Hospitalization of Pediatric Enteric Fever Cases, Dhaka, Bangladesh, 2017–2019: Incidence and Risk Factors

Shampa Saha,1 K. M. Isthiaque Sayeed,1 Senjuti Saha,12 Md Shaful Islam,1 Afifur Rahaman,1 Maksuda Islam,1 Hafizur Rahman,1 Raktim Das,1 Md Mahmudul Hasan,1 Mohammad Jamal Uddin,1 Arif Mohammad Tanmoy,1 A. S. M. Nawshad Uddin Ahmed,1,12 Stephen P. Luby,4 Jason R. Andrews,4 Denise O. Garrett,5 and Samir K. Saha1,3

1Child Health Research Foundation, Dhaka, Bangladesh, 2Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA, 3Bangladesh Institute of Child Health, Dhaka Shishu Hospital, Sher-E-Bangla Nagar, Dhaka, Bangladesh, 4Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, Stanford, California, USA, and 5Applied Epidemiology, Sabin Vaccine Institute, Washington, DC, USA

**Background.** Enteric fever causes substantial morbidity and mortality in low- and middle-income countries. Here, we analyzed Surveillance for Enteric Fever in Asia Project (SEAP) data to estimate the burden of enteric fever hospitalization among children aged <15 years and identify risk factors for hospitalization in Bangladesh.

**Methods.** SEAP used hospital surveillance paired with a community-based health-care utilization assessment. In SEAP hospital surveillance, blood was obtained for culture from children aged <15 years with ≥3 days of fever. In the hospital catchment area, a health-care utilization survey (HCUS) was conducted to estimate the proportion of febrile children hospitalized at the study hospitals. We analyzed hospital surveillance and HCUS data to estimate the health care–adjusted incidence of enteric fever hospitalization, and conducted univariable and multivariable logistic regressions.

**Results.** From July 2017 through June 2019, 2243 laboratory-confirmed enteric fever cases were detected in 2 study hospitals; 673 (30%) were hospitalized. The health care–adjusted incidence of enteric fever hospitalization among children <15 years old was 303/100,000 children/year (95% confidence interval [CI], 293–313). Salmonella Typhi contributed most to the enteric fever hospitalization incidence (277/100,000 children/year; 95% CI, 267–287). The incidence was highest among children aged 2 to <5 years (552/100,000 children/year; 95% CI, 522–583), followed by those aged <2 years (316/100,000 children/year; 95% CI, 288–344). Factors independently associated with enteric fever hospitalization included fever duration, diarrhea, vomiting, abdominal pain, and leukocytopenia.

**Conclusions.** We estimated a high burden of hospitalization due to enteric fever among children aged <5 years in Bangladesh. The introduction of a typhoid conjugate vaccine would protect children from typhoid and avert typhoid hospitalizations.

**Keywords.** enteric fever; typhoid; hospitalization; incidence; risk factors.

Typhoid and paratyphoid, collectively called enteric fever, are caused by the bacteria *Salmonella enterica* serovars Typhi and Paratyphi A, B, or C. Enteric fever remains a major cause of morbidity and mortality in low- and middle-income countries [1, 2]. In 2017, *S. Typhi* caused approximately 11 million illnesses and 117,000 deaths, whereas *S. Paratyphi* caused over 3 million illnesses and 19,000 deaths globally [3, 4]. The burden of enteric fever was greatest in South Asia and among children aged <15 years [3].

A heat-killed, phenol-preserved, whole-cell typhoid vaccine for the prevention of typhoid fever has been available since 1896. The efficacy of this vaccine was established in 1960 [5–7]. Live attenuated Ty21a and Vi typhoid polysaccharide vaccines are effective against typhoid fever, but these vaccines are not recommended for children aged <2 years and have a short duration of protection [5]. A new-generation typhoid conjugate vaccine (TCV) containing Vi polysaccharide conjugated to a tetanus-toxoid protein carrier showed 55% protective efficacy in a human challenge model [8]. Considering its improved immunologic properties, suitability for use in infants and young children, and expected longer duration of protection, the World Health Organization (WHO) Strategic Advisory Group of Experts recommended the use of TCV over other available vaccines against typhoid in October 2017 [9]. In January 2018, the WHO prequalified the first TCV for use in countries with a high burden of typhoid fever [10]. The Phase III clinical trial of the WHO-prequalified TCV in Nepal from 2017–2019 showed that a single dose of TCV was 82% effective in reducing *S. Typhi* bacteremia in children 9 months to 16 years of age [11].

For the introduction of a new vaccine into a country’s national immunization program, the disease burden is a critical consideration [12]. As the case fatality rate of typhoid fever is less than 1%, hospitalization may serve as a proxy of severe disease [13]. In resource-poor countries, there is a fierce competition for hospital
beds. For example, in Bangladesh there are only 3 beds per 10,000 people [14]. The lack of hospital beds often means that patients with serious illnesses—for example, pneumonia, meningitis, birth asphyxia, and preterm birth–related complications—are not admitted [15]. The prevention of hospitalization of enteric fever cases would free up these needed hospital beds, and would ultimately reduce the burden on the health system. Therefore, hospitalization can be a consideration for decision-making for the introduction of TCV in the national immunization program.

In Bangladesh, several studies have documented a high burden of enteric fever at hospitals and in the community [16–20]. However, data on the incidence of enteric fever hospitalization are scarce. Hospitalizations were reported in 2 population-based studies that were conducted in urban slums and were limited by representation of the urban slum population. These studies captured disease at an early stage by active surveillance in the community, hence interrupting the natural course of disease that might have led to hospitalization [19, 20]. The Surveillance for Enteric Fever in Asia Project (SEAP), a multi-country, multi-site prospective study, used a hybrid surveillance approach with facility-based surveillance paired with a community-based health-care utilization survey (HCUS) to assess the burdens of enteric fever in Bangladesh, Pakistan, and Nepal. The community-based HCUS included all socioeconomic levels and did not interrupt the natural course of disease, as it did not involve active, population-based surveillance [21]. Here, we analyzed SEAP data to estimate the burden of enteric fever hospitalization among children aged <15 years in an urban population and to identify risk factors for hospitalization in Bangladesh.

**METHODS**

**Hospital Surveillance**

**Study Design, Sites, and Procedures**

SEAP surveillance was conducted at 2 pediatric hospitals in Dhaka, Bangladesh: Dhaka Shishu (children) Hospital and Dr MR Khan Shishu Hospital. With 660 beds, Dhaka Shishu Hospital is the largest pediatric hospital in Bangladesh that provides primary to tertiary levels of care to patients aged <18 years. With 250 beds, Dr MR Khan Shishu Hospital is the second largest pediatric hospital in the country and provides patients aged <15 years with primary and secondary levels of care. A catchment area of these 2 hospitals that had been previously identified was used for the HCUS (Figure 1) [21, 22].

We enrolled children from the inpatient department (IPD), outpatient department (OPD), and the hospital laboratory. All children living in the hospital catchment area and presenting at the OPD with ≥3 days fever were eligible to participate in the study. The inpatient eligibility criteria included clinical suspicion of enteric fever by clinicians or a blood culture positive for S. Typhi or S. Paratyphi A. Eligible cases were enrolled in SEAP IPDs and OPDs if they had a blood culture in the study hospital and gave consent to participate in the study. Additional lab-confirmed cases that were identified at the hospital laboratories and missed at the IPDs and OPDs were enrolled retrospectively in the study as hospital lab–enrolled cases.

![Figure 1](https://www.oxford Academic Journals/doi/abs/10.1093/cid/ciaa443)

**Figure 1.** Maps showing population density in Bangladesh by (A) districts and location of Dhaka district, (B) location of the study catchment area in Dhaka district, and (C) location of the study hospitals in the study catchment area.
Salmonella sera (Ramel, Thermo Fisher Scientific) were used to confirm Salmonella serovar–specific anti-
cacao, and MacConkey agar plates. Standard biochemical incubation, positive samples were subcultured on sheep blood,

3rd quartile ranges (IQRs) for summarizing continuous variables of individuals with a febrile illness compatible with enteric fever—
care-seeking behavior of children aged <18 years who had symptoms consistent with enteric fever—
which included fever for >3 days in the last 8 weeks for outpatient cases—and estimated the proportion of individuals with a febrile illness compatible with enteric fever who sought care at the health facilities participating in SEAP hospital surveillance [21].

Detection of S. Typhi and S. Paratyphi in Blood Samples
A sample of 3 milliliters of blood was obtained under aseptic conditions for culture from all children enrolled in this study. Blood culture was performed utilizing the BACTEC (Becton Dickinson and Company) automated culture system. The bottle was incubated at 37°C for a maximum of 5 days. After incubation, positive samples were subcultured on sheep blood, chocolate, and MacConkey agar plates. Standard biochemical tests and agglutination with Salmonella serovar–specific antisera (Ramel, Thermo Fisher Scientific) were used to confirm Salmonella Typhi/Paratyphi isolates [16].

Health-care Utilization Survey
The hospital catchment area for the HCUS included 22 out of 90 administrative wards of Dhaka city corporation and covered approximately 51 square kilometers. The catchment area was divided into 2524 clusters by an overlaying geographic information system (GIS grids), and then 100 clusters were randomly chosen for conducting HCUS. In SEAP, 2 HCUSs were conducted; the first during April–July 2017 and the second during September–December 2018, during which a new set of clusters were selected. During both HCUSs, each household included in the selected clusters was approached for interview, with no replacement of households in cases of absence or refusal. We used standardized questionnaires to collect health care–seeking behavior of children aged <15 years who were enrolled in SEAP hospital surveillance, regardless of residence. Risk factors associated with hospitalization were analyzed using univariable and multivariable logistic regressions. We conducted 2-tailed statistical tests at an alpha level of 0.05.

Ethical Consideration
This study was approved by the Ethical Review Committee of the Bangladesh Institute of Child Health, Dhaka. Informed written consent for participation in the study was obtained from the guardian of each child. In addition, assent was obtained from the children aged ≥11 years.

RESULTS
Hospital Surveillance
A total of 11 354 children were enrolled and had a blood culture performed at IPDs and OPDs of Dhaka Shishu Hospital and Dr MR Khan Shishu Hospital (Figure 2). Among these, 1629 lab–confirmed enteric fever cases were detected: 1447 (89%) S. Typhi and 182 (11%) S. Paratyphi. Additionally, 614 enteric fever cases were identified at the hospital lab who were not enrolled at an IPD or OPD. All 275 S. Paratyphi that were isolated during the reporting period were S. Paratyphi A. Of the 2243 lab–confirmed typhoid and paratyphoid cases, 673 (30%)
were hospitalized, and 91% (n = 612) of the hospitalizations were due to S. Typhi. Enteric fever occurred throughout the year, with slight decreases in the numbers of cases and hospitalizations during winter (December–February; Figure 3). The majority (n = 523; 78%) of the hospitalized typhoid and paratyphoid cases came from the hospital catchment area where HCUS had been conducted.

Of 673 hospitalized, lab-confirmed S. Typhi and S. Paratyphi cases, 361 (54%) were aged <5 years (Table 1). All had fever at the time of hospitalization, with a median duration of 6 days (IQR, 4–8). Additional predominant clinical and laboratory findings at the time of hospitalization included vomiting (262/672, 39%), diarrhea (204/671, 30%), abdominal pain (165/672, 25%), cough (99/672, 15%), hepatomegaly (11/54, 20%), leukocytopenia (10/54, 20%), splenomegaly (25/323, 8%), and thrombocytopenia (25/323, 8%). Nearly all (667/673, 99%) isolates identified from the hospitalized children were ciprofloxacin-resistant, whereas the rate of multidrug resistance, defined as resistance to chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole, was 17% (115/673). The median duration of stay in the hospital was 7 days (IQR, 5–9). No deaths were reported among the hospitalized cases. Detailed characteristics of hospitalized and nonhospitalized children are shown in Table 1.

Figure 3. Distribution of total number of enteric fever cases (n = 2243) and hospitalizations (n = 673) by month at Dhaka Shishu Hospital and Dr MR Khan Shishu Hospital, Dhaka, Bangladesh, July 2017–June 2019.

Figure 2. Enteric fever cases aged <15 years enrolled (n = 11,968) by recruitment location, with Salmonella Typhi and S. Paratyphi isolated, and hospitalized at Dhaka Shishu Hospital and Dr MR Khan Shishu Hospital, Dhaka, Bangladesh, July 2017–June 2019. Abbreviations: IPD, inpatient department; OPD, outpatient department; S., Salmonella.
Although young children were more likely to be hospitalized, age was not identified as a risk factor for hospitalization in the multivariable logistic regression. Factors independently associated with hospitalization included fever duration, diarrhea, vomiting, abdominal pain, and leukocytopenia (Table 2). No significant differences in resistance to chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole were found between hospitalized and nonhospitalized cases.

### Community Health-care Utilization
In the hospital catchment area, the estimated number of children aged <15 years in 2017 and 2018 was 1,148,076.

Data are of hospitalized (n = 673) and nonhospitalized (n = 1,570) S. Typhi and S. Paratyphi cases isolated at Dhaka Shishu Hospital and Dr MR Khan Shishu Hospital, July 2017–June 2019.

| Characteristics                      | Hospitalized | Nonhospitalized | Total  | P value |
|--------------------------------------|--------------|-----------------|--------|---------|
| **Demographic characteristics**      |              |                 |        |         |
| Age                                  |              |                 |        |         |
| <2 years                             | 93           | 14%             | 176    | 11%     | 269     | .019* |
| 2 to <5 years                        | 268          | 40%             | 568    | 36%     | 836     |       |
| 5 to <15 years                       | 312          | 46%             | 826    | 53%     | 1141    |       |
| 6 months to <15 years                | 672          | 100%            | 1568   | 70%     | 2243    |       |
| Median age (IQR) in months           | 48 (24–84)   |                 | 60 (36–84) |       | 60 (36–84) | <.001* |
| Sex                                  |              |                 |        |         |
| Male                                 | 363          | 54%             | 866    | 55%     | 1229    | .594  |
| Resident of catchment area           | 523          | 78%             | 1438   | 91%     | 1961    | <.001* |
| **Clinical and laboratory findings** |              |                 |        |         |
| Median duration of fever (IQR) in day at the time of enrollment | 7 (5–9) |                 | 5 (4–8) |       | 6 (4–8) | .009* |
| Vomiting                             | 262          | 39%             | 274    | 17%     | 536     | <.001* |
| Diarrhea                             | 204          | 30%             | 158    | 10%     | 362     | <.001* |
| Abdominal pain                       | 165          | 25%             | 217    | 14%     | 382     | <.001* |
| Cough                                | 99           | 15%             | 319    | 20%     | 418     | .006* |
| Constipation                         | 23           | 3.4%            | 60     | 3.8%    | 83      | .615  |
| Headache                             | 18           | 2.7%            | 74     | 4.7%    | 92      | .032* |
| Rash                                 | 10           | 1.5%            | 5      | 3.3%    | 15      | .006* |
| Jaundice                             | 4            | 0.6%            | 2      | 0.1%    | 6       | .055  |
| Seizure                              | 3            | 0.4%            | 1      | 0.1%    | 4       | .055  |
| Bloody stool                         | 2            | 0.3%            | 0      | 0%      | 2       | .037* |
| Difficult breathing                  | 2            | 0.3%            | 4      | 0.3%    | 6       | .376  |
| Hepatomegaly on ultrasonogram        | 28           | 52%             | 5      | 71%     | 33      | .305  |
| Splenomegaly on ultrasonogram        | 12           | 22%             | 1      | 14%     | 13      | .645  |
| Leukocytopenia, total WBC < 4000/mm³ | 25           | 7.7%            | 10     | 1.9%    | 35      | <.001* |
| Thrombocytopenia, platelet < 150 000 µl | 25       | 7.7%            | 13     | 2.5%    | 38      | <.001* |
| **Organism**                         |              |                 |        |         |
| S. Typhi                             | 612          | 91%             | 1356   | 86%     | 1968    | .003* |
| S. Paratyphi                         | 61           | 9.1%            | 214    | 14%     | 275     |       |
| **Severity**                         |              |                 |        |         |
| Days not able to conduct usual activities due to illness | 3 (0–8) |                 | 3 (0–12) |       | 3 (0–12) | .902  |
| Hours of bed rest during worst day of illness | 3 (2–6) |                 | 2 (1–5) |       | 2 (1–5) | .003* |
| **Drug resistance**                  |              |                 |        |         |
| Ampicillin                           | 202          | 30%             | 373    | 24%     | 575     | .002* |
| Chloramphenicol                      | 126          | 19%             | 248    | 16%     | 374     | .088  |
| Cotrimoxazole                        | 118          | 18%             | 237    | 15%     | 355     | .206  |
| Ciprofloxacin                        | 667          | 99%             | 1534   | 97%     | 2201    | .042* |
| Azithromycin                         | 9            | 1.3%            | 40     | 2.5%    | 49      | .072  |
| Cefixime                             | 1            | 0%              | 3      | 0%      | 4       | .827  |
| Cefazidime                           | 0            | 0%              | 0      | 0%      | 0       |       |
| MDR                                  | 115          | 17%             | 222    | 14%     | 337     | .073  |

*Statistically significant.
2 rounds of HCUS, data on hospitalization due to febrile illness in the last 1 year were collected from 36 142 children aged <15 years living in the selected clusters (Table 3). A total of 335 (0.9%) hospitalizations due to febrile illness were identified; 177 (52.8%) were hospitalized at a study hospital.

Incidence of Hospitalization Due to Enteric Fever

The overall crude incidence of hospitalization due to enteric fever among children aged <15 years in the hospital catchment area in urban Dhaka during 2017–2018 was 46 per 100 000 children per year (95% CI, 42–49; Table 4). The estimated incidence of enteric fever hospitalization after adjustment for facility coverage, facility capture, and blood-culture sensitivity was 303 per 100 000 children per year (95% CI, 293–313).

Salmonella Typhi was the main contributing factor for hospitalization. There was no difference in the hospitalization rates between males and females. The hospitalization rate was highest among children aged 2 to <5 years, followed by those aged <2 years. The duration of fever and the presence of diarrhea, vomiting, abdominal pain, and leukocytopenia were identified as risk factors for enteric fever hospitalization.

Similar to our findings of 30% hospitalization, a study conducted from 2004 through 2016 in a similar setting reported that 32% of the typhoid cases and 21% of the paratyphoid pediatric cases required hospitalization [16]. Previous data showed that 3.6% of all admissions at large pediatric hospitals in Bangladesh were either laboratory-confirmed or clinically diagnosed enteric fever cases [23]. This could be because Bangladesh has a high burden of enteric fever, with incidence rates ranging from 2.7–18.7 per 1000 children [19, 20, 24].

In concordance with previous studies evaluating the clinical profile of enteric fever, we found that the predominant signs, symptoms, and laboratory findings of hospitalized enteric fever cases include fever, vomiting, diarrhea, abdominal pain, cough, hepatomegaly, and splenomegaly [23, 25–27]. But in contrast to the systematic review conducted by Azmatullah et al. [27]

### Table 3. Health-care Utilization Survey–Identified Hospitalizations of Children <15 Years Old for Febrile Illness at Dhaka Shishu Hospital and Dr MR Khan Shishu Hospital, Dhaka, Bangladesh, 2017–2018

| Characteristics                                      | HCUS 2017 | HCUS 2018 | Total |
|------------------------------------------------------|-----------|-----------|-------|
|                                                      | n         | %         | n     | %     |
| <15 year old children interviewed for hospitalization due to febrile illness in last 1 year |           |           |       |       |
| Hospitalized anywhere                               | 141       | .7%       | 194   | 1.2%  | 335   | .9% |
| Hospitalized at Dhaka Shishu Hospital                | 22        | 15.6%     | 49    | 25.3% | 71    | 21.2% |
| Hospitalized at Dr MR Khan Shishu Hospital           | 53        | 37.8%     | 53    | 27.3% | 106   | 31.6% |
| Hospitalized at other places                         | 66        | 46.8%     | 92    | 47.4% | 158   | 47.2% |

Abbreviation: HCUS, health-care utilization survey.
Table 4. Crude and Adjusted Incidence Rate of Hospitalization of Laboratory-confirmed *S. Typhi* and *S. Paratyphi* Among Children Aged <15 by Organism, Sex, Age Group and Recruitment Location, at the Catchment Area of Dhaka Shishu Hospital and Dr MR Khan Shishu Hospital, Dhaka, Bangladesh, July 2017–June 2019

| Characteristics | Number of hospitalized cases | Population | Crude incidence rate per 100 000/year (95% CI) | Febrile cases hospitalized at study hospitals | Health-care seeking adjusted incidence per 100 000/year (95% CI) | Facility captured febrile cases at study hospitals | Facility capture adjusted incidence per 100 000/year (95% CI) | Blood culture sensitivity adjusted incidence per 100 000/year (95% CI) | Blood culture sensitivity |
|-----------------|-----------------------------|------------|-----------------------------------------------|-----------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|-------------------------|
| **Overall enteric fever** | | | | | | | | | |
| | 523 | 1 148 076 | 46 (42–49) | 53% | 86 (81–92) | 47% | 185 (177–193) | 61% | 303 (293–313) |
| **Organism** | | | | | | | | | |
| *S. Typhi* | 478 | 1 148 076 | 42 (38–45) | 53% | 79 (71–84) | 47% | 169 (161–177) | 61% | 277 (267–287) |
| *S. Paratyphi A* | 45 | 1 148 076 | 3.9 (2.8–5.1) | 53% | 7.4 (5.8–9) | 4% | 16 (14–18) | 61% | 26 (23–29) |
| **Sex** | | | | | | | | | |
| Male | 276 | 584 730 | 47 (42–53) | 54% | 88 (80–95) | 47% | 185 (171–196) | 61% | 303 (289–317) |
| Female | 247 | 563 346 | 44 (38–49) | 51% | 86 (78–93) | 46% | 188 (176–199) | 61% | 308 (293–322) |
| **Age** | | | | | | | | | |
| <2 years | 70 | 155 915 | 45 (34–55) | 58% | 78 (64–92) | 40% | 193 (171–215) | 61% | 316 (288–344) |
| 2 to <5 years | 209 | 225 453 | 93 (80–105) | 57% | 163 (146–179) | 48% | 337 (313–361) | 61% | 552 (522–583) |
| 5 to <15 years | 244 | 766 708 | 32 (28–36) | 46% | 69 (63–75) | 50% | 138 (129–146) | 61% | 225 (215–236) |
| 6 months to <15 years | 522 | 1 110 388 | 47 (43–51) | 51% | 91 (86–97) | 47% | 195 (187–203) | 61% | 319 (309–330) |
| **Enrollment location** | | | | | | | | | |
| OPD | 106 | 1 148 076 | 9.7 (7.5–11) | 53% | 17 (15–20) | 44% | 40 (36–43) | 61% | 65 (60–70) |
| IPD | 368 | 1 148 076 | 32 (29–35) | 53% | 61 (56–65) | 84% | 72 (67–77) | 61% | 118 (112–125) |
| Hospital lab | 49 | 1 148 076 | 4.3 (3.1–5.5) | 53% | 8.1 (6.4–10) | 100% | 8.1 (6.4–10) | 61% | 13 (11–15) |

Abbreviations: CI, confidence interval; IPD, inpatient department; OPD, outpatient department; *S.*, Salmonella.
and a study conducted in Fiji [26], we observed lower proportions of children with signs and symptoms of complications, including gastrointestinal bleeding (6–8% in prior studies vs 0.3% in our study) and jaundice (2.8% in prior studies vs 0.6% in our study), and no mortality (1–6% in prior studies vs 0% in our study) due to enteric fever among children, which is possibly due to the widespread over-the-counter availability of antibiotics in Bangladesh. Relatively less severe disease in our population could also possibly be explained by a hypothesis that frequent subclinical exposure to S. Typhi and S. Paratyphi from contaminated water and food may provide a level of immunity against the disease to the people living in the endemic area. However, our data demonstrated that only fever duration, diarrhea, vomiting, abdominal pain, and leukocytopenia were associated with enteric fever hospitalization among children aged <15 years. Although there are reports on coinfections with dengue, malaria, and so forth, data on the role of coinfection with other pathogens on hospitalization of enteric fever cases is scarce [28, 29]. In the blood cultures of the enteric fever cases enrolled in SEAP, we did not find any other bacterial pathogens. However, based on the clinical criteria and advice of clinicians, only 74 cases were tested for dengue. Of them, 2 (2.7%) were positive for either an NS1 antigen test or anti-dengue immunoglobulin M. As the number of dengue-positive cases was too small, we did not include coinfection with dengue in the risk factor analysis.

We reported that the adjusted incidence of hospitalization due to typhoid and paratyphoid was 303 per 100 000 children per year in children aged <15 years. This rate is higher than the rates observed by previous studies conducted in Bangladesh, Kenya, and Spain [19, 20, 25, 30]. In Bangladesh, Brooks et al. [20] gathered 12 407 person-years worth of data for 10 months, but found no hospitalizations, complications, or deaths among blood culture–confirmed typhoid fever patients. Naheed et al. [19] observed only 4 hospitalizations among blood culture–confirmed typhoid fever patients per year. Thus, we used a 61% sensitivity rate to adjust the incidence of enteric fever hospitalization for all subgroups, as information on sensitivity rates by subgroups was not available. Sensitivity rates may vary by subgroups, and thus affect our estimates for different subgroups.

**CONCLUSIONS**

We estimated that 303 per 100 000 children aged <15 years with enteric fever require hospitalization per year. Children aged <5 years are affected most. The introduction of TCV in the national immunization program would protect children from typhoid and avert related admissions at pediatric hospitals, thus allowing children with other severe diseases to be treated. Thus, TCV would not just prevent morbidity and mortality due to typhoid fever, it would also save more lives and prevent disability from other severe diseases, and therefore reduce the burden on the health system and improve child health overall.

**Notes**

**Acknowledgments.** The authors thank all physicians, laboratory personnel, and research assistants working at Dhaka Shishu Hospital and Dr MR Khan Shishu Hospital, especially Dr Dipalok Mukharjee, Dr Shamsun Nahar, Dr Shammin Azmery, Dr Humaira Susmita, Dr Shumaiya Ferdaus, and Mr Anik Sarker, who played active roles in implementation of the Surveillance for Enteric Fever in Asia Project hospital surveillance; Ms Salma Akhter for coordination of the health-care utilization survey (HCUS); all research assistants who collected quality HCUS data; Ms Ruma Sarker for data management support; and Mr. Md. Shariful Islam and Mr Argho Sarker for data management support.
Financial support. This work was supported by the Bill and Melinda Gates Foundation (Investment ID OPP113007).

Supplement sponsorship. This supplement is sponsored by the Sabin Vaccine Institute and made possible by a grant from the Bill & Melinda Gates Foundation.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References
1. Mogasale V, Maskery B, Ochiai RL, et al. Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment. Lancet Glob Heal 2014;2:e570–80.
2. Antillón M, Warren JL, Crawford FW, et al. The burden of typhoid fever in low- and middle-income countries: a meta-regression approach. PILOS Negl Trop Dis 2017;11:e005376.
3. Stanaway JD, Reiner RC, Blacker BE, et al. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Infect Dis 2019;19:369–83.
4. Wierzba TF, Sanders JW. The global burden of enteric fevers in the age of typhoid conjugate vaccines. Lancet Infect Dis 2019;19:340–1.
5. Fraser A, Goldberg E, Acosta CJ, Paul M, Leibovici L. Vaccines for preventing typhoid fever: In: Fraser A, ed. Cochrane database of systematic reviews. Chichester, United Kingdom: John Wiley & Sons, Ltd, 2007. Available at: http://doi.wiley.com/10.1002/14651858.CD001261.pub2. Accessed 22 February 2020.
6. Yugoslav Typhoid Commission. A controlled field trial of the effectiveness of phenol and alcohol typhoid vaccines: final report. Bull World Health Organ 1962;26:357–69.
7. World Health Organization. State of the art of vaccine research and development. 2006. Available at: https://apps.who.int/iris/bitstream/handle/10665/69348/WHO_IVB_06_01_eng.pdf;jsessionid=910C9043CA1D327048D2C391905A32B?sequence=1. Accessed 22 May 2020.
8. Fraser NA, Levine MM. Typhoid vaccine development with a human challenge model. Lancet 2017;390:2419–21.
9. World Health Organization. Weekly epidemiological record. Typhoid vaccines: WHO position paper—March 2018. 2018. Available at: https://apps.who.int/iris/bitstream/handle/10665/272272/WER9313.pdf?ua=1. Accessed 12 November 2019.
10. World Health Organization. Typhar TCV® from Bharat Biotech, world’s first typhoid conjugate vaccine prequalified by WHO. 2018. Available at: https://www.who.int/medicines/news/2017/Bharat-Biotech-TypharTCV-WHO-PO-Press-Release-Global-Final.pdf?ua=1. Accessed 12 November 2019.
11. Shaky A, Colin-Jones R, Theiss-Nyland K, et al. Phase 3 efficacy analysis of a typhoid conjugate vaccine trial in Nepal. N Engl J Med 2019;381:2209–18.
12. World Health Organization. Principles and considerations for adding a vaccine to a national immunization programme. Available at: https://apps.who.int/iris/bitstream/handle/10665/115488/9789241506892_eng.pdf;jsessionid=F69C31CC406B6A1BA2647EA67DCE34?sequence=1. Accessed 15 November 2019.
13. Yu AT, Amin N, Rahman MW, Guarley ES, Rahman KM, Luby SP. Case-fatality ratio of blood culture–confirmed typhoid fever in Dhaka, Bangladesh. J Infect Dis 2018;218:5222–6.
14. World Health Organization. World health statistics 2009. 2010. Available at: https://www.who.int/whosis/whostat/2009/en/. Accessed 23 February 2020.
15. Saha S, Santosham M, Hussain M, Black RE, Saha SK. Rotavirus vaccine will improve child survival by more than just preventing diarrhea: evidence from Bangladesh. Am J Trop Med Hyg 2018;98:360–3.
16. Saha S, Islam MS, Sahib MSI, et al. Epidemiology of typhoid and paratyphoid: implications for vaccine policy. Clin Infect Dis 2019;68:S117–23.
17. Saha SK, Baqui AH, Hanif M, et al. Typhoid fever in Bangladesh: implications for vaccination policy. Pediatr Infect Dis J 2001;20:524–1.
18. Saha S, Saha S, Das RC, et al. Enteric fever and related contextual factors in Bangladesh. Am J Trop Med Hyg 2018;99:20–5.
19. Naheed A, Ram PK, Brooks WA, et al. Burden of typhoid and paratyphoid fever in a densely populated urban community, Dhaka, Bangladesh. Int J Infect Dis 2010;14:93–9.
20. World Health Organization. Weekly epidemiological record. Typhoid vaccines: importance of including different health-care utilizations to estimate enteric fever incidence: methods and challenges. J Infect Dis 2018;218:S568–76.
21. Luby SP, Balder AK, Saha SK, et al. A low-cost approach to measure the burden of vaccine preventable diseases in urban areas. Vaccine 2010;28:4903–12.
22. Saha S, Uddin MJ, Islam M, Das RC, Garrett DO, Saha SK. Enteric fever cases in the two largest pediatric hospitals of Bangladesh: 2013–2014. J Infect Dis 2018;218:S195–200.
23. Dewan AM, Corner J, Hashizume M, Ongsu ET. Typhoid fever and its association with environmental factors in the Dhaka metropolitan area of Bangladesh: a spatial and time-series approach. PILOS Negl Trop Dis 2013;7:e1998.
24. Breiman RF, Cosmas L, Nyugua H, et al. Population-based incidence of typhoid fever in an urban informal settlement and a rural area in Kenya: implications for typhoid vaccine use in Africa. PLOS One 2012;7:e29119.
25. Getahun SA, Parry CM, Crump JA, et al. A retrospective study of patients with blood culture–confirmed typhoid fever in Fiji during 2014–2015: epidemiology, clinical features, treatment and outcome. Trans R Soc Trop Med Hyg 2019;113:764–70. Available at: http://www.ncbi.nlm.nih.gov/pubmed/31638153. Accessed 15 November 2019.
26. Azmatsullah A, Qamar FN, Thaver D, Zaidi AK, Bhutta ZA. Systematic review of the global epidemiology, clinical and laboratory profile of enteric fever. J Glob Health 2015;5:020407. doi:10.7189/jogh.05.020407.
27. Sharma Y, Arya V, Jain S, Kumar M, Deka L, Mathur A. Dengue and typhoid co-infection study from a government hospital in North Delhi. J Clin Diagn Res 2013;7:e93–9.
28. Bhanezi M, Tessa M, Bherde G, Endris M, Enawagw B. Malaria, typhoid fever, and their coinfection among febrile patients at a rural health center in Northwest Ethiopia: a cross-sectional study. Adv Med 2014;2014:531074. doi:10.1155/2014/531074.
29. Gil R, Alvarez JL, Gómez C, Alvaro A, Gil Á. Epidemiology of typhoid and paratyphoid fever hospitalizations in Spain (1997–2005). Hum Vaccin 2009;5:420–4.
30. Saha S, Islam M, Saha S, et al. Designing comprehensive public health surveillance for enteric fever in endemic countries: importance of including different health-care facilities. J Infect Dis 2018;218:5227–31.
31. Saha S, Tannoy AM, Andrews JR, et al. Evaluating PCR-based detection of Salmonella Typhi and Paratyphi A in the environment as an enteric fever surveillance tool. Am J Trop Med Hyg 2019;100:43–6.