Experimental Typhoid Vaccines (Martin, 2012)

Table 2. Vaccines under early clinical development targeting *Salmonella* Typhi

Vaccine type	Rationale and indication	Vaccine	Description
Vi conjugate, injectable	Generation of T dependent immune response resulting in immunologic memory	Vi-rEPA	*S.* Typhi Vi conjugated to recombinant *P. aeruginosa* exoprotein A
	Vaccination of infants and young children		
		Vi-tetanus toxoid	*S.* Typhi Vi conjugated to tetanus toxoid
		Vi-diphtheria toxoid	*S.* Typhi Vi conjugated to diphtheria toxoid
		Vi-CRM_{197}	Citrobacter Vi conjugated to nontoxic mutant of diphtheria toxin
		O-polysaccharide conjugate	*S.* Typhi O-specific polysaccharide conjugated to diphtheria toxoin [110•]
Live-attenuated, oral	Reduce need for repeated dosing	CVD 909	Mutations in *aroC* and *aroD* and *htrA* genes; Constitutive Vi expression [111]
	No/low reactogenicity	Ty800	Gene disruption of *ssaV* and *aroC* [113]
		M01ZH09	Mutations in *PhoP/PhoQ* genes

Vaccines to Control Typhoid Fever? The Climate in the Late 20th Century

- Older generation vaccines against typhoid had been removed from the public health armamentarium
- Effective but too reactogenic
- Removal of vaccines was a public health triumph!
- Complacency about the impact of non-vaccine control measures

Vaccination against Typhoid Fever in Thailand (Bodhidatta, 1987)

- Typhoid a major problem in Thailand in the 1970s
- Government initiated vaccination of school children (7-12 years) with locally produced, single dose heat inactivated-phenol preserved parenteral vaccine (2.5×10^8 organisms)
- More than 5 million children vaccinated (1977-84)—ca. 80% coverage

Impact of School-Based Immunization on Blood Culture-Confirmed Cases of Typhoid and Paratyphoid Fever, Bangkok, Thailand, 1970-1985 (Bodhidatta, 1987)

Table 1. The number of blood culture–confirmed cases of typhoid and paratyphoid fever and the ratio of cases of typhoid to paratyphoid fever, Bangkok, Thailand, 1970–1985.

Period	No. of cases		Ratio of cases (typhoid:paratyphoid)
	Typhoid fever	Paratyphoid fever	
1970–1971	124	23	5.4:1
1972–1973	369	97	3.8:1
1974–1975	1,283	239	5.4:1
1976–1977	2,000	203	9.9:1
1978–1979	888	315	2.8:1
1980–1981	283	245	1.2:1
1982–1983	274	159	1.7:1
1984–1985	132	150	0.9:1

NOTE. Data are from Siriraj, Chulalongkorn, Ramathibodhi, and Bamrasnaradura hospitals. Overall $\chi^2 > 500$, $P < 10^{-6}$; χ^2 for trend = 378, $P < 10^{-6}$.

Modern Licensed Vaccines for Typhoid

1. Vi polysaccharide parenteral vaccine

2. Ty21A live oral vaccine

* Safe
* Effective
* Inexpensive
* Internationally licensed
* Used primarily for travellers

Comparative Features of Vi and Ty21a

Feature	Vi Vaccine	Ty21a Vaccine
Target group	≥2 years	≥6 years
Regimen	Single dose	3 doses qod
Side-Effects	Negligible	Negligible
Protection against typhoid	50-70%/ 3 years	50-80%/ 7 years
Herd protection	Yes	Yes
Protection against paratyphoid	No	Yes (B)

WHO Position on Typhoid Vaccines (WER, 2000)

- “Immunization of school-aged children is recommended in areas where typhoid fever in these age groups is a signficant public health problem, and particularly where antibiotic-resistant *S. typhi* strains are prevalent.”

- “Where affordable the old heat-inactivated whole cell vaccine should be replaced by the newer and less reactogenic vaccines.”

Updated WHO Recommendation (WER, 2008)

- “In view of the continued high burden of typhoid fever and increasing antibiotic resistance, and given the safety, efficacy, feasibility, and affordability of licensed typhoid vaccines, countries should consider programmatic use of typhoid vaccines for controlling endemic disease”
- “Given observations on the effectiveness of vaccination in interrupting outbreaks, typhoid fever vaccination is recommended also for outbreak control”

GAVI Alliance Board Minutes (December 16, 2008)

- “It was suggested that the Men A vaccine support approach be considered as a model for typhoid (limited duration of support for use of an existing polysaccharide vaccine while awaiting studies of the new conjugate vaccine). There was support to further explore this option.”
- “The SAGE Chair supported the intervention made about further exploring a bridging approach for typhoid vaccine.”
- “The Board encouraged the Secretariat to further develop a vaccine package that includes HPV, JE, rubella, and typhoid taking account of the technical advice … related to discussions of the WHO SAGE.”

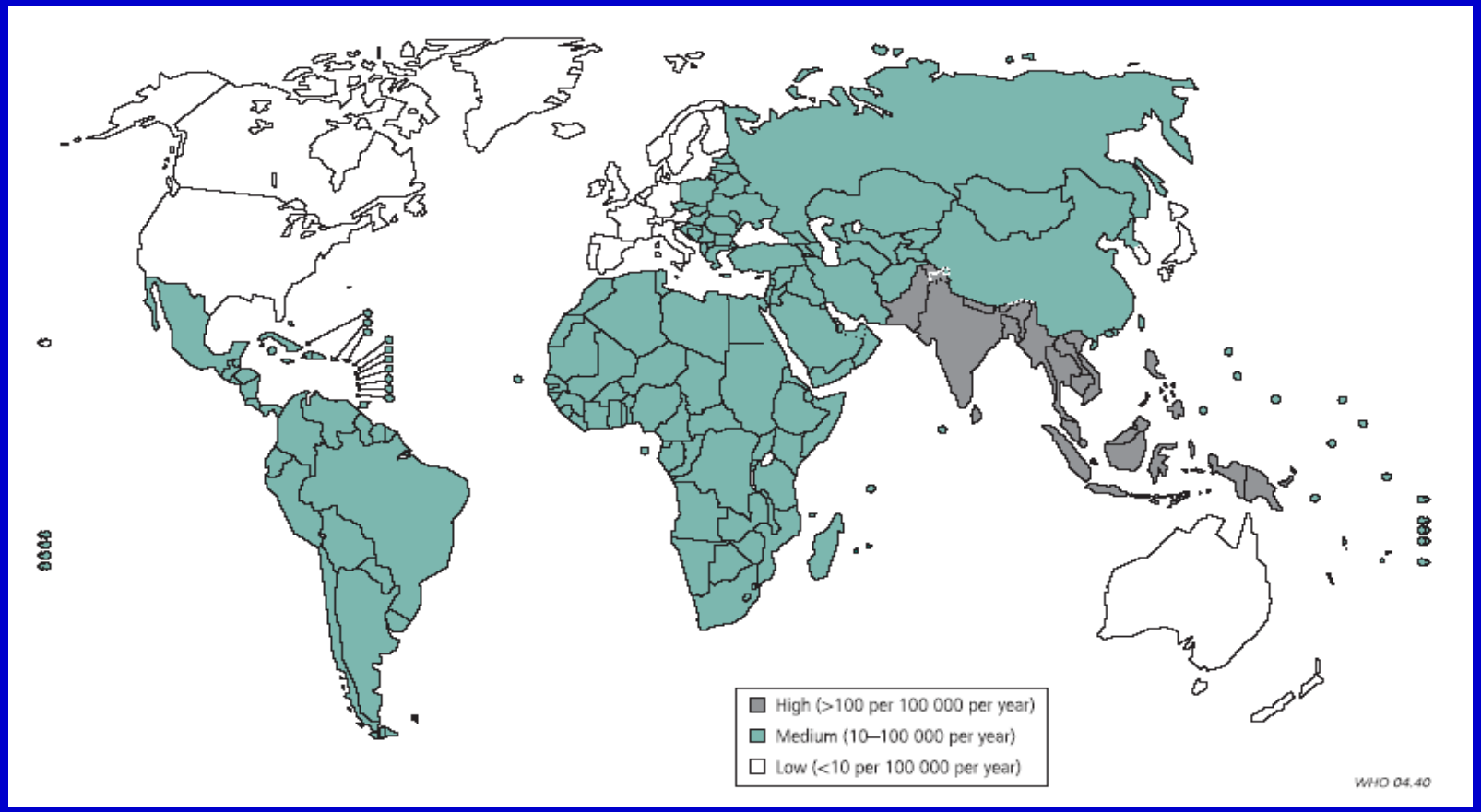
GAVI Alliance Board Minutes (November 16, 2011)

- “With regard to typhoid, because of the existence of alternative treatment options and continued uncertainty about polysaccharide’s duration of protection and timing of a conjugate vaccine, the PPC did not recommend considering the previous Board decision.”

Why the change of heart?

Has the burden of typhoid declined?

Global Burden of Typhoid Fever



Crump et al, 2004, Bulletin of WHO

- Ivanoff et al. (1994) 17 million cases and 600,000 deaths
- Crump et al. (2004) 21.7 million cases and 216,000 deaths
- Buckle et al. (2012) 26.9 million cases

Has typhoid become more treatable?

Studies on Typhoid Antibiotic Resistance (Parry, 2008)

Table 1 Occurrence of multidrug resistance and decreased ciprofloxacin susceptibility in *S. enterica* serovar Typhi and serovar Paratyphi A in recent studies

Country	Year	Serovar	No. of isolates	MDR (%)[a]	DCS or Na^R (ciprofloxacin MIC 0.1–1 mg/l) (%)	Nonsusceptible to ciprofloxacin (Cip MIC > 1 mg/l) (%)	References
Bangladesh	2002–2004	Typhi	40	38	40	0	[9]
China	2001–2002	Typhi	15	0	0	0	[8••]
England and Wales	2000–2003	Typhi	692	22	39	0	[10]
England and Wales	2006	Typhi	240	23	70	0	[11]
India	2003–2004	Typhi	122	7	57	0	[8••]
India	2005–2006	Typhi	431	15	>90	5	[12•]
Indonesia	2002–2003	Typhi	131	0	0	0	[8••]
Korea	2002–2004	Typhi	15	7	47	13	[13]
Laos	2002–2004	Typhi	50	16	0	0	[9]
Nepal	1999–2003	Typhi	3521	12	49[a]	5	[14]
Nigeria	1997–2004	Typhi	274	87	59	<1	[15]
Pakistan	2002–2004	Typhi	189	65	59	0	[8••]
Singapore	2002–2004	Typhi	26	12	39	0	[13]
Sri Lanka	2002–2004	Typhi	17	6	18	0	[13]
Taiwan	2002–2004	Typhi	15	27	40	0	[13]
The Philippines	2002–2004	Typhi	28	0	86	0	[13]
Viet Nam	2002–2003	Typhi	18	22	44	0	[8••]
Viet Nam	2002–2004	Typhi	104	74	90	0	[13]
Viet Nam	2004	Typhi	202	50	97	0	[9]
England and Wales	2006	Paratyphi A	278	2	73	0	[11]
India	2005–2006	Paratyphi A	198	0	>90	1	[12•]
Nepal	1999–2003	Paratyphi A	1810	2	86[a]	1	[14]
United States	2005–2006	Paratyphi A	146	1	87	0	[16]

DCS, decreased ciprofloxacin susceptibility; MDR, multidrug resistant (resistant to ampicillin, chloramphenicol and co-trimoxazole); MIC, minimum inhibitory concentration; Na^R, nalidixic acid resistant.[a]Nalidixic acid resistance performed on a subset of 149 *S.* Typhi and 70 *S.* Paratyphi A isolates from 2003.

Highly resistant S. typhoid with novel gyrA mutation in Nepal (Koirala, 2012)

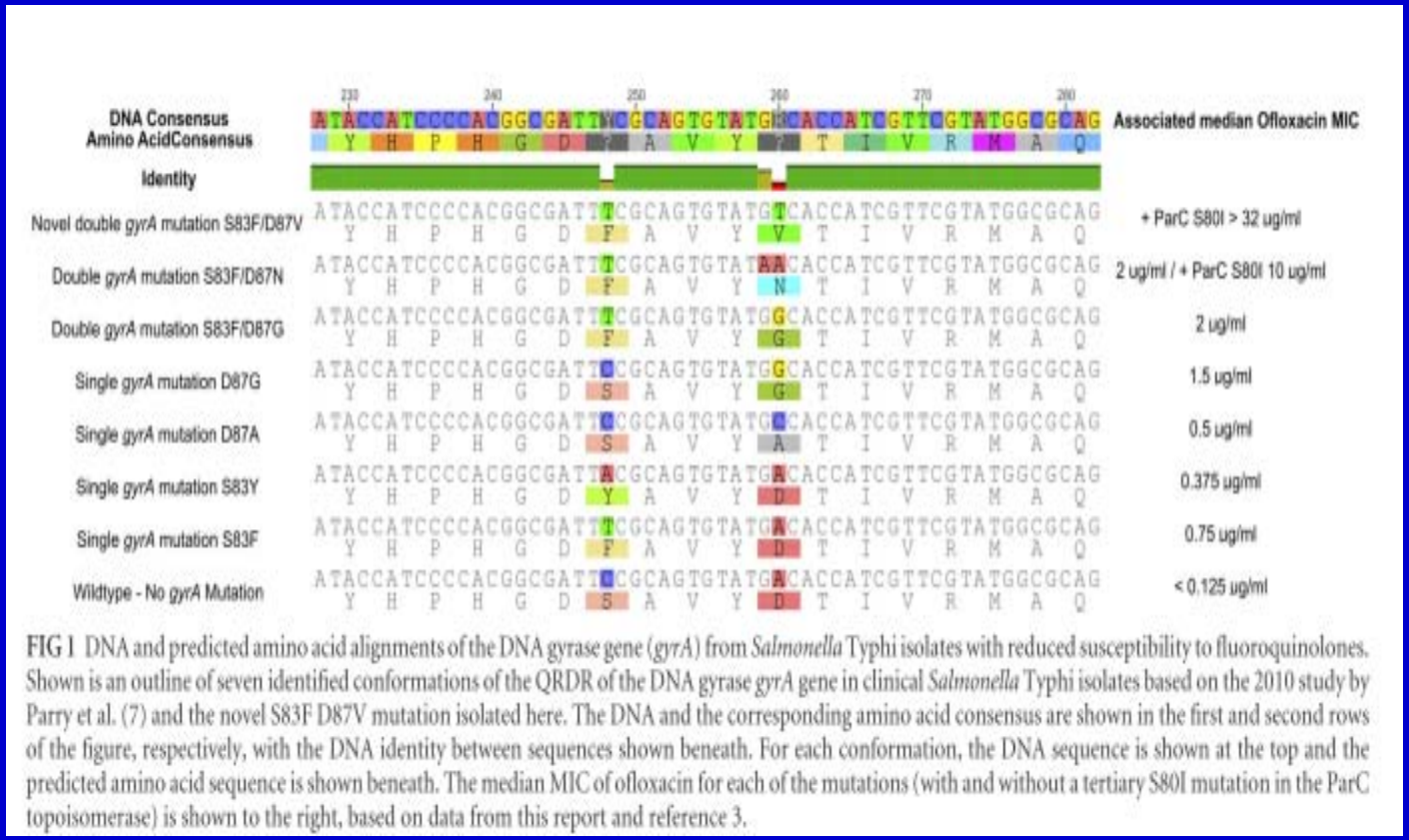


FIG 1 DNA and predicted amino acid alignments of the DNA gyrase gene (*gyrA*) from *Salmonella* Typhi isolates with reduced susceptibility to fluoroquinolones. Shown is an outline of seven identified conformations of the QRDR of the DNA gyrase *gyrA* gene in clinical *Salmonella* Typhi isolates based on the 2010 study by Parry et al. (7) and the novel S83F D87V mutation isolated here. The DNA and the corresponding amino acid consensus are shown in the first and second rows of the figure, respectively, with the DNA identity between sequences shown beneath. For each conformation, the DNA sequence is shown at the top and the predicted amino acid sequence is shown beneath. The median MIC of ofloxacin for each of the mutations (with and without a tertiary S80I mutation in the ParC topoisomerase) is shown to the right, based on data from this report and reference 3.

Are there credible doubts about the feasibility of programmatic use?

Programmatic Success Stories

- Ty21a vaccine
  - * School-based vaccination in Santiago, Chile
    - Half a million school aged children vaccinated through large school-based, randomized, controlled pre-licensure vaccine trials
  - * Post-licensure use of Ty21a in Kurdish refugees in Iran (>15,000 vaccinees)

Programmatic Success Stories

- Post-licensure use of Vi in:
  - * Vietnam: 3-10 year olds and high risk individuals in other age groups (>4 million vaccinees)
  - * Delhi State, India: 2-5 year olds (>1 million vaccinees)
  - * China (several provinces): Students and high-risk individuals in other age groups (> 36 million vaccinees)
  - * Cuba: countrywide immunization
  - * Tajikistan: Russian military (>18,000 vaccinees)

Vi Effectiveness Studies

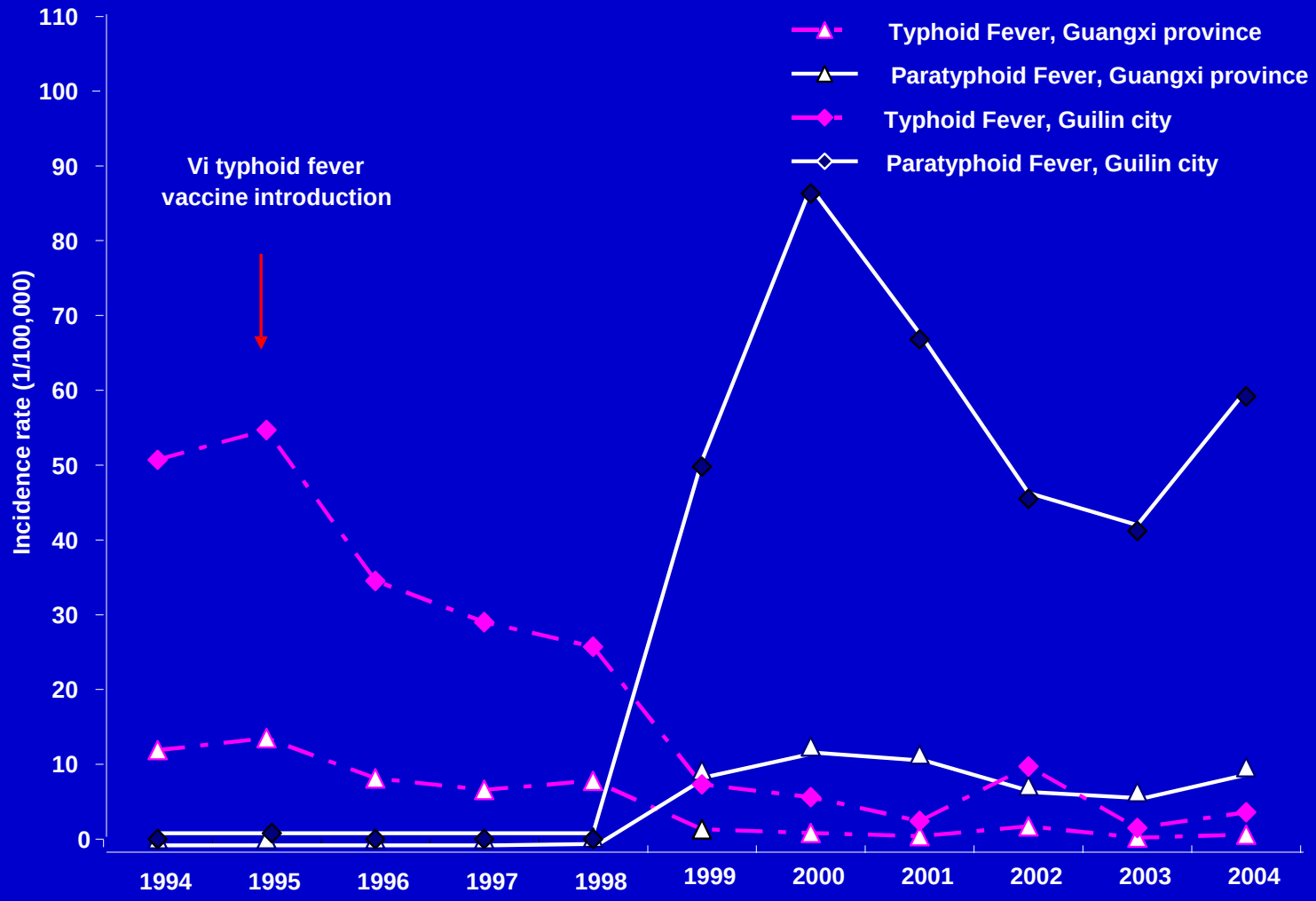
	Collaborating Institution	Setting	Target Population	Vi Vaccine	Vaccine Delivery
China	Guangxi CDC	Urban/ Rural	120,000 (General population)	Locally produced	Community-based
Pakistan	Aga Khan University	Urban (slum)	35,000 (Children)	Internationally produced	Community-based
Indonesia	NIHR&D	Urban	5,000 (Children)	Internationally produced	School-based
Vietnam	NIHE	Urban	62,000 (Children)	Internationally produced	School-based
Calcutta	NICED	Urban (slum)	50,000 (General population)	Internationally produced	Community-based

Vi Demonstration Projects Summary

- 189,665 persons were vaccinated
- Mass vaccination was feasible
- Mass vaccination was well-accepted in both community-based and school-based immunization programs

Is there reason to suspect that use of these vaccines would not be impactful?

Incidence of Typhoid and Paratyphoid in Guangxi Province (1994-2004)



Vi Vaccine Protection against a Typhoid Outbreak When Administered in a Real-Life Public Health Program

Timing of Vi Vaccination of Students	Vi Protection Against Typhoid During School Epidemic+
Before epidemic	73%*
During epidemic	71%
Before or during epidemic	71%**

+ Models simultaneously controlled for age, sex, and dining location

* P <.05; ** P<.01 (2-tailed)


Project health clinics
Households
Roads
Railways
Wards
Cluster
Ward 29
Ward 30
N
0
125
250
500 Meters

Analysis of Total Protection against Typhoid Fever by Vi Polysaccharide (Sur, 2009)

	Vi vaccinees (N=18,869)	Hep A vaccinees (N=18,804)
Typhoid Episodes	34	96
Rate (per 1,000 person-years)	0.9	2.7
Total Protection	65% (P<.0001; 95%CI:42%,79%)	-

Analysis of Indirect Protection against Typhoid Fever by Vi Polysaccharide (Sur, 2009)

	Non-vaccinees Vi clusters (N=12,206)	Non-vaccinees Hep A clusters (N=12,877)
Typhoid Episodes	16	31
Rate (per 1,000 person-years)	0.7	1.3
Indirect Protection	45% (P<.05; 95%CI:1%,70%)	-

Analysis of Overall Protection against Typhoid Fever by Vi Polysaccharide (Sur, 2009)

	All residents Vi clusters (N=31,075)	All residents Hep A clusters (N=31,681)
Typhoid Episodes	50	127
Rate (per 1,000 person-years)	0.8	2.1
Total Protection	60% (P<.0001; 95%CI:39%,74%)	

Total Protection by ViCPS Vaccine against Typhoid Fever in Children, Karachi, Pakistan, 2003-2006 (Khan, 2012)

Table 2
Total protection (adjusted and unadjusted) of ViCPS vaccine against typhoid fever in children in Karachi, Pakistan (2003–2006).

Variable	ViCPS vaccine (n = 13,238)	Hepatitis A (n = 13,993)
Typhoid fever cases	30	49
Person-days of follow up	8,382,068	8,884,898
Incidence of typhoid fever (cases/1000 person-years)	1.3	2.1
Vaccine effectiveness in children 2–16 years of age	35% (95%CI: –20%, 65%)	
Adjusted vaccine effectiveness in children 2–16 years of age	31% (–28%, 63%)	

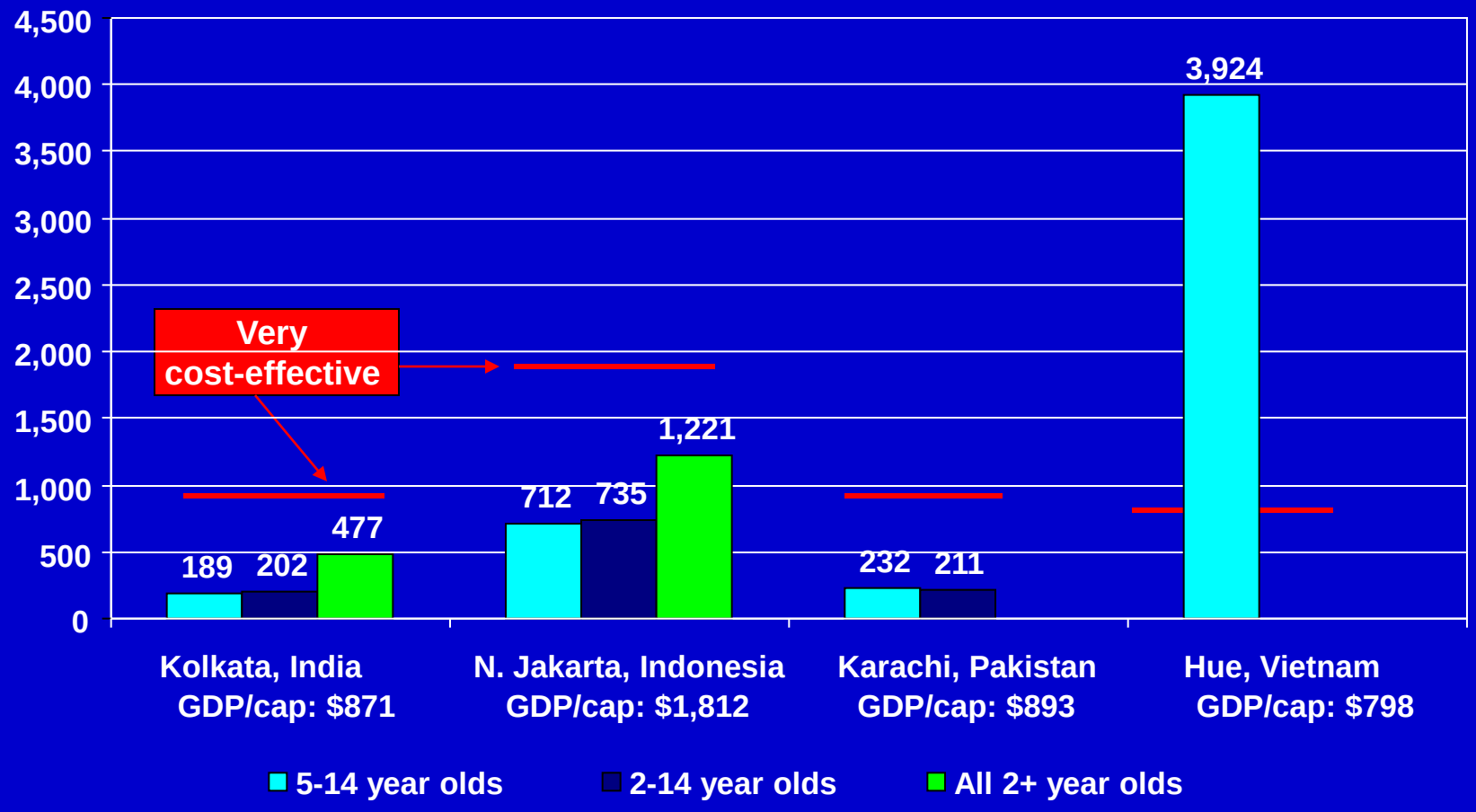
Typhoid Fever Incidence by Age Group, Karachi, Pakistan, 2003-2006 (Khan, 2012)

Table 3
Typhoid fever incidence and ViCPS vaccine total protection (adjusted and unadjusted) by age group in Karachi, Pakistan (2003–2006).

Age at baseline	Typhoid episodes (*n*/total)		*S. typhi* incidence per 1000 population		Protective effectiveness of Vi vaccine (95% confidence interval)	
	ViCPS	Hepatitis A	ViCPS	Hepatitis A	Unadjusted	Adjusted
2 to <5 years	16/3154	13/3324	3.0	2.3	–30% (–183%, 40%)	–38% (–192%, 35%)
5–16 years	14/10,084	36/10,669	0.8	1.9	59% (9%, 81%)	57% (6%, 81%)

Are the vaccines cost-effective?

Cost-Effectiveness Ratios (net public cost/DALY gained) for Vi over 3 Years (2007US$) (Cook, 2008)



Cost-Benefit Analysis of Ty21a in Children in Santiago, Chile (Ferreccio, 1989)

Net Present Value :

High incidence : saves $74.568

Low incidence : costs $ 339,316

($93,915/case prevented)

What Happened?

- Both Vi and Ty21a vaccines are cheap, feasible, safe, and effective, but neither is a “slam-dunk”
- Absence of a vocal and influential constituency
- Perception of typhoid as a non-problem- a “subterranean disease”
- The prospect of improved future vaccines- providing an excuse to let “The best be the enemy of the good”

Will Vi-Conjugate Vaccines Remedy This Situation?

- 2 Vi-conjugate vaccines are licensed or about to be licensed:
  * Biomed (Vi-TT, licensed in 2008): 2 doses for persons ≥2 mos, 4-8 week interval
  * Bharat Biotech (Vi-TT, to be licensed soon): single dose for persons ≥6 mos
- Other Vi-conjugates in clinical development

Efficacy of Vi-rEPA Conjugate Vaccine against Typhoid Fever in 2-to-5 Years Old Children, DongThap, Vietnam

Variable	Vaccine group	placebo group	Vaccine efficacy
Active surveillance (0 to 27 months)			
No. of fully immunized	5525	5566	
No. of typhoid fever	4	47	
Attack rate (case/1000/yr)	0.60	7.04	91.5 (77.1-96.6)
Passive surveillance (27 to 46 months)			
No. remain in the study	5383	5420	
No. of typhoid fever	3	19	
Attack rate (case/1000/yr)	0.362	2.34	82.4 (22.3-99.1)
Active and Passive surveillance (0 to 46 months)			
No. of typhoid cases	7	66	
Attack rate (case/1000/yr)	0.317	2.96	89.3 (76.0-96.9)

Lin FY, Ho VA, Khiem HB, Trach DD, Lanh MN, Bay PV, Thanh TC, Kossaczka Z, Robbins JB, Schneerson R, Bryla DA, Shiloach J, Szu SC. The efficacy of a Salmonella typhi conjugate vaccine in two-to-five-year-old children. NEJM 2001;344:1263-1269

Challenges

- Current pathways for licensure include studies of safety and immunogenicity without efficacy data
- Need for demonstration projects to evaluate the feasibility, acceptability, costs and impact of Vi-conjugates in realistic public health programs
- Paucity of credible ongoing surveillance for typhoid
- Persisting lack of appreciation of magnitude of typhoid by physicians and policymakers in developing countries– and lukewarm enthusiasm among international organizations

Letter to the Editor

Coalition against Typhoid (CaT): A new, global initiative to advance typhoid vaccination

Keywords:
Infectious disease
Vaccines
Typhoid