deaths among Children 59 Months of Age or Younger from July 2002 through May 2009 in Mexico, According to Age Group.

In Mexico and Brazil 35% and 22% reductions in diarrhoea-related mortality, respectively, were observed in children under 5 years, following the introduction of rotavirus vaccine

Richardson et al. NEJM 2010; 362:299; do Carmo GM et al. PLoS Med 2011; 8(4):e1001024

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New Vaccine Introductions Decision Making: Factoring in vaccine efficacy and effectiveness

- Vaccine Effectiveness more important than efficacy because it factors in issues such as vaccine coverage rates, booster dose needs and rates, herd immunity impacts, variations in immune response among different populations
  - However, less effort spent measuring vaccine effectiveness than efficacy especially for new vaccines
  - Requires high quality surveillance data or periodic community health surveys

- Other Vaccine Issues to Consider:
  - Optimal age of vaccination, number of doses required, cold storage requirements, known side effects, need for booster doses, cost of vaccine, etc.

New Vaccine Introductions Decision Making: Other Issues to Consider

Is there any alternatives ways to prevent or treat this disease?

- Yes (but each have their limitations in terms of reach/effectiveness)
  - HPV: cervical cancer screening; reduction in sexual partners/HIV
  - Malaria: vector control, bednets, prompt and aggressive tx
  - Dengue: vector control, mosquito avoidance
  - Rotavirus: ORS, Zinc, good hand hygiene
  - Pneumococcal: prompt diagnosis and antibiotic use
  - Typhoid: Proper sanitation, clean water, rapid diagnosis and tx
- No:
  - Measles, Rubella, varicella, influenza, yellow fever, hepatitis A, Hepatitis B, meningococcal meningitis

New Vaccine Introductions Decision Making: A Closer Look at Vaccine Costs

- Annual Vaccine Cost (remember to factor in the number of doses required to reach the total vaccine cost per person vaccinated)
- Donor Funding Support: None, partial, or full and for how many years?
- Vaccine Introduction Costs: To sensitize communities and train health staff on the new vaccine
- Post Marketing Surveillance for AEFIs
- Up Front Vaccine Investments: Under age 15 years MR vaccine campaign to avoid CRS paradox
- Opportunity Costs: vaccine introductions can crowd out other possible interventions due to limits in the number of staff and amount of time/energy/funds in the Ministry of Health to work on new initiatives
- Return on Investment: vaccines generally offer a good return on investment but how long it takes (i.e., HPV vs Rotavirus) and how noticeable the cost savings are (i.e.,Influenza vs. Rubella) vary quite a lot

Key Indicators of HF

	External (% of THE)	SHI (% THE)	Out-of-pocket (% THE)	THE (per capita US$)	THE (per capita PPP int$)
Malaysia	0·0	0·4	40·7	307·2	604·4
Thailand	0·3	7·1	19·2	136·5	285·7
Philippines	1·3	7·7	54·7	62·6	130·2
Indonesia	1·7	8·7	30·1	41·8	81·0
Vietnam	1·6	12·7	54·8	58·3	182·7
Laos	14·5	2·3	61·7	26·9	83·9
Cambodia	16·4	0·0	60·1	36·8	108·1
Low income	17·5	4·6	48·3	26·8	67·0
Lower middle income	1·0	15·8	52·1	80·2	181·0
Upper middle income	0·2	21·0	30·9	487·9	757·0
High income	0·0	25·6	14·0	4405·2	4145·0
Global	0·2	24·6	17·7	802·3	862·5

Summary of Future Vaccine Introductions in Indonesia

- **Single dose IVP** at 6 months of age: Late 2015 or early 2016 based on GAVI funding support.
- **Measles-Rubella (MR) vaccine and National MR Campaign 6 months to 15 years**: 2017-2018 when Biofarma MR vaccine ready
- **JE vaccine** (as an under 10 year or under 15 year campaign) in 1-5 provinces (Bali, West Kalimantan, NTB, NTT most likely): 2016/2017 depending on MoH leadership and some donor funding support and advocacy
- **New Biofarma Rotavirus vaccine**: Likely 2019 but depends on results of current Phase 2b/3 trial and increase in annual immunization budget
- **Pneumococcal** (Whole cell vaccine by Biofarma or PCV purchased globally): Likely 2017-2020 depending on efficacy of new whole cell vaccine, results of possible PCV probe study
- **Influenza Seasonal Vaccine**: Not an EPI priority but could be introduced for high risk groups and Health care workers by other sections of MoH or thru UHC or thru PPP
- **Dengue Vaccine, HPV vaccine, Typhoid Vaccine: ???**

Comparison of Potential New Vaccines for Indonesia

Vaccine	Rotavirus	PCV	HPV	Rubella	Influenza	JE	Dengue
Affected Age Group/Pop	Infants and child <5 yr	All, especially <5 years	Adult Women	Infants	All	Children Some regions?	All, especially children
Mortality	++	+++ ?	+++	++	+++	++	+
Disability	+	++ ?	+	++++	+	+++	+
Hospitalized	+++	++ ?	+	+	+++	++	+++
Other control strategies	Yes, minimally effective	Partially yes	Not really	No	No	Not really	Partially yes
Vaccine effectiveness	60% ??	??	>80%	95%	50% ?	90%	50-80% ?
Other key vaccine factors	Large cold chain need	3 doses	Given to teens	MR SIA required	annual	Many vaccines	Optimal age not clear
Costs	++/+++	+++	++++	+ SIA +++	+++	+/++	?

New Vaccine Introductions Decision Making: Looking Back at Why Vaccines Introduced

- Japanese Encephalitis: Response to outbreaks (fear)
- Inactivated Polio: Global Eradication Initiative
- Influenza: Pandemic preparedness; health insurance schemes
- Pneumococcal: MGD goal to reduce Infant mortality rate
- Rotavirus: Reduce infant hospitalizations (cost savings); MGD goal to reduce infant mortality rate
- Rubella: Global Measles/Rubella elimination goals; Advocacy groups; Pediatrics Associations
- Dengue: frequent outbreaks; clinician and community interest
- HPV: Cancer control sections of MoH and advocacy groups

New Vaccine Introduction Decision Making

Thank You !

Questions?