THE FEASIBILITY OF A SCHOOL-BASED VI POLYSACCHARIDE VACCINE MASS IMMUNIZATION CAMPAIGN IN HUE CITY, CENTRAL VIETNAM: STREAMLINING A TYPHOID FEVER PREVENTIVE STRATEGY

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Abstract. We report the coverage, safety, and logistics of a school-based typhoid fever immunization campaign that took place in Hue City, central Vietnam; a typhoid fever endemic area. A cluster-randomized evaluation-blinded controlled trial was designed where 68 schools (cluster) were randomly allocated the single dose Vi polysaccharide vaccine (Typherix®) or the active control hepatitis A vaccine (Havrix®). A safety surveillance system was implemented. A total of 32,267 children were immunized with a coverage of 57.5%. Strong predictors for vaccination were attending primary schools, peri-urban location of the school, and low family income. Human resources were mainly schoolteachers and the campaign was completed in about 1 month. Most adverse events reported were mild. Safe injection and safe sharp-waste disposal practices were followed. A typhoid fever school-based immunization campaign was safe and logistically possible. Coverage was moderate and can be interpreted as the minimum that could have been achievable because individual written informed consent procedures were sought for the first time in Hue City and the trial nature of the campaign. The lessons learned, together with cost-effectiveness results to be obtained by the end of follow-up period, will hopefully accelerate the introduction of Vi typhoid fever vaccine in Vietnam.

INTRODUCTION

South-central and Southeast Asian non-industrialized countries have some of the highest incidence rates of typhoid fever in the world. In Vietnam, typhoid fever remains a significant public health problem (Trach, 1998; Lin *et al,* 2000; Crump *et al,* 2004). Without changes in surveillance, Vietnam experienced a six-fold increase in reported cases of typhoid fever, from 4,859 cases in 1990 to 30,901 in 1995 (Trach, 1998; Ministry of Health, 1996). The estimated national disease incidence is approximately 33.4 per 100,000 per year (1991-2003). Additionally, major outbreaks involving schoolchildren have occurred in southern and central Vietnam.

The control of enteric infections requires the provision of safe drinking water and human waste removal systems, and the identification and treatment of carriers. The increasing number of *Salmonella enterica* subspecies *enterica* serovar *typhi* (*S. typhi*) strains that are resistant to multiple antibiotics is a growing threat. More than 80% of *S. typhi* strains in the Mekong Delta are now resistant to ampicillin, chloramphenicol,

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nalidixic acid or ciprofloxacin (Parry *et al,* 1998; Wain and Kidgell, 2004). Because the cost of these control measures may be beyond a developing country's health budget, typhoid fever immunization would be a realistic public health option (WHO, 2000). The World Health Organization (WHO) recommends routine immunization of school-aged children as part of the activities to reduce typhoid fever (WHO, 2003). However, immunization as a method to prevent typhoid fever is not widely used. A few countries, such as China and Vietnam, are leading the way in the use of these vaccines as a public health tool.

The Vietnamese Institute of Vaccine and Biological Substances (IVAC) has been responsible for the vaccine production for the local Expanded Program on Immunization (EPI) since 1982, and recently for other vaccines. In 1999, IVAC produced the first batch of Vi polysaccharide (Vi PS) vaccine (Robbins and Robbins, 1984). A bridging trial demonstrated that this locally produced vaccine was as safe and immunogenic as licensed Vi PS vaccines produced in developed countries (Ke NT *et al,* unpublished observations). It is anticipated that production of Vi PS will be scaled up by 2007, with a production capacity of 6-10 million doses per year. Thus, Vietnam will be self-sufficient in providing vaccines for high-risk populations such as schoolchildren nationwide. With the expanded availability of an affordable Vi PS vaccine, policy-relevant data are needed to streamline the typhoid fever vaccination strategy.

We report on the coverage, safety, and logistics of a school-based Vi PS immunization campaign in Hue City, Vietnam that was conducted in late 2003. This project, which is part of a multi-country multidisciplinary evaluation (Acosta *et al,* 2004), aims to contribute to the design and fine-tuning of a national typhoid fever immunization strategy that will in turn accelerate the introduction of the Vi PS vaccine in Vietnam.

METHODS

Study site

Hue, in central coastal Vietnam, is one of the nine districts in Thua Thien Province and has an estimated population of 281,788 (census 2003) living in an area of 67.77 km^2. Hue is becoming increasingly prosperous and is a preferred destination for national and international tourists. The city is divided into 25 communes. Primary health care is provided by commune health centers and private practitioners. Secondary and tertiary health care is provided by four polyclinics and three hospitals. The Hue Preventive Medicine Center (PMC), under the Provincial Health Service Office, is responsible for all preventive services. Typhoid fever is endemic in the region. In 1996, Hue reported 1,620 typhoid fever cases, 75% of which occurred in school-aged children, corresponding to an annual incidence rate of 596 per 100,000 population.

There are 68 schools in Hue, with 1,727 classes: 40 primary schools (grades 1-5), 19 middle schools (grades 6-9), seven high-schools (grades 10-12), one middle/high school (grades 6-12), and one small boarding high school for ethnic minorities. The median school size is 842 students: 700 (range: 228 to 1,393), 1,316 (range: 536 to 2,258) and 1,470 (range: 257 to 1,776) for primary, middle, and high schools, respectively. The combined middle/high school has 2,148 students. Hue is divided by a large river with a similar number of schools in each river basin. Fig 1 shows the spatial distribution of schools and the buffer zones (regions of influence) of the schools drawn using Thiessan polygons (Voronoi diagram); which allocates space to a point, based on spatial mathematics (Li *et al,* 1999).

Study design and vaccines

A cluster randomized evaluation-blinded controlled trial was designed to mimic the way the Vi PS vaccine would be delivered under public health program conditions (Acosta *et al,* 2005). The schools (clusters) were randomly allocated to receive either Vi PS vaccine or the active control, hepatitis A vaccine. They were stratified by type: primary *vs* middle/high schools, which also provided an adequate balance with respect to size. Eligible children were all permanent residents of Hue who attended school and whose parents or guardians agreed to participate in the study. A house-to-house census was done in Hue one year before the campaign, and updated one month prior to the immunization trial. Each household and individual was assigned an identification number. Typhoid

fever surveillance would last for 2 years.

Both vaccines, which are licensed in Vietnam, were donated by GlaxoSmithKline (GSK). Vaccines were supplied in commercial batches of pre-filled single-dose syringes. The label of each syringe listed the batch number, expiry date, route of administration, and the letter code (A or T). Typherix® is administered as a single dose. Havrix® series consists of a primary and a booster dose; the booster will be administered at the end of the study. Both vaccines are injected intramuscularly.

This project was approved by the local ethics committee of the National Institute of Hygiene and Epidemiology, Hanoi, the institutional review board of the International Vaccine Institute, and the WHO's Ethics Committee.

Information dissemination

Promotion activities were coordinated by the Hue PMC. The information campaign began two months prior to the campaign. Salient project information was distributed through the schools, by community leaders (people's committees), and through local newspaper clips, TV, and radio stories. Afterwards, informed consent forms were distributed to each student's household through schoolteachers, who then collected the forms signed by parents/guardians and kept them until vaccination.

Logistics

Forty-eight teams, consisting of a team leader (a physician), a vaccinator, and a vaccine recorder vaccinated in the schools. Training sessions emphasizing Good Clinical Practices were conducted. Twenty-five health workers from Hue PMC supervised the vaccination activities (1 supervisor per 1-2 teams) and assisted the teams with their day-to-day activities. Also, they were a liaison between the Hue PMC and the schools. The campaign started with a one-day pilot exercise in two schools on November 28, 2003. On December 2, 15 teams began vaccinating, and three days later, all 48 teams were involved.

On November 5, 2003, 74,400 doses of vaccine arrived in Hanoi from Rixensart, Belgium. The vaccine boxes were stored in two cold rooms at the National Institute of Hygiene and Epidemiology, separately by code. On November 7, 10,200 doses were transported by refrigerated EPI trucks from Hanoi to Hue, a journey that took about 27 hours. Two additional shipments, of 20,400 doses each, followed the initial delivery. Vaccines were stored in 34 refrigerators in Hue PMC. Each day, the teams carried cold boxes containing a maximum of 100 doses and three or four ice packs to schools using motorbikes. The cold chain was tracked during long-distance travel by battery-powered temperature strip-chart recorders and, at study sites, by periodic temperature charting and surprise checks.

Vaccination campaign

The campaign was planned and conducted so that it would not disturb other regular vaccination activities. Therefore, the teams did not immunize on the day when EPI vaccines are provided in Hue. Vaccinations were usually given in schools from Monday through Friday, although some schools were visited on Saturdays. Some teams organized additional days for immunization at schools, and then at the Hue PMC as a "mop-up" activity. Each vaccination team was assigned to deliver one and only one vaccine code letter (A, T). The team recorder filled in a vaccination record book, including the list of children to be vaccinated that was sorted by class and identification number. The supervisor checked this book daily for quality control. This book documented the date of vaccination, eligibility, letter code of the vaccine, and presence or absence of an immediate adverse event.

Direct observation for 30 minutes after vaccination allowed the detection of immediate serious adverse events (SAE). Non-solicited adverse events occurring within 30 days of vaccination were also monitored through passive surveillance. Additionally, a randomly selected subsample of 140 children was visited for three consecutive days for solicited adverse events. Vaccination teams were trained to manage immediate SAE (WHO, 1997) and outfitted with basic emergency equipment; transportation to a hospital was assured. SAE, as defined in the study protocol, were reported to an independent data and safety monitoring board (DSMB).

Outcome data entry and statistical analysis

Vaccine coverage was calculated, based on information from vaccination record books, as

the proportion of Hue permanent resident students (listed in the census) who received a dose of vaccine (A or T). To assess logistics, the following matters were described and quantified: (1) resources, including personnel, needed for vaccine procurement, storage, transportation, and vaccine delivery; (2) vaccine storage, transportation, and handling; and (3) monitoring of 120 randomly selected students to determine the time spent by students and teachers during vaccination. Safe vaccination practices, including vaccine administration and disposal of sharps, were also examined.

Data was processed by a FoxPro 6 (Microsoft, USA) database management system that was designed for the "Diseases of the Most Impoverished" (DOMI) typhoid fever projects.

To evaluate the statistical significance of potential factors associated with vaccination status and coverage by school, we used the chi-square test to compare proportions and obtained correlation coefficients using Spearman correlation for quantitative variables. Correspondingly, we calculated 95% confidence limits with test-based or exact methods. All p-values and confidence intervals were calculated in a two-tailed fashion. A p-value of ≤ 0.05 was considered significant. To adjust for confounding variables and to take into account the likelihood of an intra-cluster correlation in schools, we used a conditional logistic regression model using the generalized estimating equation (GEE). Most analyses were performed using STATA version 7.0 software (STATA Corporation, TX, USA). The GEE model was run using SAS version 8.1 (SAS Institute, Cary, NC, USA).

RESULTS

Vaccine coverage

Of the 68,004 students enrolled in schools in Hue, 56,076 were residents of the city and had been included in the project census, constituting our denominator. A total of 32,267 students were vaccinated, achieving an overall coverage of 57.5%: 57.0% for boys and 58.1% for girls. Coverage was significantly higher ($p < 0.001$) in primary schools (64.9%), followed by middle schools (56.9%) and high schools (36.6%) as depicted in Fig 2. Schools located in peri-urban areas had higher vaccine coverage than schools in urban areas (81.1% *vs* 53.4%, $p < 0.001$). However, no differences were observed for schools on opposite river basins. There was an inverse correlation between school size and vaccination coverage (Spearman $r = -0.58$, $p < 0.001$).

Table 1 summarizes the adjusted odds ratios for vaccination by school type, location (peri-urban *vs* urban), and family income (from project census). Overall, the stronger predictors for vaccination were attendance of primary school, school located in a peri-urban area, and low-income family.

Table 1

Adjusted odds ratios (OR) for selected factors associated with vaccination status by use of generalized estimated equations for within-school correlation. Hue City, Vietnam, Nov-Dec 2003.

Characteristic		Adjusted OR	95% Confidence interval
Type of school	Primary	Referent	-
	Middle	0.78	0.58-1.05
	High	0.49	0.27-0.88
School location	Urban	0.36	0.27-0.49
	Peri-urban[a]	Referent	-
Family income[b]	Low	Referent	-
	Medium	0.91	0.86-0.95
	High	0.80	0.74-0.86

[a] Peri-urban refers to 14 schools located in the 5 peripheral communes of Hue City.

[b] Monthly income per family (as self-reported in 2001 census)/number of household members. Low, ≤ 25th percentile (≤ 125,000 dong); medium, 25th-75th percentile (125,001-250,000 dong) and high, >75th (> 250,000 dong). Exchange rate: 15,000 dong ~ 1 USD. Family income information is missing for 113 students.

Logistics

In total, up to 2,000 persons were involved in the campaign's planning and execution; 1,800 were teachers (Table 2). Each team vaccinated one or two schools and worked a median of 4.5 days (range = 1-9), seven hours per day, and vaccinated a mean of 162 students daily. Including the time spent for preparation, the average time used in vaccination was 24 minutes. Teachers spent an average of 38 minutes for vaccination. Each class teacher had approximately 40 students. The main supplies used are listed in Table 3. Supply costs were analyzed separately. Vaccine wastage was about 1% (freezing, breakage, missing at inventory).

Table 2
Personnel involved in planning and implementation of a school-based Vi typhoid mass immunization project in Hue City, Vietnam, Nov-Dec 2003.

Function	No. of persons
Vaccination team members (48 teams)	
Vaccinators	48
Recorders	48
Group leader	48
Vaccination supervisors	25
Packing and storing vaccine	2
Transferring and distributing vaccine	2
Management	
Commune level	10
District/city level	2
Provincial level	2
Teachers	1,800

Safety

Overall, the recommended vaccine storage temperatures (2-8ºC) were maintained. In 13 instances, temperature deviations occurred, during the first vaccine shipment to the study site and during the course of the campaign. These instances were between 0-21ºC but did not exceed 8 hours, which is within the allowable margin given by GSK. Three individual vials were reportedly frozen and discarded.

In all, 138 students (0.4%) reported non-solicited, non-serious adverse events. Most reported more than one symptom/sign. These students were of all ages, and 51% were male. The most common symptom reported was headache, followed by fatigue. Local events were less frequent than systemic complaints, with pain at the injection site being the most common. All patients fully recovered in one or two days; except for one child who had diarrhea, malaise, and dizziness, and who recovered after four days.

Of the 140 students interviewed for adverse events, 13 (9.3%) reported general aches, 4 (2.9%) mild headache, 2 (1.4%) mild fatigue, 2 (1.4%) gastrointestinal symptoms and 1 (0.7%)

Table 3
Supplies employed during the school-based immunization campaign, Hue City, Vietnam, Nov-Dec 2003.

Item	Quantity
Styrofoam cool boxes with ice packs (2/team: 100-dose capacity)	100
Thermometers for cool boxes	100
Safety boxes	1,990
Cotton swabs	50 kg (in total)
Pincers (for holding cotton swabs)	100
Alcohol	173 Liters
Sugar (each student was offered drinkable water with sugar before vaccination; this procedure is normally used during vaccine campaigns)	4,080 kg
Emergency kit (2 adrenaline 1 mg/1 ml vials, 2 depersolon 30 mg vials, 1 distilled water vial, 2 syringes of 10 ml and 2 of 1 ml, 10 oral antihistamines, 1 sphygmomanometer, 1 thermometer, 1 stethoscope, and shock management guidelines in Vietnamese)	48
Other (duct tape, trash bags, stationary)	Not quantified

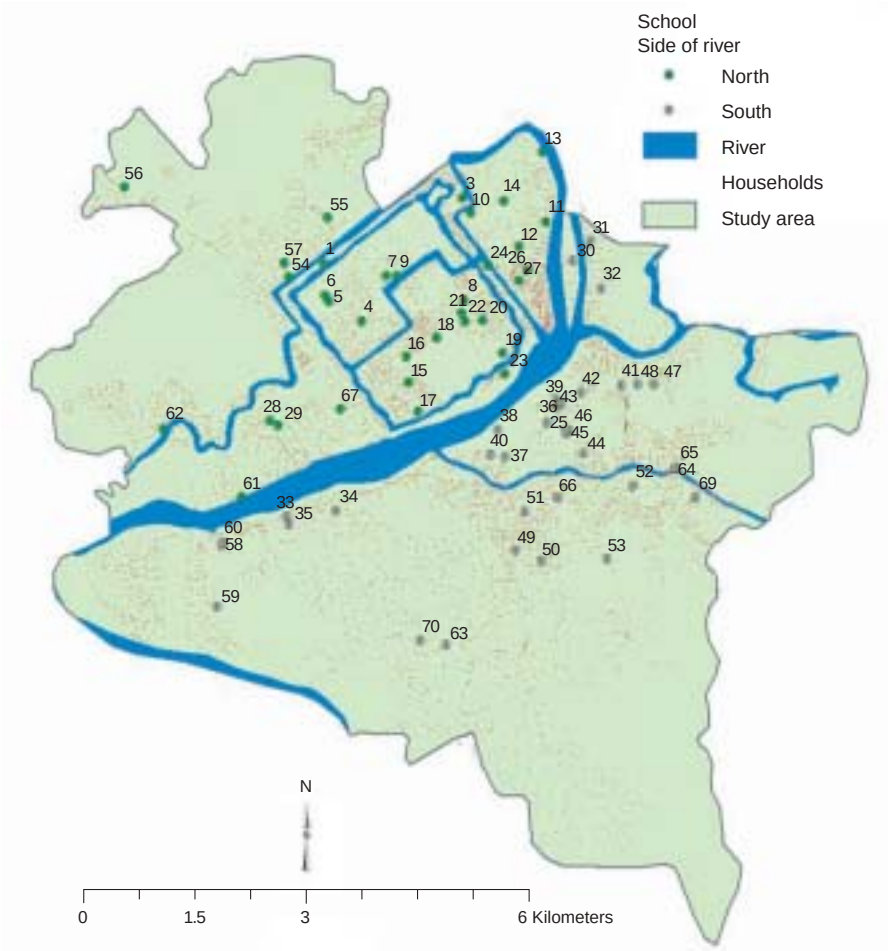


Fig 1–Map of study area showing schools (by cluster number), Hue City, Vietnam.

fever of 38ºC. When asked about local pain, overall 41 (29.3%) answered positively, and 5 (3.6%) reported that the pain was still present on the third day. Eleven (7.9%) reported redness of the injection site on the first day. Three adverse events were considered serious: an anaphylactoid reaction, a severe headache that required overnight hospitalization for observation, and a case of fever accompanied by headache and vomiting. All three students recovered fully, and the DSMB allowed continuation of the study. In addition to the above, eight children in the same class reported malaise and fatigue immediately after vaccination and one "fainted." The child who fainted was thought to experience an anxiety episode and recovered fully shortly after admission in the emergency department.

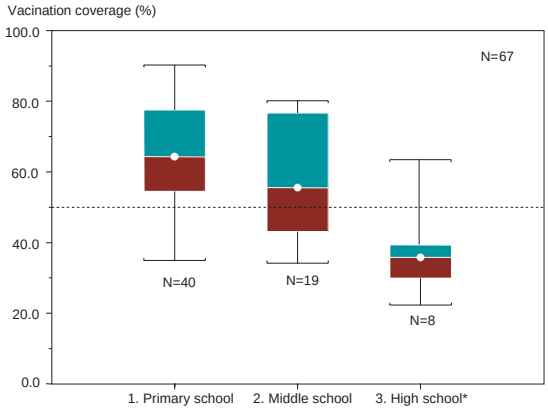
No accidental vaccinations during pregnancy or deaths following vaccination were reported. No needle-stick injuries occurred. All safety boxes were incinerated at a local hospital.

DISCUSSION

School-based immunization is an underutilized public health method for the control of typhoid fever. Our results suggested that a school-based Vi PS immunization campaign in central Vietnams was feasible because, as demonstrated in a trial in Hue, the immunization was safe and logistically possible with a minimum achievable coverage of about 60%.

The typhoid fever Vi PS vaccine has a well-established safety profile as shown by several clinical trials and post-marketing surveillance data collected over the last 10-15 years (Hessel *et al*, 1999; Zuckerman, 2001). Our study corroborates its tolerability. Vaccine safety was assessed in a detailed and comprehensive manner by passive and active surveillance. Of the approximately 32,000 immunized school-aged children, few had adverse events. However, these overall safety profile results apply to both vaccines given in this trial, Typherix® and Havrix®, because this was an ongoing blinded evaluation. Other safety considerations such as cold chain and adequate vaccine handling, including needle-stick injuries and waste disposal, were adequate.

This vaccination campaign was conducted without disrupting other local health programs, in particular the EPI program. Although the human resources employed were considerable (mainly schoolteachers), the time required was a maximum of two hours for each teacher dur-



*One boarding high-school for ethnic minorities is excluded and a school that has both secondary and high school was aggregated to the high school group.

Fig 2–Vaccination coverage for 67 schools by type of school (primary, secondary or high) plus median and 25th and 75th quartiles and data range.

ing one normal workday. Their earlier involvement information dissemination and planning was not quantified but should be considered when setting up similar programs.

The 58% vaccine coverage can be interpreted as the minimum coverage possible when targeting schools in Vietnam. Non-acceptability of the vaccine by the remaining 40% of students was reflected by not having a signed consent form, which may be due to a variety of causes. This was the first time that individual informed consent was sought in Hue. A previous immunization campaign using an oral cholera vaccine in Hue, without written individual informed consent, achieved coverage of 79% (Vu *et al*, 2003). A report that evaluated a school-based immunization program for hepatitis B vaccine in Canada indicated that a substantial limiting factor on high coverage rates was the difficulty in obtaining consent (Deeks and Johnson, 1998). At our study site, the publication of a newspaper article questioning the immunization occurred immediately after the distribution of the consent forms. Preliminary results from a post-vaccination evaluation conducted by a DOMI social science team indicate that parents who were less satisfied with the information provided, the informed consent form, and the logistics of the vaccine campaign were less likely to have their children vaccinated. In the Hue program, information dissemination to parents may have been inadequate. Hence, the vaccine coverage rate obtained most likely represented those who were willing to participate in a cluster randomized trial in Hue.

The study results indicated that a school-based strategy should first target primary schools, where the minimum expected vaccine coverage would be higher. In general, primary schools cooperation was more pronounced than in other types of school. Cooperation, although difficult to quantify, was reflected in the quality and timeliness of the return of forms and teacher support during vaccination. High school students were the least likely to be vaccinated. Anecdotal reports from the teams indicated that some high school students hid their consent forms, added “no” before “agree”, or just did not show up for vaccination. In the post-vaccination survey, some students reported refusing vaccination because their “friends were not being vaccinated.” Thus, peer pressure may have played a role in trial participation, particularly among teenagers. Our data also show that the most impoverished areas, where universal education exists, are more likely to benefit from a school-based strategy. Our findings of higher vaccination coverage in areas of lower income are similar to those of a recent analysis of vaccination uptake using geographical methods.

The experience described and the lessons learned from other limited school-based immunization programs could be utilized to gradually introduce Vi PS vaccine. Another example of available infrastructure is the school-based diphtheria-tetanus immunization program that is available only in Ho Chin Minh City. Experience with mass vaccination of schoolchildren in Thailand using an older heat-inactivated typhoid vaccine has been shown to be closely associated with a sharp decline in typhoid fever in Bangkok during an epidemic in 1985-1986 and with continuous control after the epidemic (Bodhidatta *et al*, 1987). In Vietnam, school-based Vi PS immunization could benefit from the current agreement between the Ministries of Health and Education, which has launched a 2nd measles dose for measles control. During 2002 and 2003, this campaign reached more than 20 million children aged 9 months to 10 years through schools and health facilities. The EPI has started to gradually introduce Vi PS through schools and

health facilities, but on a district-to-district basis each year. The EPI has been buying 700,000 doses for the past three years and nearly 1 million in 2004, within the framework of the collaboration between the aforementioned ministries. The Hue Vi PS vaccination study experience shows that the use of available platforms (such as the EPI cold chain and human resources) is realistic.

IVAC is building a Vi PS stand-alone production plant in Dalat, Vietnam, which should start production by 2006. Consequently a locally affordable, good manufacturing practices grade Vi PS vaccine will soon be available. The availability of the vaccine together with the encouraging results on feasibility in Hue will make the introduction of a school-based Vi PS immunization a reality in Vietnam.

ACKNOWLEDGEMENTS

This work is dedicated to the memory of Prof Dang Duc Trach. We thank GSK for donating the vaccines and providing training and support on Good Clinical Practices. We also thank the following persons: Shousun Szu, Linda Kaljee, Deok-Ryun Kim, Oak-Pil Han, John M Albert, Anne-Laure Page, Jeremy Farrar, Eun Young Kim, Sue Kyoung Jo, John Wain, Amanda Walsh, Denise DeRoeck, and the staff who worked for the following groups: National Institute of Hygiene and Epidemiology, Hue PMC; private physicians of Hue; Oxford University-Wellcome Trust, Tropical Unit, Ho Chi Minh City, Vietnam; University of Western Ontario, London, Canada; WHO, Geneva, Switzerland; and IVI, Seoul, Korea. This work was supported by the Diseases of the Most Impoverished Program, funded by the Bill and Melinda Gates Foundation.

REFERENCES

Acosta CJ, Galindo CM, Ochiai RL, *et al*. The role of epidemiology in the introduction of Vi polysaccharide typhoid fever vaccines in Asia. *J Health Popul Nutr* 2004; 22: 240-5.

Acosta CJ, Galindo CM, Ali M, *et al*. A multi-country cluster randomized controlled effectiveness evaluation to accelerate the introduction of Vi polysaccharide typhoid vaccine in developing countries in Asia: rationale and design. *Trop Med Int Health* 2005; 10: 1219-28.

Bodhidatta L, Taylor DN, Thisyakorn U, Echeverria P. Control of typhoid fever in Bangkok, Thailand, by annual immunization of schoolchildren with parenteral typhoid vaccine. *Rev Infect Dis* 1987; 9: 841-5.

Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. *Bull World Health Organ* 2004; 82: 346-53.

Deeks SL, Johnson IL. Vaccine coverage during a school-based hepatitis B immunization program. *Can J Public Health* 1998; 89: 98-101.

Hessel L, Debois H, Fletcher M, Dumas R. Experience with *Salmonella typhi* Vi capsular polysaccharide vaccine. *Eur J Clin Microbiol Infect Dis* 1999; 18: 609-20.

Li C, Chen J, Li Z. A raster-based method for computing Voronoi diagrams of spatial objects using dynamic distance transformation. *Int J Geogr Info Sci* 1999; 13: 209-25.

Lin FY, Vo AH, Phan VB, *et al*. The epidemiology of typhoid fever in the Dong Thap Province, Mekong Delta region of Vietnam. *Am J Trop Med Hyg* 2000; 62: 644-8.

Ministry of Health. Health statistics. Hanoi, Vietnam: Ministry of Health, 1996.

Parry C, Wain J, Chinh NT, Vinh H, Farrar JJ. Quinolone-resistant *Salmonella typhi* in Vietnam. *Lancet* 1998; 351: 1289.

Robbins JD, Robbins JB. Reexamination of the protective role of the capsular polysaccharide (Vi antigen) of *Salmonella typhi*. *J Infect Dis* 1984; 150: 436-49.

Trach DD. Approaches to the control of cholera and typhoid fever in Vietnam. Hanoi, Vietnam: National Institute of Hygiene and Epidemiology, 1998.

Vu DT, Hossain MM., Nguyen DS, *et al*. Coverage and costs of mass immunization of an oral cholera vaccine in Vietnam. *J Health Popul Nutr* 2003; 21: 304-8.

Wain J, Kidgell C. The emergence of multidrug resistance to antimicrobial agents for the treatment of typhoid fever. *Trans R Soc Trop Med Hyg* 2004; 98: 423-30.

World Health Organization (WHO). Surveillance of adverse events following immunization. Field Guide for managers of immunization programmes. *WHO/EPI/TRAM/93.02 REV 1.* 1997

World Health Organization (WHO). Typhoid vaccines. *Wkly Epidemiol Rec* 2000; 75: 257-64.

World Health Organization (WHO). Background document WHO/V&B/03.07: the diagnosis, treatment and prevention of typhoid fever. Geneva: WHO, 2003.

Zuckerman JN. A recently developed typhoid Vi polysaccharide vaccine: rationale and clinical profile. *BioDrugs* 2001; 15 (suppl 1): 1-4.