Typhoid fever : aspects of environment, host and pathogen interaction

Ali, S.

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Risk factors for typhoid and paratyphoid fever in Jakarta, Indonesia

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Abstract

Context: The proportion of paratyphoid fever cases to typhoid fever cases may change due to urbanization and increased dependency on food purchased from street vendors. For containment of paratyphoid a different strategy may be needed than for typhoid, because risk factors for disease may not coincide and current typhoid vaccines do not protect against paratyphoid fever.

Objective: To determine risk factors for typhoid and paratyphoid fever in an endemic area.

Design, Setting, and Participants: Community-based case-control study conducted from June 2001 to February 2003 in hospitals and outpatient health centers in Jatinegara district, Jakarta, Indonesia. Enrolled participants were 1019 consecutive patients with fever lasting 3 or more days, from which 69 blood culture–confirmed typhoid cases, 24 confirmed paratyphoid cases, and 289 control patients with fever but without *Salmonella* bacteremia were interviewed, plus 378 randomly selected community controls.

Main Outcome Measures: Blood culture–confirmed typhoid or paratyphoid fever; risk factors for both diseases.

Results: In 1019 fever patients we identified 88 (9%) *Salmonella typhi* and 26 (3%) *Salmonella paratyphi* A infections. Paratyphoid fever among cases was independently associated with consumption of food from street vendors (comparison with community controls: odds ratio [OR], 3.34; 95% confidence interval [CI], 1.41-7.91; with fever controls: OR, 5.17; 95% CI, 2.12-12.60) and flooding (comparison with community controls: OR, 4.52; 95% CI, 1.90-10.73; with fever controls: OR, 3.25; 95% CI, 1.31-8.02). By contrast, independent risk factors for typhoid fever using the community control group were mostly related to the household, ie, to recent typhoid fever in the household (OR, 2.38; 95% CI, 1.03-5.48); no use of soap for handwashing (OR, 1.91; 95% CI, 1.06-3.46); sharing food from the same plate (OR, 1.93; 95% CI, 1.10-3.37), and no toilet in the household (OR, 2.20; 95% CI, 1.06-4.55). Also, typhoid fever was associated with young age in years (OR, 0.96; 95% CI, 0.94-0.98). In comparison with fever controls, risk factors for typhoid fever were use of ice cubes (OR, 2.27; 95% CI, 1.31-3.93) and female sex (OR, 1.79; 95% CI, 1.04-3.06). Fecal contamination of drinking water was not associated with typhoid or paratyphoid fever. We did not detect fecal carriers among food handlers in the households.

Conclusions: In Jakarta, typhoid and paratyphoid fever are associated with distinct routes of transmission, with the risk factors for disease either mainly within the household (typhoid) or outside the household (paratyphoid).

Introduction

Typhoid fever, a food- and waterborne disease caused by *Salmonella enterica* serotype Typhi (*S. typhi*), is a serious public health problem in developing countries that claims 600 000 lives every year.[1] Paratyphoid fever, caused by *Salmonella paratyphi* A, B, or C, has a disease presentation similar to that of typhoid fever, but its incidence is reportedly about one tenth that of typhoid (ratio, 1:10-20).[2-3] In developing countries the identification of risk factors and relevant route of transmission for a disease such as typhoid fever is essential for the development of rational control strategies. Resources could consequently be allocated to where they count most, e.g., to the construction or expansion of water distribution networks or sewage systems, chlorination of drinking water, ensurance of food safety, hygiene education, mass vaccination campaigns, and/or the identification of carriers within or outside the households of patients.

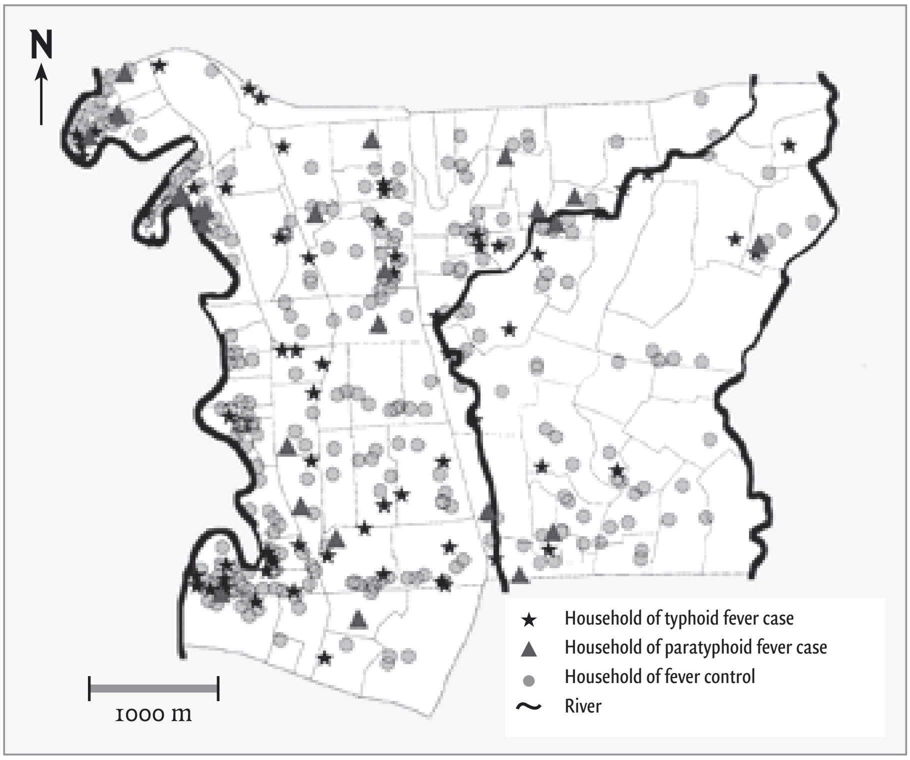
Risk factors for typhoid fever have been identified in several epidemiologic studies suggesting either waterborne[4-8] or food borne transmission.[7,9-11] Whether these factors coincide with those for paratyphoid fever has not been determined. The assumption is that in paratyphoid fever, a higher dose of bacteria is required for infection than in typhoid fever; consequently, food is implicated as the major vehicle for transmission of paratyphoid fever, since *Salmonella* bacteria can multiply in food.[12] Comparison of the transmission of both diseases is becoming increasingly relevant, because recent reports have demonstrated an increasing occurrence of paratyphoid fever.[3,13] It is not clear whether this is due to incompleteness of epidemiologic data in endemic countries or to a downward trend in the incidence of typhoid fever[1,14] and a consequent relative or absolute increase in the incidence of paratyphoid fever. In consequence, however, public health measures may well be refocused. In particular, recent interest in mass immunization as a control strategy in regions of endemicity needs to be reconsidered if the incidence of typhoid fever is decreasing and para-typhoid fever is on the rise, because current typhoid fever vaccines (i.e., parenteral Vi and oral Ty21a vaccine) do not protect against paratyphoid fever.[2]

In this community-based case-control study in an endemic area in East Jakarta, Indonesia, we compared case patients having paratyphoid and typhoid fever with random community controls to identify hygienic practices, eating habits, and environmental and household characteristics that could elucidate prevailing transmission routes. For this purpose we also examined the microbiological quality of drinking water and cultured stools of intra-household food handlers to detect transient or chronic carriers. A second control group composed of patients with non-enteric fever was used for comparison and confirmation of the results. Patients with typhoid fever, paratyphoid fever, and non-enteric fever were identified in a prospective passive-surveillance study involving hospitals and outpatient health centers in the study area.

Methods

Study Area and Population: The Jatinegara district in East Jakarta, a 10.6 km^2 area with 262 699 registered inhabitants (as of March 2002), was selected as the study area **(Figure 1)** because of its varied socioeconomic conditions and good access to *puskesmas* (i.e., public community health centers providing medical care for low-income residents of Indonesia). The local climate has 2 distinctive seasons: a rainy season (December-April) and a dry season (May-November). Three rivers cross the area, making the adjacent subdistricts prone to flooding. There is no sewage system in the area. Vaccination campaigns have not been initiated in the area.
Study Design and Selection Criteria: The study was approved by the Indonesian National Institute of Health Research and Development (*Litbangkes*) and provincial authorities. A passive surveillance system was established from June 11, 2001, to February 4, 2003. Health care facilities in the study area were approached for the surveillance study.

Figure 1. Study area (Jatinegara, Jakarta, Indonesia), showing households of cases with typhoid and paratyphoid fever and fever controls



Those participating included all 4 hospitals in the immediate vicinity, 8 of the 13 additional small private outpatient clinics in the area, and all 12 *puskesmas*. A fee of US $0.35 covers 3 days of antibiotic treatment, but cultures or Widal tests are not part of the usual diagnostic practice in *puskesmas*. Eligible patients were individuals living in the study area who consulted one of the participating health care facilities because of self-reported fever for 3 or more consecutive days. A single blood specimen for culture was collected from each eligible patient. Depending on the age of the patient, 5 to 10 mL of blood was collected into blood culture vials (aerobic) containing antibiotic-absorbing resins (Bactec; Becton Dickinson, Franklin Lakes, NJ) that were provided to the centers by the study group free of charge.

Cases were eligible patients with blood culture–confirmed *S. typhi* or *S. paratyphi* infection. All cases were subject to a household visit within a month after the febrile episode that prompted the blood culture.

Blood cultures of patients with non-enteric fever showed either no growth or bacteria other than *S. typhi* or *S. paratyphi* as cause of fever. Malaria could be excluded in the differential diagnosis of prolonged fever, because transmission does not occur in Jakarta. Every second consecutive patient with non-enteric fever was selected as a fever control and visited. Also, during the surveillance, community controls were randomly selected within a random household in every third *rukun tetangga* (i.e., the smallest administrative unit of 40-60 area households) of a total of 1140 *rukun tetanggas*. When a community control reported fever in the 30 days preceding the interview or refused participation, the house on alternating sides of the initially selected household was approached. The selection of both groups of controls was nonmatched for age, sex, or neighborhood (i.e., residence in 1 of the 8 subdistricts of Jatinegara) to limit selection bias and prevent overmatching. Four controls from both groups for every case of enteric fever were selected to increase statistical power.

Household Visits and Sample Collection: Cases and controls were interviewed by trained medical school graduates, using a standardized questionnaire that included the known risk factors from previous studies and questions from a questionnaire that was used in a similar risk factor study, which had been locally tested and validated.[6] Written informed consent was provided by all participants at the household visit. To prevent the overrepresentation of multiple-case households, only 1 patient (i.e., the first reported case or fever control) per household was interviewed. If cases or controls were younger than 13 years, the mother or guardian was interviewed. No time frame for hygiene behavior and food habits was mentioned, because it aimed at the description of usual practice. A *household* was defined as a dwelling whose inhabitants ate from the same pot. *Flooding* was defined as inundation of the house of a participant in the 12 months preceding the interview. *Intrahousehold food handlers* were defined as individuals preparing meals for cases or controls 3 or more times a week. A single stool sample of 2 g was collected from all cases, controls, and their intrahousehold food handlers in a vial with Cary-Blair transport medium and samples were processed within 24 hours after collection. Water samples of 150 mL directly from the source of running drinking water were collected in the households of 62 typhoid and 20 paratyphoid cases, 341 community controls, and 233 fever controls using World Health Organization guidelines.[15]

Laboratory Methods: Blood culture vials from outpatient facilities were transported on the day of collection to Mitra Internasional, one of the participating private hospitals with a microbiology laboratory certified by the International Organization for Standardization. Blood cultures were incubated for up to 7 days. Samples demonstrating growth were plated on blood agar medium. *Salmonella typhi* or *S. paratyphi* A were identified by use of agglutination antisera (Polyvalent, D, Vi, H, and Paratyphi A; Murex Biotech Ltd, Dartford, England) and biochemical tests (Microbact; Medvet Diagnostics, Adelaide, Australia). Susceptibility against chloramphenicol, ampicillin, cotrimoxazole, and ciprofloxacin was tested by disk diffusion on Mueller-Hinton agar. Stool samples were cultured for *Salmonella* bacteria using selenite enrichment broth (Oxoid Ltd, Hampshire, England). Suspected colonies as identified by visual inspection were plated on xylose-lysine-desoxycholate agar and *Salmonella-Shigella* agar, and on triple sugar iron agar, SIM (sulphide and indole production and motility) medium, and Simmons citrate (Oxoid). Bacterial identification was identical to that for bacteria from blood cultures.

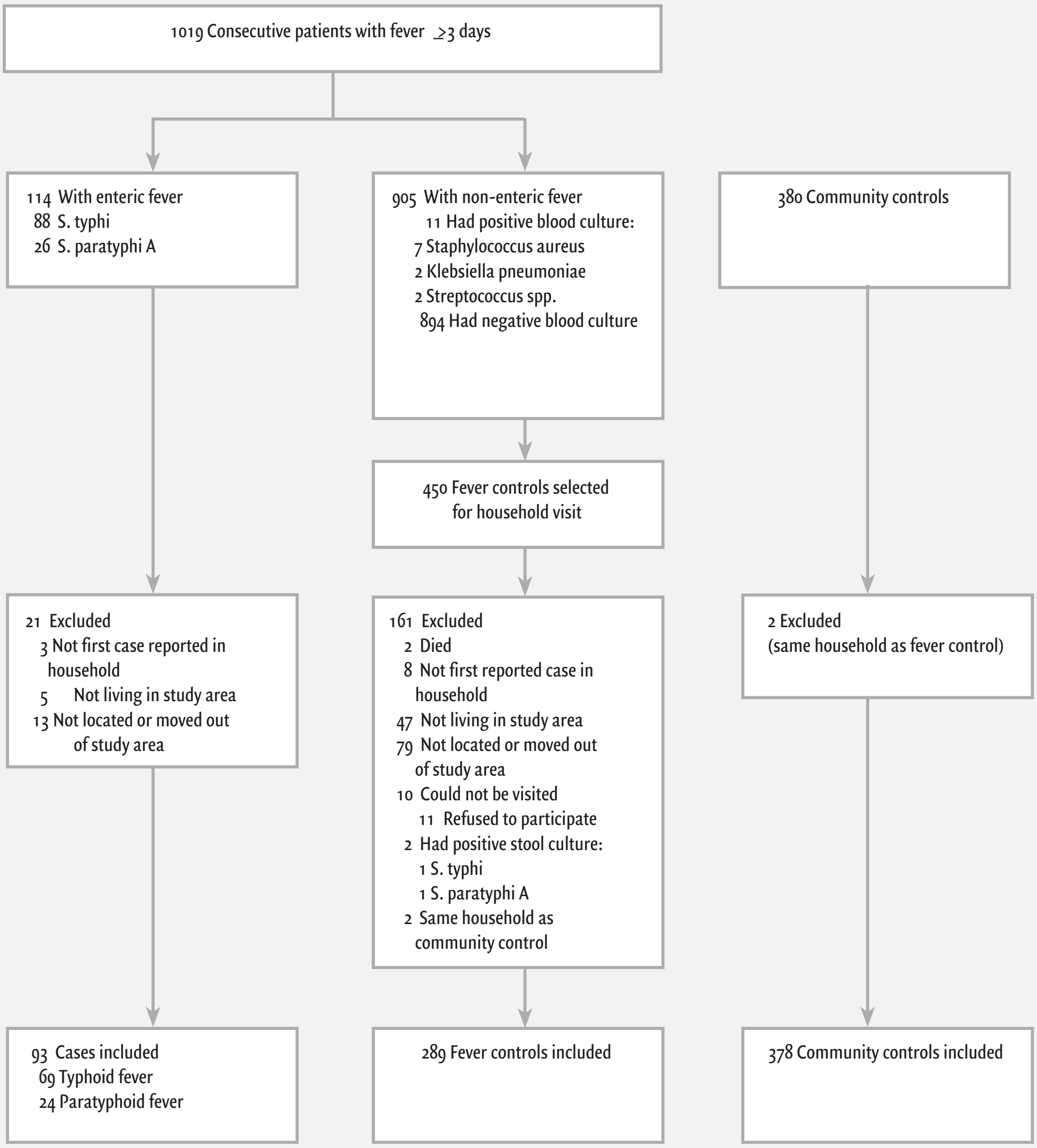
Samples from the sources of drinking water were transported on ice and processed within 6 hours after collection at the Nusantara Water Centre.[15] In samples from piped water the bactericidal effect of chlorine during transport was neutralized by 0.1 mL of 10% sodium thiosulphate. Water samples were examined for total and fecal coliforms by use of most probable number method.[15] Fecal contamination was defined as a most probable number index for fecal coliforms of 1/100 mL or greater.

Statistical Methods: Data from the questionnaires were entered twice using EpiInfo 6.04b software (US Centers for Disease Control and Prevention, Atlanta, Ga), validated, and imported into SPSS version 11.5 (SPSS Inc, Chicago, Ill) for statistical analysis. After the first 3 months of surveillance, an interim analysis was performed and the needed sample size was calculated; a minimum sample size of 80 enteric fever cases (assuming 4 times as many fever controls) was required to detect significant associations ($P<.05$) between key exposure variables and outcome, with a power of 0.80. Normally and nonnormally distributed numerical variables were analyzed using t tests and Mann-Whitney U tests, respectively. Measures for association were expressed as odds ratios (ORs) for disease with their 95% confidence intervals (CIs) for categorical variables. To control for confounding, a multivariate analysis was performed using logistic regression with a forward likelihood ratio test with the significantly associated variables from the bivariate analysis and potential confounders (e.g., age, sex, income, and neighborhood residence).[16] Sex and income were also included in the bivariate analysis; age and neighborhood residence were not. Effect modification by interaction of age, sex, or income was tested, but these terms were not significantly associated and did not change the ORs of associated variables. The attributable risk of each independently associated variable from the multivariate analysis was calculated.[17]

Results

Surveillance Study: During the study period 1019 consecutive patients with fever lasting 3 or more days were included. We identified 88 *S. typhi* and 26 *S. paratyphi* A infections. In 905 patients with non-enteric fever, 11 had bacteremia of another cause (*Staphylococcus aureus* [n = 7], *Klebsiella pneumoniae* [n = 2], and *Streptococcus* spp [n = 2]), whereas the remaining 894 patients were culture-negative (**Figure 2**). Most of the patients were treated in the *puskesmas* (n = 717 [70%]), and fewer patients in hospitals (n = 113 [11%]) and outpatient clinics (n = 189 [19%]). The relative number of patients with typhoid or paratyphoid fever among febrile patients was similar for all health care centers (P = .81). Typhoid and paratyphoid fever accounted for 114 (11%) of the febrile episodes identified. Twenty-three percent (26/114) of enteric fevers were paratyphoid fever. Three (3%) of the 88 *S. typhi* strains were resistant to chloramphenicol, ampicillin, and cotrimoxazole; all *S. paratyphi* A strains were susceptible to these antibiotics.
Patients with typhoid and paratyphoid fever reported a median of 4 days (interquartile range [IQR], 3-7) of fever before blood cultures were taken. This period was similar to that in patients with non-enteric fever (median, 4 days; IQR, 3-54). The age of all patients enrolled in the surveillance study ranged from 1 to 76 years (3-59 years for patients with enteric fever and 1-76 years for those with non-enteric fever). The number of enteric fever cases enrolled in the dry season was higher than that in the rainy season (ratio, 7:3) and this ratio was similar (P>.05) in patients with non-enteric fever (ratio, 6:4). Referring physicians reported prior use of antibiotics in 26 patients (23%) with typhoid or paratyphoid fever and in 200 patients (22%) with nonenteric fever (P = .86).
Household Visits: In total, 69 typhoid fever cases, 24 paratyphoid fever cases, 289 fever controls, and 378 community controls were available for analysis (**Figure 2**). Not all of the cases and fever controls could be interviewed. Two fever controls died. Three cases (3%) and 8 fever controls (2%) were secondary patients from households in which only the first patient was interviewed to prevent overrepresentation of these households. Five cases (4%) and 47 fever controls (10%) were not living in the study area. Some addresses could not be found or patients had migrated out of the area (13 [11%] and 79 [18%] for cases and fever controls, respectively). Due to manpower constraints, 10 fever controls

Figure 2. Study inclusion of typhoid and paratyphoid fever cases, fever controls and community controls in Jatinegara, Jakarta, Indonesia, June 2001 – February 2003



(2%) could not be visited; 11 fever controls (2%) but none of the remaining cases refused cooperation. Two fever controls had positive stool culture results (for *S. typhi* [n = 1] and *S. paratyphi* A [n = 1]) at the household visit and were therefore excluded from the analysis. Enteric fever cases and fever controls were visited a median of 24 (IQR, 21-29) days after the blood culture. Fever controls reported to be diagnosed and treated for the following diagnoses: suspected typhoid fever (n = 126 [44%]), dengue fever (n = 11 [4%]), respiratory tract infections (n = 10 [3%]), tuberculosis (n = 3 [1%]), influenza (n = 3 [1%]), gastroenteritis (n = 2), urinary tract infection (n = 1), and encephalitis (n = 1); 132 patients (46%) were not informed of the working diagnosis.

During the study period, 380 random households in the study area community were visited; 289 (76%) of the community controls agreed to participate at the first approach and the remaining 91 (24%) were the neighbors from the initially selected households. From 2 households of community controls a patient with non-enteric fever was included later in the course of the study period. These 2 households were excluded from the analysis.

Demographic Data From the Visited Cases and Controls: The median age of the typhoid cases was 16 (range, 3-57) years; of paratyphoid cases, 22 (range, 4-59) years; of community controls, 27 (range, 1-80) years; and of fever controls, 20 (range, 1-75) years (**Table 1**). Typhoid and paratyphoid fever cases and fever controls were significantly younger than the community controls (P<.01). The age of patients with typhoid fever did not differ significantly from that of those with paratyphoid fever (P = .12). Fever controls were significantly more often of male sex than were community controls (P = .003 by χ^2 test) and typhoid cases (P = .03). No significant differences in the sex ratio were found when typhoid or paratyphoid cases were compared with community controls. Compared with the number of community controls per subdistrict, who had been included proportionally to the size of the population, in 1 subdistrict proportionally more typhoid cases than community controls were enrolled (P = .07), whereas in another subdistrict more patients with paratyphoid fever were enrolled (P = .05). Within the group of patients with enteric fever itself, no significant overrepresentation of any subdistrict was found in the comparison of patients with typhoid and paratyphoid fever (P = .37).

Risk Factors for Typhoid and Paratyphoid Fever: Risk factors for typhoid and paratyphoid fever in comparison with community and fever controls are shown in **Table 1**. Compared with paratyphoid cases the typhoid cases were more often female, lived in more crowded conditions, were more frequently from a lower income category, more frequently reported recent typhoid fever among household contacts in the preceding 12 months, used ice cubes more often, shared food more often, and observed poor handwashing hygiene. Flooding and eating food purchased from street vendors were more frequently reported by patients with paratyphoid fever than by those with typhoid fever. Among the 2 control groups, fever controls were more often male, from a lower income group, observed

Table 1. Risk factors for typhoid and paratyphoid fever in Jakarta

	Cases		Controls	
Risk factor	**Typhoid fever (n=69)**	**Paratyphoid fever (n=24)**	**Community (n=378)**	**Fever (n=289)**
Age, median (range), y	16 (3-57)	22 (4-59)	27 (1-80)	20 (1-75)
Female sex	40 (58%)	9 (38%)	211 (56%)	126 (44%)
Low family income [a]	40 (58%)	9 (38%)	182 (48%)	174 (60%)
Household size, median (range) [b]	6 (3-200)	5 (2-8)	6 (1-50)	6 (1-20)
Crowding [c]	34 (49%)	8 (33%)	137 (36%)	101 (35%)
Recent typhoid fever in the household	11 (16%)	3 (13%)	23 (6%)	27 (9%)
No use of soap for hand washing	49 (71%)	15 (63%)	214 (57%)	183 (63%)
No toilet in household	15 (22%)	5 (21%)	33 (9%)	38 (13%)
Eating food from street vendors	22 (32%)	13 (54%)	85 (23%)	59 (20%)
Consumption of iced drinks	17 (25%)	5 (21%)	51 (14%)	62 (22%)
Consumption of ice cubes	45 (65%)	14 (58%)	176 (47%)	131 (45%)
Sharing food from same plate	31 (45%)	7 (29%)	102 (27%)	101 (35%)
Eating with hands	33 (48%)	11 (46%)	121 (42%)	164 (43%)
Drinking water: piped water	7 (10%)	2 (8%)	77 (20%)	42 (15%)
Faecal contamination of drinking water source [d]	30 (48%)	11 (55%)	192 (56%)	125 (54%)
Flooding	26 (38%)	14 (58%)	79 (21%)	99 (34%)

a: Defined as below the median monthly income of the community controls (900,000 Rupiah [US $105]).
b: Includes 2 outliers: an orphanage with 200 individuals and a dormitory with 50 individuals in the typhoid cases and community controls, respectively.
c: Defined as more than the median number of household members of community controls (median, 6)
d: Water samples obtained from 62 typhoid and 20 paratyphoid cases, 341 community and 233 fever controls.

Table 2. Bivariate analysis of risk factors for typhoid and paratyphoid fever in comparison with community controls and fever controls

Risk factor	**Odds ratio (95% Confidence interval)**			
	Typhoid fever		**Paratyphoid fever**	
	Community controls	**Fever controls**	**Community controls**	**Fever controls**
Female sex	1.09 (0.65-1.84)	1.78 (1.05-3.04)	0.48 (0.20-1.11)	0.78 (0.33-1.83)
Low family income	1.49 (0.88-2.50)	0.91 (0.54-1.55)	0.65 (0.28-1.51)	0.40 (0.17-0.94)
Crowding	1.71 (1.02-2.86)	1.81 (1.06-3.07)	0.88 (0.37-2.11)	0.93 (0.39-2.25)
Recent typhoid in the household	2.93 (1.36-6.32)	1.84 (0.86-3.92)	2.21 (0.61-7.94)	1.39 (0.39-4.95)
No use of soap for hand washing	1.88 (1.07-3.28)	1.42 (0.80-2.52)	1.28 (0.55-2.99)	0.97 (0.41-2.28)
No toilet in household	2.90 (1.48-5.70)	1.84 (0.94-3.57)	2.75 (0.97-7.85)	1.74 (0.61-4.93)
Eating food from street vendors	1.61 (0.92-2.83)	1.83 (1.02-3.26)	4.07 (1.76-9.42)	4.61 (1.96-10.81)
Consumption of iced drinks	2.10 (1.13-3.90)	1.20 (0.65-2.22)	1.69 (0.60-4.72)	0.96 (0.35-2.68)
Consumption of ice cubes	2.15 (1.26-3.68)	2.26 (1.31-3.91)	1.61 (0.67-3.71)	1.69 (0.73-3.93)
Sharing food from same plate	2.21 (1.31-3.74)	1.52 (0.89-2.59)	1.11 (0.45-2.77)	0.77 (0.31-1.91)
Drinking water: piped water	0.44 (0.19-1.01)	0.66 (0.29-1.55)	0.36 (0.08-1.54)	0.54 (0.12-2.36)
Faecal contamination of drinking water source	0.73 (0.42-1.25)	0.81 (0.46-1.42)	0.95 (0.38-2.35)	1.06 (0.42-2.64)
Flooding	2.29 (1.33-3.95)	1.16 (0.67-2.00)	5.30 (2.27-12.38)	2.69 (1.15-6.27)

poorer handwashing hygiene, had fewer toilets and connections to the water mains in their houses, shared food more frequently, were more likely to consume iced drinks, and were more likely to report flooding than were community controls (**Table 1**).
In addition, for all interviewed participants, low income was significantly associated with purchasing food from street vendors (OR, 1.58; 95% CI, 1.03-2.41). When ice cubes were used, these were purchased from ice vendors by equal proportions in the groups: 41 (69%) patients with typhoid or paratyphoid fever, 107 (61%) community controls, and 93 (71%) fever controls (P = .12).

Bivariate Analysis

Risk Factors for Typhoid Fever: Bivariate analysis of risk factors comparing typhoid cases with community controls showed the following significantly associated risk factors for typhoid fever: crowding (>6 household members) and recent typhoid fever of household contacts (**Table 2**). The association of recent typhoid fever of household contacts and typhoid fever also remained significant in a subgroup of households with more than 6 household members: from the 34 typhoid cases, 8 (24%) reported recent typhoid fever in a household contact, whereas from 137 community controls, 9 (7%) did (OR, 4.38; 95% CI, 1.54-12.40). In the comparison with community controls, other significantly associated risk factors for typhoid fever were no use of soap for handwashing, no toilet in the household, and flooding. With respect to eating habits, typhoid was not significantly associated with eating food from street vendors, but a significant association was found with consuming iced drinks, use of ice cubes, and sharing food from the same plate. Sharing of food occurred mostly with household contacts: 84% (26/31) of typhoid cases and 84% (85/101) of community controls and in lower frequencies in all groups at work or school.
Female sex was associated when typhoid cases were compared with fever controls, which was likely due to the overrepresentation of males in the fever control group (**Table 2**).
In the fever-control comparison crowding was associated with typhoid fever, as was eating foods from street vendors and use of ice cubes. None of the hygiene-related risk factors (i.e., no use of soap for handwashing, no toilet in the household) was significantly associated with typhoid in comparison with fever controls.

Risk Factors for Paratyphoid Fever: In comparison with community controls and fever controls, paratyphoid fever among cases was significantly associated with eating foods from street vendors and flooding. Fever controls had a lower family income than did patients with paratyphoid fever.
Water Examination: During the study period, 656 samples from the sources of running drinking water of cases and controls were collected; 358 (55%) contained fecal coliforms (median, 30; IQR, 6-250 per 100 mL). Fecal contamination of drinking water was not

significantly associated with either typhoid or paratyphoid fever in comparison with both control groups (**Table 2**). Also, bacterial numbers in water samples were not significantly different for typhoid or paratyphoid fever cases vs those for fever controls ($P = .54$ and $P = .90$, respectively, by Mann-Whitney U test) or community controls ($P = .43$ and $P = .95$, respectively). All respondents reported that they boiled drinking water before consumption and that they kept water boiling for several minutes.

Food Handlers: A food handler was not present in all households of cases or controls because some cases and controls always ate outside of the household or cooked their own food. No *S. typhi* or *S. paratyphi* A were isolated in the single stool samples that could be obtained from 96% of the 78 food handlers of (para)typhoid cases, 246 of the fever controls, and 298 of the community controls, respectively.

Multivariate Analysis

Residence of participants in 1 of the 8 subdistricts was not evaluated in the bivariate analysis, but was included in the multivariate analysis as a potential confounder. In this analysis, neighborhood residence was not independently associated with either typhoid fever or paratyphoid fever. The significant risk factors for typhoid and paratyphoid fever from the bivariate analysis that were evaluated in the multivariate analysis are shown in **Table 3.**

Risk Factors for Typhoid Fever: Using the community control group, typhoid fever continued to be independently associated with hygienic practices (no use of soap for hand-washing, sharing of food, and no toilet in the household) and recent intrahousehold typhoid fever in the preceding 12 months. These are presented in order of decreasing magnitude of attributable risk (**Table 3**). Typhoid cases were significantly younger than community controls, suggesting that either exposure to *S. typhi* or susceptibility to symptomatic infection when exposed is greater among young people.

Using the fever controls for comparison, we identified ice cubes and female sex (related to the high percentage of male participants in the fever control group) as independent risk factors for typhoid fever. Hygiene-related factors were not independently associated.

Risk Factors for Paratyphoid Fever: In the multivariate analysis, paratyphoid fever continued to be independently associated with eating foods from street vendors when paratyphoid cases were compared with both control groups (**Table 3**). Flooding also remained a significant risk factor for paratyphoid fever. The individual contribution of eating habits and flooding as calculated by the attributable risk alternated in importance for both control groups. Low income was inversely associated with paratyphoid fever in the comparison with fever controls.

Table 3. Multivariate analysis of independent risk factors for typhoid and paratyphoid fever in comparison with community controls and fever controls

	Typhoid fever (n=69)		Paratyphoid fever (n=24)	
Risk factor	**OR (95% CI)**	**Attributable Risk, %**	**OR (95% CI)**	**Attributable risk, %**
Comparison with community controls (n=378)				
No use of soap for handwashing	1.91 (1.06-3.46)	34	NA	
Sharing food from same plate	1.93 (1.10-3.37)	22	NA	
No toilet in household	2.20 (1.06-4.55)	12	NA	
Recent typhoid in household	2.38 (1.03-5.48)	9	NA	
Young age	0.96 (0.94-0.98)		0.9 9 (0.96-1.02)	
Flooding	1.65 (0.88-3.08)		4.52 (1.90-10.73)	45
Eating food from street vendors	NA		3.3 4 (1.41-7.91)	38
Use of iced drinks	1.12 (0.55-2.26)		NA	
Consumption of ice cubes	1.34 (0.73-2.44)		NA	
Crowding	1.54 (0.88-2.72)		NA	
Comparison with fever controls (n=289)				
Consumption of ice cubes	2.27 (1.31-3.93)	36	NA	
Female sex	1.79 (1.04-3.06)	26	1.1 0 (0.43-2.84)	
Low income	0.85 (0.49-1.49)		0.2 8 (0.11-0.71)	49
Eating food from street vendors	1.62 (0.88-2.98)		5.17 (2.12-12.60)	48
Flooding	NA		3.2 5 (1.31-8.02)	42
Crowding	1.60 (0.92-2.76)		NA	

Abbreviations: CI, confidence interval; OR, odds ratio.
NA: not significantly associated in the bivariate analysis and not included in the multivariate analysis.

Comment

The main finding of this study is that in Jatinegara, Jakarta, typhoid and paratyphoid fever largely follow distinct routes of transmission. Typhoid is spread predominantly within the household, whereas paratyphoid is mainly transmitted outside the home. No fecal carriers among food handlers in the households were detected and there was no association between the level of contamination of drinking water and either typhoid or paratyphoid fever. Apparently, *S. typhi* is introduced into households by convalescent cases transiently excreting the bacterium. Consistent with this, independent risk factors for the intrahousehold spread of typhoid were poor handwashing hygiene and sharing of food from the same plate. On the other hand, risk factors for transmission of paratyphoid were outside the household (i.e., flooding, consumption of foods from street vendors). Furthermore, in this community-based passive surveillance study, paratyphoid comprised 23% of all enteric fever cases, an apparent rise in relative incidence of paratyphoid compared with earlier studies.

To reach the conclusion concerning the distinct route of transmission of paratyphoid and typhoid fever, we compared characteristics of cases with those of community controls and fever controls. Some potential pitfalls that may affect complete recruitment of patients in the area, and individual classification of cases and fever controls, need to be considered. Not all eligible fever patients might have been included, although we performed blood cultures free of charge to preclude economic barriers for inclusion. Self-treatment with over-the-counter antibiotics and an atypical presentation of enteric fever (e.g., as observed in young children) may have influenced inclusion.[18] Even so, the proportional representation of typhoid fever of 8.6% of illnesses with fever for 3 or more days is comparable with rates in other active and passive surveillance studies for typhoid fever using the same inclusion criteria (4.6%-8.5%).[19-23] Furthermore, the sensitivity of the microbiological methods never reaches 100%.[24] However, because most patients with fever were included in the first week of illness, the sensitivity of blood culture comes close to that of quantitation in bone marrow and is superior to the Widal test.[25,26] Also, the interference of antibiotics, which can yield false-negative results, was limited due to this short period before inclusion and to the antibiotic-neutralizing resins in the blood culture vials. Accordingly, equal proportions of typhoid and paratyphoid fever cases and non-enteric fever controls had previously taken antibiotics. To further minimize misclassification of fever controls, stool cultures were performed 3 to 4 weeks after blood culture (i.e., at a time when bacteria may still be excreted in feces of patients with typhoid or paratyphoid fever). The 2 febrile patients with negative blood culture results at inclusion, whose stool cultures yielded *S. typhi* and *S. paratyphi* A, were accordingly excluded from the analysis. Another potential limitation of this study concerns the screening for *Salmonella* carriers by a single stool culture that might not suffice because of intermittent excretion of the bacteria in stools.[12]

The use of a representative community control group allowed us to determine the prevalence of risk factors in the whole population at risk. Our study demonstrates that risk estimates from case-control studies could be affected by the selection of the control-group used for comparison. For instance, when typhoid fever cases were compared with community controls, most of the independent risk factors for typhoid fever were intrahousehold factors (i.e., no use of soap for handwashing, sharing of food, and recent typhoid fever in a household member), whereas those factors were not associated in the comparison with fever controls. This suggests that hygiene practices of both cases and fever controls were of a standard below that of community controls. In addition, partially overlapping routes of transmission of typhoid fever and other febrile illnesses could be interdependent and result in the demonstrated similar intrahousehold risk profile of typhoid fever cases and fever controls with similar socioeconomic characteristics.

Food obtained from street vendors was a likely vehicle for extrahousehold transmission of paratyphoid fever because it contributed significantly to transmission in contrast to hygiene-related risk factors. This is consistent with the notion that multiplication of paratyphoid bacteria in food is required to reach a number sufficient to cause disease. Street vendors have only limited facilities for cooled storage of foods and for washing of hands, foods, and dishes. The low hygienic standards could therefore contribute not only to the transmission of paratyphoid fever but of other foodborne diseases such as typhoid, as well.[7,11,27-29] Due to the Asian economic crisis starting in 1997, the expanding urban population became even more dependent on inexpensive food obtained from street vendors, which may explain the relatively high proportion of paratyphoid fever in enteric fever in Jakarta. Low-income groups more frequently ate food obtained from street vendors than did individuals with high income, but all income groups who purchase food from street vendors may be at risk.

In contrast to the largely extra-household transmission of paratyphoid fever, typhoid fever was more of an intrahousehold affair introduced by recent typhoid cases in the households and facilitated by poor hand-washing hygiene and sharing of food from the same plate, consistent with an earlier report.[10] The association of poor handwashing hygiene and typhoid fever was shown before in Indonesia and India.[6,9,11] A recent review stressed the importance of the use of soap for the reduction of the incidence of diarrheal diseases.[30] In our study we also identified a significant association between not using soap for handwashing and all febrile illnesses (OR, 1.40; 95% CI, 1.05-1.88). The combination of poor handwashing hygiene, eating with hands, and sharing food from the same plate can understandably facilitate transmission of typhoid, but apparently the infective dose to allow transmission of paratyphoid is only infrequently met. Because we observed no intrahousehold outbreaks and detected no fecal carriers among the food handlers in the households of cases, intrahousehold person-to-person spread through convalescent patients observing poor hygiene seems a more likely scenario than transmission by chronic carriers among food handlers in households.

Apart from the above-mentioned risk factors, some additional observations should be considered. First, the total number of interviewed patients with typhoid and paratyphoid fever in our study was limited, which may have influenced the statistical power of the analysis, especially in small subgroups, and the demonstrated associations of specific risk factors. Second, food purchased from street vendors could be implicated as a vehicle for transmission of typhoid as well, as shown in the bivariate analysis. Also, the consumption of ice cubes obtained from street vendors might expose clients to *Salmonella* bacteria because these bacteria can survive in ice.[31] Another extrahousehold location of acquisition of typhoid fever could be public toilets, which generally lack handwashing facilities. Third, there was an association between flooding and paratyphoid fever.

Two hypotheses may explain this association: flooding could introduce bacteria from contaminated surface water into sources of drinking water. However, since most cases of typhoid and paratyphoid fever occurred during the dry season, flood-related waterborne transmission seemed not to play a major role. Alternatively, flooding may be an income-associated geographic marker that coincides with the distribution of carriers among food vendors in the area. This could also explain the clustering of paratyphoid fever cases in some regions, but since community controls were nonmatched for subdistrict neighborhood residence, this assumption could not be verified. Finally, although a considerable proportion of the sources of drinking water contained fecal coliforms that were used as indicator organisms, contamination itself was not associated with enteric fever. Dilution of *S. typhi* or *S. paratyphi* in water might generate too low a dose to infect partially immune residents. More likely, however, the entrenched habit of boiling drinking water from the water mains or groundwater pumps explains the lack of an association between water contamination and enteric fever and should certainly be continued to prevent possible outbreaks of disease, in combination with proper storage of boiled water to prevent domestic contamination.

In conclusion, the present findings suggest that public health policies for control of typhoid and paratyphoid fever in Jakarta should focus on hygiene education as well as monitoring of the street-food trade, although such strategies would have to be tested in intervention trials to prove their value. First, instruction on proper handwashing hygiene using soap could reduce the overall incidence of infectious diseases in Jakarta and especially preclude transmission of typhoid fever among contacts of cases. Second, prevention of bacterial contamination of street food and ice cubes could contribute to containment of enteric fever, paratyphoid in particular. Follow-up of enteric fever cases, especially among food vendors, should be prioritized to reduce the role of transient or chronic carriers in the foodborne transmission.

If vaccination were to be considered as a means of controlling typhoid, an individualized approach rather than mass vaccination (i.e., targeted vaccination of young household contacts of cases) may be a cost-effective approach when public health resources are scarce.[32] But, because of the increasing incidence of paratyphoid fever in Jakarta, as well as readily available antibiotic treatment and the potentially effective intervention of education to increase appropriate handwashing, mass immunization programs for typhoid fever in Jakarta may not be appropriate at this time.

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