THE ROLE OF DISEASE BURDEN IN THE DECISION MAKING PROCESS: THE HIB VACCINE EXPERIENCE

Brad Gessner, MD
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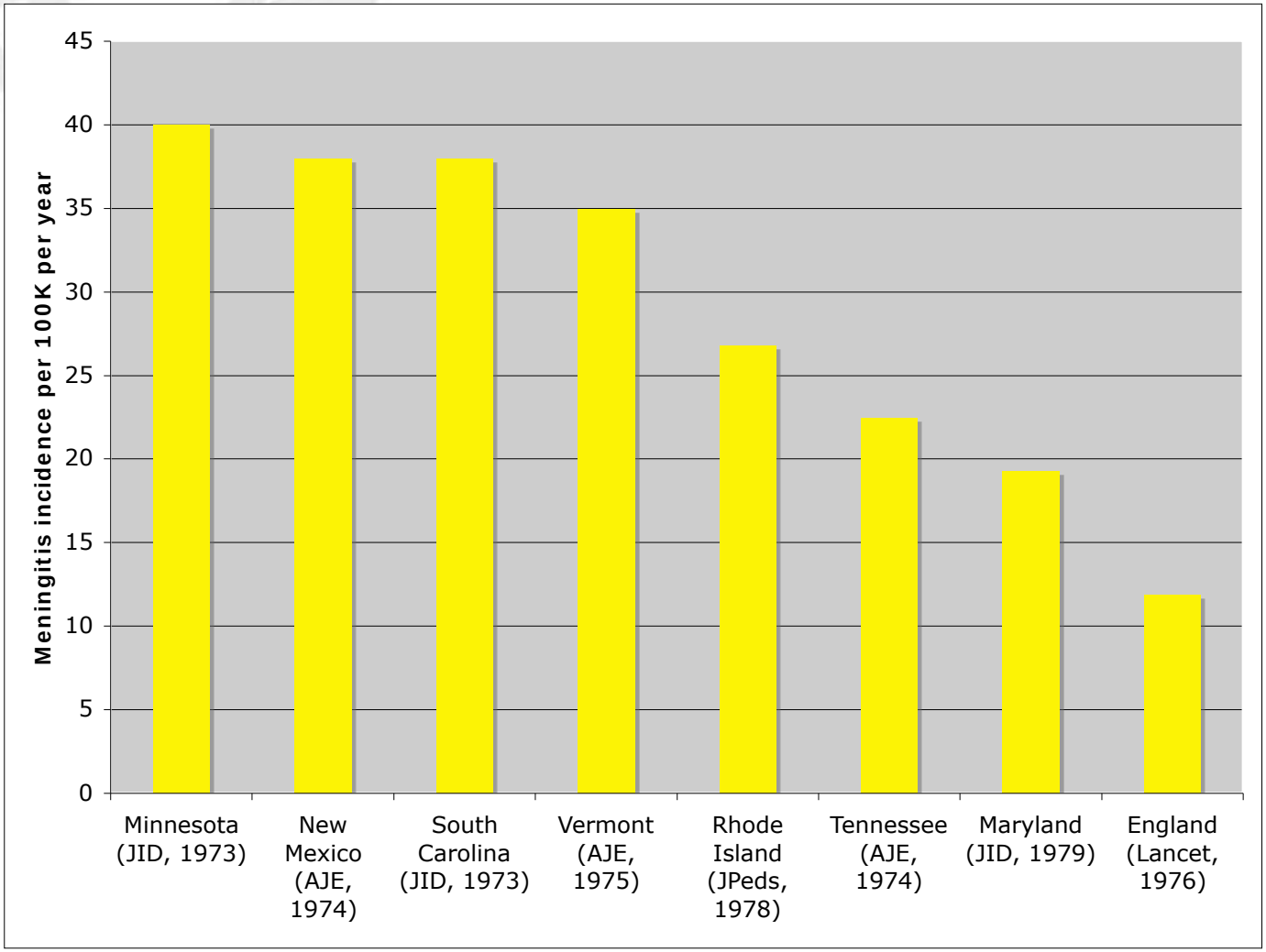
INDUSTRIALIZED COUNTRIES

1970s: Hib incidence from hospital based surveillance in the US/England



- Eight studies in 1970s, all but one in US
- High incidence
- 1 in 200 to 500 with invasive Hib disease
- Many sequelae
- High CFR

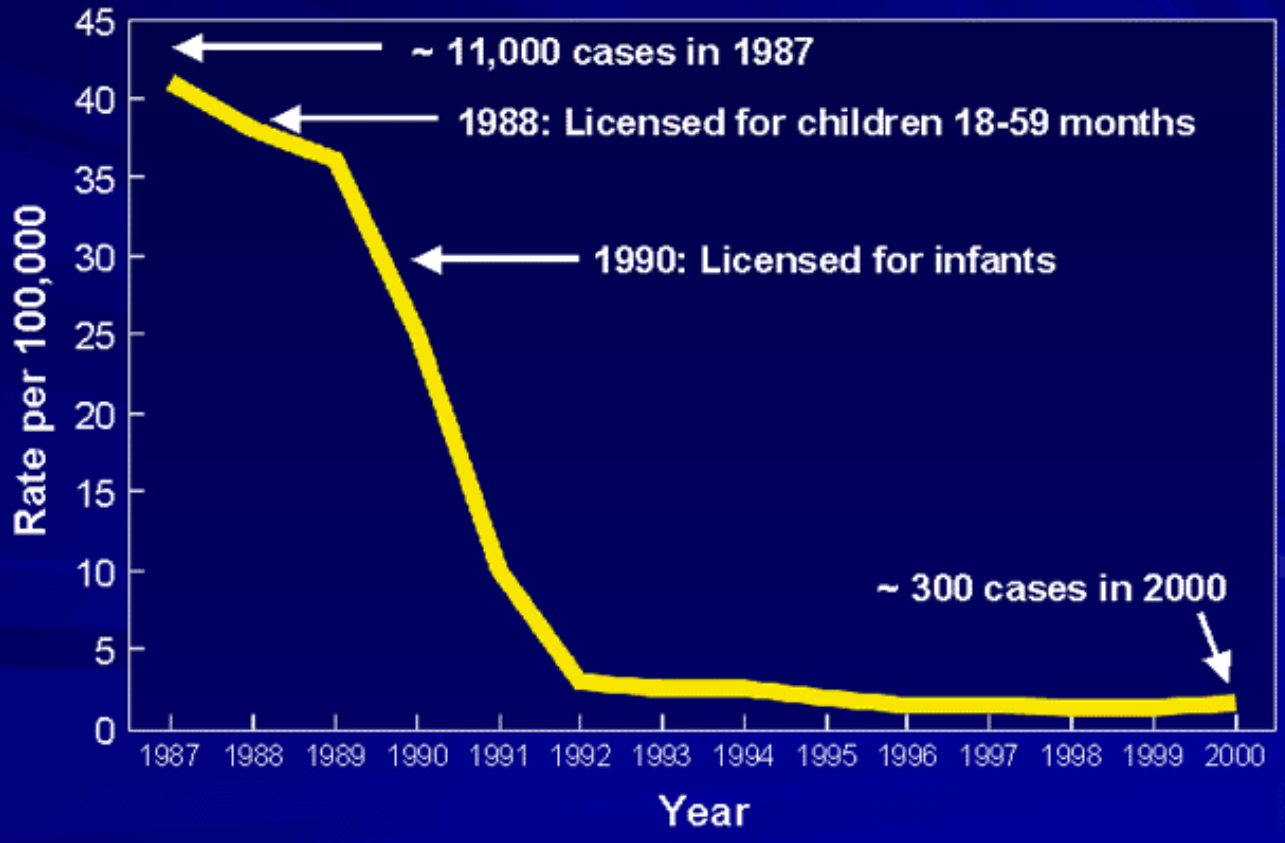
ACIP Recommendation Introduction

Haemophilus influenzae type b (Hib) is the leading cause of invasive bacterial disease among children in the United States. Before effective vaccines were introduced, one in 200 children developed invasive Hib disease by the age of 5 years. Sixty percent of these children had meningitis; 3%-6% died. Permanent sequelae, ranging from mild hearing loss to mental retardation, affect 20%-30% of all survivors of meningitis. Ninety-five percent of the cases of invasive H. influenzae disease among children less than 5 years of age are caused by organisms with the type b polysaccharide capsule. Approximately two-thirds of all cases of Hib disease affect infants and children less than 15 months of age, a group for which a vaccine has not previously been available.

MMWR 1991; 40(RR01):1-7

Reducing Invasive Haemophilus Influenzae Disease with Hib Vaccine

(developed by NIH-funded scientists)

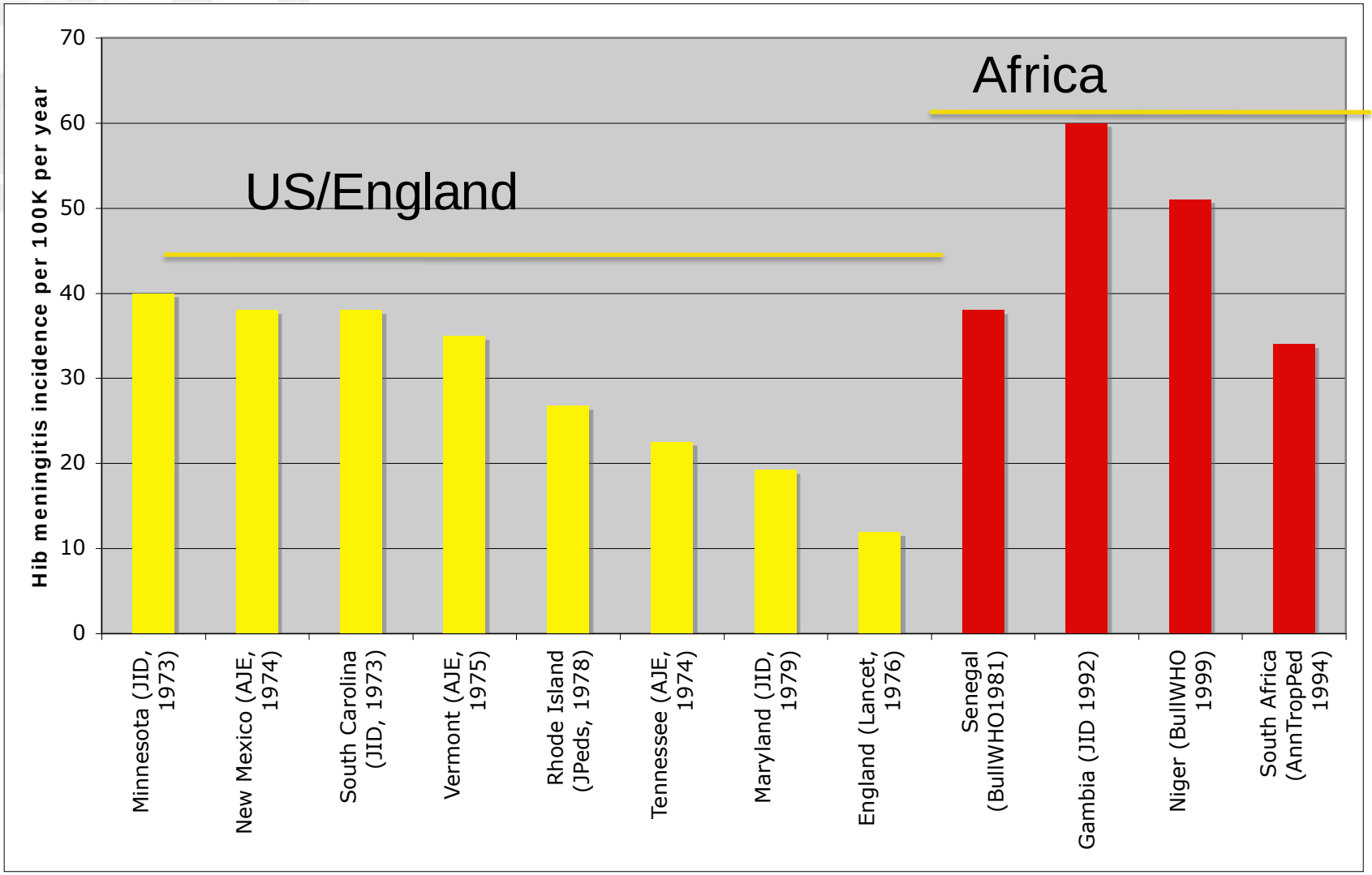


Summary

- Where
  - disease is perceived as common and severe
  - occurs in wealthy countries with robust decision making processes
  - vaccine widely accepted
- Burden based on surveillance data alone may be sufficient to motivate
  - research and development
  - NITAG recommendations
  - universal vaccine introduction
  - provider vaccine acceptance

SUB-SAHARAN AFRICA

Pediatric Hib meningitis incidence



Difficulties

- Relativity matters
  - "Common" is relative
  - Cost is relative
- Pneumonia more important problem
  - Hib known to be a cause of pneumonia
  - But…
    - Great majority non-bacteremic
    - Lung puncture, trans-tracheal aspirate not available in most of Africa

The Gambia Hib RCT

Lancet 1997;349:1191-7

	PRP-T	Control	Vaccine preventable proportion
Severe pneumonia	873	913	4.4%
Radiologically defined	198	251	21.1%
Lobar pneumonia	86	115	25.2%
Hypoxic pneumonia	36	40	10.0%

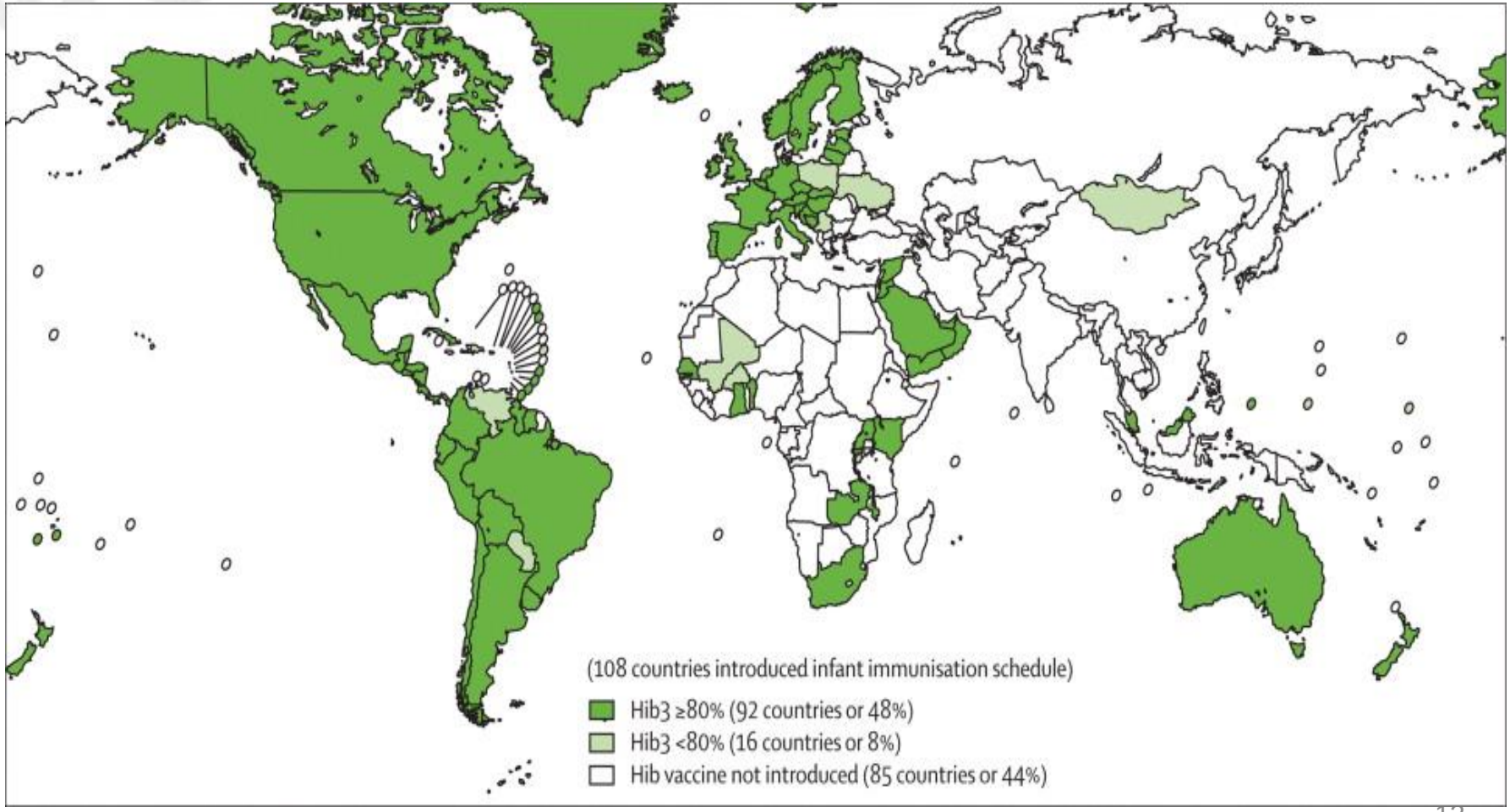
AS OF 2000, AND OTHER THAN SPECIAL CASE OF THE GAMBIA, SOUTH AFRICA WAS THE ONLY SUB-SAHARAN AFRICAN COUNTRY USING HIB VACCINE

International developments

- GAVI
  - 2000: Launch
  - 2001: First countries to introduce Hib containing pentavalent vaccine with GAVI support
- WHO, 1998 position statement (WER, 1998, 61-73):

In view of the demonstrated safety and efficacy of the Hib conjugate vaccines, Hib vaccine should be included, as appropriate to national capacities and priorities, in routine infant immunization programmes. In geographical regions where the burden of Hib disease is unclear, efforts should be made to evaluate the magnitude of this problem.

Hib Vaccine Use in 2006



Summary

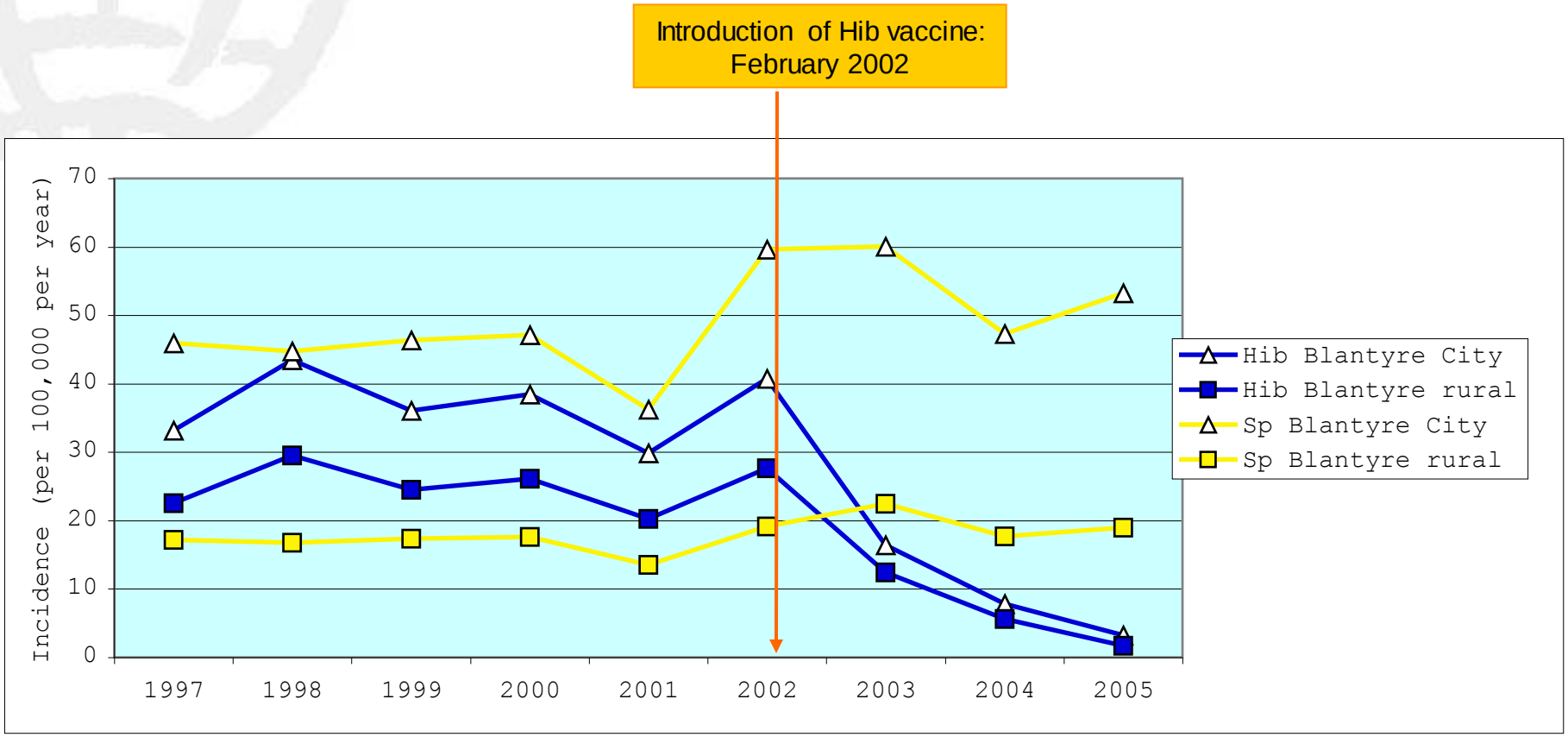
- Disease burden data can motivate international community, including mobilization of financial support
- BUT:
  - where national decision making processes are weak and
  - poor communication of burden data occurs
  - financing and disease burden data may not lead to vaccine use

International developments

GAVI ALLIANCE

Saving children's lives and protecting people's health by increasing access to immunisation in poor countries

Malawi: trends in Hib and *Streptococcus pneumoniae* (Sp) meningitis incidence

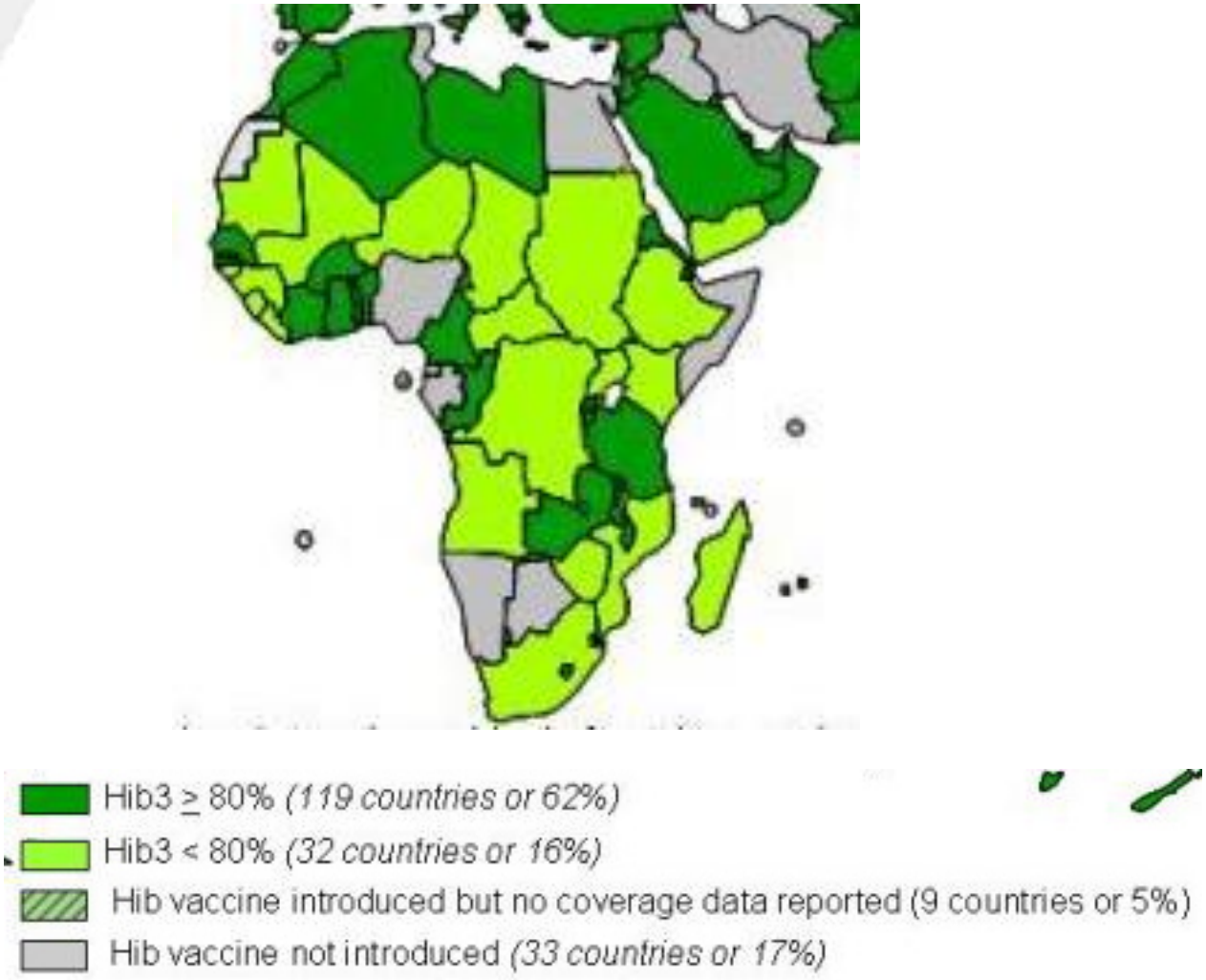


- Data provided by PBM Network, WHO-Malawi and Queen Elizabeth Hospital, Blantyre, Malawi
- Vaccine 2006;24:6232-9.

- 2006: “In view of their demonstrated safety and efficacy, conjugate Hib vaccines should be included in all routine infant immunization programmes. Lack of local surveillance data should not delay the introduction of these vaccines, especially where regional evidence indicates there is a high burden of disease.”

Hib vaccine introduction (and infant Hib coverage, 2009)

Source:
WHO/UNICEF



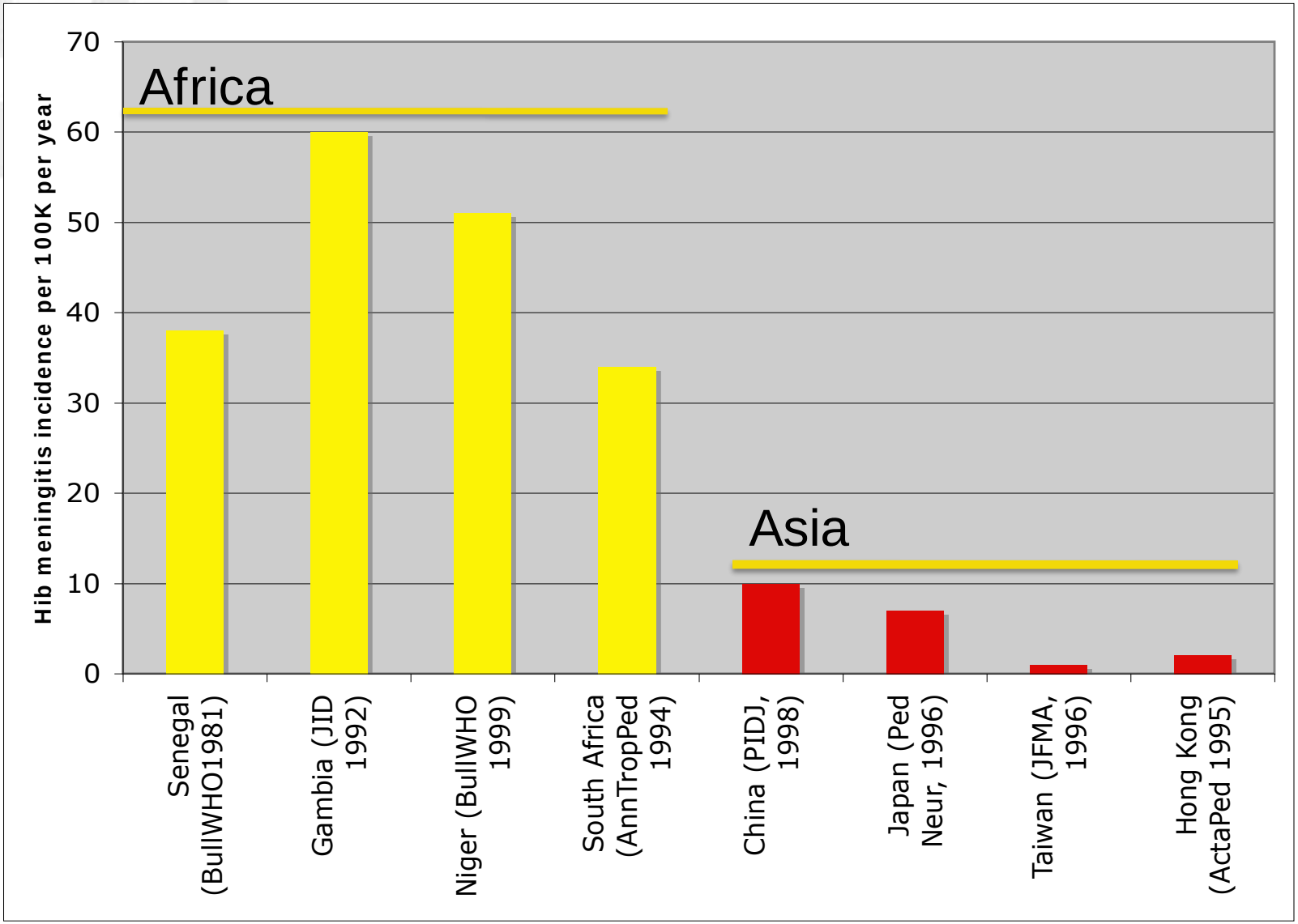
Summary

- Where
  - Financing exists
  - Resources exist to access financing
  - Social marketing and advocacy occur
  - The international community is united
  - Vaccine acceptance is high

- Robust burden data ⇒ vaccine introduction
  - Even in the absence of robust decision making processes

ASIA

Surveillance data up to 1998



Summary statement: The First International Conference on Hib infection in Asia: 1996

- "The incidence and burden of Hib disease in Asia are not yet well-defined."
- "Countries considering implementation of Hib immunization into their routine childhood immunization programs should examine the burden of disease and the costs of vaccine and its provision, to determine the impact on resource availability for health care in contrast with the benefits from the prevention of Hib-related diseases. In planning introduction of Hib immunization, early liaison with manufacturers…is essential."

Salisbury, PIDJ, 1998

Vaccine probe study

- An approach, not a method
  - Conceptually, evaluates an aspect of disease rather than vaccine
  - Ideally RCT
- Main outcome: vaccine preventable disease incidence (vaccine attributable rate reduction)
  - Equals: $Incidence_{control}$ - $Incidence_{intervention}$
  - Equivalent: VE * $Incidence_{control}$

Lombok, Indonesia trial: meningitis data

Lancet 2005;365:43-52

	Prevented proportion	Control group incidence*	Vaccine preventable disease incidence* (95% CI)
Confirmed Hib (n=7)	86%	19	16 (1.4 to 31)
Probable bacterial meningitis (n=47)	55%	86	47 (13 to 81)
Possible bacterial meningitis (n=76)	50%	134	67 (22 to 112)
Lumbar puncture (n=229)	26%	346	89 (10 to 167)
Meningitis hospitalization or clinic seizure assessment (n=467)	22%	701	158 (42 to 273)

***per 100,000 person-years**

.

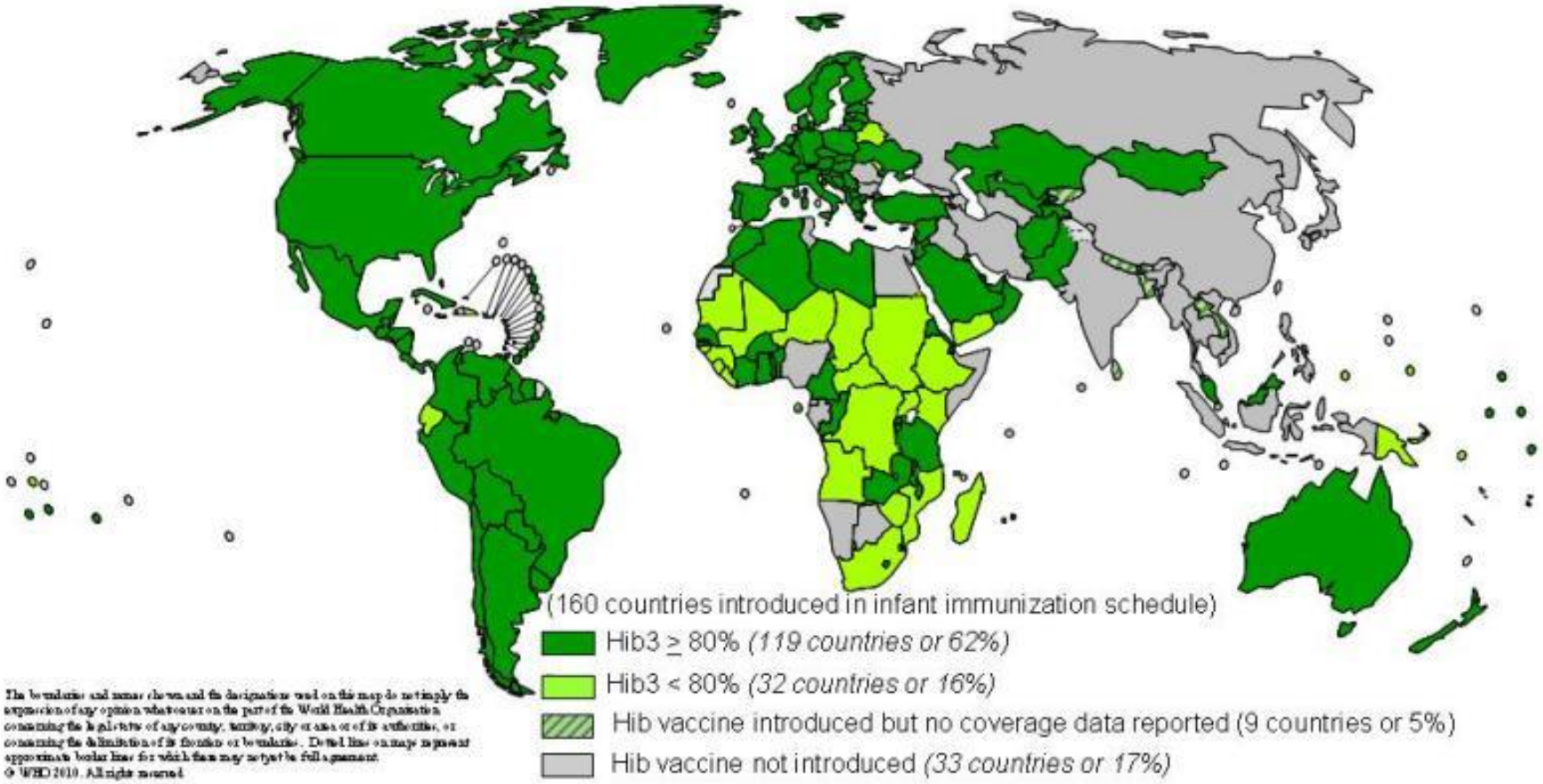
International developments

GAVI ALLIANCE

Saving children's lives and protecting people's health by increasing access to immunisation in poor countries

World Health Organization

Countries having introduced Hib vaccine and infant Hib coverage, 2009



Source: WHO/UNICEF coverage estimates 1980-2009, July 2010-Date of slide:27 July 2010

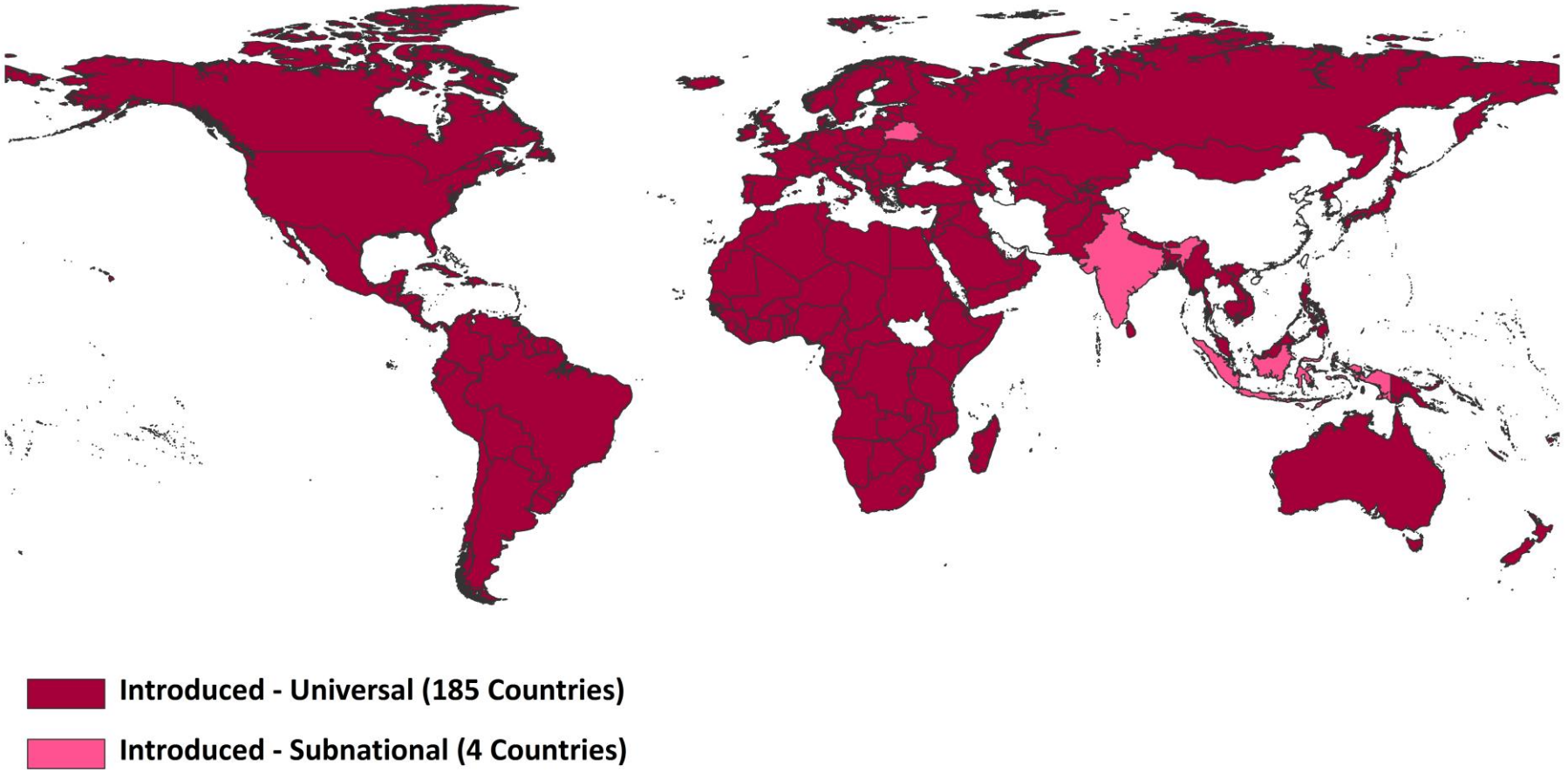
Regional developments

- Existing well-functioning NITAGs
  - 1970: Thailand
  - 1982: China
  - 1992: Republic of Korea
  - 2001: India
- New Hib conjugate vaccine producers
  - Three in India (one joint venture with Indonesian producer)
  - One Republic of Korea
  - Two domestic producers in China

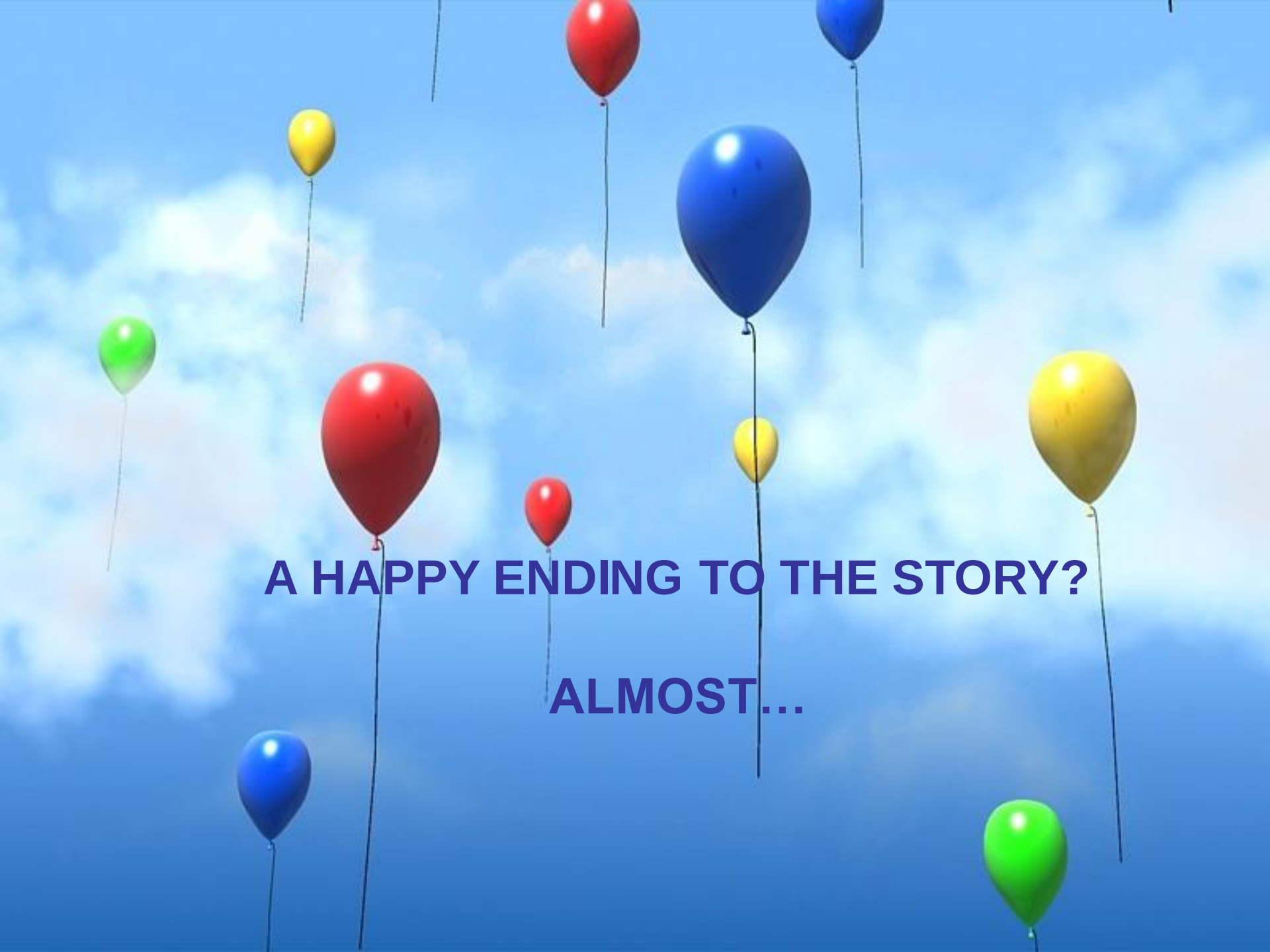
Summary

- Where
  - Disease burden difficult to interpret
  - History of local vaccine production exists
  - NITAGs and local decision-making take precedence over WHO recommendations
- All resources may be needed
  - Burden and cost data
  - Advocacy
  - Decision making processes
  - Financing
  - Local vaccine production

Global Introduction Status of Hib Vaccine: 2014

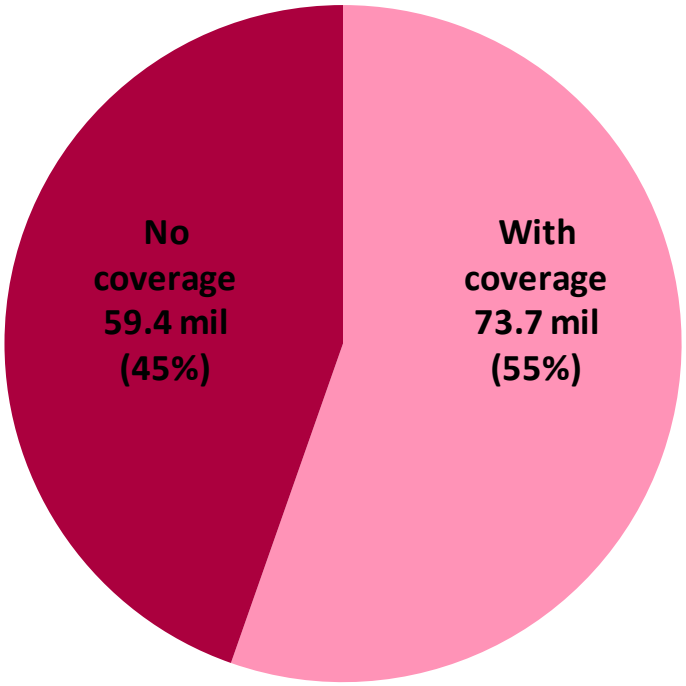


Source: International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. Vaccine Information Management System (VIMS) Global Vaccine Introduction Report, March 2014.

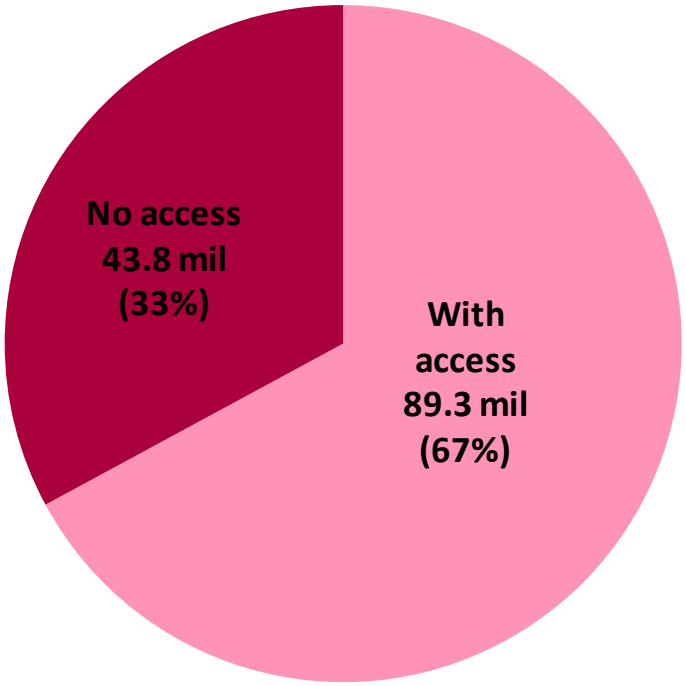

A HAPPY ENDING TO THE STORY?
ALMOST…

Global Coverage and Access to Hib Vaccine: 2014

Present Hib Coverage
(Global Surviving Infants)



Present Hib Access
(Global Surviving Infants)



Source: International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. Vaccine Information Management System (VIMS) Global Vaccine Introduction Report, March 2014.

POSTSCRIPT 1: A PUBLIC HEALTH BATTLE OVER DISEASE BURDEN INTERPRETATION

NTAGI Subcommittee Recommendations on *Haemophilus influenzae* Type b (Hib) Vaccine Introduction in India

SUBCOMMITTEE ON INTRODUCTION OF HIB VACCINE IN UNIVERSAL IMMUNIZATION PROGRAM, NATIONAL TECHNICAL ADVISORY GROUP ON IMMUNIZATION, INDIA

Correspondence to: Dr Lalit Kant, Head, Division of ECD, Indian Council of Medical Research, Ansari Nagar, New Delhi 110 029, India. lalitkant@icmr.org.in

Background: WHO estimates that *Haemophilus influenzae* type b (Hib) caused over 8 million cases of serious disease and 376,000 deaths globally in the year 2000. The introduction of Hib vaccines has essentially eliminated Hib disease in countries where they are routinely used. Now, almost all Hib disease cases and deaths occur in countries where Hib vaccines is not incorporated in the routine immunization program.

Process: The Hib and Pneumococcal subcommittee of National Technical Advisory Group on Immunization (NTAGI) in India met in April 2008. This paper focuses on the discussions regarding Hib vaccine introduction; the pneumococcal vaccine discussion is being published separately. The subcommittee reviewed the available published and unpublished literature as well as consulted prominent Hib experts to make an informed decision regarding the introduction of Hib vaccine into the routine Universal Immunization Program (UIP) in India.

Objectives: The meeting was conducted with the objectives of reviewing the existing Indian, regional and global data on Hib disease (meningitis and pneumonia), the data on safety and immunogenecity of Hib vaccines manufactured in India, as well as the programmatic and operational requirements for the introduction of Hib vaccine in India, with the goal of making a recommendation on the introduction of Hib vaccine into the UIP.

Recommendations: The committee noted that Hib diseases burden is suffiently high in India to warrant prevention by vaccination. Hib vaccines have been demonstrated to be safe, both globally and in India, and extremely efficacious in all settings where they have been used. Hib vaccine fits into the UIP immunization schedule. Several Indian manufacturers are currently producing Hib vaccines, and a detailed analysis showed that supplier capacity would be sufficient to meet the present and future demand for India if given sufficient lead time to increase production. Recognizing that it is the poorest children that are most at risk, the Indian Academy of Pediatrics has already recommended this vaccine for routine use in India. This subcommittee strongly recommended that Hib vaccine should immediately be introduced in India's UIP.

Key words: *H. influenzae*, Hib vaccine, India, Recommendations.

Indian J Med Res 132, July 2010, pp 1-3

Editorial

Introducing pentavalent vaccine in the EPI in India: A counsel for caution

The story of how pharmaceutical companies influenced scientists and official agencies like the World Health Organization (WHO) in the recent swine flu scare[1] and the saga of the undeclared conflicts of interests of members of the WHO's Strategic Advisory Group of Experts[2] has set off alarm bells around the world. When trusted advisors are less than honest, the potential for harm is great, and the feeling of betrayal is poignant.

A similar feeling of sadness and betrayal was evoked by the report of National Technical Advisory Group on Immunization (NTAGI) sub-committee on *Haemophilus influenzae* B (Hib) published recently[3]. On December 14, 2009, the Health Secretary chaired a meeting to discuss the policy framework for vaccine preventable disease in the country. Invited to this meeting were the chairperson, vice-chairperson and Indian Academy of Pediatrics representative to the NTAGI Hib sub-committee. Data from an ICMR study in Anaicut block of Vellore, obtained under the Right to Information Act were presented. The study showed that the incidence of all-cause pneumonia was 30 per 1000

in this multi-center study were reviewed by the sub-committee, but it was left out from the report.

WHO directive on Hib

The latest WHO position paper on Hib says 'Hib vaccine should be included in all routine immunization programmes'[5]. This suggests that Hib vaccine should be included in the immunization programme universally, irrespective of an individual country's disease burden, not withstanding of natural immunity attained within the country against the disease, and not taking into account the rights of sovereign States to decide how they use their limited resources. The mandate and wisdom of issuing such a directive, for a disease that has little potential of becoming a pandemic, needs to be questioned.

The directive has come after a number of failed attempts to convince the scientific community of the need for this vaccine in Asia[6,7]. We present this as a case study on the visible and invisible pressures brought to bear on governments to deploy expensive new vaccines.

India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From Tehelka Magazine, Vol 7, Issue 24, Dated June 19, 2010
CURRENT AFFAIRS
cover story
More Than A Pinprick
THE RISK TO INDIA'S NEWBORNS
A SLY FUDGING OF FACTS IS PUSHING INDIA INTO BUYING VACCINES BACKED BY THE WHO THAT MAY HAVE KILLED CHILDREN IN OTHER COUNTRIES
BY VIJAY SIMHA

SUPPLEMENT www.jpeds.com • THE JOURNAL OF PEDIATRICS

Impact and Cost-Effectiveness of *Haemophilus influenzae* Type b Conjugate Vaccination in India

Andrew D. Clark, MA[1], Ulla K. Griffiths, PhD[1], Syed Shahid Abbas, MBBS, MPH[2], Krishna D. Rao, PhD[2], Lois Privor-Dumm, MIBS[3], Rana Hajjeh, MD[4], Hope Johnson, PhD[3], Colin Sanderson, MA, MSc, PhD[1], and Mathuram Santosham, MD, MPH[3]

Objective To estimate the potential health impact and cost-effectiveness of nationwide *Haemophilus influenzae* type b (Hib) vaccination in India.

Study design A decision support model was used, bringing together estimates of demography, epidemiology, Hib vaccine effectiveness, Hib vaccine costs, and health care costs. Scenarios favorable and unfavorable to the vaccine were evaluated. State-level analyses indicate where the vaccine might have the greatest impact and value.

Results Between 2012 and 2031, Hib conjugate vaccination is estimated to prevent over 200 000 child deaths (~1% of deaths in children <5 years of age) in India at an incremental cost of US$127 million per year. From a government perspective, state-level cost-effectiveness ranged from US$192 to US$1033 per discounted disability adjusted life years averted. With the inclusion of household health care costs, cost-effectiveness ranged from US$155-US$939 per discounted disability adjusted life year averted. These values are below the World Health Organization thresholds for cost effectiveness of public health interventions.

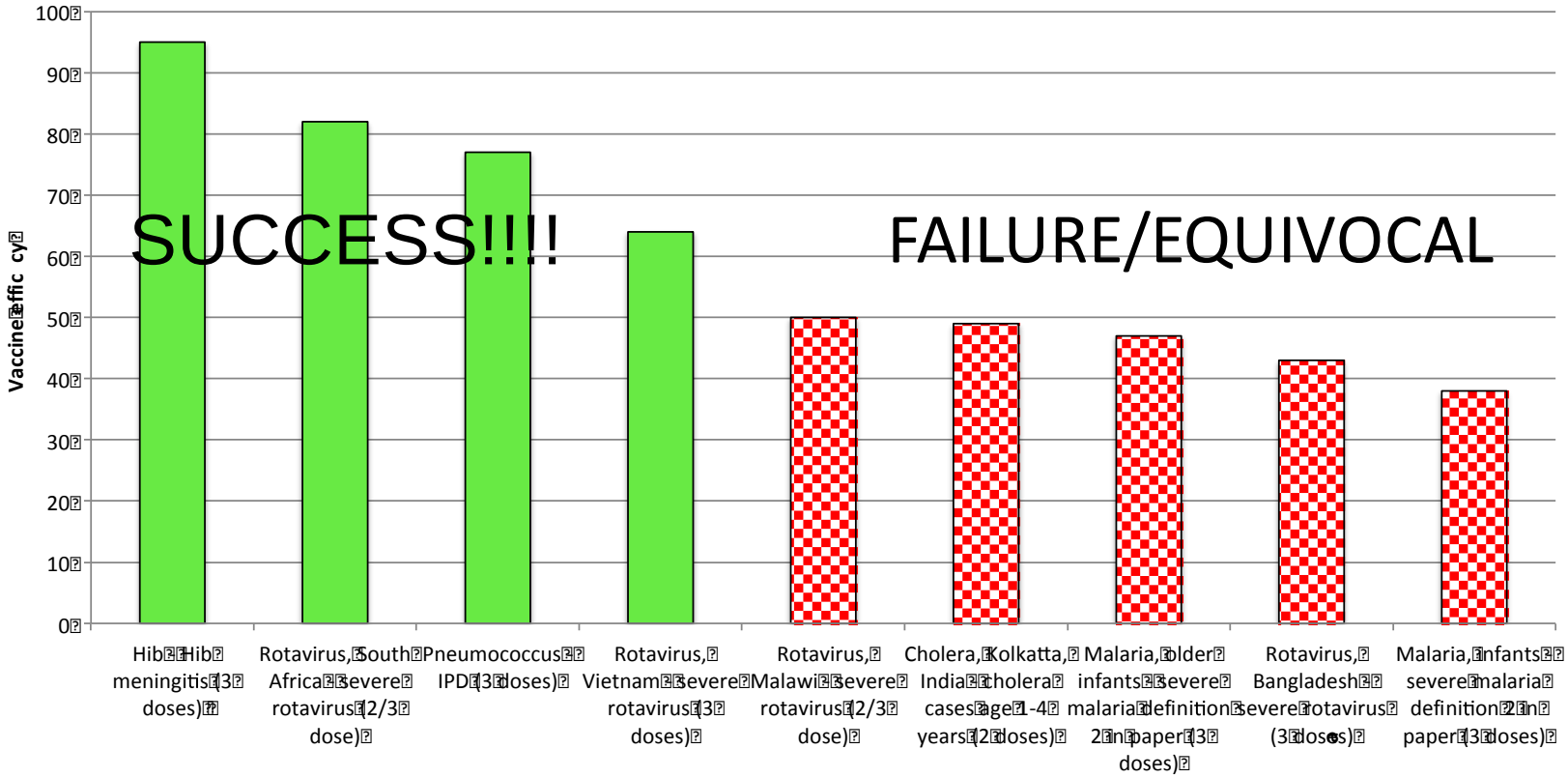
Conclusions Hib conjugate vaccination is a cost-effective intervention in all States of India. This conclusion does not alter with plausible changes in key parameters. Although investment in Hib conjugate vaccination would significantly increase the cost of the Universal Immunization Program, about 15% of the incremental cost would be offset by health care cost savings. Efforts should be made to expedite the nationwide introduction of Hib conjugate vaccination in India. *(J Pediatr 2013;163:S60-72).*

Response

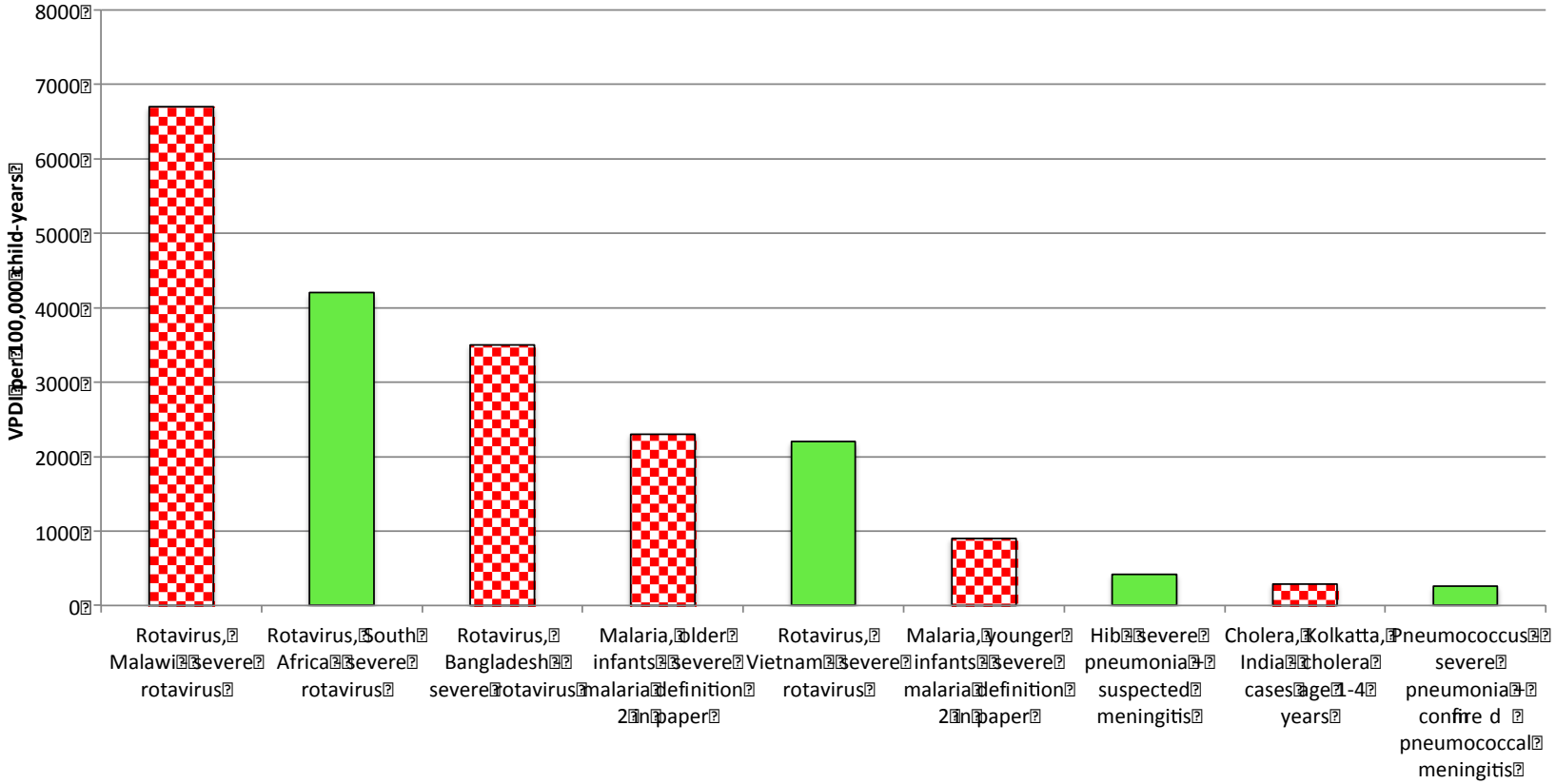
- Jacob Puliyel, J Peds 2014 Feb
- Conclusion: We hope the authors will be able to provide a more accurate base-case estimate of costs and benefits in the light of the above discussion. Such a base case estimate must include cost of treating the 1.9% increase in pneumonia in the vaccinated and also include the increased deaths from pneumonia.
- http://www.ncbi.nlm.nih.gov.offcampus.lib.washington.edu/pubmed/23773596

POSTSCRIPT 2: RETHINKING HOW TO ASSESS A VACCINE'S VALUE

PER PROTOCOL ANALYSIS OF VE



PER PROTOCOL ANALYSIS OF VPDI



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

Conclusions

- Disease burden the foundation of most vaccine decision-making
- {Incidence x severity x cost}
- Incidence best measured by vaccine preventable disease incidence?
- Burden data interpretation can be subtle and contextual
- Burden data rarely enough to drive policy
- Burden data part of ongoing assessment of vaccine usefulness

This is perhaps the most beautiful time in human history; it is really pregnant with all kinds of creative possibilities.