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

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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.
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 healthcare 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 healthcare 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

<table>
<thead>
<tr>
<th>Study type</th>
<th>Description</th>
<th>Location</th>
<th>Collaborating institutions</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptive</td>
<td>Disease burden prospective studies Population: urban; all age groups; 160,000 individuals</td>
<td>North Jakarta, Indonesia</td>
<td>NIHRD, NAMRU-2</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>Population: urban; age: 5-60 years; 120,000 individuals</td>
<td>Hechi city, Guangxi province, China</td>
<td>Guangxi CDC</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>Population: slum; age: 2-16 years; 35,000 individuals</td>
<td>Sultanabad-Hijrat, Bilal, Karachi, Pakistan</td>
<td>Aga Khan University</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>Population: urban; age: 7-26 years; 70,000 individuals</td>
<td>Hue city, Viet Nam</td>
<td>NIHIE</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>Population: slum; all age groups; 50,000 individuals</td>
<td>Wards 29 and 30, eastern Kolkata, West Bengal, India</td>
<td>NICEF</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>Population: slum; all age groups; 20,000 individuals</td>
<td>Dhaika, Bangladesh</td>
<td>ICDDR,B Centre for Health and Population Research</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Existent data collection to determine burden of disease</td>
<td>Data originate from: national surveillance systems and statistics, published scientific literature, and unpublished reports</td>
<td>Bangladesh, China, India, Indonesia, Pakistan, Vietnam, and Thailand</td>
<td></td>
<td>Ongoing</td>
</tr>
<tr>
<td>Observational</td>
<td>Retrospective studies of long-term Chinese Vi PS efficacy/effectiveness</td>
<td>Follow-up of individually-randomized double-blind placebo-controlled trials conducted in 1994</td>
<td>Baoying county, Jiangsu province, China</td>
<td>Public Health College of Southeast University, Nanjing</td>
</tr>
<tr>
<td></td>
<td>Follow-up of individually-randomized double-blind placebo-controlled trials conducted in 1995</td>
<td>Quanzhou county, Guangxi province, China</td>
<td>Guangxi CDC</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>Case-control study</td>
<td>Baoying county, Jiangsu province, China</td>
<td>Jiangsu CDC</td>
<td>Completed</td>
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<tr>
<td></td>
<td>Vi PS effectiveness studies</td>
<td>Hue city, Viet Nam</td>
<td>NIHIE</td>
<td>Completed</td>
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<tr>
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<td>Completed</td>
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<td>North Jakarta, Indonesia (slum area)</td>
<td>NIHRD, NAMRU-2</td>
<td>Completed</td>
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<td>Jiangsu CDC</td>
<td>Completed</td>
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<tr>
<td>Clinical trials of new Vi PS formulations</td>
<td>Safety and immunogenicity after re-injection, individually-randomized controlled trial</td>
<td>Guangxi province, China</td>
<td>Wuhan Biological Institute NIH-USA</td>
<td>Planned for 2004</td>
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</table>
| CDC: Center for Disease Prevention and Control; NAMRU-2: Naval Medical Research Unit No. 2; NICEF: National Institute of Cholera and Enteric Diseases; NIH: National Institutes of Health; NIHIE: 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. In 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.

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