

Optimal safety assessment system for future vaccines against poverty-related diseases (PRD:HIV, malaria, TB) in developing countries

International Association for Biologicals
Barcelona, Spain
April 27-28, 2011

Robert T. Chen MD. MA
HIV Vaccine & Special Studies Team
Centers for Disease Control & Prevention

Disclaimer

“The findings and conclusions in this presentation have not been formally disseminated by the CDC and should not be construed to represent any agency determination or policy”

Life-saving vaccines on the horizon

(source: www.path.org)

Research and development pipeline

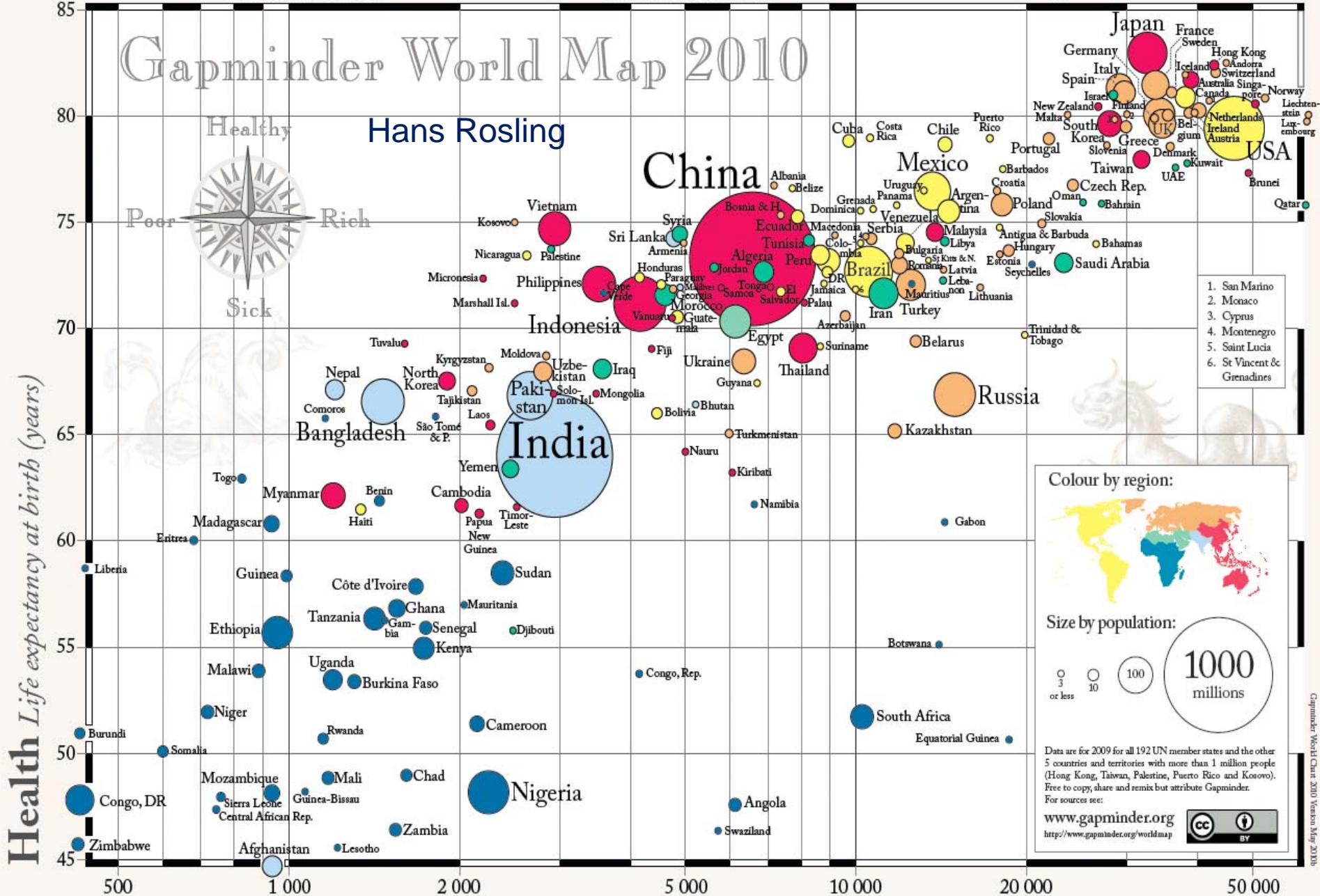
		Number killed per year	Candidate vaccines	Research and development pipeline			
	Disease			Research	Predclinical	Clinical/regulatory approval	Registration
Diarrheal	Enterotoxigenic <i>Escherichia coli</i> (ETEC)	380,000	6	[Progress bar]			
	Rotavirus*	527,000	7	[Progress bar]			
	Shigellosis	1 million	7	[Progress bar]			
Respiratory	Influenza*	300,000–500,000	11	[Progress bar]			
	Pneumococcus*	2 million	5	[Progress bar]			
	Tuberculosis	1.6 million	11	[Progress bar]			
Vector-borne	Japanese encephalitis (JE)**	10,000–15,000	4	[Progress bar]			
	Malaria	1.3 million	23	[Progress bar]			
Other	HIV/AIDS	2.8 million	20	[Progress bar]			
	Human papilloma virus (HPV)	250,000	9	[Progress bar]			
	Meningococcal A*	6,000–20,000***	4	[Progress bar]			

Gapminder World Map 2010

Low-income countries

Middle-income countries

High-income countries



1. San Marino
2. Monaco
3. Cyprus
4. Montenegro
5. Saint Lucia
6. St Vincent & Grenadines

Colour by region:

Size by population:

3 or less
10
100
1000 millions

Data are for 2009 for all 192 UN member states and the other 5 countries and territories with more than 1 million people (Hong Kong, Taiwan, Palestine, Puerto Rico and Kosovo). Free to copy, share and remix but attribute Gapminder. For sources see: www.gapminder.org <http://www.gapminder.org/worldmap>

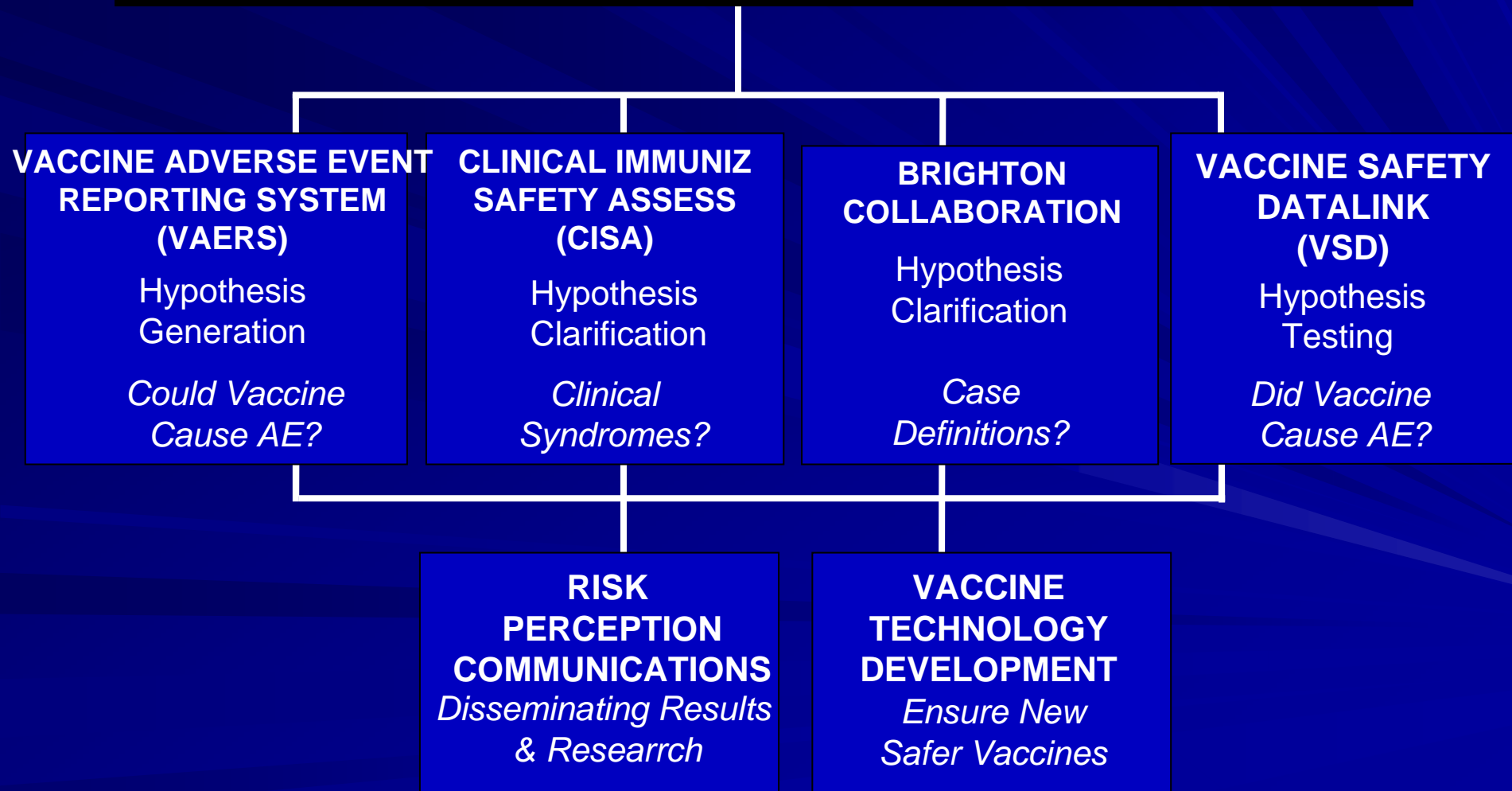
Gapminder - World Chart 2010 Version May 2010

Money GDP per person in US dollars (purchasing power adjusted) (log scale)

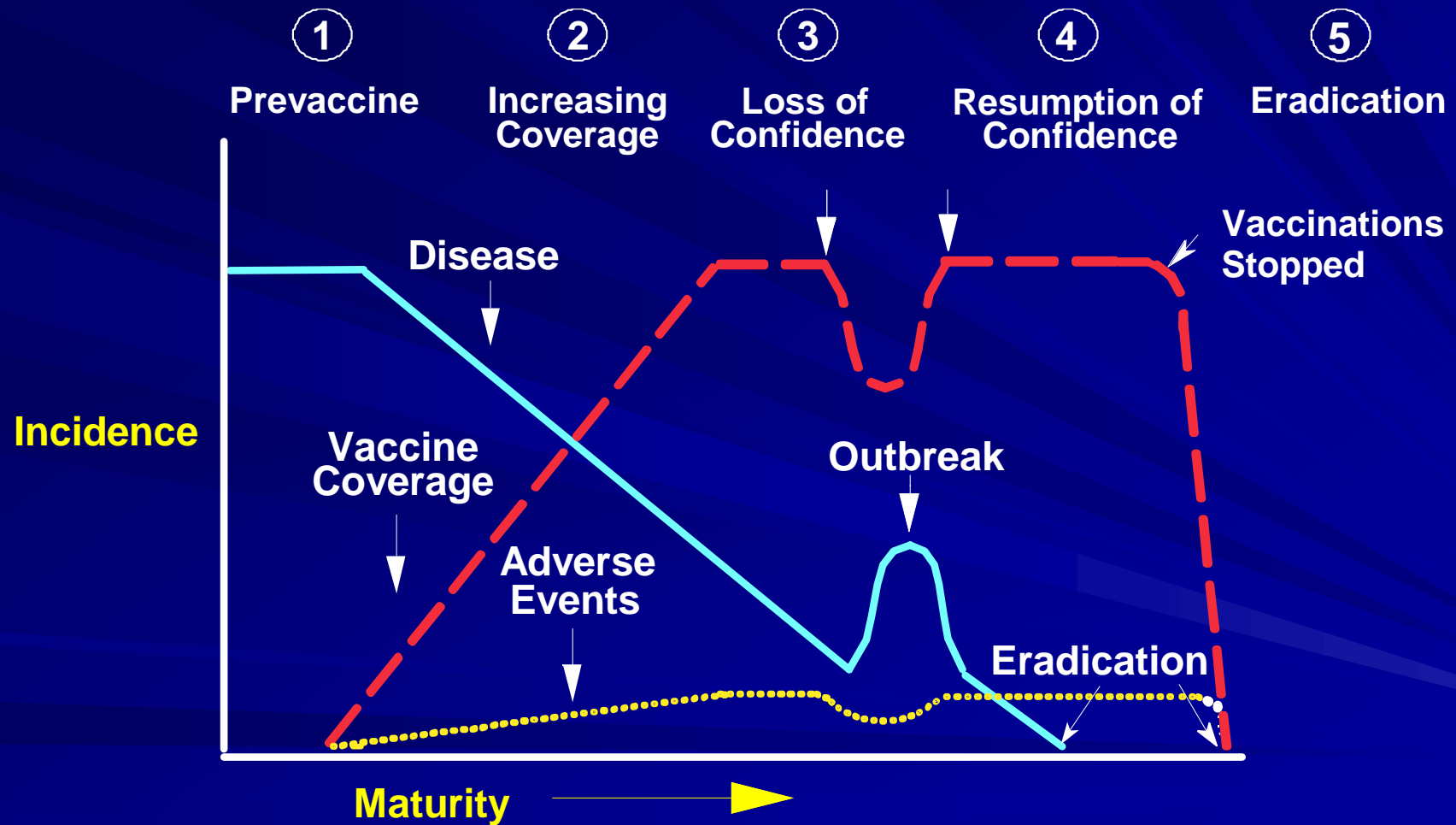
GAPMINDER

SAFETY MONITORING FLOW DIAGRAM IMMUNIZATION SAFETY BRANCH

How best to Adapt to Less Developed Settings?



Evolution of an Immunization's Use and Safety Concerns



New vaccine iprogram = less mature; impact era of rapid communications?

Editors' Introduction: Vaccine Safety Throughout the Product Life Cycle

AUTHORS: Daniel A. Salmon, PhD, MPH,^a Andrew Pavia, MD, FAAP, FIDSA^b and Bruce Gellin, MD, MPH^a

^aNational Vaccine Program Office, Office of the Assistant Secretary for Health, Office of the Secretary, US, Department of Health and Human Services, Washington, DC; ^bDivision of Pediatric Infectious Disease, Department of Pediatrics, University of Utah

www.pediatrics.org/cgi/doi/10.1542/peds.2010-1722U

doi:10.1542/peds.2010-1722U

Accepted for publication Nov 29, 2010

Address correspondence to Daniel Salmon, PhD, MPH, National Vaccine Program Office, Office of Public Health and Science, Office of the Secretary, Department of Health and Human Services, 200 Independence Ave SW, Room 715H, Washington, DC 20201. E-mail: daniel.salmon@hhs.gov

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2011 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

The development and widespread use, in the United States and globally, of safe and effective vaccines has been one of the greatest achievements in science, medicine, and public health—saving lives, preventing disabilities, contributing to improvements in life expectancy, and reducing health care costs. Serious and once common childhood infections are increasingly joining the ranks of “vaccine-preventable diseases.” The number of childhood and adolescent diseases prevented by vaccines has increased from 10 to 16 in just the last 10 years. Moreover, we now have vaccines that can prevent the infections that can lead to cervical and liver cancer.

Ironically, as the threat of disease has been diminished by vaccines, there has been increasing attention on the risks, both real and perceived, from vaccines. When vaccines are used effectively, the incidence of vaccine-preventable diseases declines, and over time, the diseases that vaccines have prevented are less common. The result is that there is a subtle shift in the benefit/risk ratio. With the recent addition of new vaccines to the recommended childhood

Opportunities to Improve Vaccine Safety Data

	Pre-Licensure	Post-Licensure
Developed Settings	a	b
Less Developed Settings	c	d

Table 2. Sample sizes needed to detect increases in rates of rare events after vaccination

Rates (%)	Sample size*	No. potentially affected	Percentage of US birth cohort
0.1 vs 0.2	50 000	4000	1.25
0.1 vs 0.3	17 500	8000	0.44
0.05 vs 0.1	100 000	2000	2.5
0.01 vs 0.02	500 000	400	12.5
0.01 vs 0.03	175 000	800	4.4

*Two-arm trial, power=80%, alpha (2-sided) = 5%.

“The most reliable way to assess causality is in a controlled study, but clinical trials of new vaccines are typically too small to detect rare but serious effects. If the size of these trials were increased, much more could be learned about the safety of a vaccine prior to its exposure to entire populations. “

Ellenberg SS.Pharmacoepidemiol Drug Saf. 2001;10:411-5.

Some Ideas to Improve PRD Vaccine Safety during Pre-Licensure Clinical Trials

- Lessons from Rotashield and Intussusception:
 - Larger (vs. maximizing value of available) sample size
 - Single DSMB/integrated safety oversight of candidate vaccine
 - Ensure DSMB includes safety/rare disease epi expertise
- Use data linkage and pattern recognition to complement traditional clinician attribution of causality in clinical trials
- Specimen collection for pharmacogenomic studies
- Use/develop standardized Brighton Collaboration case definitions + other processes?

New Brighton Collaboration (BC) Pre-Licensure Working Groups

- INYVAX: Safety Elements of a Protocol for Clinical Trial of Vaccines in Resource Limited Countries
 - EC funded, Launched March 2009
 - Lead: Jan Bonhoeffer + Uli Heininger
 - Future:
 - target disease-specific (HIV, Malaria, TB) vaccines
 - Vector-specific (e.g., adeno-, pox-, DNA)
- Viral Vector Vaccines Safety Working Group (V3SWG)
 - Cross-cutting issues currently
 - Launched Sept 2008: ~100 => 30 volunteers
 - Lead: Bob Chen
 - Future: vector-specific (e.g., adeno-, pox-, DNA)

Example of V3SWG Template Content

3. Characteristics of wild type agent

- 3.1. Please list any disease(s) caused by wild type, the strength of evidence, severity, and duration of disease in
- healthy people
 - Immunocompromised
 - neonates, infants, children
 - During pregnancy
 - in the unborn
 - any other susceptible populations
 - In Animals

Characteristics of proposed vaccine vector

- 4.1. What is the basis of attenuation/inactivation?
- 4.2. What is the risk of reversion to virulence or recombination with wild type or other agents?
- 4.3. Is the vector genetically stable during multiple passages?
- 4.4. What is known about the genetic stability during in vivo replication?
- 4.5. Will a replication competent agent be formed?
- 4.6. What is the potential for shedding and transmission?

Recs on issues needing study: 2003 WHO informal consultation on characterization/ quality aspect of vaccines based on live viral vectors

1. The potential for vector recombination with wild type pathogenic strains
2. Implications of prior infections on safety
3. Genetic stability of replicating vaccine viruses in vivo
4. Potential changes of vaccine viral tropism
6. Tests for absence of reversion to virulence
7. Absence of replication-competent virus when replication incompetent vectors are used
8. Vaccine effects on innate immunity and on the induction of an immuno-suppressive window or immune-activation
9. Length of time for monitoring adverse events
10. Possible secondary transmission of vaccine virus
11. Inclusion of adventitious agents in cell culture

Added by V3SWG

Vaccine Safety Datalink (VSD) Data Linkages

**Vaccination
Records**

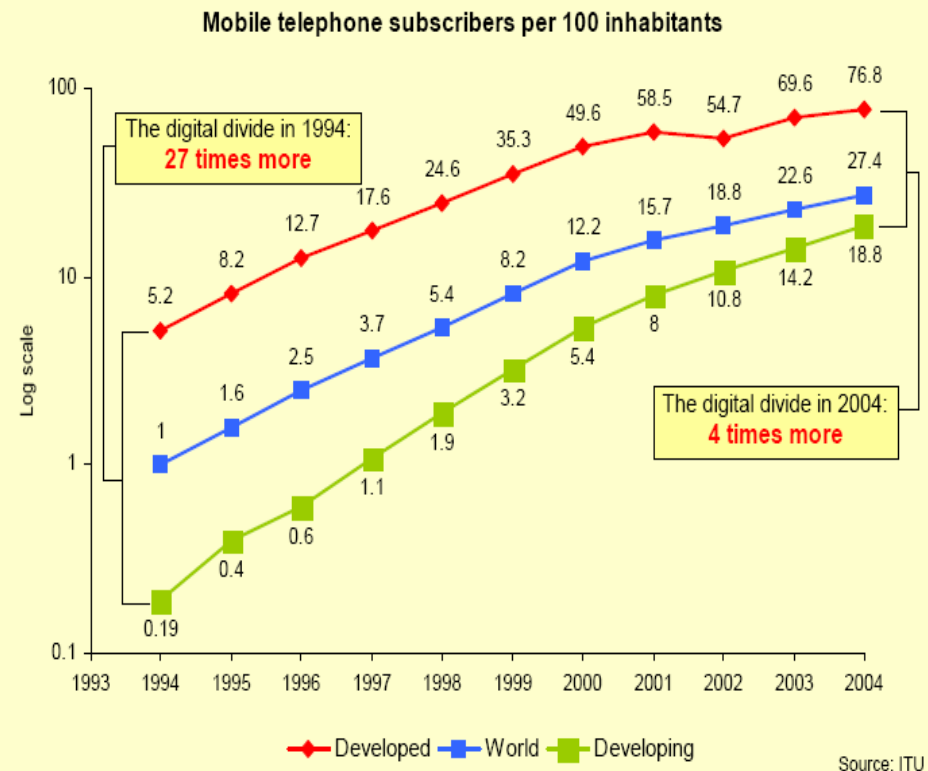
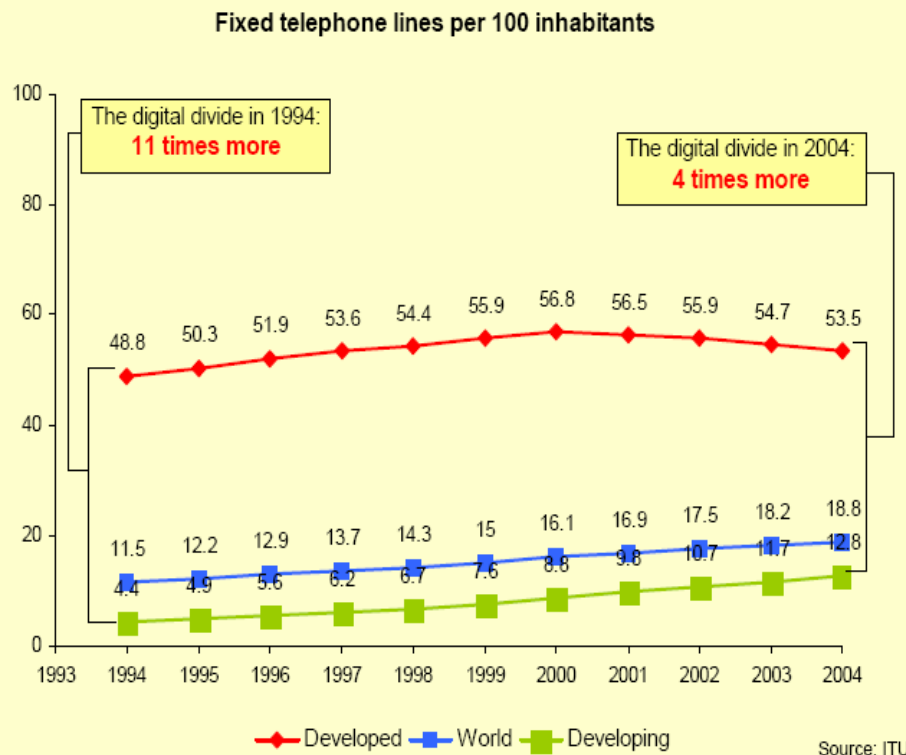
**Health
Outcomes**
(Hospital) (ER)
(OPD)

**Patient
Characteristics**
(Birth Tapes)
(Census)

How to Extend to Less Developed Countries?

VSD Linked Analysis Database

Digital Divide: Fixed and Mobile Phones



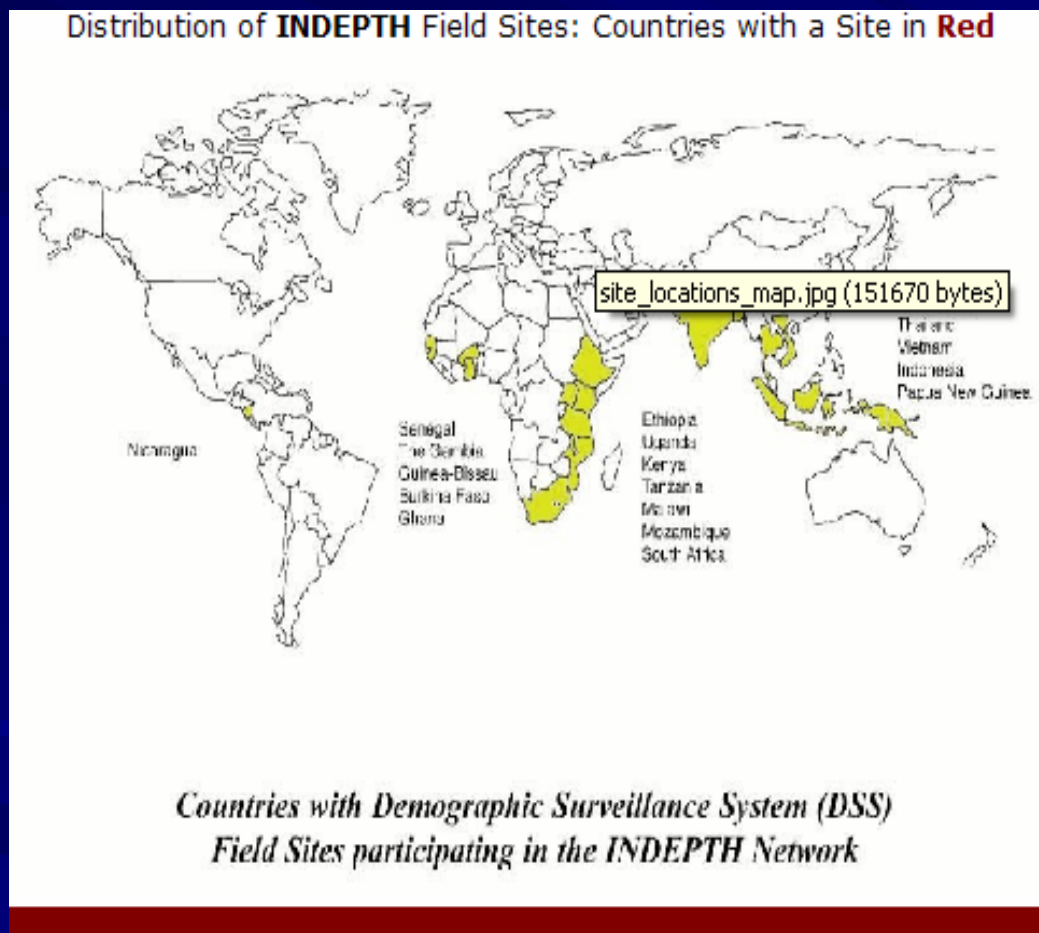
- Definition: Gap between those who benefit from digital technology and those who do not.
- **TRUTH #8:** Midlevel countries in relatively advanced emerging markets, not the poorest countries, are the best settings for experimental efforts to close the Divide. (www.digitaldivide.org)



Global Vaccine Safety DataNet in Less Developed Settings?

- Digital divide likely lesser issue in middle-income countries (e.g., Brazil, China, India) = mix of developed & developing settings, many with large populations
- Challenge will be low-income countries:
 - Needs:
 - VPD with too low an incidence in middle-income countries (e.g., malaria)
 - VPD with unique strains in low-income countries (e.g., HIV)
 - Potential good news:
 - Substantial global resources for “orphan” diseases R&D, clinical trials + AIDS care => foundation for post-licensure infrastructure?
 - Rapid spread cell phone technology (humans love talking)
 - Existing Demographic Surveillance System (DSS) = core for VSD

INDEPTH (www.indepth-network.org): International Network of field sites with continuous Demographic Evaluation of Populations and Their Health in developing countries



- Vision: an international platform of sentinel demographic sites that provides health and demographic data and research to enable developing countries to set health priorities and policies based on longitudinal evidence. INDEPTH's data and research will guide the cost effective use of tools, interventions and systems to ensure and monitor progress towards national goals.
- Mission: To harness the collective potential of the world's community-based longitudinal demographic surveillance initiatives in resource constrained countries to provide a better, empirical understanding of health and social issues, and to apply this understanding to alleviate the most severe health and social challenges.

Closest analogy to VSD/MCO for LDC's? use for P3/P4 studies of new vaccines

Some Ideas to Improve PRD Vaccine Safety during Post-Licensure

- Improve accuracy of vaccine exposure ascertainment:
 - Peel off vaccine barcode labels scanned by cell phone => computerized immunization registry

Products Deals Travel Login using




Search for: Find it

related: mobile phone scanner, unlocked cell phones, pda palm barcode scanner, more...

s > PDA, Tablets & Handhelds > digital cell phone scanner

Found it! Save: Share: Showing 1 - 30 of 65 matches, Sorted by Price: Low to High

Compare To show Tax and Shipping, enter your ZIP code

<input type="checkbox"/>	 Wasp Tech WPA1000 + MOBILEASSET LICENSE Scanner - Mobile Phone, SD/MMC Memory Card ★★★★★ Add to List More Like This TechForLess	\$363 Free shipping Compare Prices
<input type="checkbox"/>	 Janam Technologies XP20 Batch Mobile Computer 32 MB Memory - PDA - Palm OS - Keypad, Scanner - Mobile Phone, Palm Expansion ★★★★★ Add to List More Like This GeminiComputers:\$526 Consutronix:\$557	\$526 to \$557 Compare Prices at 2 Sellers
<input type="checkbox"/>	 Janam Technologies XP20 Batch Mobile Computer 32 MB Memory - PDA - Palm OS - Keyboard, Keypad, Scanner - Mobile Phone, Palm Expansion, SD/MMC Memory Card ★★★★★ Add to List More Like This Consutronix:\$568 GeminiComputers:\$532	\$532 to \$568 Compare Prices at 2 Sellers

Post-marketing Surveillance Network for Vaccines

Jerry Labadie

The UMC is a partner in an exciting WHO project which will help to boost the number and quality of reports of adverse events following immunization (AEFI): The Global Network for Post-marketing Surveillance of Newly Pre-qualified Vaccines (PMS Network). UMC tools VigiFlow and Vigibase are key elements in the reporting, management and analysis of the reports of the AEFI. Through the Global PMS Network, enhanced reporting of vaccine safety data to the UMC is expected in coming years. In turn this will assist ongoing efforts (supported by WHO's Global Advisory Committee on Vaccine Safety) to use the resources and experience of UMC for data mining and signal detection to improve global vaccine safety monitoring.

standardized case definitions, methods of analysis, reports to the network) to ensure comparability of safety data among network countries.

VigiFlow in use

AEFI reports from the PMS Network countries will be sent to the global database of the WHO-UMC programme by VigiFlow. VigiFlow has been modified to capture vaccine specific data. The reported AEFI will be subjected to UMC's routine data mining procedures. This will improve the vaccine safety monitoring capacity and data-mining tools at UMC.

EXPERT
REVIEWS

Global Vaccine Safety DataNet Meeting

Expert Rev. Vaccines 7(1), 15–20 (2008)

Steven Black

279 So South Street,
Wilmington, OH 45177, USA
stevblack@gmail.com

Global Vaccine Safety DataNet Meeting

Annecy, France, 12–13 September 2007

An international meeting was held at the Merieux Foundation in Annecy, France, on 12–13 September 2007, to discuss the establishment of a Global Vaccine Safety DataNet. Invitations were extended to experts from developed and developing countries that currently, or will soon, collect computerized information on vaccine exposure and clinical outcomes, as well as representatives of public health agencies and pharmaceutical companies. The goals of the meeting included assessing current capabilities and interest in establishing a global vaccine safety data network, exploring the infrastructure and funding required to bring such a project to fruition and discussing the best approach to implementation.

Establishing Causal Link: Adverse Event and Vaccine

Can we maximize value of data in LDC's?

- Unique lab result
- Unique clinical syndrome
- Epidemiologic study
(or large clinical trial)

		Illness or Syndrome	
		Yes	No
Vaccination	Yes	a	b
	No	c	d

Vaccine Adverse Event reports < "a"
due to under- + biased reporting

Rate in vaccinated

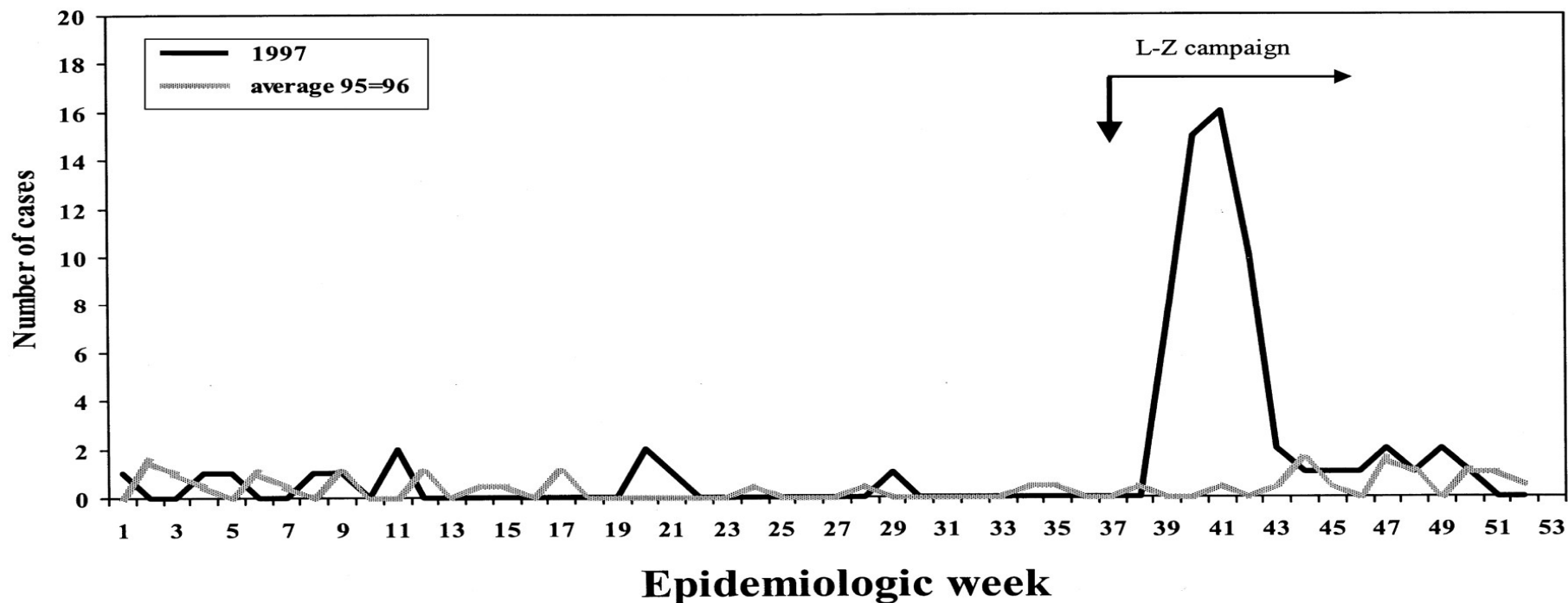
$a/a+b$

Rate in unvaccinated

$c/c+d$

Aseptic meningitis (all causes) among children 1-11 years, by week and year of onset, five selected municipalities, Rio Grande do Sul, Brazil 1995-1997

da Silveira, C. M. et al. *Int. J. Epidemiol.* 2002 31:978-982; doi:10.1093/ije/31.5.978



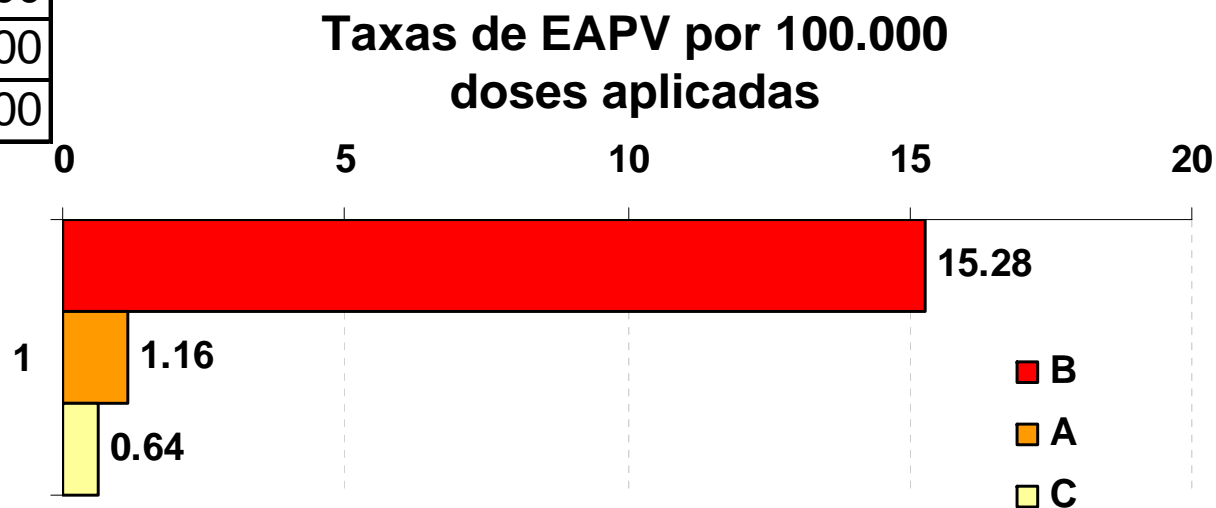
- The risk of vaccine-associated aseptic meningitis ~ 1 case per 3390 doses administered.
- Mass campaign strategy facilitated detection of events that might have gone undetected.

Eventos Adversos de Hipersensibilidade Vacina Tríplice Viral

Reações de hipersensibilidade ocorridas em até 24 horas após vacinação (campanha de seguimento contra sarampo 2004)

Estimativa de doses aplicadas

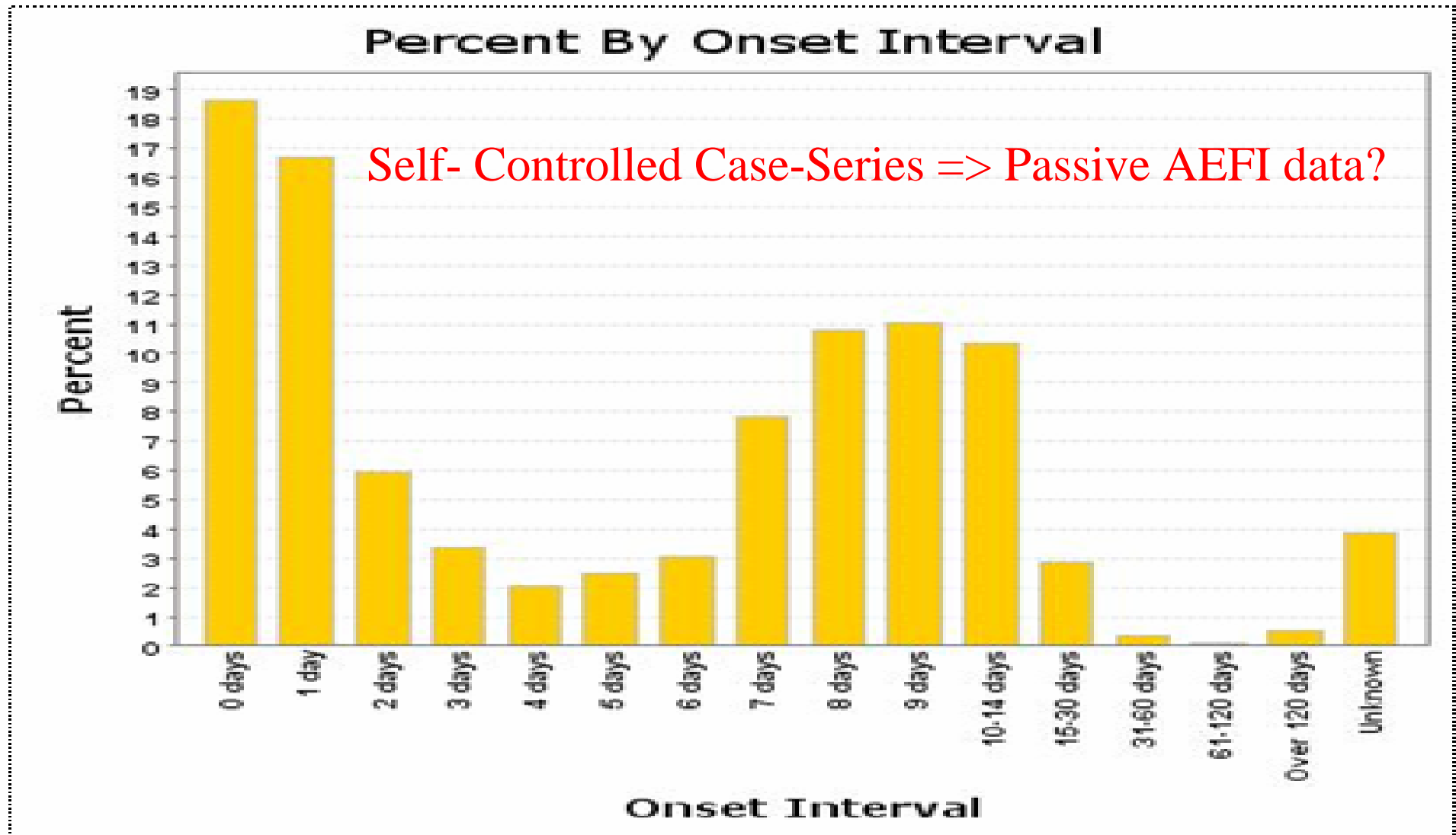
A	5,000,000
B	2,500,000
C	4,200,000
Total	11,700,000



Valor $p < 0,0001$

Fonte : CGPNI

Onset Interval of Febrile Convulsions After MMR Vaccine, VAERS, 1990-2011



RV1: Post-marketing IS studies

RV1 (Rotarix)					
Study Population	Investigators	Study info	Results (selected)	Incidence Rate Ratio	95% CI
Mexico	GSK	Self-controlled case series	DOSE 1 Interim results 0-30 days	IRR 1.8	(99% CI) 1.0, 3.1
Mexico/Brazil PAHO/CDC		Self-controlled case series (+ case-control)	DOSE 1 1-7 days	IRR 4.6	2.5, 8.8
			1-21 days	IRR 1.6	0.9, 2.8
			Brazil	DOSE 1 1-7 days	IRR 1.1
		1-21 days	IRR 0.75	0.35, 1.6	
Australia	APSU/PAEDS	Expected IS cases from historical rates	DOSE 1 Age 1 - <3 months 1-7 days 1-21 days	(Relative Risk) RR 3.45 RR 1.53	0.71, 10.1 0.42, 3.92

8



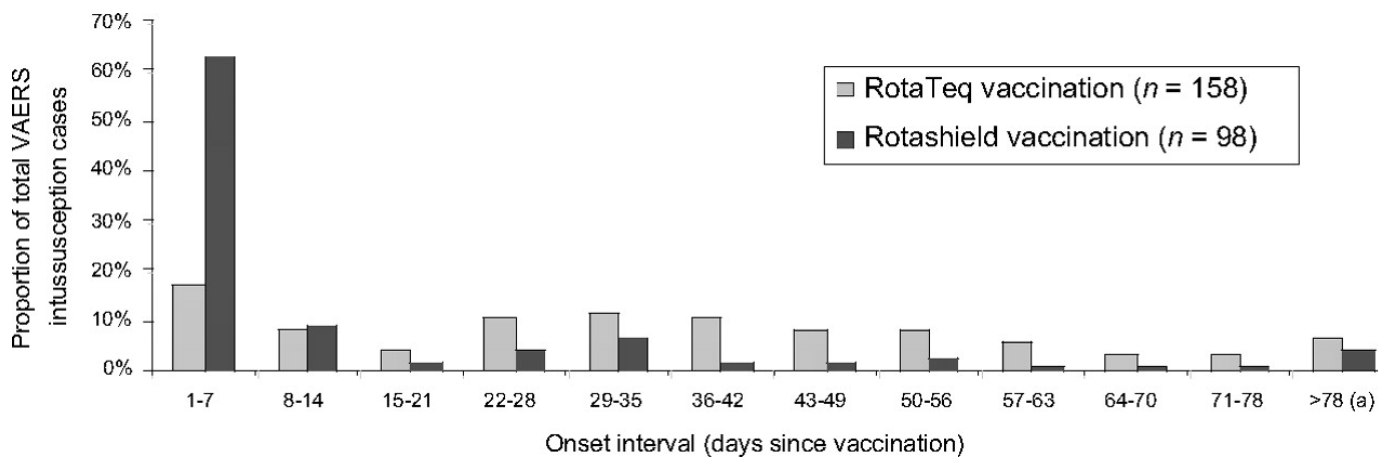
RV5: Post-marketing IS studies

RV5 (RotaTeq)					
Study Population	Investigators	Study info	Results (selected)	RR	95% CI
US: VSD pop	CDC/VSD	Controls: concurrent other vaccine recipients	DOSE 1 (unconfirmed cases) 1-7 days 1-30 days	RR 0.65 RR 1.40	0.03, 38.04 0.38, 7.64
US: insured pop	Merck	Controls: concurrent DTaP recipients	DOSE 1,2,3 combined 1-7 days (exploratory) 0-30 days	RR 2.8 RR 0.8	0.3, 139.5 0.2, 3.5
Australia	APSU/PAEDS	Expected IS cases from historical rates	DOSE 1 Age 1 - <3 months 1-7 days 1-21 days	RR 5.26 RR 3.5	1.1, 15.4 1.3, 7.6

9



FIGURE 2 Proportions of total reports to the VAERS of intussusception cases after RotaTeq (February 1, 2006, to September 25, 2007) and RotaShield (October 1, 1998, to August 15, 1999) vaccination, according to onset interval



Haber, P. et al. Pediatrics 2008;121:1206-1212

Mullooly J et al. Quality Assessments of HMO Diagnosis Databases Used to Monitor Childhood Vaccine Safety. *Methods of Information in Medicine* 2004; 43: 163-170.

Conclusions: The misclassification error rates for automated screening outcomes substantially reduce the power of screening analyses and limit usefulness of screening analyses to moderate to strong vaccine-outcome associations. Medical record verification of outcomes is needed for definitive assessments.

Misclassification => bias towards the null

Factors contributing to misclassification of clinical outcomes in less developed settings
= Achille's Heel for PRD vaccine safety studies?

- High underlying burden morbidity + mortality
- Understaffing relative to demand for services (worsened by brain drain)
- Poor training
- Poor diagnostic capabilities
- Poor referral networks
- Under-resourcing of health care sector in economy overall
- Not easy problem to solve

Risk of febrile seizure after measles-containing vaccination, various database studies

Country	Vaccine Type	Doses	Onset Interval (Days)	Relative Risk (95%CI)	Attributable Risk	Reference
UK	Urabe MMR	77,200	6-11	2.70 (1.81,4.01)	1:3000	Farrington P. Lancet 1995; 345: 567-69
UK	Jeryl-Lynn MMR	20,100	6-11	3.77 (1.95, 7.30)	1:3000	Farrington P. Lancet 1995; 345: 567-69
US	Jeryl-Lynn MMR	137,457	8-14	2.83 (1.44, 5.55)	1:2941	Barlow W, NEJM2001;34 5:656-61
VN	Measles	53,256	0-14	2.4 (0.9-6.1) (Viral Fever)	?	Ali M. Bull WHO 2005; 83:604-10

Summary

- Urgent global need vaccines vs. PRD (HIV, malaria, TB, etc.)
- Many of these vaccine candidates will use “high tech” approaches with limited past human experience.
- Increasing ability to capture safety data in pre- and post- licensure needed, especially in countries with highest incidence.
- Ease: middle > lower income countries
 - Positive: increase in cell phone, R&D on orphan diseases, DSS
 - Negative: poor specificity of Dx = Achille’s heel? Major need in staff training /development
 - Challenge: catalyze/harness positive > negative
- Mass campaign in context of good AEFI surveillance may serve as good interim proxy