J HEALTH POPUL NUTR 2004 Sep;22(3):240-245
ISSN 1606-0997 $ 5.00+0.20

The Role of Epidemiology in the Introduction of Vi Polysaccharide Typhoid Fever Vaccines in Asia

Camilo J. Acosta[1], Claudia M. Galindo[1], R. Leon Ochiai[1], M. Carolina Danovaro-Holliday[1], Anne-Laure Page[1], Vu Dinh Thiem[2], Jin Kyoung Park[1], Eunsik Park[1], Hyewon Koo[1], Xuan-Yi Wang[1], Remon Abu-Elyazeed[3,4], Mohammad Ali[1], M. John Albert[5], Bernard Ivanoff[1,6], Tikki Pang[7], Zhi-Yi Xu[1], and John D. Clemens[1,8]

[1]International Vaccine Institute, Seoul, Republic of Korea, [2]National Institute of Hygiene and Epidemiology, Hanoi, Viet Nam, [3]Epidemiology Unit, Enteric Disease Research Program, U.S. NAMRU-3, Cairo, Egypt, [4]GlaxoSmithKline Biologicals, Singapore, [5]Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait, [6]Vaccines and Other Biologicals, and [7]Research Policy and Cooperation, World Health Organization, Geneva, Switzerland, and [8]National Institute of Child Health and Human Development, Bethesda, MD, USA

ABSTRACT

Despite the availability of at least two licensed typhoid fever vaccines—injectable sub-unit Vi polysaccharide vaccine and live, oral Ty21a vaccine—for the last decade, these vaccines have not been widely introduced in public-health programmes in countries endemic for typhoid fever. The goal of the multidisciplinary DOMI (Diseases of the Most Impoverished) typhoid fever programme is to generate policy-relevant data to support public decision-making regarding the introduction of Vi polysaccharide typhoid fever immunization programmes in China, Viet Nam, Pakistan, India, Bangladesh, and Indonesia. Through epidemiological studies, the DOMI Programme is generating these data and is offering a model for the accelerated, rational introduction of new vaccines into health programmes in low-income countries. Practical and specific examples of the role of epidemiology are described in this paper. These examples cover: (a) selection of available typhoid fever vaccines to be introduced in the programme, (b) generation of policy-relevant data, (c) providing the 'backbone' for the implementation of other multidisciplinary projects, and (d) generation of unexpected but useful information relevant for the introduction of vaccines. Epidemiological studies contribute to all stages of development of vaccine evaluation and introduction.

***Key words*:** Typhoid fever; Vaccine; Epidemiology; Vaccinology; *Salmonella* Typhi; Asia

INTRODUCTION

Epidemiology is an essential tool to evaluate biomedical innovations, such as vaccines. The role of epidemiology is not just confined to pre-licensure evaluations of efficacy of vaccines (Phase I, II and III trials), as it also plays a key role in both introduction and post-licensure evaluations. Here, we report the epidemiological studies designed and conducted by the Diseases of the Most Impoverished (DOMI) typhoid fever programme in Bangladesh, China, India, Indonesia, Pakistan, and Viet Nam. The goal of the DOMI Programme is to provide evidence to accelerate the development and introduction of new-generation vaccines against cholera, typhoid fever, and shigellosis. The typhoid fever studies of the programme aim to generate policy-relevant data to facilitate the rational introduction and use of the licensed Vi polysaccharide vaccine (Vi PS vaccine) against typhoid fever.

Correspondence and reprint requests should be addressed to:
Dr. Camilo J. Acosta
International Vaccine Institute
San 4-8 Bongcheon-7-dong
Kwanak-gu, Seoul 151-818, Korea
Email: Camilo_acosta2003@yahoo.com
Fax: (82) (2) 872.2803

Background

The burden of typhoid fever has recently been estimated for 2000 as approximately 21,700,000 cases and 220,000 deaths (1). Although this estimate may not be accurate, the burden is considerable. High annual incidence rates have been reported recently in some countries of Asia: 198 per 100,000 in Viet Nam (Mekong Delta) (2) and 980 per 100,000 in India (Delhi) (3). The burden of the disease has been aggravated by the emergence of multi-drug-resistant strains, limiting treatment options (4). In the absence of an affordable programme to assure safe water and better sanitation conditions in developing countries, vaccination of high-risk populations is considered to be the most promising strategy for the control of typhoid fever (5,6). Two new-generation licensed vaccines for typhoid fever—live, attenuated oral vaccine, Ty21a (7) and injectable subunit vaccine, Vi PS vaccine (8)—have shown to be moderately efficacious without significant side-effects. Although Phase III individual randomized controlled trials have documented the safety and efficacy of both the vaccines in several countries, neither vaccine has been widely adopted in the public-health programmes in developing countries with endemic typhoid fever.

DOMI TYPHOID FEVER STUDIES

The table shows the salient features of the epidemiological studies launched by the DOMI typhoid fever programme, consisting of descriptive, observational and experimental studies.

Descriptive prospective studies

Data on the burden of typhoid fever are being collected in selected areas of six Asian countries. In brief, after a *de jure* census of a defined catchment population and assignment of individual identification numbers, a population-based typhoid fever surveillance system was implemented in 2001. Efforts were put in place to include the majority of different levels of the health-care system. Medical personnel interviewed, examined, and obtained a venous blood specimen for culture and serological assessment of *Salmonella enterica* subsp. *enterica* serovar Typhi (*S.* Typhi) for all persons with fever of ≥3 days living in the study area. Relevant clinical information was recorded using standard procedures and forms. Printed census booklets at the health facilities under study were used for identifying individuals and noting their unique identification numbers. Culture-proven cases or those with positive serologic tests were visited at home 7, 14, 30, and 90 days after onset of illness to confirm the identification of the patient and to gather information on typhoid fever-related disability. Deaths were documented through the project healthcare system, censuses, and national death reports. Regardless of the site of death, an infectious disease-focused verbal autopsy form was filled in to determine the cause of all deaths (9,10). All the study sites employed common surveillance and microbiologic methods to permit comparison of the burden of disease among countries. After a surveillance of 1-2 year(s) and completion of an additional census, Vi PS vaccine-effectiveness studies were launched at the same sites.

Collection of existing data

Data on the burden of typhoid fever during 1991-2000 have been collected from national surveillance systems and statistics, published scientific literature, and unpublished reports, in Bangladesh, China, India, Indonesia, Pakistan, Viet Nam, and Thailand. National surveillance systems are diverse in different countries and register cases of typhoid fever based on various combinations of blood culture, serology, or clinical criteria. Additionally, they are not comprehensive and do not include all health-care systems. Nevertheless, because prospective disease-burden assessments can be performed only in limited populations and generalization of the results of these prospective studies outside the populations under study may be uncertain, summarization of existing data in conjunction with the prospective assessments can offer more complete countrywide assessments of disease burden.

Retrospective observational studies

The DOMI Programme is conducting three retrospective studies to help determine the duration of protection provided by a locally-produced Chinese Vi PS vaccine. Two follow-up studies of individually-randomized double-blind placebo-controlled trials—one in Baoying county, Jiangsu province and another in Quanzhou county, Guangxi province—were conducted in 1994 and 1995 (11,12). Health records originating from the local disease surveillance system in a span of six-year post-immunization were reviewed to detect cases of serologically-confirmed (Widal) typhoid fever. Cases of typhoid fever were ascertained blinded to the vaccine status. Incidence rates of typhoid fever in vaccinees versus controls will be determined. In the third

Table. DOMI typhoid fever programme

Study type	Description	Location	Collaborating institutions	Status
Descriptive				
Disease burden prospective studies	Population: urban; all age groups; 160,000 individuals	North Jakarta, Indonesia	NIHRD, NAMRU-2	Completed
	Population: urban/rural; age: 5-60 years; 120,000 individuals	Hechi city, Guangxi province, China	Guangxi CDC	Completed
	Population: slum; age: 2-16 years; 35,000 individuals	Sultanabad-Hijrat, Bilal, Karachi, Pakistan	Aga Khan University	Completed
	Population: urban; age: 2-16 years; 70,000 individuals	Hue city, Viet Nam	NIHE	Completed
	Population: slum; all age groups; 50,000 individuals	Wards 29 and 30, eastern Kolkata, West Bengal, India	NICED	Completed
	Population: slum; all age groups; 20,000 individuals	Dhaka, Bangladesh	ICDDR,B: Centre for Health and Population Research	Ongoing
Existing data collection to determine burden of disease	Data originate from: national surveillance systems and statistics, published scientific literature, and unpublished reports	Bangladesh, China, India, Indonesia, Pakistan, Viet Nam, and Thailand		Ongoing
Observational				
Retrospective studies of long-term Chinese Vi PS efficacy/effectiveness	Follow-up of individually-randomized double-blind placebo-controlled trials conducted in 1994	Baoying county, Jiangsu province, China	Public Health College of Southeast University, Nanjing	Completed
	Follow-up of individually-randomized double-blind placebo-controlled trials conducted in 1995	Quanzhou county, Guangxi province, China	Guangxi CDC	Completed
	Case-control study	Baoying county, Jiangsu province, China	Jiangsu CDC	Completed
Experimental				
Vi PS effectiveness studies	Open cluster-randomized controlled effectiveness trial	Hechi city, Guangxi province, China	Guangxi CDC	Vaccination: April-May 2003 Ongoing disease surveillance
	Evaluator-blinded cluster-randomized controlled effectiveness trial	Sultanabad-Hijrat, Bilal colonies (slum area), Karachi, Pakistan	Aga Khan University	Sultanabad-Hijrat Vaccination: August-September 2003 Ongoing disease surveillance Bilal Colony Vaccination: planned for August 2004
	Evaluator-blinded cluster-randomized controlled effectiveness trial	Hue city, Viet Nam	NIHE	Vaccination: November-December 2003 Ongoing disease surveillance
	Evaluator-blinded cluster-randomized controlled effectiveness trial	Wards 29 and 30, eastern Kolkata, West Bengal, India	NICED	Vaccination: planned for September 2004.
	Logistic and feasibility; single arm study	North Jakarta, Indonesia (slum area)	NIHRD, NAMRU-2	Completed
Clinical trials of new Vi PS formulations	Safety and immunogenicity after re-injection; individually-randomized controlled trial	Suzhou city, Jiangsu province, China	Jiangsu CDC	Completed
	Safety and immunogenicity study of combined Vi PS-meningococcal A PS; individually-randomized controlled trial	Guangxi province, China	Wuhan Biological Institute NIH-USA	Planned for 2004

CDC: Center for Disease Prevention and Control; NAMRU-2: Naval Medical Research Unit No. 2; NICED: National Institute of Cholera and Enteric Diseases; NIH: National Institutes of Health; NIHE: National Institute of Hygiene and Epidemiology; NIHRD: National Institute of Health and Research Development

study, rates of earlier Vi PS vaccination in typhoid fever cases versus age- and sex-matched disease-free controls are being compared to estimate the long-term effectiveness of a Vi PS vaccine provided through the public-health system since 1996 in Suzhou city, Jiangsu, China.

In addition to the above studies, the DOMI Programme had the opportunity to analyze the effectiveness of the Vi PS vaccine during an outbreak of typhoid fever in 1999 in a middle school in Xing-An county, Guangxi province (13). Before the outbreak, some students had received the Vi PS vaccine through a school-based immunization programme. 1n 1999, during the outbreak, students who had not been vaccinated previously were vaccinated. Effectiveness analysis took into account the time-dependent nature of vaccination and illness. The protective efficacy of the Vi PS vaccine given before or during the epidemic was 76% (13).

Clinical trials of new Vi PS vaccine formulation and uses

Due to uncertainties about reactions following re-injection of Vi PS vaccine (14), the DOMI Programme conducted a study in Suzhou city, Jiangsu province, China. This study evaluated the safety and immunogenicity of re-injection of a Chinese Vi PS vaccine three years after the initial vaccination. The study was an individually-randomized double-blind placebo-controlled clinical trial involving approximately 1,000 children aged 9-14 years. An individually-randomized controlled trial of safety and immunogenicity of a combined Vi PS/ meningococcal A PS vaccine administered to children aged 4-6 years in China has been designed. If the combination shows an adequate safety and immunogenic profile, the goal would be to reduce production costs and insert the newly-formulated vaccine into the national immunization schemes.

Vi PS vaccine-effectiveness demonstration projects

A core activity of the DOMI typhoid fever programme is the conduction of cluster-randomized, evaluator-blinded controlled trials in China, Pakistan, Viet Nam, and India. These trials are being carried out after the prospective descriptive studies at the same sites. They were designed to provide scientifically sound evidence of the protective impact and cost-effectiveness of the Vi PS vaccine delivered through the existing public-health systems. The unit of allocation is a cluster of individuals. The boundaries demarcating the clusters are selected to resemble a unit to be targeted for vaccination under ordinary conditions (geographic area or schools). Eligibility for participation corresponds to the anticipated eligibility for a public-health programme: school-age children for Viet Nam; all populations aged above five years for China; and those aged above two years for India and Pakistan. The formulation of the vaccine, its mode of delivery, safety measures, constitution of vaccine teams, and choice of venue for vaccinating simulate programmatic conditions. Cases of typhoid fever are being documented through the passive case-detection surveillance developed in the lead-in prospective surveillance. Adverse events following immunization are documented for a one-month period following dosing.

Parenteral inactivated whole-cell typhoid vaccines were reported to have significantly decreased the number of cases of typhoid fever among non-vaccinated groups in Thailand (15). The cluster-design approach will also permit testing whether such indirect effects occur after immunization with the Vi PS vaccine.

CONCLUSION

Epidemiological data contribute to all stages of development of a vaccine programme (16). Before a vaccine is licensed, its safety and efficacy must be established using controlled clinical trials. Post-licensing evaluation is of equal importance. These last studies identify changes in vaccine efficacy when vaccination is delivered through the existing public-health systems, assess the duration of protection, and detect rare or new adverse events. Epidemiology, defined as "the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems" (17), fulfils its most relevant role when introducing and fine-tuning a new vaccination programme to reduce the burden of a given disease. The DOMI typhoid fever programme highlights four practical roles of epidemiological studies in the spectrum of the introduction of vaccines in such countries.

First, epidemiological evidence derived from pre-licensure studies of protective efficacy guided the selection of available typhoid fever vaccines to be introduced in the programme. The consistent efficacy results of Vi PS vaccine in different settings (11,12,18,19) identified this vaccine as the best option. Additionally, the Vi PS vaccine has other advantages in relation to acceptance and delivery, such as a single-dose scheme and less-stringent cold chain. Second, post-licensure studies

being conducted in the DOMI Programme will generate policy-relevant data, such as re-injection safety, effectiveness, and duration of protection, to tailor the use of the Vi PS vaccine in public-health programmes. Additionally, the ongoing large-scale effectiveness trials will provide information on the acceptability of the Vi PS vaccine, programmatic feasibility of administration, selection of a delivery strategy, and expected levels of vaccine coverage—all central for decision-makers. Furthermore, the observational study in China that evaluated the effectiveness of the Vi PS vaccine during an epidemic in a school-setting (13) confirmed the magnitude of protective efficacy as observed from the previous phase III trials, provided insights about Vi PS as a tool to be used in epidemics, and gave re-assurance about the quality of a locally-produced vaccine compared to one produced by international pharmaceutical companies.

Third, the DOMI typhoid fever epidemiological studies have provided the 'backbone' for the implementation of other central multidisciplinary projects, such as economic analysis, behavioural studies, vaccine policy studies, molecular epidemiology, and analysis of geographical information systems. Data on cost of illness are obtained from cases of culture- and serology-proven typhoid fever ascertained in the prospective disease-burden studies. Behavioural, willingness-to-pay and vaccine demand surveys have been conducted in representative (simple random sampling) households drawn from the already-conducted census in areas where cluster-randomized trials have been launched. Technology transfer for the production of vaccines by qualified local producers in Asia is being facilitated with the aim of carrying out bridging clinical studies for regulatory approval.

Fourth is the generation of unexpected but useful information. Preliminary incidence data from the prospective studies have shown lower-than-expected figures for blood culture-proven typhoid fever. The low sensitivity of blood culture to detect *S.* Typhi (20) in areas where antibiotics are sold over-the-counter is one plausible explanation. The combined use of the traditional (Widal tube agglutination assays) and newer-generation typhoid fever serology-based detection methods in culture-negative febrile patients seems to suggest that the burden of culture-negative typhoid fever in these Asian countries may be two or three times that revealed by the use of blood culture methods only. The development of a more sensitive but yet specific case definition of typhoid fever, using a combination of serological test results as well as blood culture results, can provide a more accurate burden estimate, while still providing an unbiased measurement of vaccine's protective efficacy. Data from the DOMI prospective studies on burden of typhoid fever also indicate that *Salmonella enterica* subsp. *enterica* serovar Paratyphi A (*S.* Paratyphi A) is emerging as a major pathogen in some parts of Asia. If this trend continues, consideration must be given to developing a bivalent (*S.* Typhi-*S.* Paratyphi A) enteric fever vaccine for some areas in Asia.

The DOMI typhoid fever programme is an enormous and ambitious one. All planned epidemiological studies have been launched, and the majority have been completed. Huge economic and human resources have been mobilized, and a great effort has been made to follow the international research guidelines (21). Many lessons will be learnt when the programme is concluded, and the data generated by the above epidemiological studies will strongly contribute to the accelerated introduction of the Vi PS vaccine in Asia.

ACKNOWLEDGEMENTS

This work was supported by the Diseases of the Most Impoverished (DOMI) Programme, funded by the Bill and Melinda Gates Foundation and coordinated by the International Vaccine Institute, Seoul, Republic of South Korea.

This work is dedicated to the memory of Prof. Dang Duc Trach. We thank: Allan Donner, Jeremy Farrar, Yang Honghui, Wang Bangui, Veraprasad Reddy, Dong Baiqing, Duc Anh, Do Gia Canh, Yang Jin, Nirmal Kumar Ganguly, Lalit Kant, Sujit Kumar Bhattacharya, Dipika Sur, Byomkesh Manna, Zhou Weizhong, Wang Nin, Zulfiqar Ahmed Bhutta, Nizami Qamaruddin, Afia Zafar, Rumina Hasan, Cyrus Simanjuntak, Magdarina Agtini, Narain Punjabi, Yanning Gao, Hasbullah DVM, Lorenz von Seidlein, Jacqueline Deen, Hyejon Lee, Luis Jodar, Moshaddeque Hussein, Paul Kilgore, Kok-hai Ong, T. Afifah Ibrahim, Michael Goon, Eun Young Kim, Sue Kyoung Jo, John Wain, Amanda Walsh, Hans Bock, Robert Breiman, Didier Leboulleux, and more than 500 personnel working for the following institutions: Guangxi Center for Prevention and Disease Control (CDC), China; Jiangsu CDC, China; South East Univer-sity, Nanjing, China; Lanzhou Institute, China; National Institute of Hygiene & Epidemiology, Viet Nam; Oxford University-Wellcome Trust, Tropical Unit, Ho Chi Minh City,

Viet Nam; Indian Council of Medical Research, India; National Institute of Cholera and Enteric Diseases, India; Society for Applied Studies, India; Aga Khan University, Pakistan; NIHRD and U.S.-NAMRU-2, Indonesia; ICDDR,B: Centre for Health and Population Research, Bangladesh; GlaxoSmithKline; Shanta Biotechnics, India; University of North Carolina, USA; University of Western Ontario, Canada; and World Health Organization, Switzerland.

REFERENCES

1. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. *Bull World Health Organ* 2004;82:346-52.
2. Lin FY, Vo AH, Phan VB, Nguyen TT, Bryla D, Tran CT *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.
3. Sinha A, Sazawal S, Kumar R, Sood S, Reddaiah VP, Singh B *et al*. Typhoid fever in children aged less than 5 years. *Lancet* 1999;354:734-7.
4. Rowe B, Ward LR, Threlfall EJ. Multidrug-resistant *Salmonella typhi*: a worldwide epidemic. *Clin Infect Dis* 1997;24(Suppl 1):S106-9.
5. World Health Organization. Typhoid vaccines. *Wkly Epidemiol Rec* 2000;75:257-64.
6. World Health Organization. Background document: the diagnosis, treatment and prevention of typhoid fever. Geneva: World Health Organization, 2003. 38 p. (WHO/V&B/03.07).
7. Germanier R, Fürer E. Isolation and characterization of Gal E mutant Ty 21a of *Salmonella typhi*: a candidate strain for a live, oral typhoid vaccine. *J Infect Dis* 1975;131:553-8.
8. 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.
9. World Health Organization. A standard verbal autopsy method for investigating causes of death in infants and children. Geneva: World Health Organization, 1999. 78 p. (WHO/CDS/CSR/ISR/99.4).
10. United Kingdom. Department for International Development. Overview of census and verbal autopsy methods. *In*: Policy implications of adult morbidity and mortality: end of phase 1 report. Chapter 8. 1997. (http://www.ncl.ac.uk/ammp/site_files/public_html/ammp_rep/ammp_rpt.pdf, accessed on 15 June 2004).
11. Wang ZG, Zhou WZ, Shi J. [Efficacy and side effects following immunization with *Salmonella typhi* Vi capsular polysaccharide vaccine]. Zhonghua Liu Xing Bing Xue Za Zhi 1997;18:26-9.
12. Yang HH, Wu CG, Xie GZ, Gu QW, Wang BR, Wang LY *et al*. Efficacy trial of Vi polysaccharide vaccine against typhoid fever in south-western China. *Bull World Health Organ* 2001;79:625-31.
13. Yang HH, Kilgore PE, Yang LH, Park J-K, Pan Y-F, Kim Y *et al*. An outbreak of typhoid fever, Xing-An county, People's Republic of China, 1999: estimation of the field effectiveness of Vi polysaccharide typhoid vaccine. *J Infect Dis* 2001;183:1775-80.
14. 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.
15. 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.
16. Begg N, Cutts FT. The role of epidemiology in the development of a vaccination program. *In*: Cutts FT, Smith PG. Vaccination & world health. Chichester: Wiley, 1994:123-37.
17. Last JM. A dictionary of epidemiology. 3d ed. Oxford: Oxford University Press, 1995. 180 p.
18. Klugman KP, Koornhof HJ, Robbins JB, Le Cam NN. Immunogenicity, efficacy and serological correlate of protection of *Salmonella typhi* Vi capsular polysaccharide vaccine three years after immunization. *Vaccine* 1996;14:435-8.
19. Acharya IL, Lowe CU, Thapa R, Gurubacharya VL, Shrestha MB, Cadoz M *et al*. Prevention of typhoid fever in Nepal with the Vi capsular polysaccharide of *Salmonella typhi*. A preliminary report. *N Engl J Med* 1987;317:1101-4.
20. Wain J, Phan VB, Ha V, Nguyen NM, To SD, Walsh AL *et al*. Quantitation of bacteria in bone marrow from patients with typhoid fever: relationship between counts and clinical features. *J Clin Microbiol* 2001;39:1571-6.
21. International Conference on Harmonisation. Harmonized tripartate guideline. Guideline for good clinical practice E6. (http://www.ich.org/MediaServer.jser?@_ID=482&@_MODE=GLB, accessed on 15 June 2004).