Clinical trials: an overview of issues to be considered

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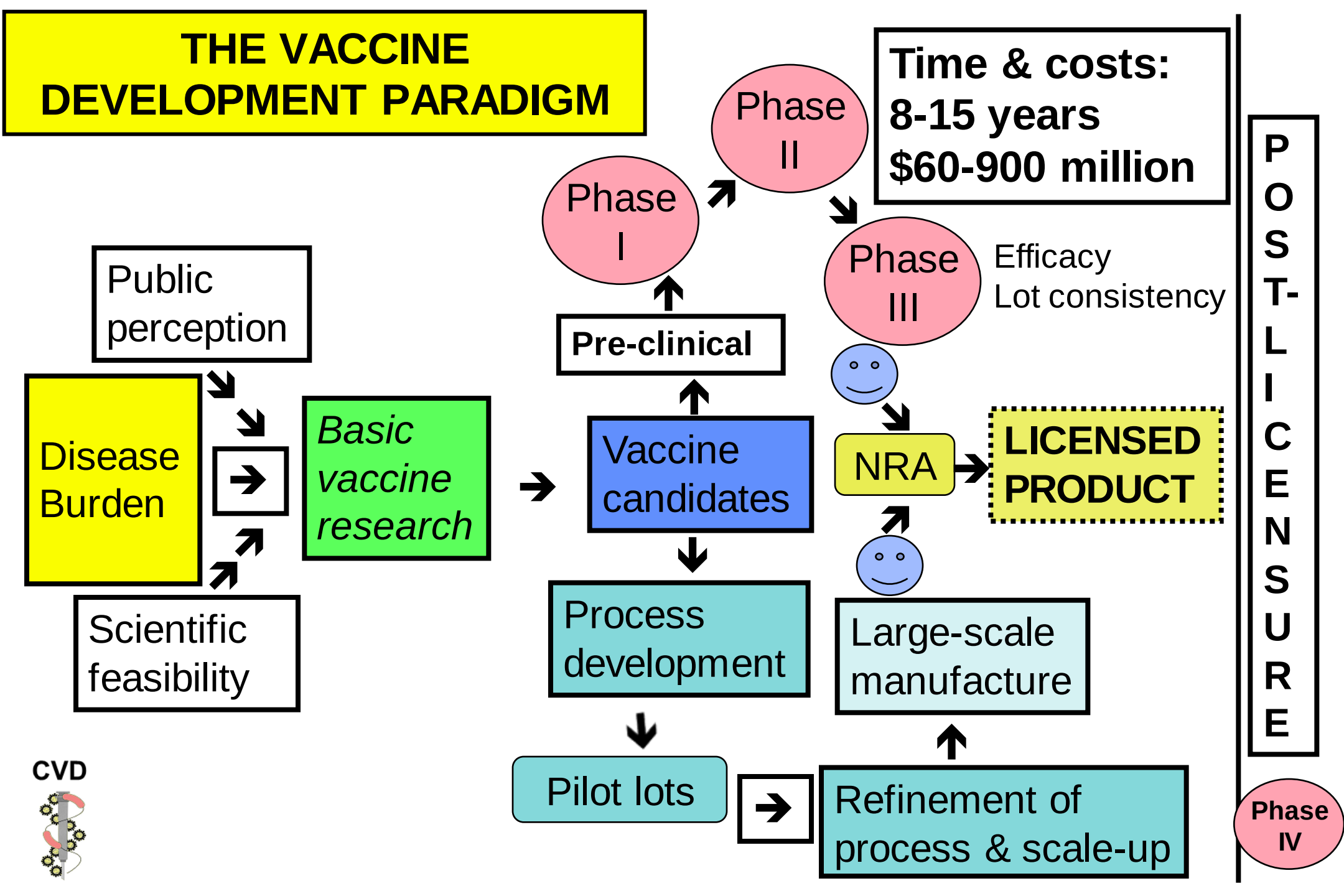
THE VACCINE DEVELOPMENT PARADIGM
Time & costs:
8-15 years
$60-900 million
Phase II
Phase I
Phase III
Efficacy
Lot consistency
Public perception
Disease Burden
Scientific feasibility
Basic vaccine research
Pre-clinical
Vaccine candidates
Process development
Pilot lots
Refinement of process & scale-up
Large-scale manufacture
NRA
LICENSED PRODUCT
POST-LICENSURE
Phase IV
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The vaccine trials paradigm

- **Phase I -** Preliminary safety & immune response in small numbers of subjects
- **Phase II -** Safety & immunogenicity in larger groups; target populations; determine immunization schedule; choose the formulation; show compatibility with concomitant vaccines
- **Phase III** - Efficacy in large-scale trials (randomized, controlled, double-blind design, when possible)

LICENSURE

- **Phase IV -** Impact & safety post-licensure under real-life conditions; modifications in formulation and immunization schedule

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DISEASE BURDEN, MARKETS & VACCINE DEVELOPMENT

"Global market vaccines" - e.g., Hepatitis B, Hib, rotavirus, pneumo

- Burden in both industrialized and developing countries
- Markets in industrialized countries drive development

"Industrialized market vaccines" - e.g., Lyme disease; nicotine

- Burden & markets in industrialized countries drive development

"Impeded vaccines" - e.g., RSV, group A streptococcus

- Markets exist but safety questions raise the risk and create barriers

"Developing market vaccines" - e.g., malaria, *Shigella*, *Leishmania*

- Burden in developing countries; few "reliable" or "mature" markets

"Biodefense vaccines" - e.g., anthrax rPA, tularemia, smallpox, etc.

- Burden is theoretical and governments create the market

"Pandemic vaccines" - e.g., Swine flu 1976 & 2009, Avian flu 2006

- Burden sometimes unclear; gov'ts must guarantee a market

"Special" Phase I vaccine trials

- **What is the ultimate target population?**
  - Infant vaccines often require small step-wise Phase I studies in older children before descending to infancy
- **Live viral and bacterial vaccines**
  - Often require special precautions (e.g., **physical containment**)
  - Preliminary assessment of **excretion and transmission** to contacts
- **Impeded vaccines**
  - (e.g., RSV, group A *Streptoccoccus pyogenes*)
  - Trials involve particularly intensive clinical surveillance and regulatory oversight
- **Unusual vaccines**
  - (e.g., "edible vaccines" derived from transgenic plants)

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Phase II vaccine trials

- **"Bread & butter"** trials of vaccine development
- **Pave the way** for pivotal Phase III trials
- Often **less "visible"** than Phase I and III trials
- Sites and populations for Phase II trials
- Carefully **select and validate the immune response(s)** to be measured
- **Finalize formulation** as soon as possible
  - Communication with process developers
  - Communication with immune response measurers
- **Harmony** with existing immunization schedules
- **Compatibility** with concomitant vaccines

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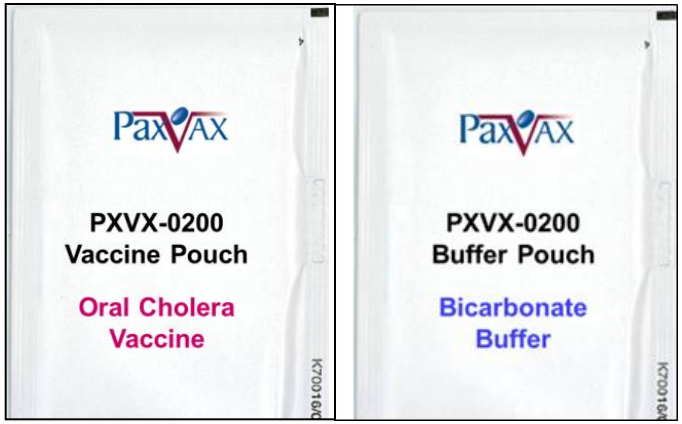
Phase II vaccine trials

Live vaccines

- Shedding pattern
- Transmissibility to contacts
- Environmental impact (GMOs)
- Genetic stability of isolates



Phase IIB tudies

- Characterize se to wild type pat allenge)
- Measure **eff**
- Identify vacc ion
- Where challe
  - Pre-erythro
  - Cholera vac
  - *Shigella* vac
  - Enterotoxig
  - Influenza va
  - Typhoid vac

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Efficacy of PAXVAX0200 (CVD 103-HgR) in preventing moderate and severe El Tor cholera when challenged 10 days after ingestion of a single oral dose of vaccine

Cholera

Attack Rate	Vacc	Ctrls	Efficacy
Moderate/severe	2/35	20/33	91%
(i.e., > 3.0 liters)	5.7%	60.6%	

Challenge with 10^5 CFU of NIH El Tor Inaba N16961 frozen inoculum

This study design was requested by the FDA

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Assessing vaccine efficacy pre-licensure

- "**Gold Standard**" -- Large-scale, adequately-powered, randomized, controlled, double-blind trial with allocation at the level of the individual
- Trials with **cluster randomization** of larger units such as classes, schools, families, villages
- **Seroprotection** (immunologic correlate of protection known) or **serological non-inferiority**
- Mass interventions; **"before and after" analysis**
- **Volunteer challenge studies**
- FDA **"Animal model rule"** (e.g., biodefense vaccines, intermittent unpredictable burden, etc.)

Large-scale Phase III vaccine field trials

- Selection and preparation of the study site
  - Impetus; incidence rate, seasonality, modes of transmission, adequacy of health care and microbiology infrastructure, census, migration data, etc.
- Protocol design (**"pivotal study"**)
- **Financing** large-scale trials (industry; public; partners)
- Some **ethical issues**
- **Nurturing political commitment and ownership**
- Execution of the trial (**logistics & management**)
- Interaction with the **DSMB**
- **Analysis** of the data
- **Post-trial commitments** (to subjects & Ministry)

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Phase III study protocol

Primary aim(s)

- Must be clear, precise, achievable
- Must provide the evidence base for:
  - Licensure
  - Public health use
- Sample size influenced by:
  - Number of study groups and comparisons
  - Out migration
  - Power to detect a true difference
  - Alpha value
  - Lower Limit of the 95% CI for vaccine efficacy
  - Herd immunity effect on incidence

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Reasons to randomize by units other than individual subjects

- Nature of the vaccine:
  - Live vaccine with potential for person-to-person transmission
  - Vaccine functions at the community level (e.g., transmission-blocking malaria vaccine)
- Logistics and practicality
- Attempt to measure herd immunity

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Intervention with live oral (SmD) *Shigella sonnei* vaccine in a *S. sonnei*-endemic institution

	Year		*Shigella sonnei* cases
	1968		50
	1969		38
	1970		36
	1971		88
→	1972	Vaccine trial	0

Levine et al, Am J Epidemiol 1976

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Allocation to treatment groups in Santiago field trials of Ty21a

- Randomly allocated whole classes to receive Ty21a oral vaccine or oral placebo
- All children of consenting parents in a given class received the same product and regimen
- Vaccination during springtime (before school summer recess)
- Peak typhoid incidence during summer

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Efficacy of liquid formulation of Ty21a, Area SurOriente & Area Norte, Santiago

	Ty21a	Placebo
No. children	36,623	10,302
Incidence/10^5 children	63	272
Efficacy	77%	-
(95% CI)	(60-87%)	-
No. classes	2,369	687
Classes with typhoid /10^2 classes	0.97	3.93
Efficacy	75%	-
(95% CI)	(56-85%)	-

3 oral doses, every other day interval. 3 years of follow-up. Levine et al, Lancet 1990

Selecting the control preparation for vaccine efficacy trials

- ***True placebo***
- A ***licensed vaccine*** against another infection that will have no effect on the study outcome events
  - provides a benefit for control subjects
  - sometimes difficult to find a suitable vaccine
  - may compromise double blindness
- An ***experimental vaccine*** against another infection that will have no effect on the study outcome events
  - good for efficacy but not for safety evaluation

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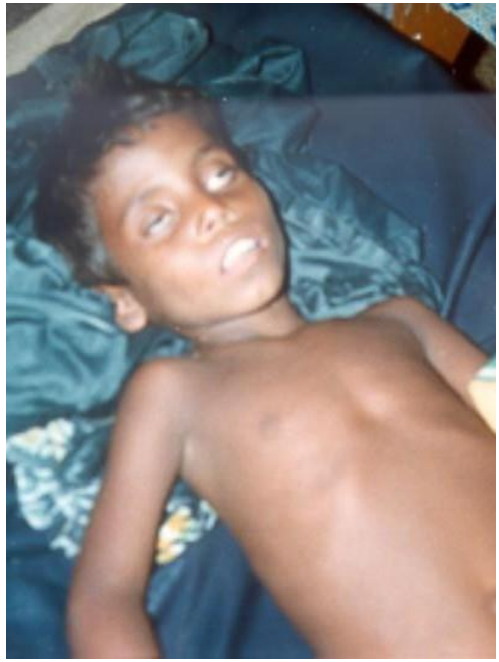
Role of “luck” in large-scale vaccine field trials

- **Year to year variation** in disease incidence (e.g., cholera)
- **Antigenic change** in the circulating pathogen (e.g., influenza virus)
- **Geographic variability** within an endemic zone (e.g., meningococcus)
- Sometimes disease “hot spots” turn cold without precise explanations (e.g., malaria in some places in sub-Saharan Africa)



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Strengthening infrastructure to support large-scale vaccine trials

- In large-scale trials in developing countries:
  - Microbiologic infrastructure often has to be strengthened
  - Health care infrastructure must often be reinforced

Automated blood culture machines introduced, Gabriel Touré Hospital bacteriology lab,- Bamako, Mali, 2002

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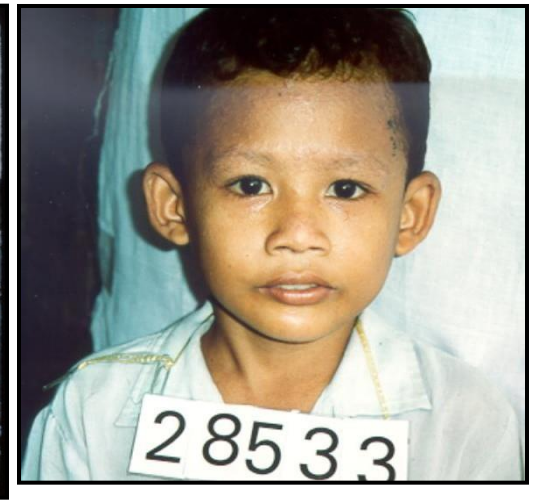
“Politics” and large-scale vaccine field trials

- Like it or not, in one way or another, politics always impinge on large-scale vaccine field trials
- The political aspects of vaccine trials must be recognized, considered and addressed

Ex-President of Mali, Amadou Toumani Toure

Organizing and executing large-scale vaccine field trials
It's the LOGISTICS, darn it!!!



Technical advances that have revolutionized large-scale field trials:

- Cell phones
- Notebook computers, tablet computers & PDAs
- Internet
- Skype & equivalent
- ICH (harmonization of Good Clinical Practices, etc.)

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Good Clinical Practice (GCP)

The comprehensive regulations and guidelines for conducting clinical trials that must be followed for results of those trials to be contained within an application requesting licensure of the vaccine.

Protocol design	Informed consent
Record keeping	Data reporting
Laboratory SOPs	Adverse event reporting

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Performing vaccine trials

- The **TRIAL PROTOCOL**, a key document, is a "bible" for those conducting the study
- **WRITE** in the protocol exactly what you propose to do
- **DO** what you wrote you would do
- **LEAVE** a pristine document trail so that an independent interested party, monitor or auditor can verify that you **DID WHAT YOU WROTE YOU WOULD DO**

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Assessing vaccine safety during efficacy trials

Nested reactogenicity/immunogenicity trial

- Reactogenicity/immunogenicity of actual field trial lots
- Typically includes 1-5% of total trial participants
- Usually involves active surveillance

Surveillance for serious adverse events (SAEs)

- All hospitalizations and deaths monitored
- Adapt surveillance to fit local setting
- In developing country settings, repeated census and verbal autopsies may be required

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Unexpected morbidity and mortality detected during pre-licensure efficacy trials

Phase III trials of formalin-inactivated RSV vaccine, USA

Increased incidence of severe RSV disease in vaccinees vs controls

Chin J et al 1969; Fulginiti et al 1969; Kapikian et al 1969

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Post-licensure impact and safety of vaccines

- *Disappointment -*

- *Serendipity -*

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Post-licensure impact and safety of vaccines

- *Disappointment* - Rotashield®
  (intussusception)

- *Serendipity* - Hib & pneumo conjugates
  (indirect protection)

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Phase IV surveillance to document product safety and impact

- Surveillance for rare adverse events
- Effectiveness/impact
  - Fall in incidence
  - Case/control studies
  - Large-scale post-licensure selective vaccination and intensive surveillance

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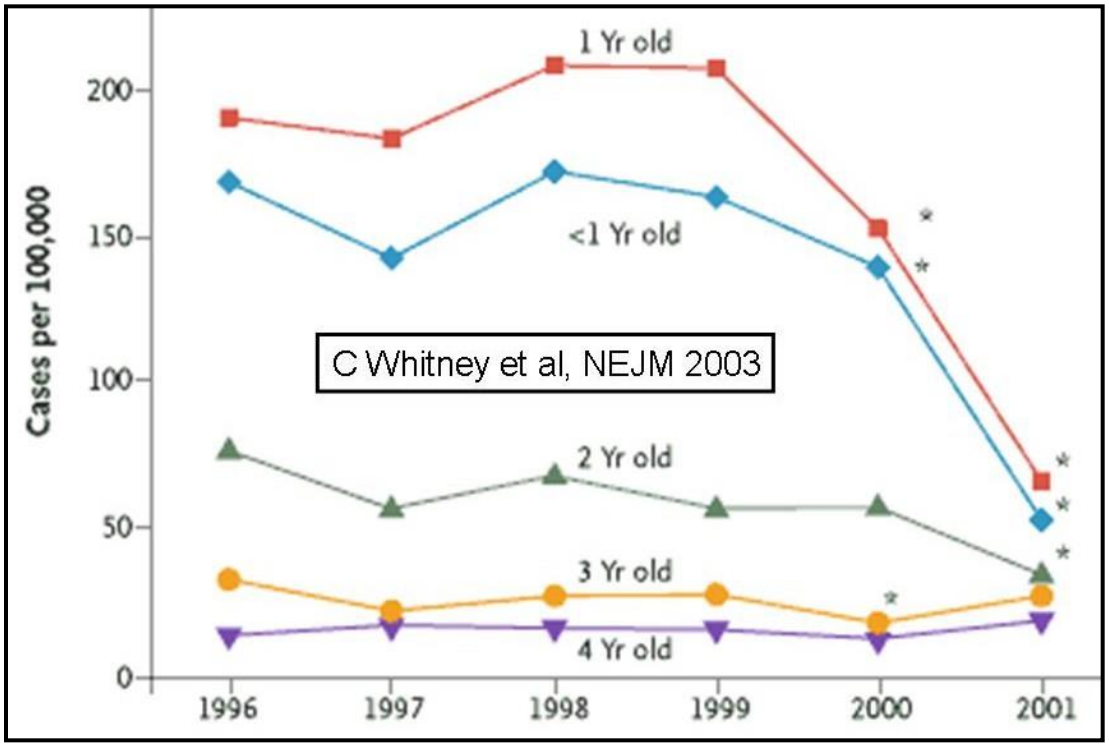
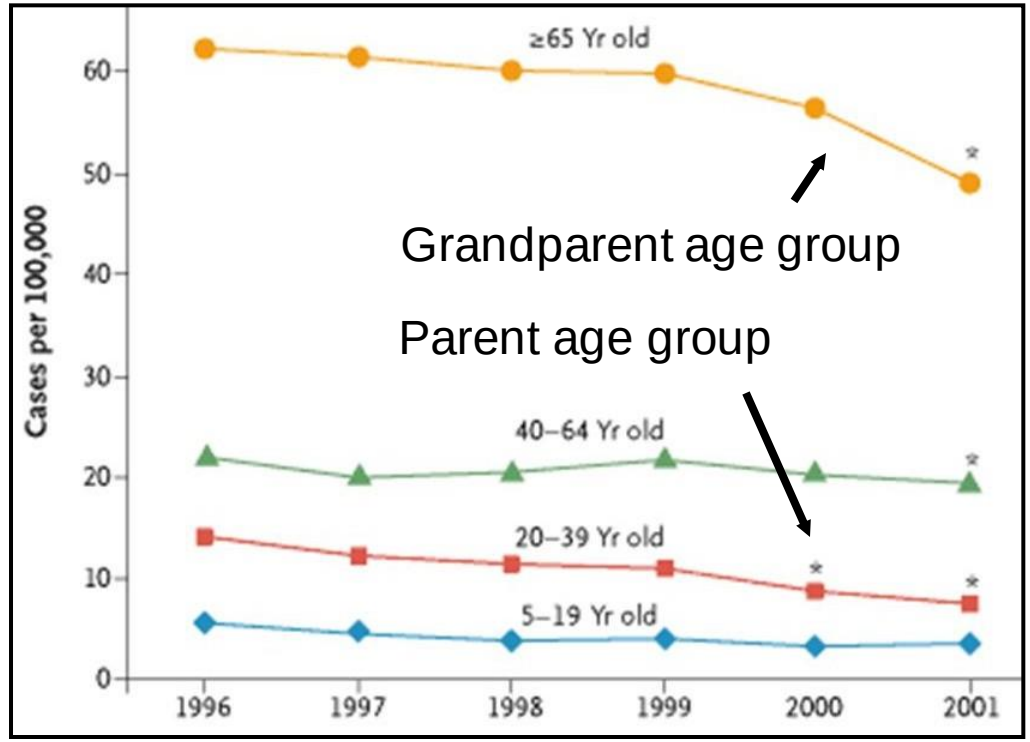
Post-licensure impact of Prevnar® on invasive pneumococcal disease in USA





C Whitney et al, NEJM 2003

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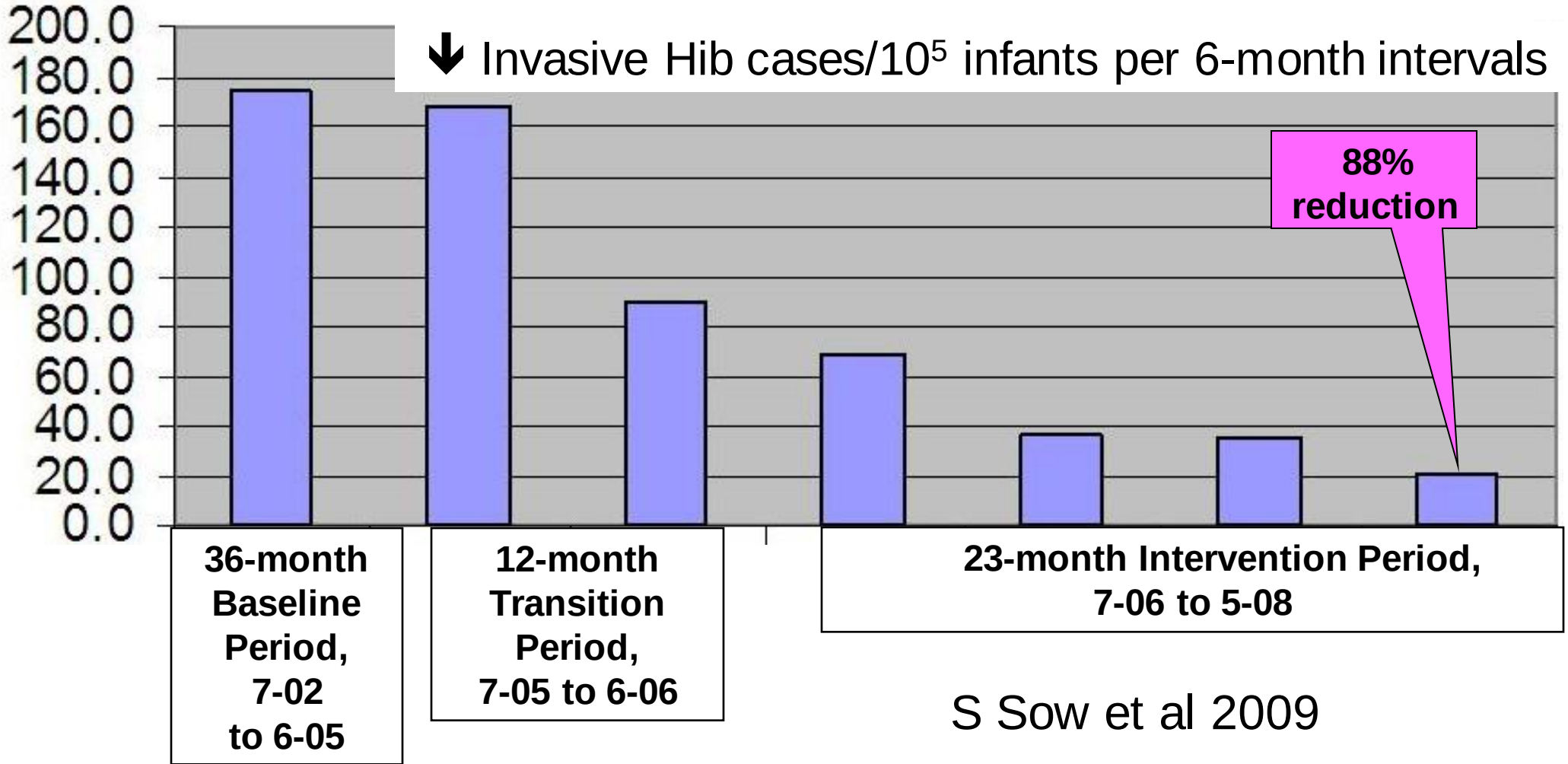
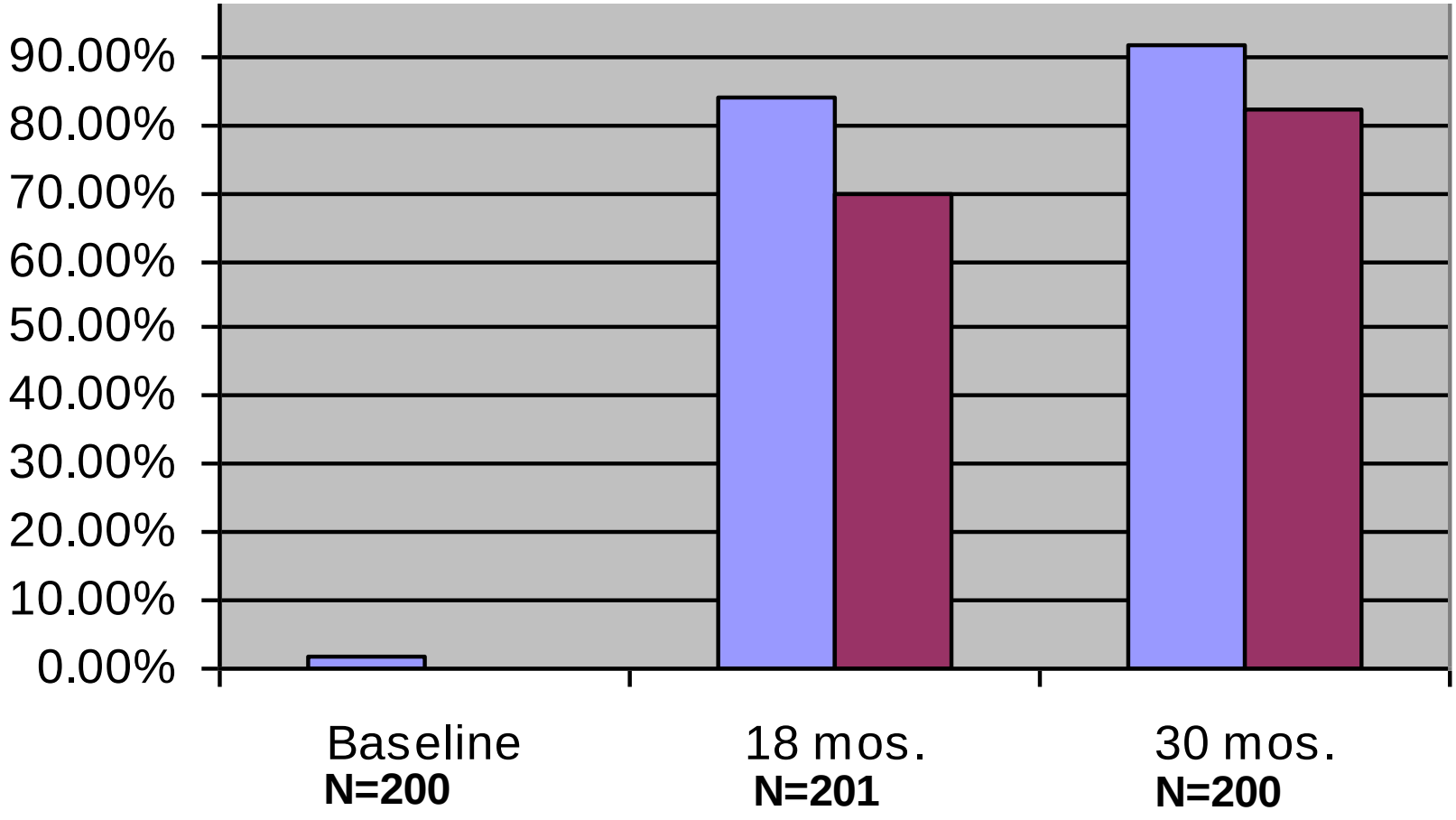
Impact of Hib vaccine introduction on invasive Hib disease in infants, Bamako, Mali



S Sow et al 2009

Prevalence of serum Hib PRP antibodies in Malian infants 6-7 months of age before and 18 & 30 months after the introduction of Hib conjugate into the EPI for Malian infants



S Sow et al, AJTMH 2009

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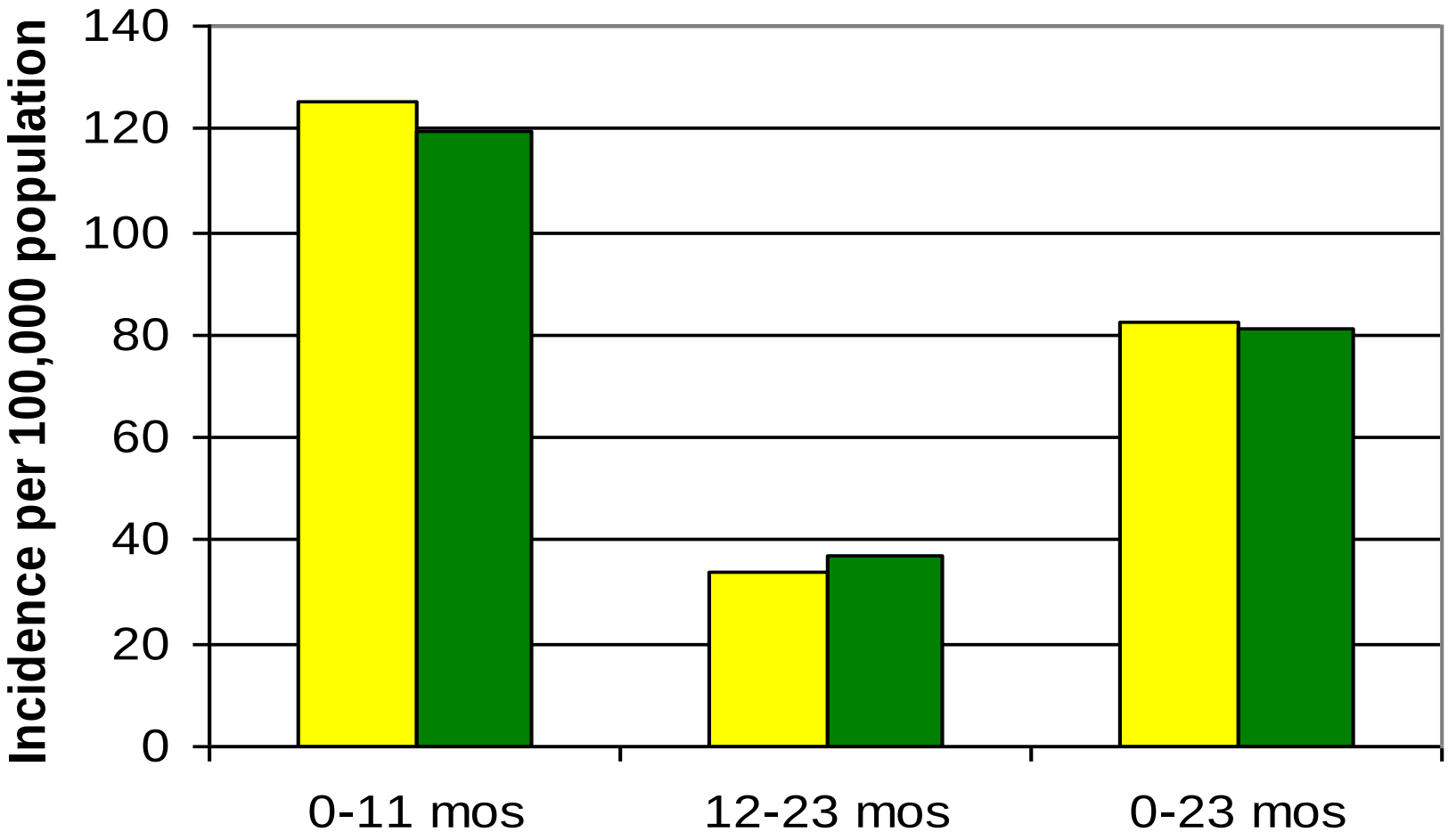
Lack of impact of Hib vaccine introduction on invasive pneumococcal hospitalizations



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Vaccine effectiveness -- Hib cases during 30 mos. of follow-up among children assigned to the two sets of health centers during the selective vaccination

	Santiago Health Centers: DTP (N=35)	DTP/PRP-T (N=36)	
Assigned population:	46,948	48,080	
No. Hib cases	40	4	p<.001
Effectiveness		90% (CI=75-100%)*	

* (95% Confidence Interval)
Lagos et al, Ped Infect Dis J 1996
Santiago, Chile

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Post-licensure effectiveness of oral cholera vaccines

Micronesia outbreak, Pohnpei, 2000

- WHO evaluation of live oral cholera vaccine CVD 103-HgR
- Retrospective cohort study of Pohnpei target population vaccinated
- Cholera case records & vaccination registries matched
- 47% of population vaccinated during mass campaign
- Cholera incidence 5x higher in non-vaccinees
- **Vaccine Efficacy = 79% (CI, 72-85%)**
  (Vaccine 2004)

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Post-licensure maternal immunization effectiveness trials are currently ongoing in 3 developing countries: Nepal, South Africa, Mali

- 3rd trimester immunization of pregnant women
- **Primary aim** is to determine if infants born to immunized mothers are protected against laboratory-confirmed influenza
- Randomized (level of individual) controlled trials:
  - Nepal & S Africa – flu vaccine vs plbo (3000 & 2100 women,)
  - Mali – flu vaccine vs quadrivalent meningococcal conjugate (Menactra™) (4192 women)

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Enjoy ADVAC 2014
and Lake Annecy!!

Thanks
Merci
Gracias
Grazie
Danke
Obrigado

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