Assessing public health impact through "vaccine probe" analyses

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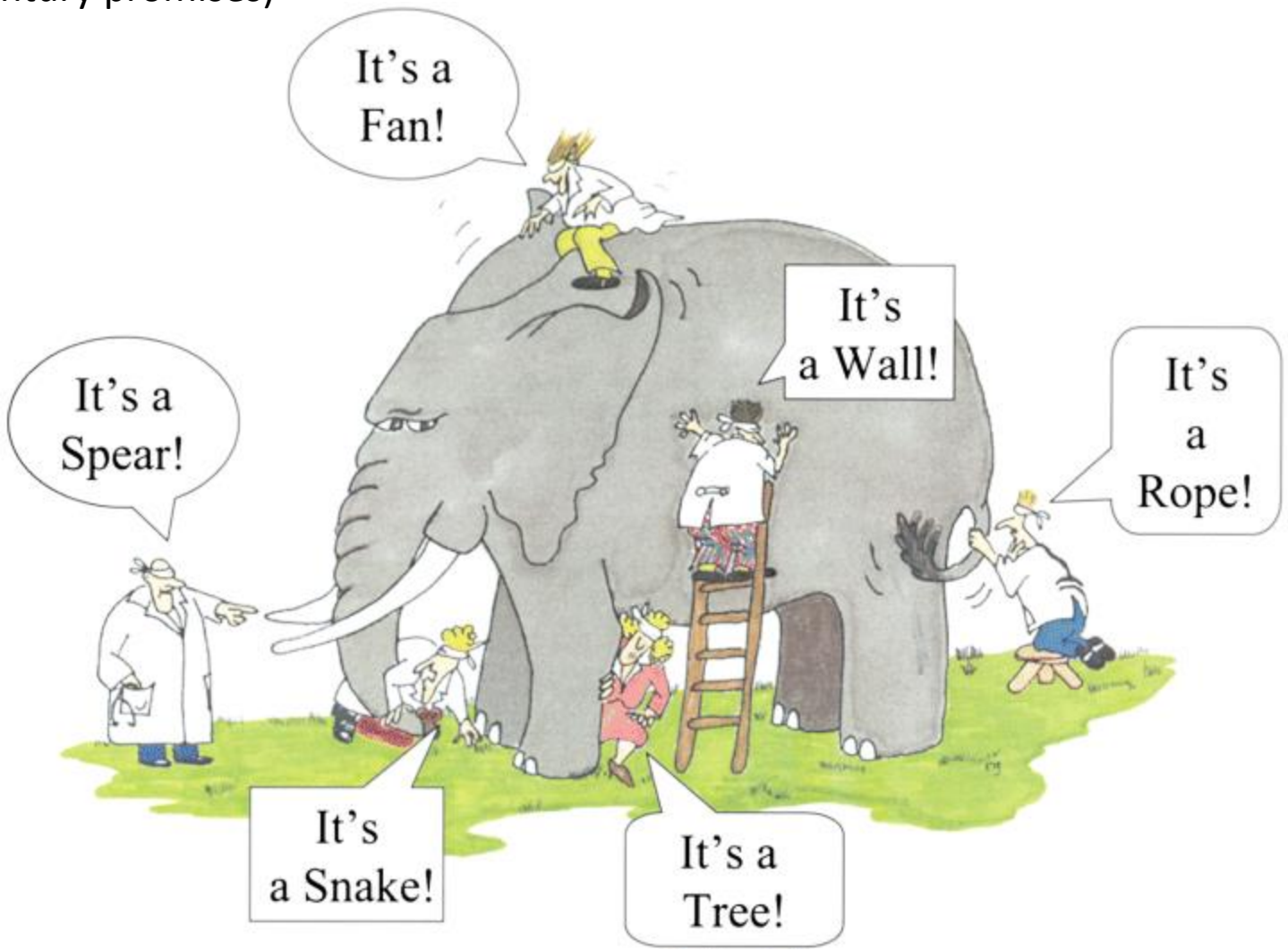
State of understanding the relative role of pathogens in major disease syndromes and entities (despite 21st century promises)



https://sidewayslookatscience.wordpress.com/2013/12/27/blindfoldedly-feeling-an-e-lephant-why-studying-the-internet-has-got-me-all-confused/

Yet understanding the elephant is important

- For priority setting
  - Research
  - Development (especially vaccines and chemotherapeutics)
  - Public health prevention and control programs especially where there are limited resources
- For designing targeted prevention strategies (i.e. vaccines)
- Once you have a package of vaccines, what evidence do you use to decide which ones to spend your limited funds on

Chun-Ju Chiang, Ya-Wen Yang, San-Lin You, Mei-Shu Lai, Chien-Jen Chen, SEP 4, 2013

From 1977-1980 to 2001-2004, age- and sex-adjusted rate s for individuals aged 5 to 29 years decreased by more than 90% for chronic Liver disease and hepatocellular carcinoma (HCC) (95% CI=66-98%) mortality and by more than 80% for HCC incidence (95% CI=35-94%).

RESEARCH LETTER

Thirty-Year Outcomes of the National Hepatitis B Immunization Program in Taiwan

Hepatitis B virus (HBV) infection causes infant fulminant hepatitis (IFH), and chronic HBV infection may progress to chronic liver disease (CLD) and hepatocellular carcinoma (HCC). Taiwan launched a nationwide HBV immunization program for newborns in July 1984,[1] which has successfully lowered the prevalence of chronic HBV carriers, incidence of HCC, and mortality of IFH in vaccinated birth cohorts.[2-4] The mortality of CLD before and after HBV immunization has never been examined. We assessed the 30-year outcomes of the immunization program.

Methods | From July 1984 to June 1986, the immunization program covered only newborns with high-risk mothers who were seropositive for HBV surface antigen. Coverage was extended to all newborns in July 1986, preschool children in July 1987, and primary school children in 1988-1990. Recombinant HBV vaccines replaced plasma-derived vaccines in 1992. The immunization coverage rates for birth cohorts from 1984 to 2010 was 88.8% to 96.9%.[2,5]

The mortality of IFH, CLD, and HCC and the incidence of HCC were compared among birth cohorts born before and after the launch of the program. The National Death Certificates Database (1977-2011) was used to derive the mortality rates of IFH (*International Classification of Diseases, Ninth Revision* [*ICD*-9] code 570), CLD (*ICD*-9 code 571), and HCC (*ICD*-9 codes 1550 and 1552); the National Cancer Registry Database (1977-2009) was used to derive the incidence rates of HCC (*International Classification of Diseases for Oncology* code C220).[6] Infant fulminant hepatitis was analyzed in birth cohorts to 2009-2011, whereas other outcomes were analyzed in birth cohorts to 2001-2004 (age range: 5-29 years in 2009). To control sex and duration of HBV infection, sex-adjusted or age- and sex-adjusted incidence and mortality rate ratios were calculated using Poisson regression models (SAS version 9.2; SAS Institute Inc). Two-sided $P < .05$ was considered statistically significant. This study was approved by the data release review board of the Bureau of Health Promotion, which waived the requirement for informed consent.

Results | Infant fulminant hepatitis mortality rates and sex-adjusted rate ratios declined significantly for infants born from 1977-1980 to 2009-2011 (**Table**). The decline was greatest from 1981-1984 to 1985-1988 and from 1989-1992 to 1993-1996, coincident with the launch of the national immunization program in 1984 and the change to recombinant vaccines in 1992. Compared with 1977-1980, the sex-adjusted rate ratio declined to 0.88 (95% CI, 0.65-1.21) in

Table. Mortality Rates of Infant Fulminant Hepatitis, Chronic Liver Diseases, and Hepatocellular Carcinoma and Incidence Rates of Hepatocellular Carcinoma of Birth Cohorts Born Before and After the Launch of Hepatitis B Immunization Program in 1984 in Taiwan

	Mortality in Ages 5-29 y												Hepatocellular Carcinoma Incidence in Ages 5-29 y			
	Infant Fulminant Hepatitis					Chronic Liver Disease				Hepatocellular Carcinoma						
Birth Years	PY Under Observation	No. of Cases	MR[a]	Sex-ARR (95% CI)	PY Under Observation	No. of Cases	MR[a]	Age- and Sex-ARR (95% CI)		No. of Cases	MR[a]	Age- and Sex-ARR (95% CI)		PY Under Observation	No. of Cases	IR[b]	Age- and Sex-ARR (95% CI)
1977-1980	1 492 223	86	5.76	1 [Reference]	39 962 223	260	0.65	1 [Reference]		325	0.81	1 [Reference]		39 962 223	454	1.14	1 [Reference]
1981-1984	1 433 854	73	5.09	0.88 (0.65-1.21)	37 443 552	147	0.39	0.65 (0.53-0.79)[c]		209	0.56	0.70 (0.59-0.83)[c]		36 301 908	278	0.77	0.73 (0.63-0.85)[c]
1985-1988	1 210 040	32	2.64	0.46 (0.31-0.69)[c]	26 428 945	35	0.13	0.40 (0.28-0.57)[c]		78	0.30	0.43 (0.33-0.55)[c]		25 146 138	94	0.37	0.48 (0.38-0.60)[c]
1989-1992	1 236 620	33	2.67	0.46 (0.31-0.69)[c]	21 172 702	5	0.02	0.12 (0.05-0.28)[c]		36	0.17	0.27 (0.19-0.39)[c]		19 895 132	46	0.23	0.37 (0.27-0.51)[c]
1993-1996	1 207 901	8	0.66	0.11 (0.06-0.24)[c]	16 201 336	11	0.07	0.39 (0.02-0.73)[d]		20	0.12	0.21 (0.13-0.34)[c]		14 908 280	33	0.22	0.43 (0.30-0.62)[c]
1997-2000	1 125 123	4	0.36	0.06 (0.02-0.17)[c]	10 046 542	3	0.03	0.16 (0.05-0.50)[d]		12	0.12	0.21 (0.12-0.38)[c]		8 867 241	15	0.17	0.37 (0.21-0.62)[c]
2001-2004	907 460	2	0.22	0.04 (0.01-0.16)[c]	4 084 224	1	0.02	0.11 (0.02-0.80)[e]		2	0.05	0.08 (0.02-0.34)[c]		3 391 623	3	0.09	0.20 (0.06-0.65)[e]
2005-2008	767 813	3	0.39	0.07 (0.02-0.21)[c]													
2009-2011	527 323	1	0.19	0.03 (0.01-0.24)[d]													

Abbreviations: ARR, adjusted rate ratio; PY, person-years.

[a] Indicates mortality rate (MR) per 100 000 PY.

[b] Indicates incidence rate (IR) per 100 000 PY.

[c] $P < .001$.

[d] $P < .01$.

[e] $P < .05$.

Recombinant HBV vaccines replaced plasma-derived vaccines in 1992.

Immunization coverage rates for birth cohorts from 1984 to 2010 was 88.8% to 96.9%.

Cluster randomized trial

94-95% efficacy against
Chronic hep B infection
18-22 years later

Impact on liver cancer analysis
expected in 2017

Herd immunity will have
to be considered

Peto et al. BMC Infectious Diseases 2014, 14:7
http://www.biomedcentral.com/1471-2334/14/7

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Efficacy and effectiveness of infant vaccination against chronic hepatitis B in the Gambia Hepatitis Intervention Study (1986–90) and in the nationwide immunisation program

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Abstract

Background: Gambian infants were not routinely vaccinated against hepatitis B virus (HBV) before 1986. During 1986–90 the Gambia Hepatitis Intervention Study (GHIS) allocated 125,000 infants, by area, to vaccination or not and thereafter all infants were offered the vaccine through the nationwide immunisation programme. We report HBV serology from samples of GHIS vaccinees and unvaccinated controls, and from children born later.

Methods: During 2007–08, 2670 young adults born during the GHIS (1986-90) were recruited from 80 randomly selected villages and four townships. Only 28% (753/2670) could be definitively linked to their infant HBV vaccination records (255 fully vaccinated, 23 partially vaccinated [1–2 doses], 475 not vaccinated). All were tested for current HBV infection (HBV surface antigen [HBsAg]) and, if HBsAg-negative, evidence of past infection (HBV core-protein antibody [anti-HBc]). HBsAg-positive samples (each with two age- and sex-matched HBsAg-negative samples) underwent liver function tests. In addition, 4613 children born since nationwide vaccination (in 1990-2007) were tested for HBsAg. Statistical analyses ignore clustering.

Results: Comparing fully vaccinated vs unvaccinated GHIS participants, current HBV infection was 0.8% (2/255) vs 12.4% (59/475), $p < 0.0001$, suggesting 94% (95% CI 77-99%) vaccine efficacy. Among unvaccinated individuals, the prevalence was higher in males ($p = 0.015$) and in rural areas ($p = 0.009$), but adjustment for this did not affect estimated vaccine efficacy. Comparing fully vaccinated vs unvaccinated participants, anti-HBc was 27.4% (70/255) vs 56.0% (267/475), $p < 0.00001$. Chronic active hepatitis was not common: the proportion of HBsAg-positive subjects with abnormal liver function tests (ALT > 2 ULN) was 4.1%, compared with 0.2% in those HBsAg-negative. The prevalence of antibodies to hepatitis C virus was low (0.5%, 13/2592). In children born after the end of GHIS, HBsAg prevalence has remained low; 1.4% (15/1103) in those born between 1990–97, and 0.3% (9/35150) in those born between 1998–2007.

Conclusions: Infant HBV vaccination achieves substantial protection against chronic carriage in early adulthood, even though approximately a quarter of vaccinated young adults have been infected. This protection persists past the potential onset of sexual activity, reinforcing previous GHIS findings of protection during childhood and suggesting no need for a booster dose. Nationwide infant HBV vaccination is controlling chronic infection remarkably effectively.

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ORIGINAL ARTICLE

Effectiveness of Maternal Influenza Immunization in Mothers and Infants

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ABSTRACT

BACKGROUND

Young infants and pregnant women are at increased risk for serious consequences of influenza infection. Inactivated influenza vaccine is recommended for pregnant women but is not licensed for infants younger than 6 months of age. We assessed the clinical effectiveness of inactivated influenza vaccine administered during pregnancy in Bangladesh.

METHODS

In this randomized study, we assigned 340 mothers to receive either inactivated influenza vaccine (influenza-vaccine group) or the 23-valent pneumococcal polysaccharide vaccine (control group). Mothers were interviewed weekly to assess illnesses until 24 weeks after birth. Subjects with febrile respiratory illness were assessed clinically, and ill infants were tested for influenza antigens. We estimated the incidence of illness, incidence rate ratios, and vaccine effectiveness.

RESULTS

Mothers and infants were observed from August 2004 through December 2005. Among infants of mothers who received influenza vaccine, there were fewer cases of laboratory-confirmed influenza than among infants in the control group (6 cases and 16 cases, respectively), with a vaccine effectiveness of 63% (95% confidence interval [CI], 5 to 85). Respiratory illness with fever occurred in 110 infants in the influenza-vaccine group and 153 infants in the control group, with a vaccine effectiveness of 29% (95% CI, 7 to 46). Among the mothers, there was a reduction in the rate of respiratory illness with fever of 36% (95% CI, 4 to 57).

CONCLUSIONS

Inactivated influenza vaccine reduced proven influenza illness by 63% in infants up to 6 months of age and averted approximately a third of all febrile respiratory illnesses in mothers and young infants. Maternal influenza immunization is a strategy with substantial benefits for both mothers and infants. (ClinicalTrials.gov number, NCT00142389.)

From the International Centre for Diarrheal Disease Research, Dhaka, Bangladesh (K.Z., E.R., S.E.A., M.R., R.R., N.S.S., R.E.B.); and the Bloomberg School of Public Health (E.W., S.B.O., M.C.S.), Institute for Vaccine Safety (S.B.O.), and Department of Pediatrics, School of Medicine (M.C.S.) — all at Johns Hopkins University, Baltimore. Address reprint requests to Dr. Steinhoff at the Children's Global Health Center, Cincinnati Children's Hospital, 3333 Burnet Ave., MLC 2048, Cincinnati, OH 45229, or at m.steinhoff@gmail.com.

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N Engl J Med 2008;359:1555-64.

Randomized Double-Blind Trial of inactivated influenza vaccine given to mothers in third trimester, Bangladesh

Variables	Episodes		Effectiveness (95% CI)
Infants	"Control" vaccine	Influenza vaccine	
Person-months	870	881	
Febrile Resp Illness	153	110	28.9 (6.9-45.7)
Diarrhea	138	137	1.9 (-30.0-26.0)
Clinic Visit	92	54	42.0 (18.2 (58.8)
Influenza test ordered	79	41	48.7 (25.4-64.7)
Influenza test positive	16	6	62.8 (5.0-85.4)

Pneumococcal Disease Burden in Developing Countries "Vaccine Probe" Approach

- Concept—Using a highly effective vaccine, it is possible to estimate burden of disease by the reduction of targeted syndromes (like pneumonia) in the vaccinated

- Blood culture is very insensitive

  —But, how do you interpret the vaccine probe data?

  - Very carefully… may depend on factors occurring at time of study, that are not universal

Randomized, Double-blind Trial of a nine-valent Pneumococcal Conjugate Vaccine The Gambia

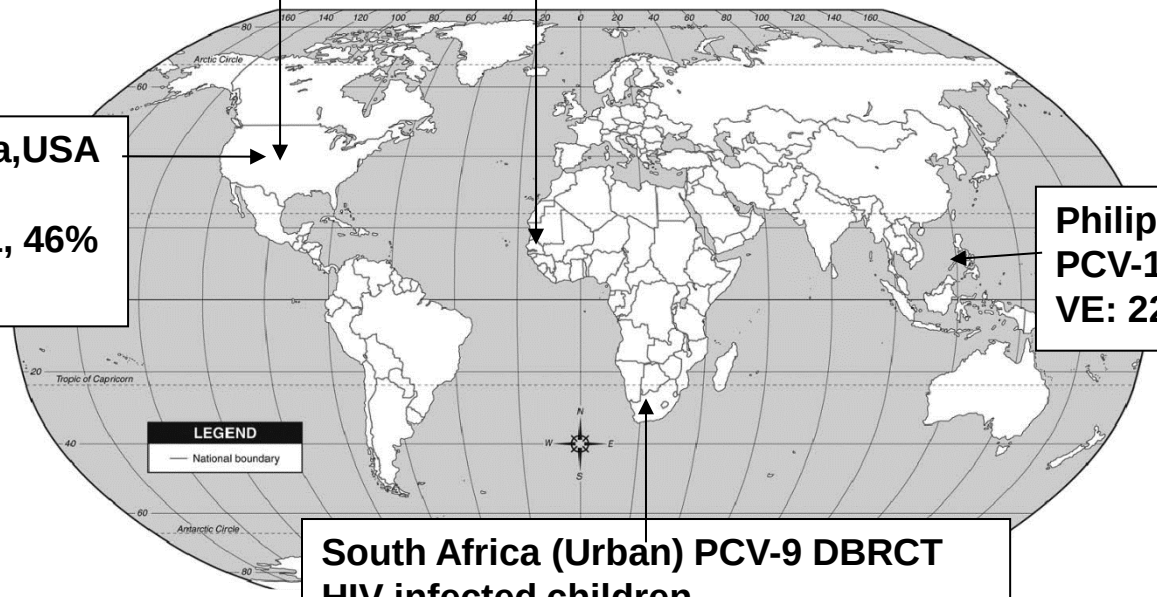
- From 2000-2003, 8,718 received vaccine and 8,719 received placebo
- Efficacy against blood-culture confirmed pneumococcal disease (caused by vaccine serotypes): 77% (95% CI 51-90)
- Invasive (blood culture confirmed) pneumococcal disease (all types): 50% (95% CI 21-69)
- Chest x-ray confirmed pneumonia: 37% (95% CI 25-48)
- Hospitalizations: 15% (95% CI 7-21)
- All cause mortality 16% (95% CI 3-28)

Cutts FT, et al. *Lancet* 2005;365:1139-46

PCV Efficacious in Reducing Radiologically Confirmed Pneumonia in Children

Navajo, USA (Rural)
American-Indians
PCV-7 Cluster randomised
VE: -2%; P>0.05

The Gambia (Rural)
PCV-9 DBRCT
VE: 37%; 95%CI 25-48



Northern California,USA
PCV-7 DBRCT
VE: 30%; 95%CI 11, 46%

Philippines (Rural)
PCV-11 DBRCT
VE: 22.9; 95%CI -1, 41

South Africa (Urban) PCV-9 DBRCT
HIV infected children
VE: 9% (95%CI -15 to 27)

HIV non-infected children
VE: 25% (95%CI 4 to 40)

Black S et al. PIDJ 2001/ Hansen J PIDJ 2006; Klugman KP et al. NEJM 2003; Cutts F et al. Lancet 2005; Lucero et al PIDJ 2009

Most bacteriologic studies from children with pneumonia (developing world) suggested that pneumococci caused 30-50% of pneumonias

- If PCV prevents 50% of cases of invasive pneumococcal disease
- And it prevents 37% of radiographic pneumonia
- Then, 74% (with confidence intervals) of x-ray confirmed pneumonia in the Gambian study site at the time of the trial were associated with pneumococcal infection

Efficacy of PRV against RVGE in Africa and Asia Combined 5 Country Analyses

RVGE	Year 1 Efficacy (95% CI)	Year 2 Efficacy (95% CI)	Total Follow-up Period Efficacy (95% CI)
"Very Severe" (Vesikari ≥15)	67.1% (37.0, 83.9)	33.8% (-15.7, 62.8)	**51.2% (26.3, 68.2)**
Severe (Vesikari ≥11)	58.9% (40.0, 72.3)	28.1% (2.3, 47.2)	**42.5% (27.4, 54.6)**
Any severity	51.2% (36.6, 62.6)	21.1% (3.7, 35.5)	**33.9% (22.7, 43.5)**

Efficacy of PRV against All Cause Gastroenteritis (GE) in Africa and Asia Combined 5 Country Analyses

All Cause GE	Year 1 Efficacy (95% CI)	Year 2 Efficacy (95% CI)	Total Follow-up Period Efficacy (95% CI)
Very Severe (Vesikari ≥15)	35.9% (5.4, 57.0)	40.7% (-6.4 , 67.8	**27.4% (2.7, 46.0)**
Severe (Vesikari ≥11)	23.0% (5.4, 37.3)	11.2% (-17.7, 33.0)	**15.3% (1.7, 27.1)**
Any severity	9.4% (0.0, 17.9)	4.8% (-10.9, 18.3)	**8.2% (0.3, 15.4)**

Calculation of Proportion of Severe Acute Gastroenteritis Caused By Rotavirus

based on the equation: $VE_r = VE_{ge}/GE_{rv}$ where:

VE_r= Vaccine efficacy against severe rotavirus gastroenteritis,

VE_{ge}= Vaccine efficacy against all cause severe gastroenteritis

GE_{rv}= the proportion of severe gastroenteritis due to rotavirus;

thus, $GE_{rv} = VE_{ge}/VE_r$

Calculating the proportion of severe gastroenteritis due to rotavirus without using diagnostic tests

$$GE_{rv} = VE_{ge}/VE_{r}$$

For severe disease: The proportion of AGE due to rotavirus = 23%/59%= 39%

For very severe disease: 35.9%/67.1% = 53.5%

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Calculating the proportion of febrile respiratory infection (FRI) in infants due to Influenza without using diagnostic tests

$FRI_I = VE_{FRI} / VE_I$

Where FRI_i= Febrile Respiratory Infection due to Influenza

VE_{FRI}= Vaccine efficacy against febrile respiratory infection

VE_i= Vaccine efficacy against influenza

Thus, the proportion of febrile respiratory infection that was due to influenza was* = 28.9/62.8= 46% (!)

* At the time of the study

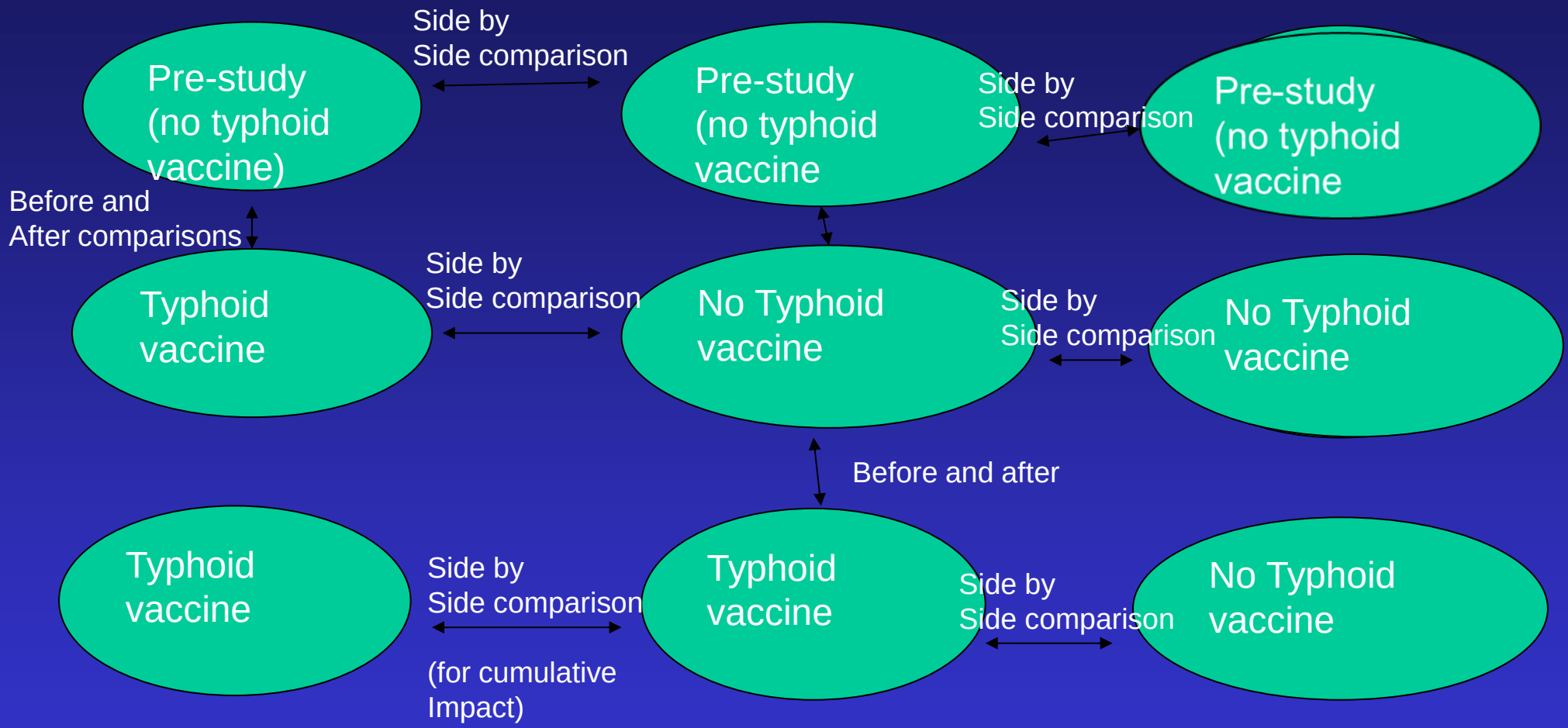
Assumptions for a typhoid conjugate vaccine probe study with primary outcome of hospitalization with 5 days of fever

- Incidence of hospitalization with 5 days of all cause fever
  - —1000/100000 (1 per 100)/ Four years of observation
- 40% of all cause prolonged fever caused by *S. T*yphi
- Vaccine efficacy against S. Typhi bacteremia=80%*
  - —Thus, 32% of all cause prolonged fever hospitalization would be prevented in immunized patients if assumption is correct
- Cluster design
  - —to measure indirect effect within clusters and to minimize indirect effect leading to underestimated burden in controls*

* If this is a licensure study to measure efficacy against laboratory confirmed disease, probe variables can be nested

Gessner BD, Halloran ME, **Khan** I. **The case for a typhoid vaccine probe study and overview of design elements.** Vaccine. 2015 Jun 19;33 Suppl 3:C30-C35.

Use of cluster demonstration step-wedge design to study large population impact considering indirect effect and temporal changes



Immunized population (sample size) required for typhoid vaccine probe study

- With lower bound of efficacy >0
- 100 people per cluster
- >100 clusters per arm
- About 11,000 people in each arm
  - —with four year follow-up
- Require good hospital surveillance for febrile admissions
- Best done as a demonstration project
  - —After trials are completed (Phase II immunogenity/safety?)
  - —Or in a place where incidence of typhoid febrile illness is much higher

Typhoid in Kibera in children <10

- Incidence of typhoid associated febrile illness was was 2,000 per 100,000 per year
- 3% of blood cultures positive for typhoid
  - —So febrile illness incidence is 66,000/100,000 per year
- Vaccine that prevents 80% of typhoid might be expected to reduce typhoid incidence to 400/100,000 per year
  - —But that would only reduce overall febrile illness rate to 64,400/100,000
- So need more specific clinical case definition or a very huge demonstration project

So…

- Vaccines can/should be used to assess public health impact
  - —i.e. against syndromes or disease states, not just the pathogen alone (unless the pathogen represents the disease state)
  - —Best done via RCTs to minimize ecologic data OR large cluster designed demonstration projects
- Vaccines of known efficacy against a pathogen can be used to assess proportion of a syndrome caused by that pathogen
- Where incidence or overall numbers (in a country/region) of a disease or syndrome is known, vaccine probe data add evidence to potential public health impact for a vaccine program