THE EPIDEMIOLOGY OF TYPHOID FEVER IN THE DONG THAP PROVINCE, MEKONG DELTA REGION OF VIETNAM

FENG-YING C. LIN, VO ANH HO, PHAN VAN BAY, NGUYEN THI THANH THUY, DOLORES BRYLA, TRAN CONG THANH, HA BA KHIEM, DANG DUC TRACH, AND JOHN B. ROBBINS

National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland; Dong Thap Provincial Hospital, Dong Thap Province, Pasteur Institute in Ho Chi Minh City, and the National Institute of Hygiene and Epidemiology, Ministry of Health, Hanoi, Vietnam

Abstract. A population-based surveillance for typhoid fever was conducted in three rural communes of Dong Thap Province in southern Vietnam (population 28,329) for a 12-month-period starting on December 4, 1995. Cases of typhoid fever were detected by obtaining blood for culture from residents with fever ≥ 3 days. Among 658 blood cultures, 56 (8.5%) were positive for Salmonella typhi with an overall incidence of 198 per 10^5 population per year. The peak occurrence was at the end of the dry season in March and April. The attack rate was highest among 5–9 year-olds (531/10^5/year), and lowest in > 50 year-olds (39/10^5/year). The attack rate was 358/10^5/year in 2–4 year-olds. The isolation of S. typhi from blood cultures was highest (17.4%) in patients with 5 to 6 days of fever. Typhoid fever is highly endemic in Vietnam and is a significant disease in both preschool and school-aged children.

INTRODUCTION

Typhoid fever is endemic in Southeast and Far East Asia, the Indian subcontinent, the Middle East, Africa, and Central and South America. It is estimated that more than 33 million cases and more than 500,000 deaths due to typhoid fever occur each year. Ingestion of food or water contaminated by acutely infected persons or chronic typhoid carriers is the most common form of transmission. As a result, typhoid fever is prevalent where unsafe drinking water or contaminated food is common.

Typhoid fever continues to be a major cause of morbidity and mortality in Vietnam. Due to the lack of laboratory facilities in most provinces, the diagnosis of typhoid for purposes of national surveillance is based on the clinical criteria of prolonged fever without localizing signs of infections. Without a change in the method of surveillance, Vietnam, particularly in the southern provinces, experienced a greater than six-fold increase in reported cases of typhoid fever from 1990 (4,859 cases) to 1995 (30,901). Most cases (~90%) were reported from the southern region which consists of 17 provinces that comprise about 39% of the total population of Vietnam.

Typhoid fever has become difficult and expensive to treat. In southern Vietnam, about 90% of Salmonella typhi isolates are now resistant to multiple antibiotics including chloramphenicol, ampicillin and co-trimoxazole.4 More recently, 76% of blood culture isolates of S. typhi were reported to be resistant to nalidixic acid.5 The improvement of sanitation, the provision of safe drinking water, and the elimination of chronic carriage is not expected to be achieved quickly. Accordingly, vaccination against typhoid fever has become a national public health priority. This study was undertaken to describe the epidemiology of typhoid fever in a defined population in southern Vietnam and to prepare a field site for vaccine trials of an improved Vi capsular polysaccharide vaccine.6

MATERIALS AND METHODS

Three communes (MH, MT, and MX) in Cao Lanh District of Dong Thap Province in the Mekong Delta region of southern Vietnam were selected for this study because of their potential as a field site for vaccine trials. There is a high endemicity of typhoid fever (the annual incidence of about 850 per 10^5 population) and an excellent health care infrastructure in place. It is located near the Provincial Hospital’s microbiology laboratory and there is a strong commitment to the control of typhoid fever from both the local community leaders and the Ministry of Health of Vietnam.

Each commune has a health center that provides primary and preventative health care. The district has a health center which has inpatient, outpatient, and emergency services. The District Health Center is located at study commune MT. There are private doctors available as well. Almost all private doctors are medical staff from the health centers/hospitals who have private clinics after government office hours. The tropical climate has two seasons: a rainy season from May to November, and a dry season from December to April. The area is primarily rural with 95% of the population engaged in agriculture. Rivers, canals, and tributaries are the major modes of transportation and the primary source of drinking water. Typhoid fever, dengue/dengue hemorrhagic fever, pneumonia/influenza, diarrhea, and rabies/exposure to rabid animals are the five most commonly reported diseases in southern Vietnam.

Surveillance included obtaining a blood sample for culture from all individuals with fever (axillary temperature ≥ 38.5°C) for 3 days who sought medical care at one of the study health facilities: Commune Health Centers, Cao Lanh District Health Center, and the Provincial Hospital between December 4, 1995 and December 3, 1996.

After verbal consent, a five mL blood sample was placed in a DifcoBACTO blood culture bottle (# 0936–37–6) containing 50 mL of trypticase soy broth under a partial vacuum and CO2. Blood culture bottles were transported on the day of collection to the Microbiology Laboratory of the Provincial Hospital for culture and identification. Cultures were incubated at 35 to 37°C for 7 days and checked at 1, 2 and 7 days for growth. Suspicious colonies were confirmed as S. typhi by standard biochemical reactions and serological tests. All S. typhi isolates were independently verified by Dr. Vee Gill at the Clinical Microbiology Laboratory, The National...
Institutes of Health. Demographic, clinical, and laboratory data were recorded for each case of fever.

Before the commencement of surveillance, a census was taken and a household survey of sewage disposal, water source, and treatment in each household was conducted by door-to-door survey. Households were visited by community health workers who also explained the program and encouraged the acceptance of blood culture for diagnosis of typhoid fever at the health facilities. Private doctors were requested to refer fever cases to the health center for blood culture. The study was approved by the Institutional Review Board of the Ministry of Health of Vietnam and the National Institute of Child Health and Human Development, National Institutes of Health.

Only individuals who resided in the three study communes were included in the data analyses. Clinical typhoid fever was defined as fever ≥3 days without localizing signs of tonsillitis, bronchitis, pneumonia, dengue fever, hemorrhagic fever, meningitis, or encephalitis. An index case was defined as the initial case, and 90% of the households used "fish pond latrines".

RESULTS

Study population and environment. A census taken in October 1995 revealed a total of 28,329 persons living in 5,494 households in the three communes; of these, 48% were males. Household surveys showed that river water and rain water were the primary sources of water; less than one percent of households used well water. Seventy-one percent of the households boil water routinely, 22% occasionally, and 7% never boil water for drinking. There is no sewage system, and 90% of the households used "fish pond latrines".

TABLE 1
Recovery of Salmonella typhi from blood culture in cases of clinical typhoid fever, Dong Thap Province, Vietnam, December 4, 1995–December 3, 1996

<table>
<thead>
<tr>
<th>Duration of fever (days)</th>
<th>Number of cases blood cultured</th>
<th>No.</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>368</td>
<td>17</td>
<td>4.6</td>
</tr>
<tr>
<td>4</td>
<td>148</td>
<td>17</td>
<td>11.5</td>
</tr>
<tr>
<td>5–6</td>
<td>70</td>
<td>12</td>
<td>17.1</td>
</tr>
<tr>
<td>≥7</td>
<td>72</td>
<td>10</td>
<td>13.9</td>
</tr>
<tr>
<td>Total</td>
<td>658</td>
<td>56</td>
<td>8.5</td>
</tr>
</tbody>
</table>

*B: Prior antibiotic intake, duration of fever, and blood culture positivity

<table>
<thead>
<tr>
<th>Duration of fever (days)</th>
<th>Status</th>
<th>No. of cases</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Yes</td>
<td>75</td>
<td>4</td>
<td>5.3</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>86</td>
<td>5</td>
<td>5.8</td>
</tr>
<tr>
<td>≥4</td>
<td>Yes</td>
<td>75</td>
<td>12</td>
<td>16.0</td>
</tr>
<tr>
<td>≥4</td>
<td>No</td>
<td>29</td>
<td>4</td>
<td>13.8</td>
</tr>
<tr>
<td>Total</td>
<td>265</td>
<td>25</td>
<td>9.4</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.001 by Chi square test

Over one-third of these connect directly to the river. Seven hundred and thirteen persons (2.5%) reported having had fever ≥3 days in the month preceding the survey.

Fever cases and blood cultures. During the 12 month study period, 973 fever-cases (age 3 months to 87 years) were evaluated, including 669 patients with clinical typhoid fever (69%); 199 with bronchitis (20%); 56 with pneumonia (6%); 20 with dengue fever (2%); and 29 (3%) with other diagnoses. Blood cultures were obtained from 667 (69%) of fever patients (658 cases of clinical typhoid fever, and 9 others). Seventy-three percent of blood samples were obtained at the commune health centers, 20% at the District Health Center, and 7% at the Provincial Hospital. The proportion of fever cases who had blood cultures done increased with age from 42.1% in <2 year-olds, 52.5% in 2–4 year-olds, and 74.1% in 5–9 year-olds to 80.4% in 10–14 year-olds.

Recovery of S. typhi from blood culture. Among 658 cases of clinical typhoid fever who had blood drawn for culture, 56 (28 males, 28 females) had S. typhi recovered from their blood, resulting in an overall isolation rate of 8.5% and an overall annual incidence of 198 per 10^4 population. The rate of recovery of S. typhi increased with the duration of fever prior to blood sampling and went from 4.6% in patients with 3 days of fever to 17.1% in patients with 5 to 6 days of fever (P < 0.001), and then decreased slightly to 13.9% in patients with fever ≥7 days (Table 1A). A history of antibiotic use prior to blood culture was available in 265 cases who were cultured: 150 (57%) had taken antibiotics and 115 had not. Salmonella typhi was recovered from 16 (10.7%) of 150 cases of clinical typhoid fever who had taken antibiotics compared with 9 (7.8%) of 115 cases who had not (P > 0.05, Chi square test). When stratified among patients with 3 days of fever, S. typhi was recovered from 5.3% of patients with prior antibiotic intake versus 5.8% without prior antibiotics. In patients with fever for ≥4 days, the recovery of S. typhi was 16.0% in those with prior antibiotic intake versus 13.8% without prior antibiotic intake (P > 0.05) (Table 1B).

Age-specific attack rate. The age-specific attack rate of clinical typhoid fever paralleled the attack rate of blood-culture-positive typhoid fever except for the age group under 2 years (Figure 1). The attack rate of typhoid fever was highest among children 5 to 9 years of age (531/10^4 for
culture-positive typhoid fever and $4717/10^3$ for clinical typhoid fever). The attack rate of clinical typhoid fever for persons < 2 years of age was comparable to the 20 to 29 year olds (1814 versus 1912/10^3). None of the 16 blood cultures from < 2 year-olds were positive.

**Seasonality.** The occurrence of blood-culture-positive typhoid fever by month and its relation to the amount of rainfall are shown in Figure 2. The number of blood-culture-positive cases of typhoid fever was highest at the end of the dry season in March and April, and lowest during the rainy season in July–September. The percent of blood cultures positive for S. typhi was also highest in March (24%) and April (29%) and lowest in May (3%).

**Clinical manifestations.** Fever, malaise, headache, and anorexia were the most common symptoms in both blood-culture-positive and culture-negative cases. Several symptoms were more prevalent in culture-positive than culture-negative cases: malaise (84% versus 67%, $P = 0.01$), anorexia (71% versus 57%, $P = 0.03$), constipation (21% versus 9%, $P = 0.02$), and diarrhea (21% versus 11%, $P = 0.02$). Conversely, cough and rales were more frequent in culture-negative cases than positive cases. In one case, a 6 year-old child had a relapse 6 weeks after the first episode, and S. typhi was isolated from blood cultures during both episodes. None of the cases was reported to have intestinal bleeding or perforation. No deaths attributed to S. typhi were reported among either clinical typhoid fever or culture-positive cases.

**Transmission within schools and families.** Among the 56 culture-positive cases, 26 were children from six schools in the study communes, with each school having from one to 10 cases. Blood-culture–positive cases occurring within one month of each other were noted in two schools in MT Commune involving five and six cases each, and in another school in MX Commune involving 9 cases. Four families each had a secondary case; in two, both the index and secondary cases were culture-positive; in the other two, the secondary case was culture-negative.

**DISCUSSION**

This population-based study quantifies the incidence of clinical and blood-culture-positive typhoid fever in three villages in the Dong Thap Province of southern Vietnam during one year. These data confirm the national clinical surveillance report that typhoid fever is highly endemic in southern Vietnam. The overall incidence of clinical typhoid fever in this study was about 12 times higher than that of culture-positive typhoid fever ($2,323$ versus $198/10^3$/year) and about three times higher than the national clinical surveillance in the previous year ($2,323$ versus $850/10^3$/year). The clinical diagnosis of typhoid fever is not obvious. Fever and malaise without localizing signs are too inclusive. Therefore, we believe that the incidence of clinical typhoid fever is an overestimate of typhoid fever. In May, when dengue fever is prevalent, only 3% of blood cultures obtained from cases of clinical typhoid fever were positive for S. typhi, whereas 24 to 28% were positive in March and April. This difference may be due to lack of specificity in the diagnosis of clinical typhoid fever.

Microbiologic diagnosis of S. typhi infection by blood culture is not precise. Using the standard of culture of bone marrow aspirations as 100%, only 50% of blood samples are positive for S. typhi. Thus, it is possible that the incidence of typhoid fever based upon blood culture is only one-half of the actual level. It is likely that we missed microbiological confirmation in patients who presented to the health center with a short duration of fever and mild illness because the isolation of S. typhi from blood culture is significantly higher in patients whose blood sample was taken after 4 days of fever. Fifty-six percent of blood cultures in this study were obtained at 3 days, mostly without a repeat blood culture. Furthermore, because the surveillance was based on the contact of fever cases with the health system, it is likely that we missed cases who did not seek medical care at the health centers. For example, using the data of fever cases reported in the household survey (713 cases in one month), and the average number of fever cases (81) seen at the study health facilities, we estimate that only about 11.4% of fever cases came in contact with the study health facilities.

Typhoid fever in young children has been thought to be uncommon and mild. However, in this study, 6 (11%) of 56 culture-positive cases were under 5 years of age. Several hospital-based studies, a hospital outpatient-based prospective study of febrile patients, and a disease surveillance in Chicago showed that about one-quarter to one-third of pediatric typhoid fever cases were under 5 years old, and 6 to 21% were under 2 years of age (Table 2). In this study, no culture-positive typhoid fever was detected in persons < 2 years of age. The apparent absence of culture-positive typhoid fever in children less than 2 years of age may be due to the difficulty and reluctance of doctors to draw five mL blood from a small child. Data from the inpatient service of Dong Thap Provincial Hospital, where medical staff are more experienced with blood drawing in young children, showed that 60 (33%) of 182 blood-culture–positive cases of typhoid fever admitted in 1996 were less than 5 years of age; six (3%) were < 2 years of age. These data showed that typhoid fever is a significant disease in children under 5 years of age.

Salmonella typhi is spread by the fecal–oral route. Following acute infections, patients may continue to excrete S. typhi for several weeks or for years as a chronic carrier. Nearly half of the culture-positive typhoid fever in this study oc-
curred in March and April, the two months at the end of the dry season. The water level progressively gets lower during the dry season, especially in smaller waterways. The water becomes more stagnant and shallow and deteriorates as the weather becomes hotter. Similar observations were also made in Indonesia where increased rainfall in December and January was followed by a peak of typhoid fever cases five months later when the rainfall was the lowest. Considering that typhoid fever is endemic and one-third of fish livers in the study area connect directly to the river in the study areas, one would expect the contamination of river water by S. typhi. Since almost all households use river water as the main source of water for drinking and for washing vegetables which are often served raw, and about 30% of households occasionally or never boil water for drinking, the likelihood of ingesting S. typhi from contaminated water is high. While the use of contaminated water could be the source of infection, the spread within the four families and the continued transmission in three schools could also be a result of person-to-person spread.

These data corroborate the national clinical case surveillance findings that typhoid fever is highly endemic in Vietnam with the highest incidence occurring in school-aged children followed by preschool children. Although none of the 16 children < 2 years of age clinically diagnosed as having typhoid fever was culture-positive, the hospital data showed that 3% of culture-positive cases were under 2 years of age. Based on these observations, vaccination for typhoid fever should include children under 5 years of age. However, all three licensed typhoid vaccines (whole cell heat-phenol inactivated vaccine, oral live-attenuated vaccine (Ty21a), and the Vi capsular polysaccharide vaccine) have limitations that restrict their use for routine childhood immunization because none confer protection in children under 5 years. The development of a typhoid vaccine that can confer immunity when administered to infants as part of their routine immunization is essential for successful control of this disease.

Acknowledgments: The authors gratefully acknowledge the medical staff at the Commune Health Centers, Cao Lanh District Health Center, and the Infectious Disease Department of the Provincial Hospital for their participation in this study. We also thank the local community leaders for their support of the study, and Dr. David Taylor for his critical review of this manuscript.

Table 2: Reported frequency of typhoid fever in children < 5 years of age

<table>
<thead>
<tr>
<th>Study</th>
<th>Country, year</th>
<th>Age (years)</th>
<th>Total cases</th>
<th>% &lt; 2 years old</th>
<th>% &lt; 5 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galloway and others*11</td>
<td>United Kingdom, 1964</td>
<td>0–12</td>
<td>86</td>
<td>9.3</td>
<td>31.4</td>
</tr>
<tr>
<td>Scragg and others12</td>
<td>South Africa, 1959–1967</td>
<td>Pediatric</td>
<td>316</td>
<td>5.6</td>
<td>23.7</td>
</tr>
<tr>
<td>Mulligan13</td>
<td>Nigeria, 1964–1969</td>
<td>0–19</td>
<td>249</td>
<td>20.5</td>
<td>36.5*</td>
</tr>
<tr>
<td>Johnson and others14</td>
<td>Nigeria, 1972–1978</td>
<td>0–12</td>
<td>117</td>
<td>–</td>
<td>17.1</td>
</tr>
<tr>
<td>Thyskorn and others15</td>
<td>Thailand, 1977–1984</td>
<td>Pediatric</td>
<td>163</td>
<td>–</td>
<td>47.2</td>
</tr>
<tr>
<td>Chow and others16</td>
<td>Hong Kong, 1978–1983</td>
<td>0–12</td>
<td>111</td>
<td>–</td>
<td>20.7</td>
</tr>
<tr>
<td>Ellis and others17</td>
<td>South Africa, 1977–1983</td>
<td>0–13</td>
<td>456</td>
<td>8.2</td>
<td>–</td>
</tr>
<tr>
<td>Lepage and others22</td>
<td>Rwanda, 1984–1985</td>
<td>Pediatric</td>
<td>47</td>
<td>17.0</td>
<td>31.9</td>
</tr>
<tr>
<td>Verma and others23</td>
<td>India, 1989–1994</td>
<td>Pediatric</td>
<td>409</td>
<td>10.9</td>
<td>–</td>
</tr>
<tr>
<td>Velema and others24</td>
<td>Indonesia, 1990–1991</td>
<td>0–13</td>
<td>356</td>
<td>–</td>
<td>19.7</td>
</tr>
<tr>
<td>Mirsa and others25</td>
<td>Chicago, IL, 1988–1994</td>
<td>0–18</td>
<td>55</td>
<td>–</td>
<td>35*</td>
</tr>
<tr>
<td>This study</td>
<td>Southern Vietnam, 1995–1996</td>
<td>0–87</td>
<td>56</td>
<td>0</td>
<td>10.7</td>
</tr>
</tbody>
</table>

* 0–5 years

Financial support: This study was supported by a contract from National Institute of Child Health and Human Development, National Institutes of Health (NOI-HD-52325).


REFERENCES