Original Article

Enteric fever burden in North Jakarta, Indonesia: a prospective, community-based study

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Abstract

Introduction: We undertook a prospective community-based study in North Jakarta, Indonesia, to determine the incidence, clinical characteristics, seasonality, etiologic agent, and antimicrobial susceptibility pattern of enteric fever.

Methodology: Following a census, treatment centre-based surveillance for febrile illness was conducted for two-years. Clinical data and a blood culture were obtained from each patient.

Results: In a population of 160,261, we detected 296 laboratory-confirmed enteric fever cases during the surveillance period, of which 221 (75%) were typhoid fever and 75 (25%) were paratyphoid fever. The overall incidence of typhoid and paratyphoid cases was 1.4, and 0.5 per thousand populations per year, respectively. Although the incidence of febrile episodes evaluated was highest among children under 5 years of age at 92.6 per thousand persons per year, we found that the burden of typhoid fever was greatest among children between 5 and 20 years of age. Paratyphoid fever occurred most commonly in children and was infrequent in adults.

Conclusion: Enteric fever is a public health problem in North Jakarta with a substantial proportion due to paratyphoid fever. The results highlight the need for control strategies against enteric fever.

Key words: enteric fever; typhoid fever; paratyphoid fever; incidence

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Introduction

We undertook a prospective study of enteric fever in all age groups in North Jakarta, Indonesia. Previous reports from Indonesia [1,2,3,4,5,6], including partial results from this surveillance study [7,8], indicate that enteric fever is an important public health problem in the country. In this paper, we present the data from two years of surveillance in North Jakarta on the incidence and characteristics of enteric fever by etiologic agent and by age group, as well as the seasonality and antimicrobial susceptibility patterns of the isolates. Such detailed information on burden of disease is important to inform policy decisions regarding disease control strategies.

Methodology

Study area and population

The study was conducted in an impoverished, congested area of North Jakarta, where the average annual income per person was US$ 689 in 2000 [9]. Water supply and sanitation is inadequate with only 57% to 65% of the population having access to tap water [10]. Many residents use water from either a communal tap or a local river for washing and buy water from vendors for consumption. Many of the houses are temporary structures with no toilets. There is no separate sewage system for human waste disposal in the area.

North Jakarta is divided into seven sub-districts (*kecamatans*). The sub-districts of Tanjung Priok and Koja were targeted for this surveillance study based on the expected high incidence of enteric disease, accessibility, and previous research experience in the area [11]. The study also incorporated cholera and shigellosis surveillance, the results of which have been previously reported [12]. The total population enumerated by a study census in 2001 was 160,261 individuals of whom 15,741 (10%) were younger than 60 months of age [13].

Health care system

The first-level health-care facility in Indonesia is a primary health center or Puskesmas. There are 54 primary health centers in North Jakarta, 22 of which are located in Tanjung Priok and Koja, equipped to conduct preventive measures and treat mild diseases. More severe conditions are referred to hospitals. The Infectious Disease Hospital and Koja Hospital are the main government referral hospitals in North Jakarta. In 2001, there were 314 private practitioners, 36 polyclinics, 32 maternal clinics, and 29 small private hospitals in the study area.

Surveillance procedures

The surveillance was conducted from August 2001 to July 2003. We invited patients of all age groups residing in the study area and presenting to a participating health-care provider (primary health centers in the study area, the Infectious Disease Hospital, and Koja Hospital) with fever for three days or diarrhoea to join the surveillance. A blood culture examination for *Salmonella* species was offered free of charge. A blood sample (8-10 ml) blood was collected from each adult participant with fever lasting three days or longer and used to immediately inoculate a culture bottle with 10% ox-gall media during the initial phase of the study or Bactec plus F/Aerobic bottle (BD Bactec system, Franklin Lakes, USA) starting on the seventh month of the surveillance. From children younger than 12 years of age with fever of longer than three days, 3-5 ml ml of blood were collected and immediately inoculated in a culture bottle with 10% ox-gall solution during the initial phase of the study or a Bactec Peds Plus bottle (BD Bactec system, Franklin Lakes, USA) starting the seventh month of the surveillance.

Treatment was provided in accordance with national guidelines. The participants paid the regular nominal visiting fee of about US$ 0.20 at the health centers and US$ 0.30 at the hospitals. Periodic meetings were held with representatives of all the health centers and hospitals.

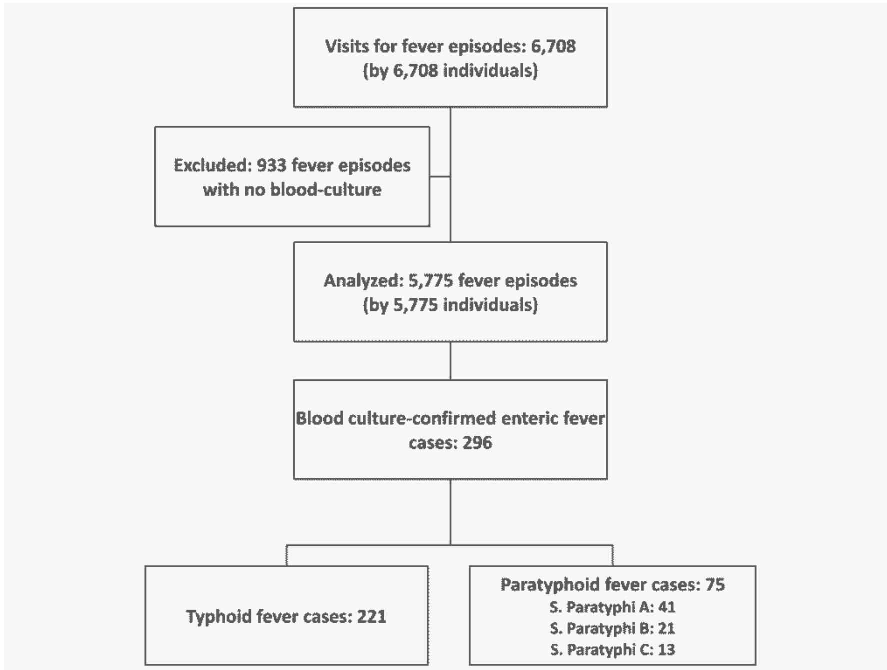
Laboratory procedures

The inoculated bottles were transported twice daily to the U.S. Naval Medical Research Unit No. 2 laboratory and processed according to standard procedures for the isolation and identification of *Salmonellae* [6,14]. The bottles with 10% ox-gall media were incubated at 37°C and sub-cultured onto MacConkey and SS agar plates on days 1, 4, and 7. The Bactec bottles were incubated in a Bactec machine and when bacterial growth was detected, a small aliquot of media was sub-cultured onto MacConkey and Salmonella-Shigella (SS) agar plates on days 1, 4 and 7. The MacConkey and SS agar plates were incubated at 37°C for 18 to 24 hours. On MacConkey agar, *Salmonellae* were identified as non-lactose-fermenting smooth colonies. On SS agar, *Salmonellae* were identified as non-lactose-producing, non-fermenting colonies with a black center. Suspected colonies were screened using Kligler's iron agar, motility indole ornithine, and citrate utilization tests. Colonies giving biochemical reactions suggestive of *Salmonellae* were confirmed serologically by slide agglutination test with polyvalent O Salmonella, specific O and Vi antisera (Difco Laboratories, Franklin Lakes, USA).

The bacterial isolate was then tested by slide agglutination test for H antigen factor d, a, b and c for *S.* Typhi, *S.* Paratyphi A, *S*. Paratyphi B and *S.* Paratyphi C, respectively. Unusual isolates were confirmed by biochemical reactions in an API 20E strip.

Antimicrobial susceptibility testing of *S.* Typhi and *S*. Paratyphi against ampicillin, trimethoprim/sulfamethoxazole, chloramphenicol, tetracycline, ceftriaxone, cephalothin, ciprofloxacin and nalidixic acid was conducted using standard antimicrobial discs (Becton, Dickinson and Co., Sparks, USA) using the Kirby Bauer disc diffusion method on Muller-Hinton agar [15]. *Salmonella* isolates were verified at a reference laboratory, Balitvet (Veterinarian Research Laboratory), Bogor, Indonesia, and the University of Oxford, Wellcome Trust Clinical Research Unit, Ho Chi Minh City, Vietnam.

Figure 1. Flow of patients visiting the participating treatment centers for fever in the North Jakarta study site, 1 August 2001 to 31 July 2003



Data management, definitions, and analysis

The case report forms were double-entered into a custom-made data entry program using FoxPro software (Microsoft, Seattle, USA). The data management program included error, range, and consistency check programs.

A fever episode was defined as a reported history of fever. The onset was taken as the day on which fever was reported to have begun. All fever episodes regardless of duration with a positive culture for *Salmonellae* were included in the analysis. Multiple visits for fever within seven days by the same individual was considered a single fever episode. A typhoid and paratyphoid fever case was defined as fever with isolation by blood culture of *S.* Typhi or *S.* Paratyphi, respectively.

We estimated the annual incidence of fever episodes, typhoid and paratyphoid fever cases using the 2001 study census as the denominator, assuming that each individual in the census contributed 24 months to the denominator and assuming a balance between in- and out-migration during the surveillance period. We used the age-specific number of fever episodes, typhoid and paratyphoid fever cases among the residents of the study area as the numerator. The 95% confidence intervals of the incidence were calculated using an exact method based on the binomial distribution [16]. Odds ratios were calculated to compare individual characteristics between typhoid and paratyphoid fever cases. All p-values and 95% confidence intervals were interpreted in a two-tailed fashion. Statistical significance was designated as a p-value less than 0.05. Statistical analyses were performed using Stata 7 (Stata Corporation, College Station, USA) software.

Ethics

After the project's purpose was explained, patients, or in the case of minors, their parents or guardians, gave verbal consent prior to participation in the study. The study was approved by the Ethics Committee of the Ministry of Health, Indonesia; the Institutional Review Board, National Institute of Health Research and Development, Ministry of Health, Jakarta, Indonesia; the Institutional Review Board, United States Naval Medical Research Unit No 2, Jakarta, Indonesia; and the Secretariat Committee on Research Involving Human Subjects, World Health Organization, Geneva, Switzerland

Results

During the surveillance period, there were 6,708 visits for fever at the participating treatment centers by residents of the study area (Figure 1). After excluding 933 (14%) visits with no blood culture obtained, 5,775 (86%) fever episodes were included in the analysis.

Figure 2. Number of culture-confirmed typhoid and paratyphoid fever by month in the North Jakarta study site, 1 August 2001 to 31 July 2003

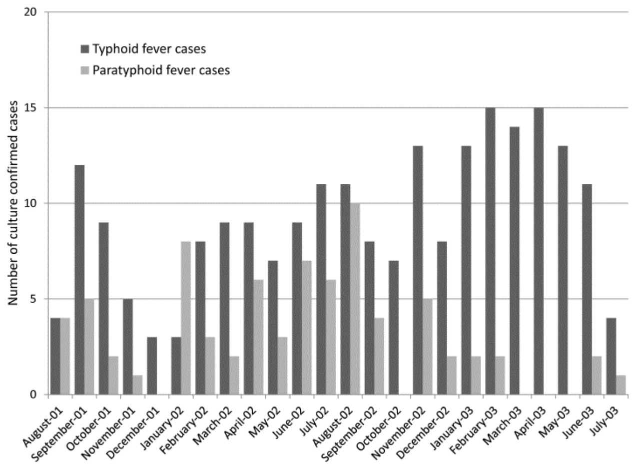
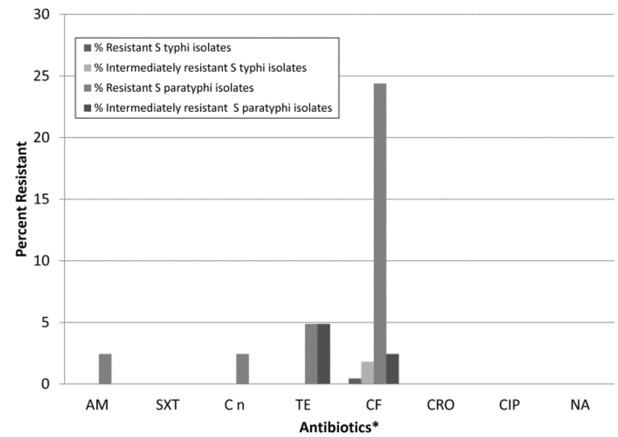


Figure 3. Antimicrobial resistance patterns of Salmonella enterica serotype Typhi isolates (n = 221) and Salmonella enterica serotype Paratyphi A isolates (n =41) in the North Jakarta study site



* AM = ampicillin, SXT = trimethoprim/sulphamethoxazole, C n = chloramphenicol, TE = tetracycline, CF =cephalothin, CRO = ceftriaxone, CIP = ciprofloxacin and NA = nalidixic acid

Among the fever episodes, we detected 296 enteric fever cases, of which 221 (74.66%) were typhoid fever and 75 (25.34%) were paratyphoid fever. Of the latter cases, 41 (54.67%) were due to *S*. Paratyphi A, 21 (28.00%) to *S.* Paratyphi B, and 13 (17.33%) to *S.* Paratyphi C. Over the course of the two-year surveillance period, typhoid or paratyphoid cases occurred nearly all year round with no seasonal pattern (Figure 2).

The overall incidence of detected fever episodes, typhoid, and paratyphoid cases was 41.9, 1.4, and 0.5 per thousand populations per year, respectively (Table 1). The incidence of febrile episodes was highest among young children. The burden of typhoid fever was greatest among those 5 to 20 years old with 128 (58%) cases diagnosed in this age group. In children under 2 years of age the incidence of paratyphoid fever (2.4 per thousand per year; 95% CI 1.4 - 3.9) was significantly higher than the incidence of typhoid fever (0.1 per thousand per year; 95% CI 0.0 to 0.08).

We compared other characteristics between typhoid and paratyphoid cases (Table 2). There was no significant difference in clinical presentation except for diarrhea, which was less frequently reported among typhoid fever cases (8.6%) compared to paratyphoid fever cases. Four cases required hospitalization, all of which were typhoid fever cases.

In general, the *S*. Paratyphi isolates displayed greater antimicrobial resistance than *S.* Typhi (Figure 3). The *S.* Typhi isolates showed emerging resistance to ceftriaxone but remained susceptible to other antimicrobial agents. Multi-resistant *S*. Typhi was not isolated from the study site during the surveillance period.

Discussion

Utilizing a passive surveillance program, we detected an enteric fever annual incidence of about one case per thousand populations per year, of which 25% were paratyphoid. There has been an increasing trend, or perhaps increasing recognition, of paratyphoid fever in Indonesia [4,5,7,8], as well as in other parts of Asia [7,8,17,18,19,20]. This emergence of paratyphoid fever has been attributed to improved microbiologic isolation methods, changes in the virulence of the organism, shifts in herd immunity, and widespread typhoid vaccination, but the true reason remains unknown. In addition, our results are notable for the detection of other *S.* Paratyphi B and C, since studies in other sites have mainly detected *S*. Paratyphi A [7,8,17,18,19,20].

Our reported incidence of typhoid and paratyphoid fever probably underestimates the true burden of disease. We used passive case detection and some of the enteric fever patients in the study area may not have used the treatment centers participating in the surveillance and thus remained undetected. A study in a Delhi slum utilizing active surveillance by visiting homes twice weekly found typhoid fever incidence among children under 5 years and those between 5 to less than 20 years of age at 27 and 12 per thousand populations per year, respectively [21]. Differences in study methodology as well as the epidemiology of the

Table 1: Age-specific incidence (per 1,000 persons per year) of fever episodes and culture-confirmed typhoid fever and paratyphoid fever in the North Jakarta study site, 1 August 2001 to 31 July 2003

Age at illness	Population	Fever episodes	Incidence of fever (95% CI)		Typhoid fever cases	Typhoid fever incidence (95% CI)		Paratyphoid fever cases	Paratyphoid fever incidence (95% CI)	
Under 5 years	**15994**	**1926**	**120.4**	**(115.4, 125.6)**	**23**	**1.4**	**(0.9, 2.2)**	**20**	**1.3**	**(0.8, 1.9)**
under 2 years	6959	1243	178.6	(169.7, 187.8)	1	0.1	(0, 0.8)	17	2.4	(1.4, 3.9)
2 to 4.9 years	9035	683	75.6	(70.2, 81.2)	22	2.4	(1.5, 3.7)	3	0.3	(0.1, 1)
5 to under 20 years	**47378**	**2010**	**42.4**	**(40.6, 44.3)**	**128**	**2.7**	**(2.3, 3.2)**	**24**	**0.5**	**(0.3, 0.8)**
5 to 9.9 years	14674	689	47.0	(43.5, 50.5)	36	2.5	(1.7, 3.4)	2	0.1	(0, 0.5)
10 to 19.9 years	32704	1321	40.4	(38.3, 42.6)	92	2.8	(2.3, 3.5)	22	0.7	(0.4, 1.0)
20 to under 40 years	**63785**	**2059**	**32.3**	**(30.9, 33.7)**	**63**	**1.0**	**(0.8, 1.3)**	**24**	**0.4**	**(0.2, 0.6)**
20 to 29.9 years	37182	1425	38.3	(36.4, 40.3)	54	1.5	(1.1, 1.9)	14	0.4	(0.2, 0.6)
30 to 39.9 years	26603	634	23.8	(22.0, 25.7)	9	0.3	(0.2, 0.6)	10	0.4	(0.2, 0.7)
40 years and older	**33104**	**713**	**21.5**	**(20.0, 23.2)**	**7**	**0.2**	**(0.1, 0.4)**	**7**	**0.2**	**(0.1, 0.4)**
40 to under 60 years	26905	540	20.1	(18.4, 21.8)	5	0.2	(0.1, 0.4)	6	0.2	(0.1, 0.5)
60 years and older	6199	173	27.9	(23.9, 32.3)	2	0.3	(0.1, 1.2)	1	0.2	(0, 0.9)
All ages (total)	**160261**	**6708**	**41.9**	**(40.9, 42.9)**	**221**	**1.4**	**(1.2, 1.6)**	**75**	**0.5**	**(0.4, 0.6)**

Table 2: Comparison of characteristics between the culture-confirmed typhoid and paratyphoid cases in the North Jakarta study site

	Typhoid fever n = 221	*Paratyphoid fever n = 75*	*P-value*	*OR (95% CI) p-value*
Mean (median; SD) age	16.5 (14.5 ; 10.1)	18.5 (16.4 ; 14.9)	0.3	1.0 (0.9,1.0)
No (%) female	107 (48.4)	37 (49.3)	0.9	1.0 (0.6,1.8)
No (%) with nausea	153 (69.2)	50 (66.7)	0.7	1.1(0.6,2.0)
No (%) with vomiting	104 (47.1)	30 (40.0)	0.3	1.3 (0.8, 2.3)
No (%) with abdominal pain	12 (5.4)	5 (6.7)	0.7	0.8 (0.3, 2.4)
No (%) with constipation	18 (8.1)	5 (6.7)	0.7	1.2 (0.4, 3.5)
No (%) with diarrhea	19 (8.6)	38 (50.7)	<.0001	0.1 (0.1, 0.2)
No (%) with abdominal distention	29 (13.1)	8 (10.7)	0.6	1.3 (0.6, 2.9)
No (%) with abdominal tenderness	29 (13.1)	8 (10.7)	0.6	1.3 (0.6, 3.0)
No (%) referred for hospitalization	4 (1.8)	0	0.6	1.0 (0.9, 1.0)

disease between the study sites probably account for the lower incidence observed in Jakarta than in Delhi.

A study from Vietnam utilizing passive surveillance showed a culture-confirmed typhoid fever incidence similar to our findings: 3.6, 5.3, and 4.3 per thousand populations per year among those 2 to under 5 years, between 5 to 9 years, and between 10 to 19 years, respectively [22].

A previously published study from Jakarta [4] suggested that paratyphoid fever is predominantly transmitted outside the household, in contrast to the in-household transmission of typhoid fever. However, we found that 18 enteric fever episodes in children under 2 years of age were caused by paratyphoid fever. This finding suggests possible transmission within the household.

Four episodes of enteric fever required hospitalization, all of which were typhoid cases. This difference was not statistically significant and may have been due to chance. Paratyphoid cases presented significantly more frequently with diarrhea than typhoid fever episodes. In general, however, the clinical appearance of typhoid and paratyphoid cases in our study was similar, indicating that the infections could not be differentiated based on presenting signs and symptoms. Surprisingly, the majority of isolates from our study remain susceptible to antimicrobial agents despite the ubiquitous availability of antibiotics without prescription.

The age distribution of typhoid fever patients suggests that children and young adults are at highest risk for typhoid fever and should be targeted for control strategies such as vaccination. None of the licensed typhoid vaccines protect against paratyphoid fever. However, a candidate paratyphoid vaccine consisting of a modified O-specific polysaccharide of its lipopolysaccharide conjugated to tetanus toxoid has been developed and undergone Phase I and II trials in Vietnamese adults and children [23]. This North Jakarta study site could be a potential area for the evaluation of paratyphoid vaccines.

In summary, enteric fever, both typhoid and paratyphoid, is a problem in Jakarta. Our findings highlight the need for control strategies against the disease.

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