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# Burden of typhoid and paratyphoid fever in a densely populated urban community, Dhaka, Bangladesh

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ABSTRACT

*Background:* We conducted blood culture surveillance to estimate the incidence of typhoid and paratyphoid fever among urban slum residents in Dhaka, Bangladesh.
*Methods:* Between January 7, 2003 and January 6, 2004, participants were visited weekly to detect febrile illnesses. Blood cultures were obtained at the clinic from patients with fever (≥38 °C). Salmonella isolates were assayed for antimicrobial susceptibility.
*Results:* Forty Salmonella Typhi and eight Salmonella Paratyphi A were isolated from 961 blood cultures. The incidence of typhoid fever was 2.0 episodes/1000 person-years, with a higher incidence in children aged < 5 years (10.5/1000 person-years) than in older persons (0.9/1000 person-years) (relative risk = 12, 95% confidence interval (CI) 6.3–22.6). The incidence of paratyphoid fever was 0.4/1000 person-years without variation by age group. Sixteen S. Typhi isolates were multidrug-resistant (MDR). All S. Paratyphi isolates were pan-susceptible. The duration of fever among patients with an MDR S. Typhi infection was longer than among patients with non-MDR S. Typhi (16 ± 8 vs. 11 ± 4 days, $p = 0.02$) and S. Paratyphi (10 ± 2 days, $p = 0.04$) infections.
*Conclusions:* Typhoid fever is more common than paratyphoid fever in the urban Bangladeshi slum; children < 5 years old have the highest incidence. Multidrug resistance is common in S. Typhi isolates and is associated with prolonged illness. Strategies for typhoid fever prevention in children aged < 5 years in Bangladesh, including immunization, are needed.


## 1. Introduction

Typhoid fever occurred in more than 20 million people in the year 2000 and causes approximately 200 000 deaths annually.[1] More than 90% of typhoid fever cases are estimated to occur in Asia. The challenges of reliably diagnosing typhoid fever have led to varying estimates of the disease burden and epidemiology in Asia. In India and Bangladesh, the highest incidence has been observed among children aged <5 years, while in Vietnam, the peak incidence has been found to occur in children aged 5–9 years.[2–4] The recent increase in fluoroquinolone resistance of *Salmonella enterica* serotype Typhi has raised concerns due to the limited treatment options available in typhoid endemic countries;[5–8] as a result, the World Health Organization (WHO) is beginning to focus resources on the promotion of typhoid immunization for children in endemic countries in Asia.[9] Population-based incidence data are helpful in identifying high-risk populations, regions, and age groups for targeted vaccination programs for the prevention of typhoid fever in resource-limited, developing countries.

Because the transmission of S. Typhi often involves factors such as hygiene, water quality, and food handling, which impact transmission of other enteric pathogens, additional information on the disease burden of invasive non-Typhi Salmonella could provide a basis for more aggressive programs to minimize transmission of all Salmonella. An increase in the incidence of S. Paratyphi has been reported from some Asian countries where typhoid fever is endemic.[10] Several Asian countries have reported the emergence of fluoroquinolone resistance among S. Paratyphi.[11–17] The overall situation has heightened the need to identify prevention measures, including vaccines, against a variety of invasive enteric pathogens.[10,18,19] However, a vaccine against paratyphoid fever is not yet available, and immunization with currently available vaccines against typhoid fever does not provide cross-protection against paratyphoid fever.

In Bangladesh, no epidemiologic data on paratyphoid fever have been available. We conducted blood culture surveillance in an

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impoverished, densely populated urban community in Dhaka to estimate the incidence and determine the antimicrobial susceptibility patterns of S. Typhi and S. Paratyphi. We also studied strain heterogeneity of S. Typhi by pulsed-field gel electrophoresis (PFGE) subtyping to determine the extent of genetic variation among drug-resistant strains.

## 2. Methods

### 2.1. Study sites

In 2000, the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) established a surveillance system in Kamalapur, a densely populated informal settlement in Dhaka, for the purposes of conducting active fever surveillance on a portion of the population. The area was divided into 377 clusters for the convenience of surveillance, and 85 clusters were randomly selected for this study. The 85 clusters included in the surveillance were proportionally distributed across the entire study area and were representative of the population residing in all 377 clusters. All inhabitants of households within the selected clusters were approached and enrolled following written consent; a household was defined as all persons that ate from the same cooking pot. People moving into one of the 85 clusters at any point during the study period were included in the surveillance. An individual's participation was terminated due to migration out of the cluster under surveillance, death, or withdrawal of consent.

### 2.2. Active fever surveillance

During the study period, between January 7, 2003 and January 6, 2004, field research workers conducted weekly visits to participating households to obtain a history of fever during the past 7 days. All participants who had consented to participate in the surveillance had access to free medical care at the study clinic (located within the surveillance area, $\leq$3 km from each participating household) and were offered free medical care there by eight trained study physicians and eight nurses. Children aged $<$5 years with a history of fever of any duration, and persons $\geq$5 years of age with fever of $\geq$3 days duration, were referred to the study clinic for clinical assessment by qualified study physicians. Study physicians obtained blood for culture from the patients with a history of fever, if the axillary temperature was $\geq$38 °C when assessed at the clinic.

### 2.3. Microbiology

Blood was collected aseptically at the study clinic, inoculated into commercially available blood culture medium (Hemoline performance diphasique, bioMérieux, France), and processed at the ICDDR,B microbiology laboratory, as described elsewhere.[20] Standard procedures were used to identify S. Typhi and S. Paratyphi A and B. Antimicrobial susceptibility of the Salmonella strains was assessed using disk diffusion according to the Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS) guidelines for the following agents: ampicillin, chloramphenicol, trimethoprim–sulfamethoxazole, nalidixic acid, ciprofloxacin, and ceftriaxone.[21] The minimum inhibitory concentrations (MIC) were measured using the Etest when an isolate was resistant to one or more antibiotics tested (AB Biodisk, Solna, Sweden). An isolate was defined as multidrug-resistant (MDR) if resistance was observed to all three first-line antibiotics (chloramphenicol, ampicillin, and trimethoprim–sulfamethoxazole). All other isolates were labeled as non-MDR.

PFGE was performed on S. Typhi isolates at the ICDDR,B laboratories following standard procedures.[22,23] PFGE analysis of S. Paratyphi isolates was not performed.

### 2.4. Treatment

All febrile patients were clinically managed at the study clinic according to a standardized treatment algorithm and had equal opportunity for receiving free health care irrespective of severity of illness or compliance with blood culture. Participants who underwent blood culture were visited at their homes daily until they were afebrile for 3 consecutive days. A clinical diagnosis of typhoid fever was made for the following clinical presentations: documented fever $\geq$38 °C (axillary) with a history of fever of any duration in children $<$ 5 years old or of at least 3 days for persons $\geq$5 years old, and without a focus of infection. Persons with clinically diagnosed typhoid fever or other Salmonella infection were treated with ampicillin or trimethoprim–sulfamethoxazole. Ciprofloxacin and ceftriaxone were reserved for MDR infections. If a patient's condition worsened while on antibiotics or did not improve clinically after 48 h of therapy, s/he was referred to the ICDDR,B hospital for further management.

### 2.5. Data analysis

The incidences of typhoid and paratyphoid fever were calculated by dividing the number of blood culture-confirmed episodes by the person-years of observation.[24,25] The actual number of days were added to calculate person-days of observation for each individual while s/he was under active surveillance, and were divided by 365 days to calculate the person-years of observation. We calculated the incidence of typhoid fever in two ways. First, we calculated the incidence of typhoid fever among the study population based on the febrile episodes when a blood culture was obtained, in order to extrapolate the lowest possible estimate of typhoid fever incidence in the study population. Second, we assumed that the persons who did not provide a blood culture would yield S. Typhi in blood culture at a similar rate as those who did provide a blood culture. So we applied the observed S. Typhi isolation rate to those who did not have a blood culture and calculated additional S. Typhi cases in order to compute the highest possible estimate of typhoid fever incidence among the study population.

Continuous variables were reported as mean value $\pm$ standard deviation (SD) or median value and range, and were compared across groups using unpaired sample *t*-tests or non-parametric tests. Differences between groups with respect to categorical variables were assessed using the Pearson Chi-square or Fisher's exact test.

### 2.6. Ethical issues

Written informed consent was obtained from heads of participating households on behalf of all household members at the time of enrollment, before initiation of active surveillance; it covered consent for weekly home visits, blood culture for persons with a febrile episode, and collection of clinical data following culture. Each individual participant had the right to withdraw her/his consent at any time.

This study was approved by the Ethics Review Committee of ICDDR,B and the Institutional Review Board of the Centers for Disease Control and Prevention (CDC; Atlanta, GA, USA).

## 3. Results

During the study period, 26 583 persons were living in the randomly selected clusters and total of 24 893 individuals (94%) were enrolled from 5513 households in the active surveillance for febrile illness; 1690 persons (6%) declined participation in the surveillance. The mean age ($\pm$ SD) of the population under surveillance was 25 years ($\pm$ 17) including 3520 children aged $<$5

**Table 1**
Features of patients who did and did not provide blood for culture among patients with fever in the active surveillance for Salmonella infection, Bangladesh, 2003–2004 ($N$ = 1148)

| Main features | Blood culture performed ($n$ = 863) | Blood culture not performed ($n$ = 285) | $p$-Value |
|---|---|---|---|
| Age, median (range) years | 4.4 (0–82) | 2.6 (0–70) | <0.001 |
| Children <5 years, $n$ (%) | 483 (56) | 220 (77) | <0.001 |
| Male, $n$ (%) | 442 (51) | 138 (48) | 0.2 |
| Clinical diagnosis of typhoid fever, $n$ (%) | 213 (25) | 6 (2) | <0.001 |
| Axillary temperature, mean (± SD) °C | 38.9 (± 0.7) | 39.9 (± 0.7) | 0.5 |

SD, standard deviation.

years (14%); 50% were male. On average, an individual stayed in the surveillance project for 10 months (± 3). Among the enrolled individuals, 20 765 persons (83%) lived in the surveillance area throughout the entire study period; 2334 persons (9%) migrated into the surveillance clusters, 1700 persons (7%) migrated out of the surveillance clusters, 48 persons (0.2%) died, and 46 persons (0.2%) withdrew consent before the study period ended. During 12 months of surveillance, 19 710 person-years were observed, including 2381 person-years among children aged <5 years.

Study physicians identified 1333 fever episodes among 1148 persons visiting the study clinic in 12 months (67.6 fever episodes/1000 person-years), including 868 fever episodes (65%) in children <5 years old. Physicians obtained 4 ml (± 0.4) of blood for culture during 961 episodes (72%) from 863 persons (including 96 patients with >1 fever episode). Of the samples collected for blood culture, 564 were from episodes in children aged <5 years (59%). Blood culture could not be obtained for 372 fever episodes (28%) among 285 persons (25%), and 304 episodes (82%) were among children aged <5 years. The reasons for not obtaining a blood culture were: parent/legal guardian did not approve a blood culture ($n$ = 338, 91%), the legal guardian was not present to provide valid consent ($n$ = 17, 5%), doctor postponed blood culture due to lack of adequate supplies for culture ($n$ = 11, 3%), and information was not available for six (2%) episodes. The patients from whom a culture was not obtained were younger in age and were less likely to have a clinical diagnosis of typhoid fever than those who had a blood culture (Table 1).

Of the 961 episodes, an antimicrobial was reported to have been taken in 91 (10%) before the blood specimen was collected. A bacterial pathogen was isolated from 70 episodes yielding an isolation rate of 7.3%. The bacterial isolation rate among the persons who were treated with an antimicrobial drug ($n$ = 11) prior to blood culture was not different than among those who were not treated with an antimicrobial drug ($n$ = 59) prior to blood culture (12% vs. 7%; $p$ = 0.09). S. Typhi was isolated from blood cultures of 40 episodes in 40 persons, yielding an isolation rate of 4.2%; 25 isolates were yielded among children <5 years old (isolation rate of 4.4%). S. Paratyphi A was isolated from eight episodes in eight persons (11%), including one child <5 years old (13%); no S. Paratyphi B, S. Paratyphi C, or other Salmonella serotypes were identified.

### 3.1. Incidence

S. Typhi was isolated from blood cultures every month, with the greatest number of cases occurring in April, August, and December (Figure 1). The overall incidence of blood culture-confirmed typhoid fever was 2.0 episodes (95% confidence interval (CI) 1.5–2.8)/1000 person-years. The incidence in children < 5 years old was 10.5 episodes (95% CI 6.8–15.5)/1000 person-years, which was 12-fold greater than the incidence among persons ≥5 years of age (0.9 episodes (95% CI 0.5–1.4)/1000 person-years; relative risk (RR) = 12, 95% CI 6.3–22.6). Among children < 5 years old, the highest incidence was observed among children aged ≥12 months (11.5 episodes (95% CI 7.3–17.2)/1000 person-years). The incidence

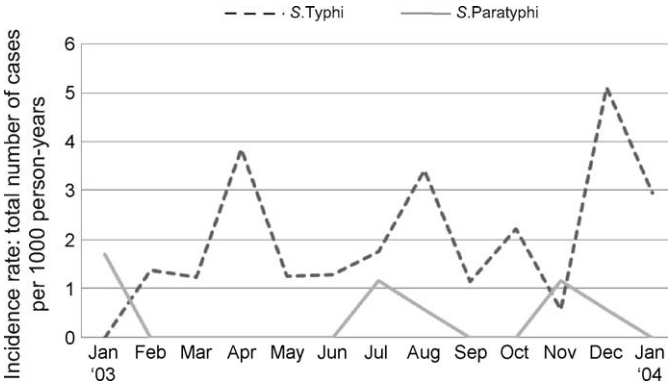


**Figure 1.** Incidence of typhoid and paratyphoid fever by month, 2003–2004.

of S. Paratyphi infection was 0.4 episodes (95% CI 0.2–0.8)/1000 person-years, and did not differ between children < 5 years old and those aged ≥5 years old.

When we applied the overall isolation rate of S. Typhi (4.2%) among the persons who did not have a blood culture ($n$ = 372), we detected an additional 15 (372 × 0.042) S. Typhi cases, and the overall incidence of typhoid fever in the study population was estimated to be 2.8 episodes/1000 person-years. With a similar calculation, we detected an additional 13 (304 × 0.044) S. Typhi cases among children aged < 5 years and three (68 × 0.038) S. Typhi cases among persons ≥5 years old. Hence, the highest incidence of typhoid fever was estimated to be 16.0 episodes/1000 person-years among children aged <5 years and 1.0 episodes/1000 person-years among those aged ≥5 years.

### 3.2. Antimicrobial susceptibility and PFGE patterns

Of the 40 S. Typhi isolates, 17 were resistant to trimethoprim–sulfamethoxazole (43%), 17 to chloramphenicol (43%), 16 to ampicillin (40%), and 16 to nalidixic acid (40%). Sixteen isolates (40%) were resistant to all three first-line antibiotics (MDR). Two isolates (5%) had single resistance to nalidixic acid (NAR) and one isolate (3%) was sensitive to ampicillin but resistant to trimethoprim–sulfamethoxazole, chloramphenicol, and nalidixic acid. Eight of 40 S. Typhi isolates (20%) had reduced susceptibility to ciprofloxacin (MIC 0.19–0.38 μg/ml); five of them were MDR, three were non-MDR, and seven were NAR S. Typhi strains. All 40 S. Typhi isolates were susceptible to ceftriaxone. Twenty-one S. Typhi isolates (53%) and all eight S. Paratyphi isolates (100%) were susceptible to all drugs tested.

PFGE analysis of 40 S. Typhi yielded 10 patterns; 20 (50%) isolates belonged to a single type (homogeneous), and the remaining 20 belonged to nine different types (heterogeneous). Sixteen of 20 homogeneous isolates (80%) were MDR. Thirteen of the 16 MDR homogeneous isolates (81%) and three of the four non-MDR homogeneous isolates were NAR strains. All 20 hetero-

**Table 2**
Comparison of demographic and clinical features of patients with typhoid and paratyphoid fever and patients with other febrile illness in active surveillance for Salmonella infection, Bangladesh, 2003–2004

| Clinical characteristics | Salmonella Typhi ($n$ = 40) | Salmonella Paratyphi A ($n$ = 8) | Other febrile illness ($n$ = 913)[a] |
|---|---|---|---|
| Male | 19 (48) | 7 (88) | 469 (51) |
| Children <5 years | 25 (63) | 1 (13)[b] | 538 (59)[c] |
| Antibiotic taken at home | 8 (20) | 1 (3) | 82 (9)[b] |
| Cough | 22 (55) | 2 (25) | 678 (74)[b,c] |
| Runny nose | 28 (70) | 5 (63) | 558 (61) |
| Vomiting | 7 (18) | 1 (13) | 143 (16) |
| Headache | 10 (25) | 7 (88)[b] | 364 (40)[c] |
| Myalgia | 6 (15) | 6 (75)[b] | 290 (32)[c] |
| Tenesmus | 8 (20) | 0 | 74 (8)[b] |
| Constipation | 1 (3) | 2 (25) | 63 (7) |
| Watery stool | 10 (25) | 0 | 105 (12)[b] |
| Bloody stool | 2 (5) | 0 | 16 (2) |
| Abdominal pain | 10 (25) | 2 (25) | 161 (18) |
| Abdominal tenderness | 1 (3) | 0 | 16 (2) |
| Irritability | 5 (13) | 2 (25) | 233 (26) |
| Loss of appetite | 24 (60) | 3 (38) | 606 (66) |
| Hospitalization | 4 (10) | 0 | 13 (1)[b] |
| Duration of fever between onset and resolution, days | 13 (± 7) | 10 (± 2)[b] | 7 (± 5)[b,c] |

Results are $n$ (%) or mean (± standard deviation).
[a] Eight Salmonella Paratyphi A cases were excluded from other febrile illness.
[b] $p < 0.05$ when compared to Salmonella Typhi.
[c] $p < 0.05$ when compared to Salmonella Paratyphi.

geneous isolates and one homogeneous isolate were susceptible to all antimicrobial drugs tested.

### 3.3. Clinical features

Clinical manifestations of patients with typhoid fever were generally similar to those of other febrile patients who did not have Salmonella bacteremia. However, the patients with S. Typhi infections more frequently reported tenesmus, watery stool, and required hospitalization, than the patients who did not have S. Typhi infection (Table 2). At initial presentation to the clinic, the duration of fever among patients with S. Typhi infection was longer than in the patients who did not have Salmonella infection (5 ± 3 days vs. 4 ± 3 days, $p = 0.002$). The patients with S. Paratyphi infection were older in age, more frequently reported headache and myalgia, and became afebrile earlier than the patients with S. Typhi infection. Tenesmus, watery stool, bloody stool, abdominal tenderness, and hospitalization were not reported by any patients with S. Paratyphi infection (Table 2). No deaths were reported among patients who had presented with a febrile illness at the study clinic during the surveillance period.

Among children <5 years old, children who had S. Typhi infections had more frequently reported being treated with antibiotics ($n$ = 7, 28% vs. $n$ = 40, 7%; $p = 0.003$), having watery stool ($n$ = 8, 32% vs. $n$ = 71, 13%; $p = 0.02$), and requiring hospitalization ($n$ = 4, 16%, $p = 0.002$) than the children who did not have S. Typhi infection. However, clinical features among persons ≥5 years old did not differ between those who had S. Typhi infection and those who did not have S. Typhi infection (data not shown).

Clinical presentations among patients with S. Typhi infection were not different between those aged <5 years and those aged ≥5 years, except that children <5 years of age more frequently reported a runny nose (60% vs. 20%; $p = 0.02$) and vomiting (28% vs. 0%; $p = 0.03$) than persons ≥5 years of age. On examination, five children (20%) were less active or irritable, one had abdominal tenderness (4%), and four required hospitalization (16%), which were not reported among persons ≥5 years old.

### 3.4. Clinical response to antimicrobial therapy

Among 40 patients with S. Typhi infection, 26 recovered (65%) with first-line therapy (ampicillin or trimethoprim–sulfamethoxazole), 12 recovered (30%) with ciprofloxacin, and two recovered (5%) with ceftriaxone. Among 24 patients infected with non-MDR S. Typhi infection, 21 (88%) recovered after outpatient treatment with ampicillin/trimethoprim–sulfamethoxazole; one patient (4%) recovered without any antimicrobial treatment, two patients, both children <5 years old, were hospitalized (8%); one hospitalized child recovered with ampicillin and the other recovered with ceftriaxone treatment in hospital. The three patients who had reduced susceptibility to ciprofloxacin recovered after outpatient treatment with trimethoprim–sulfamethoxazole.

Among 16 patients with MDR S. Typhi infection, 11 recovered (69%) after outpatient treatment with ciprofloxacin, three recovered (19%) after outpatient treatment with ampicillin/trimethoprim–sulfamethoxazole, and two, both children aged <5 years, were hospitalized (12%); one hospitalized child recovered with ciprofloxacin treatment and the other with ceftriaxone treatment. All five patients who had reduced susceptibility to ciprofloxacin recovered after treatment with ciprofloxacin, including the one who required hospitalization. All patients infected with S. Paratyphi recovered after outpatient treatment with a first-line agent without developing any complication.

The clinical features between patients with MDR S. Typhi infection and non-MDR S. Typhi infection were generally similar at initial presentation, except that patients with MDR S. Typhi infection were more frequently treated with antibiotics before coming to the study clinic and had a longer total duration of fever (Table 3). However, the overall duration of the febrile episode among the patients with an MDR S. Typhi infection was longer than that of the patients who had a non-MDR S. Typhi infection (16 ± 8 days vs. 11 ± 4 days, $p = 0.02$) despite treatment with antimicrobial drugs. Although not statistically significant at the 0.05 level, there was a difference in illness duration following treatment between the patients infected with NAR S. Typhi strains and patients infected with non-NAR S. Typhi strains (15 ± 8 days vs.11 ± 5 days; $p = 0.06$).

## 4. Discussion

The incidence of invasive salmonellosis was found to be high among the residents of the densely populated urban slum community in Dhaka. S. Typhi bacteremia represents the bulk of these cases, and S. Paratyphi A bacteremia represents the remainder. The incidence of acute typhoid fever was higher

**Table 3**
Comparison of clinical features of patients with non-MDR and MDR Salmonella Typhi infection, 2003–2004

| Clinical features | Patients with non-MDR Salmonella Typhi ($n$ = 24) | Patients with MDR Salmonella Typhi ($n$ = 16) | $p$-Value |
|---|---|---|---|
| Children <5 years | 17 (71) | 8 (50) | 0.2 |
| Male | 11 (46) | 8 (50) | 0.8 |
| Antibiotic taken before culture | 2 (8) | 6 (38) | 0.04 |
| Duration of fever at the time of sample collection, days | 4 (± 2) | 6 (± 4) | 0.05 |
| Body temperature, °C | 39 (± 1) | 39 (± 1) | 0.9 |
| Cough | 13 (54) | 9 (56) | 0.8 |
| Runny nose | 11 (46) | 7 (44) | 0.9 |
| Vomiting | 4 (17) | 3 (19) | 0.9 |
| Headache | 6 (25) | 4 (25) | 0.7 |
| Myalgia | 4 (17) | 2 (13) | 0.6 |
| Tenesmus | 3 (13) | 5 (31) | 0.1 |
| Constipation | 1 (4) | 0 | 0.4 |
| Watery stool | 4 (17) | 6 (38) | 0.1 |
| Bloody stool | 2 (8) | 6 (38) | 0.3 |
| Abdominal pain | 4 (17) | 6 (38) | 0.3 |
| Abdominal tenderness | 0 | 15 (94) | 0.3 |
| Irritability | 4 (17) | 1 (6) | 0.3 |
| Loss of appetite | 16 (67) | 8 (50) | 0.3 |
| Total duration of fever between illness onset and resolution, days[a] | 11 (± 4) | 16 (± 8) | 0.02 |
| Hospitalization | 2 (8) | 2 (13) | 0.6 |

Results are $n$ (%) or mean (± standard deviation). MDR, multidrug-resistant.

among children <5 years of age than among persons aged ≥5 years, as we noted in a previous study conducted in the same population.[3] Infection with MDR S. Typhi resulted in a longer duration of illness episodes despite treatment with antimicrobial drugs to which the isolate was susceptible, as has been observed in other studies.[26,27] Multidrug and nalidixic acid resistance add to the burden of typhoid fever and to the urgency of prevention efforts.

While the incidence of invasive paratyphoid illness was considerably lower, its documentation adds to the burden of disease that could be prevented with effective programs aimed at improving hygiene, sanitation, and water quality. The previous study conducted in 2001 in the same study location of Kamalapur[3] found a nearly two-fold higher incidence of S. Typhi bacteremia compared to the incidence described here (3.9 episodes/1000 person-years vs. 2.0 episodes/1000 person-years). The opposite trend was seen with the incidence of paratyphoid fever, which nearly doubled from 2001 to the present (0.2 episodes/1000 person-years vs. 0.4 episodes per 1000 person-years; RR = 0.7, 95% CI 0.3–1.8). Despite recent increases in S. Paratyphi A infection in a few countries in Asia, S. Typhi infection remained the more common of the two in our study setting, as has been observed in other urban settings in India and Pakistan.[28,29] In the present study children aged <5 years more frequently suffered from typhoid fever than paratyphoid fever, and, on average, typhoid fever caused more severe illness among children <5 years old than persons ≥5 years old. Thus interventions that would reach those aged <5 years are important in order to reduce the overall disease burden.

Resistance to nalidixic acid among S. Paratyphi isolates was recently found to be more common than among S. Typhi isolates obtained from hospitalized patients in India and Nepal, while MDR was relatively rare among both pathogens.[15–17] In contrast, all S. Paratyphi A isolates identified in this study were susceptible to all antimicrobial agents tested, while 40% of S. Typhi isolates were MDR. This study further observed an association between MDR S. Typhi strains and prior antibiotic use, which has been demonstrated previously with other Gram-negative enteric pathogens.[30–32] In settings such as Kamalapur where over-the-counter antibiotic use is common, it is possible that persons who report prior use of antibiotics and are infected with non-MDR strains would not show evidence of S. Typhi infection on blood culture. In contrast, individuals who report prior use of antibiotics but are infected with an MDR strain would yield S. Typhi on blood culture. The PFGE types of all MDR S. Typhi strains were similar, as has been previously shown in studies from Bangladesh, Pakistan, Vietnam, and Hong Kong.[33–36] Although we did not observe treatment failure with ciprofloxacin, two recent reports from Bangladesh noted full resistance of MDR NAR S. Typhi strains to ciprofloxacin.[37,38] These developments underscore the importance of monitoring antimicrobial susceptibility patterns, reviewing options for guiding empirical therapy for typhoid fever, and expanding efforts to prevent infection.

Similar to earlier studies, we also found that S. Typhi and S. Paratyphi infections were not distinguishable clinically.[39,40] However, several patients with S. Typhi infection required hospitalization despite antimicrobial therapy guided by blood culture, which was not observed for the patients with S. Paratyphi infection. We did not document the occurrence of invasive non-typhoidal Salmonella (such as Salmonella Enteriditis and Salmonella Typhimurium) disease, which was consistent with other studies in South Asia,[3,17] but contrasted with the high incidence of non-typhoidal Salmonella demonstrated in Africa.[41,42] These findings highlight the potential significance of geographic location for defining and addressing the burden of invasive Salmonella disease. Since food and water are primary vehicles for Salmonella transmission, access to safe water, use of soap for hand washing, and safe food handling practices would likely substantially reduce the disease burden of Salmonella diseases and benefit the entire population.[43–49]

This study had several limitations. First, we relied on blood culture for the diagnosis of typhoid fever. Blood culture is only 50–80% sensitive and, thus, we may have underestimated the incidence of typhoid fever by not capturing true cases.[50–52] Second, we were unable to obtain blood cultures from about a third of the febrile episodes, primarily in very young children, a group in whom typhoid fever incidence is high in Bangladesh and elsewhere.[2] We demonstrated that the incidence of typhoid fever would have been higher at 16 episodes per 1000 person-years, rather than our observed incidence of 11 episodes per 1000 person-years. Third, we identified ill patients via an active population-based surveillance system and, hence, we likely detected and treated patients earlier than they might have been detected and treated in routine clinical care settings. This may have led us to detect more cases of Salmonella bacteremia that are only

mildly symptomatic than we would have detected had we used a facility-based passive surveillance approach. Earlier detection and the resulting earlier clinical intervention may have helped avert more severe illness and death, again leading to underestimation of disease burden. Fourth, this study detected a limited number of S. Typhi and S. Paratyphi isolates. Because of this, we had limited power to fully compare the clinical characteristics of patients with S. Typhi, S. Paratyphi, and other febrile illnesses. However, even with a small sample size we identified significant differences in some clinical characteristics across the three groups. Despite these limitations, we confirmed a continuing high incidence of typhoid fever in this population. Our findings underscore the importance of prevention of typhoid fever in urban Bangladesh and in similar settings.

We conclude that typhoid fever is endemic in an urban setting in Bangladesh, resulting in significant illness among pre-school children. Paratyphoid fever, while occurring less frequently, may increasingly contribute to the overall disease burden. As low income workers are increasingly attracted to urban centers with available jobs, the population residing in informal settlements such as Kamalapur will continue to overwhelm the available water and sanitary infrastructure. Targeted vaccination against S. Typhi would be a valuable immediate step to reduce disease burden, especially in urban Bangladeshi slums. The incidence of S. Paratyphi demonstrates the need for longer term investment in improved water and sanitation services to reduce the burden of multiple fecal–oral transmitted pathogens in these communities.

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