RATIONALE FOR INTERNATIONAL COLLABORATION IN EPIDEMIOLOGICAL VACCINE SAFETY STUDIES

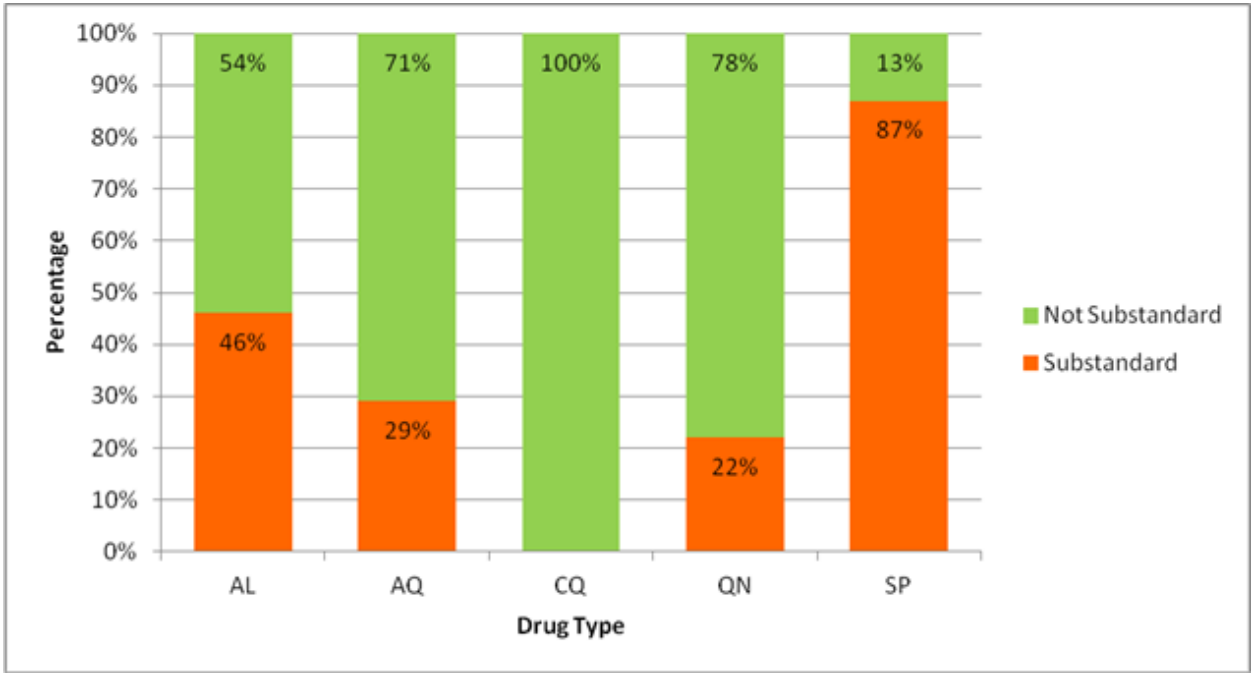
Presented by:

Hector S. Izurieta, MD, MPH
FDA

Are safety and effectiveness issues the same for vaccines and for drugs?

- Vaccines usually administered to:
  - Healthy People
    - Low tolerance for adverse events
  - Large population segments
    - Even rare adverse events can affect thousands
- Therefore:
  - With some exceptions, vaccines expected to be:
    - very safe
      - Otherwise the population trust is unsustainable
    - Clearly beneficial
      - Otherwise the population won't seek them

Are safety and effectiveness issues the same for vaccines and for drugs? Example

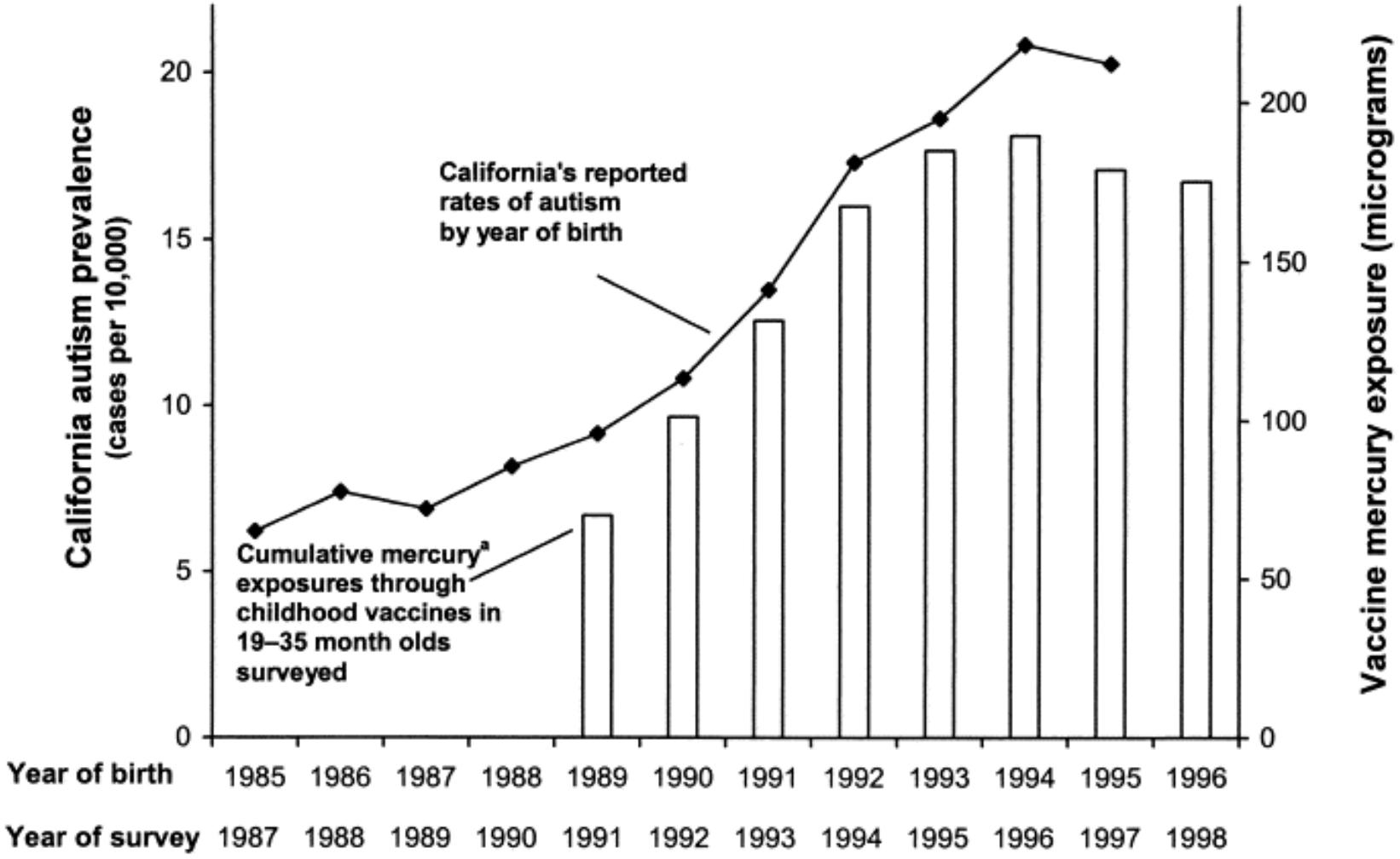


Example prevalence of substandard drugs – Country X
Antimalarials:
AL (coartem)
Amodiaquine
Cloroquine
Quinine
SP (Fansidar)

The extraordinary success of vaccinations comes at a price

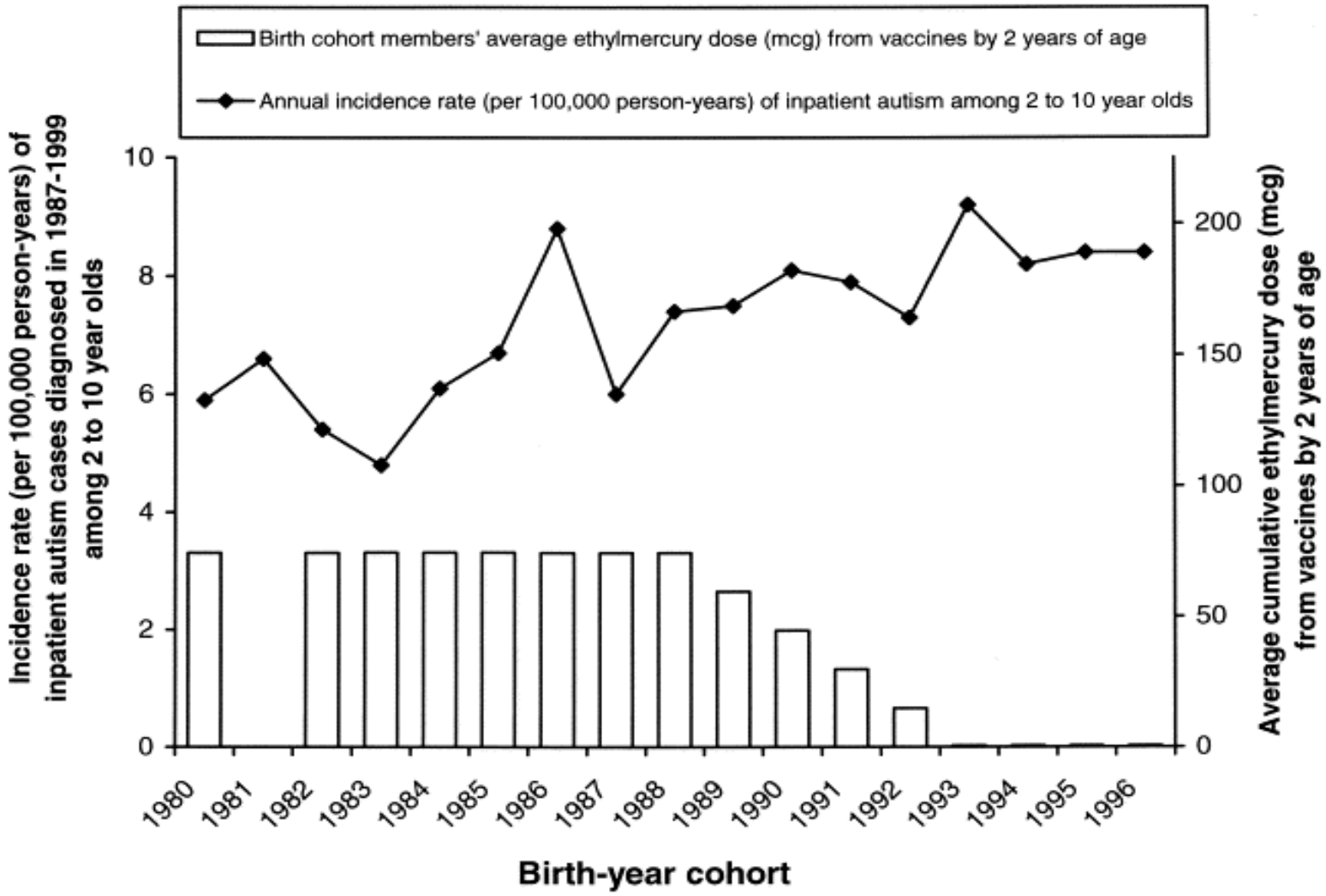
- Vaccines are amongst most effective public health interventions
- In many areas of the world, effectiveness of vaccines has eradicated public memory of the diseases they were designed to prevent
  - examples include smallpox, polio, tetanus, meningitis and many others.
- Therefore, today, most communities worldwide have low tolerance for vaccine adverse events
- Safety scares have potential to rapidly compromise vaccine programs worldwide

Estimated Prevalence of Autism and Mercury Exposure in Vaccines, California, 1985-98



Reference: Stehr-Green P et al. *Am J Prev Med* 2003; 25:101-106

Incidence of Autism in Sweden & Cumulative Thimerosal in Vaccines



Reference: Stehr-Green P et al. *Am J Prev Med* 2003; 25:101-106

Autism and MMR Vaccines (The Wakefield LANCET Paper)

- Selection Bias:
  - Several parents had gotten referred to the lawyer, Richard Barr, and through him to Wakefield, by an anti-vaccine group called JABS, which suspected a link between autism and MMR vaccine. Thus, in his research, Wakefield had not examined a random sample of children who had received MMR vaccine. Rather, he obtained most of his patients because they had developed autism or intestinal disorder around the time they received MMR and their parents suspected a connection.

Reference: http://www.markpine.us/?tag=selection-bias

Current Issues

- Most LMIC countries have limited capacity to implement epidemiological vaccine safety studies
  - In the past, most countries have relied on assessments from developed countries, where vaccines have been usually licensed initially, or in results from passive surveillance
- Increasing trend towards introduction of new vaccines into LMIC even before they are licensed in Europe or the U.S.
  - Rotavirus vaccine in Latin America
  - Meningitis A vaccine in Africa

(Very) Good News

Example: Meningitis In Burkina Faso (A)

Adverse Event	Reported Rate in Enhanced Passive Surveillance** (N= 11,466,950 vaccinees/ 3 countries)	Baseline Rate (N= 97,715surveyed)
Convulsions	0.15	26.60
Urticaria	0.73	21.49
Anaphylaxis	None	0.00
Any Adverse Event	12.83	

Rates are per 100,000 individuals

Meningitis In Burkina Faso*
Passive and active surveillance

Adverse Event	Rate in Active Surveillance (N= 107,493 vaccinees)	Reported Rate in Enhanced Passive Surveillance** (N= 11,466,950 vaccinees/ 3 countries)	Baseline Rate (N= 97,715surveyed)
Convulsions	29.76	0.15	26.60
Urticaria	16.74	0.73	21.49
Anaphylaxis	None	None	0.00
Any Adverse Event	52.10	12.83	

Rates are per 100,000 individuals

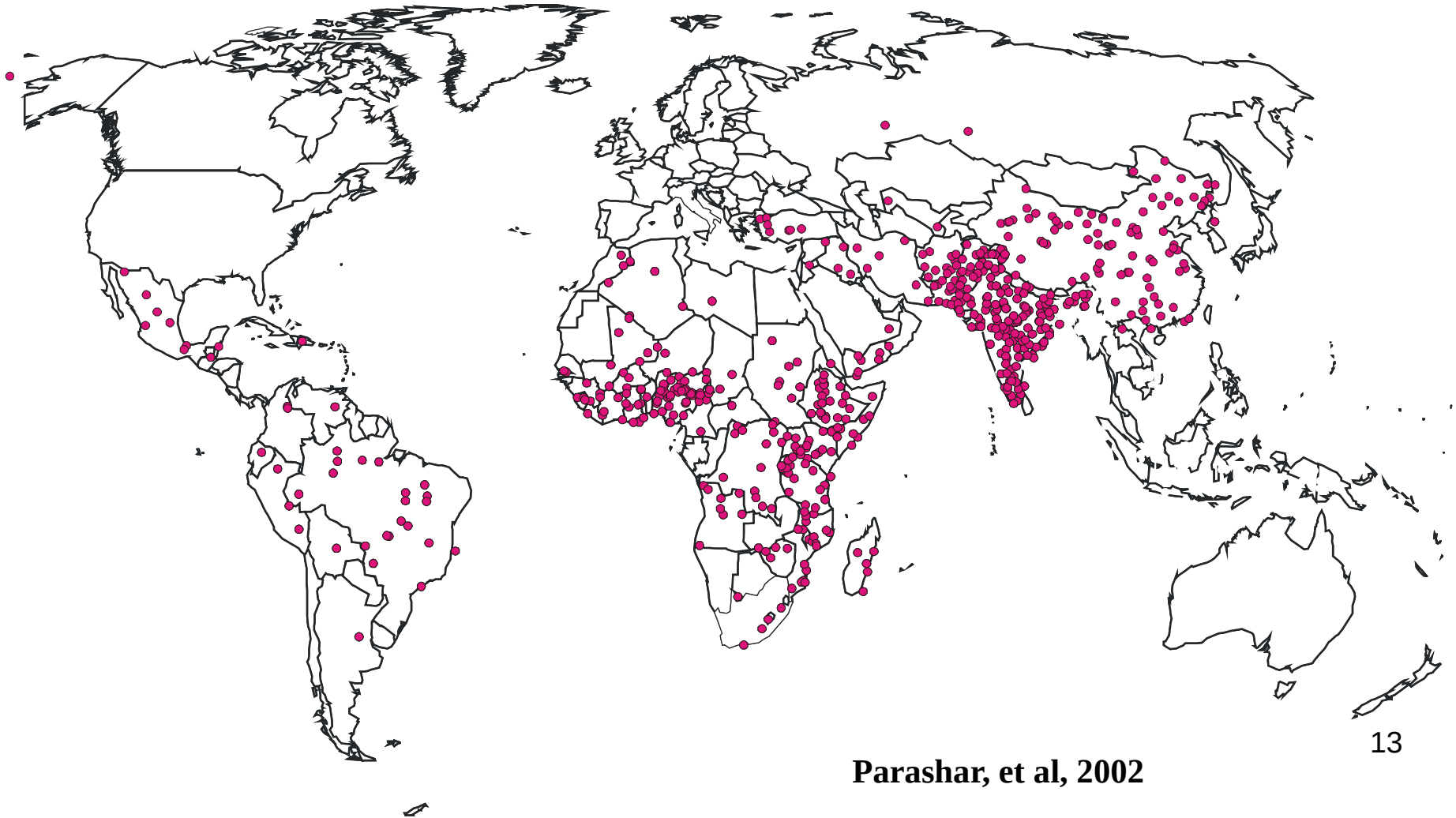
Adverse events following immunization during mass vaccination campaigns at first introduction of a meningococcal A conjugate vaccine in Burkina Faso, 2010, **in press, *Vaccine***

Sample Sizes Needed to Detect Increases in Rates of Rare Events*

Rate difference	Sample size	% Birth cohort*	# Potentially Affected
5% vs. 15%	320	0.008%	400,000
5% vs. 10%	950	0.024%	200,000
0.2% vs. 0.6%	8,750	0.22%	16,000
0.2% vs. 0.4%	25,000	0.625%	8,000
0.01% vs. 0.03%	175,000	4.4%	800
0.01% vs. 0.02%	500,000	12.5%	400

Two-arm trial, power=80%, alpha (2 sided) = 5%
Ellenberg SS. Drug Saf 2001b; 10:411-415. * U.S. Birth cohort = 4 million

Global Distribution of Rotavirus Deaths (n=440,000)



Parashar, et al, 2002

Differences in Rotavirus Epidemiology

	Developed countries	Developing Countries
Age - median	9-15 mo.	6-9 mo.
- % <1year	65%	80%
Seasonality	Winter	Year-round
Rv Strains	4-5 common	Diverse
Co-infections	Uncommon	Common
Mortality	Low	High
Co-morbidity	Uncommon	HIV, Malnutrition

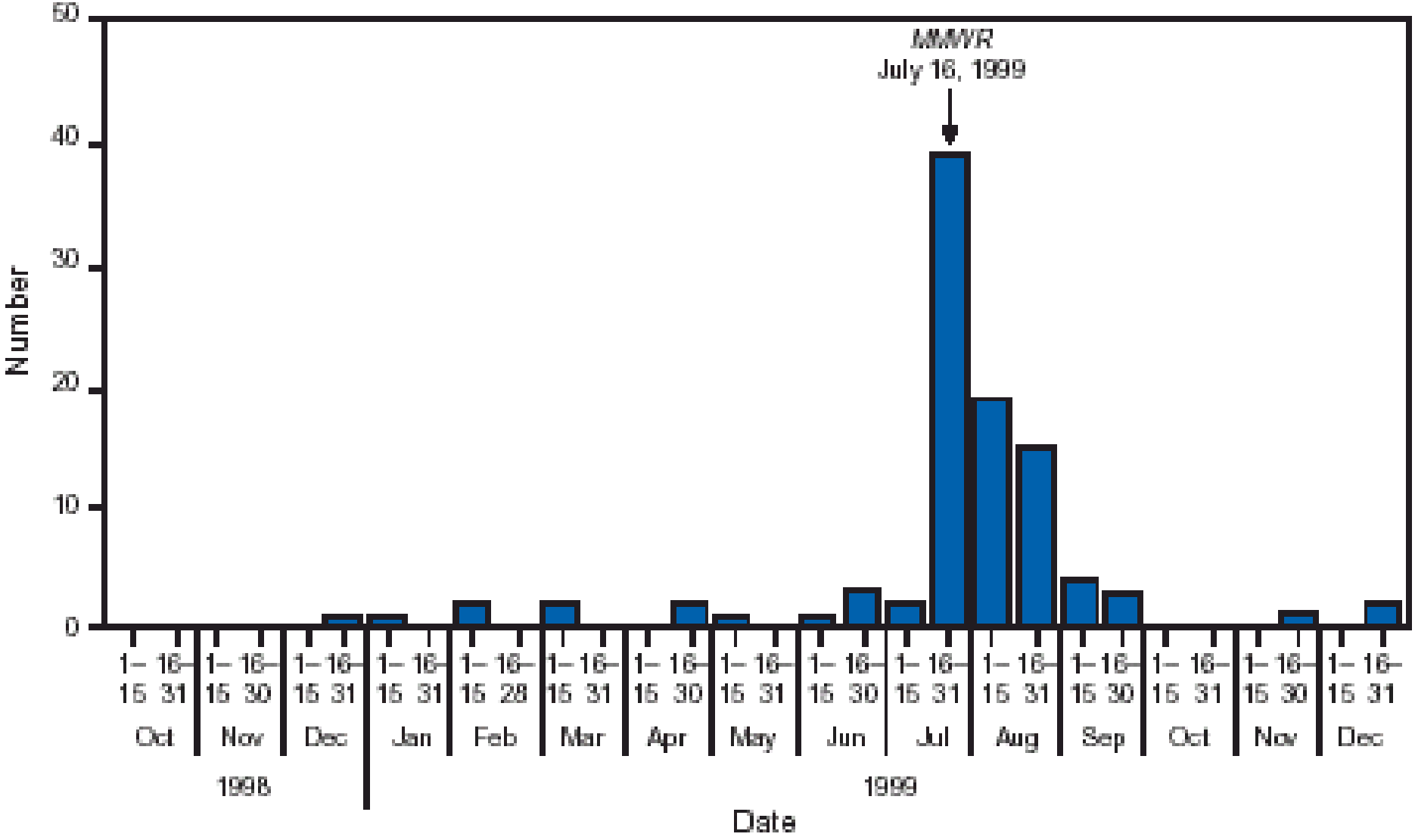
Courtesy Umesh Parashar, CDC

Rotavirus Vaccines, History

- Aug l998 — RotaShield® approved
- July 1999 — RotaShield® withdrawn
- Jan 2001 — Rotateq REST Study initiated
- Sept 2004 — 70,000th subject enrolled
- April 2005 — BLA submitted to U.S.FDA
- Feb 3, 2006 — Rotateq BLA approved (U.S)
- 2008 — Rotarix BLA approved (U.S) *

- * Approval of Rotarix in Latin America preceded U.S. licensure

FIGURE 1. Number* of confirmed cases of intussusception after implementation of rhesus-human rotavirus reassortant-tetravalent vaccine, by date reported to the Vaccine Adverse Event Reporting System — United States, October 1, 1998–December 31, 1999



Intussusception Randomized Study

	All cases of IT		Vaccine Dose #1		Vaccine Dose #2		Vaccine Dose #3	
Days Post Dose	Rota	Pla	Rota	Pla	Rota	Pla	Rota	Pla
0-7	1				1			
0-14	1	1			1			1
0-21	3	1			3			1
0-42	6	5		1	4	1	2	3
0-60	8	6	1	1	5	2	2	3
0-462	13	19						

Expected (Extrapolated) & Observed IT Cases per Vaccine Dose, 1-21 Days Post-vaccination in Study

Days Post vaccine Dose	IT Cases After Vaccine Dose 1*		IT Cases After Any Vaccine Dose	
	Observed among vaccinees	Expected based on background rate**	Observed	Expected **
1-7	0	0.34	1	1.01
8-14	0	0.34	0	1.01
15-21	0	0.34	2	1.01

** Background rate used =1 case per 2,000 person-years (50 per 100,00)

Risk of Intussusception for the New Rotavirus Vaccines

- In some studies, a small association was found, but the vaccines remained in the market
- Attributable risk:
  - CDC: “if a risk does exist of the magnitude seen in Mexico, 1 case of intussusception caused by rotavirus vaccine would occur per 100,000 infants vaccinated following age recommendations”*
- Age at vaccination, background risk of intussusception and rates of rotavirus hospitalization and death change (often dramatically) by country
  - Safety evaluations (and eventually benefit risk assessments) should be applicable to the specific Region/Country in which the vaccine is being used

** http://www.cdc.gov/vaccines/vpd-vac/rotavirus/intussusception-studies-acip.htm*

Need for Country and Subpopulation Specific Data

- Limited data for 1st dose at age >12 weeks or 3rd dose beyond age 34 weeks
- Initial Rotavirus trials do not address use in infant populations such as:
  - children with HIV
  - underlying gastrointestinal disorders
  - infants who reside in areas outside the U.S. where the standard of care is to give live oral polio vaccine.

Help is on the way..

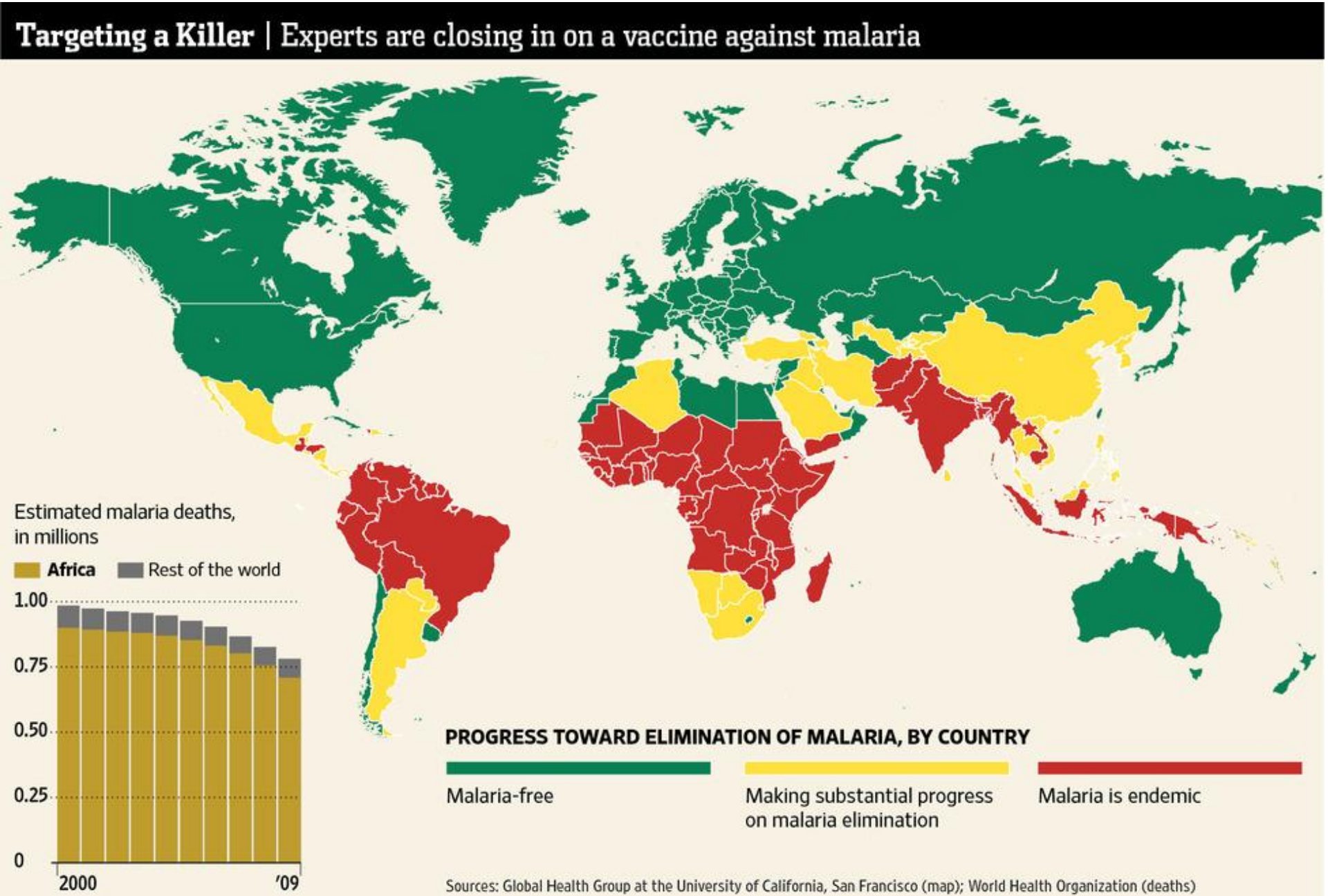
- Safety of the pentavalent vaccine (Rotateq) in Kenya including among HIV-infected and HIV-exposed infants
  - Laserson et al, Vaccine 2012, in press

  - Conclusion:SAEs were not significantly more common among HIV-infected or HIV-exposed children, however the low number of HIV-infected infants did not provide sufficient power to assess safety among HIV-infected vaccine recipients

New Vaccines for LMIC

- Many vaccines may be introduced in the next decade against diseases such as typhoid, malaria, and dengue.
- Tuberculosis cases will continue to burden mainly developing countries, there are efforts towards overcoming obstacles to make available new and powerful TB vaccines
- People living in high risk countries are in need of vaccines to treat neglected diseases such as hookworm infection, Chagas, sleeping sickness, which are in early stages of development

Example: Malaria

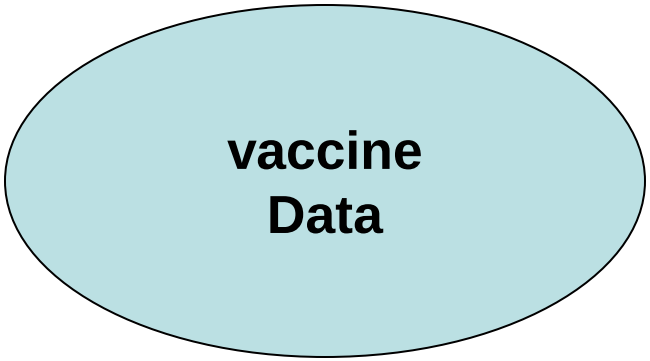


A Promising New Malaria Vaccine

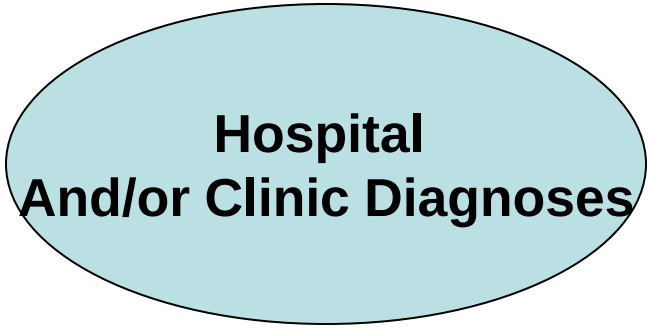
- A new malaria vaccine is being developed by a public–private partnership between GlaxoSmithKline and PATH, supported by the Gates Foundation*
- Intended primarily for use in infants and young children in sub-Saharan Africa.
- Randomized study in Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique and Tanzania.
- Preliminary results show that in children aged five to 17 months, the vaccine:
  - Lowered risk of clinical malaria by 56% during the 12 months after vaccination.
  - Cut risk of severe malaria by 47%

*** NEJM, 2011**

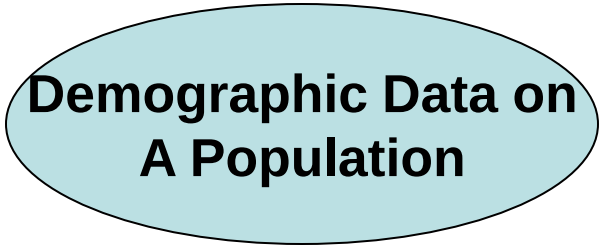
What Data is Needed for a Network?



Exposure information at a minimum for cases



Outcome or Possible "Adverse Event"



NOTE:

- **Can do SCCS (and obtain RR) with Outcome and Vaccine data or case control if demographics also available**
- **With all three, can calculate rates and attributable risk**

Importance of Broad Based Participation

- With globalization of vaccine manufacturing, globalization of evaluation is required.
- Increasing focus on development of vaccine targeting the developing world requires safety evaluation infrastructure in the same geographic area.
- Potential variability in susceptibility to adverse events requires a diverse population to evaluate vaccine safety

Summary of Benefits of a Global Vaccine Safety Network

- An unsubstantiated vaccine safety scare could incapacitate a valuable vaccine program.
- Without a ready infrastructure, responding to such a scare or safety issue could take so long that the program could be dead by the time an analysis is done.
- Lack of participation of local experts can undermine credibility of results
- Allow evaluations of safety concerns across a large population
- Allow retesting of results from one country in another setting
- Provide a basis for mentoring and facilitating development of infrastructure where it currently does not exist.
- Support evidence-based decision making by the WHO GACVS and other bodies.


Thanks