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Incidence of Typhoid Bacteremia in Infants and Young Children in Southern Coastal Pakistan

Aatekah Owais, MPH[1], **Shazia Sultana, MBBS**[1], **Umber Zaman, MBBS**[1], **Arjumand Rizvi**[1], and **Anita K M Zaidi, MBBS, SM**[1]

[1] Department of Paediatrics and Child Health. Aga Khan University, Karachi, Pakistan

Keywords

typhoid; incidence; pre-school children; Pakistan

INTRODUCTION

Typhoid is the most common bacteremic illness in highly endemic countries, such as Pakistan. A systemic bacterial disease with insidious onset of symptoms, the clinical presentation of typhoid fever in infants and young children can be varied and non-specific. Typhoidal illness can range from a mild, non-specific febrile illness, to clinical or radiologic pneumonia, or severe illness with features of the classic typhoidal syndrome (high fever, toxicity, hepatomegaly, and splenomegaly) which can be fatal.(1–8)

The purpose of this paper is to describe the incidence of typhoid bacteremia in Pakistani infants and children < 5 years old, and consider the implications of these findings for immunization policies in highly endemic countries.

Incidence estimates of typhoid fever in Pakistan are available from older children and estimated to cause 452 cases per 100 000 person-years among 2–15 year-olds, with an increased risk of disease among 2–4 year-olds (573 cases per 100,000 person-years).(9) Although there are limitations in trying to estimate the overall burden of typhoid for a demographically and geographically diverse country like Pakistan, accumulating data from several population-based studies in and near Karachi are collectively beginning to provide broad estimates of the incidence of typhoid for this region of Pakistan.(9,10) However, limited population-based surveillance data are available for the burden of typhoid fever and/or bacteremia among children < 2 years old, and especially among infants younger than 12 months.(10–14) Furthermore, an array of different surveillance methods has been used in

Correspondence to: Dr. Anita Zaidi, MBBS, SM, FAAP, Professor of Paediatrics and Child Health, and Microbiology, Department of Paediatrics and Child Health, Aga Khan University, Stadium Road, PO Box 3500, Karachi 74800, Tel: 021-493-0051, ext 4734, Fax: 021-493-4294, Cell: 0300-823-4427, anita.zaidi@aku.edu.

Author contribution in this article was as follows: A. Owais provided the design and execution of the data analysis of this study, as well as preparing the manuscript.
S. Sultana was responsible for the overall supervision of the project operations.
U. Zaman supervised field operations.
Arjumand Rizvi conducted the statistical analysis.
A. K. M. Zaidi was the principal investigator and contributed to the design and execution of the data analysis, and manuscript preparation.

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these studies, ranging from active household surveillance in urban Dhaka and Delhi, to passive, augmented surveillance in Karachi, and passive facility-based surveillance in Bangladesh and Vietnam.

Robust data on burden of disease in young children are necessary to develop and implement typhoid vaccine policies for highly endemic countries. *Salmonella enterica* serovar Typhi is a human only pathogen. Therefore, vaccines are a very promising disease control tool. However, the two currently licensed vaccines, Ty21a, a live oral vaccine, and Vi polysaccharide, a parenteral vaccine, are only effective in older children and adults. A Vi conjugate vaccine has been shown to be effective in large clinical trials in young children but is not available commercially.(15,16) New generation oral typhoid vaccines, utilizing genetically attenuated strains of *S.* Typhi are also under clinical development and may be effective in infants and young children.

MATERIALS AND METHODS

The Aga Khan University's Department of Pediatrics and Child Health, in partnership with PneumoADIP, conducted population-based surveillance for invasive pneumococcal disease from February 1, 2007 to May 12, 2008. The surveillance was carried out in two low socioeconomic, contiguous coastal areas located 20 km outside of Karachi, where the Department of Pediatrics and Child Health has been conducting several studies related to neonatal health and outcomes since 2003. Both areas are semi-urban to rural settings, with fishing and livestock rearing as the major income generating activities. Biomass, specifically cow dung, is the major source of household fuel used for cooking in a large number of households. There is a 30-bed public sector hospital, but it is barely functioning and does not admit patients overnight.

Of the estimated 11,000 less than 5 years old children in these areas, a dynamic cohort of approximately 6,000 was targeted for enrollment, based on a conservative expected combined annual pneumonia, severe pneumonia, and very severe disease rates of 0.25 (95% CI: 0.24–0.26) per child per year.(17) Community health workers (CHW) carried out weekly house-to-house visits to identify sick children < 5 years old, as defined by WHO/UNICEF Integrated Management of Childhood Illness (IMCI) Guidelines.(18) Children thus identified, and whose parent(s)/primary caretakers gave consent, were triaged at the study's local community health center. Blood for culture was obtained from children with documented fever ≥ 38°C at the clinic, as well as any child identified as possible pneumococcal clinical syndrome (using core case definitions developed by the PneumoADIP investigator's group (19); Table, Supplemental digital content 1, http://links.lww.com/INF/A510). All children diagnosed with clinical pneumonia or prolonged febrile illness, were treated with oral antibiotics, regardless of their blood culture results. Those with a diagnosis of pneumonia were treated with amoxicillin, orally.

Blood was drawn for culture using aseptic precautions. Approximately 2–3 ml of blood was obtained from those who gave consent. Samples were inoculated into BACTEC Peds Plus® (Becton Dickinson, Sparks, MD, USA) bottles on-site and transported to an AKU laboratory collection site approximately 30 minutes away from the study sites. Every effort was made to ensure that bottles got loaded into the BACTEC 9240 (Becton Dickinson) system within 4 hours of collection. Standard isolation and antimicrobial susceptibility testing procedures were utilized, with appropriate recording and timely reporting of results, as per usual practice.

Statistical analysis was performed using SPSS 16.0 and OpenEpi 2.3.(20) Clinical signs and symptoms, nutritional status (as measured via height-for-age and weight-for-age z-scores),

antibiotic use before presentation at study clinic, and treatment outcome at 1 week, were compared for typhoid bacteremia, other bacteremia, and non-bacteremia cases. Medians (range) were computed for continuous variables. Due to large variation in sample size across groups, for continuous variables Kruskal-Wallis test were used for comparison among groups. Dunn's test was performed for post-hoc comparisons. Mann-Whitney test was used for subset comparison within groups. Proportions were calculated for categorical variables. Chi-square test and Fisher's exact test was used for testing of association between groups as appropriate.

A child's observation period began at consent and continued for 52 weeks, or until the child reached the age of 5 years, whichever came first. Incidence was calculated as the number of cases per person-years of observation. Seasonality was plotted as mean incidence per month.

The study was approved by the Ethical Review Committee of AKU and confidentiality of patients was maintained at all times.

RESULTS

During the study period, 5,570 children contributed 3,949 observation years. Overall, there were 3,372 episodes of febrile illness eligible for blood culture, but families of only 1,388 (41.2%) cases consented to visit the study's health center during their febrile episode. Of these, families of 1,165 (83.9%) cases consented for blood cultures. *Salmonella enterica* serovar Typhi was isolated in 16 cases, *Salmonella enterica* Paratyphi A in 2 cases, and *Salmonella enterica* Paratyphi B in 1 case. No non-typhoidal *Salmonella* serovars were isolated. Other bacteria were isolated in 17 cases, including 1 *Streptococcus pneumoniae*, 8 *Acinetobacter spp.*, 1 *Pseudomonas spp.*, 1 *E. coli*, 3 *Campylobacter jejuni*, 1 *Hemophilus influenzae* type b, 1 *Kingella spp.*, and 1 β-hemolytic Group B *Streptococcus*. Of the total culture-positive *Salmonella* Typhi cases in the cohort, 7 (43.7%) occurred in children < 2 years old, with 4 cases occurring in children < 12 months old. The age range of children with typhoid bacteremia was 10–56 months. Among children < 12 months old, cases occurred at 10 (3 cases) and 11 months of age.

The incidence of typhoid bacteremia in children < 2 years of age was 443.1 (95% CI: 193.8–876.5) per 100,000 child-years and in infants under 12 months of age was 506.4 cases per 100,000 child years (95% CI: 160.9–1222.0). The overall incidence of typhoid bacteremia in children < 5 years old was 405.1 (95% CI: 239.8–643.8) per 100,000 child-years (Table 1). The incidence of bacteremia due to enteric fever pathogens (S. Typhi, Paratyphi A and B combined) in children < 5 years old was 481.1 (95% CI: 298.2–737.4) cases per 100,000 child-years.

Of the 1,388 febrile illness cases who presented at the study clinic, a total of 1,172 (84.4%) were classified as possible pneumococcal syndrome. Out of these, 1,060 (90.4%) were classified as pneumonia clinical syndrome, 85 (7.3%) had pneumonia danger signs, and 27 (2.3%) had general danger signs (See Table, Supplemental digital content 1, http://links.lww.com/INF/A510). Blood for culture from 216 (15.6%) cases was obtained because of febrile illness only (no localizing signs or symptoms). The proportion of all blood cultures growing *S*. Typhi was 1.4%.

The most common clinical diagnosis given to children with typhoid or paratyphoid bacteremia was pneumonia (n = 15, 78.9%), followed by enteric fever (n = 2, 10.5%), upper respiratory infection (n = 1, 5.3%) and 1 (5.3%) case of febrile illness of unknown origin. Among all children given a diagnosis of pneumonia (n = 1,035), 15 (1.4%) grew *Salmonella* Typhi or Paratyphi. None of the 19 cases of typhoid or paratyphoid bacteremia required referral to tertiary care facility and were managed as out-patients, with oral amoxicillin (n =

17, 89.5%), oral cephalexin (followed by intramuscular ceftriaxone; n = 1, 5.3%), and other injectable antibiotics (n = 1, 5.3%).

We also compared the clinical signs and symptoms, nutritional status, antibiotic use before presentation at study clinic, and treatment outcome at 1 week, for typhoid bacteremia, other bacteremia, and non-bacteremia cases (Table 2). The median (range) age of *S.* Typhi bacteremia cases was 24(10–56) months, with a median (range) temperature of 38.5(37.4–40.5) °C. There were no deaths among children with typhoid bacteremia.

Incidence rates of bacteremia with enteric fever organisms varied seasonally (Figure, Supplemental digital content 2, http://links.lww.com/INF/A511). The highest incidence of the disease (810.3 per 100,000 child-years; 95% CI: 376.3–1,539.0) occurred during the monsoon months (July – October). A lower incidence rate of 607.7 (95% CI: 246.3–1,264.0) was observed during the post-monsoon season. The least number of cases (31.6%) were detected during months prior to the start of the monsoon season, for an incidence rate of 253.2 (95% CI: 92.8–561.3) per 100,000 child-years.

Antimicrobial susceptibility, determined by Kirby-Bauer disk diffusion method, showed susceptibility to ampicillin, chloramphenicol, trimethoptrim-sulfamethoxazole in 81% of the *Salmonella* Typhi isolates. Neither of the 2 *Salmonella* Paratyphi A isolates was susceptible to these 3 classes of drugs. Only 54% of the *Salmonella* Typhi isolates were fully susceptible to ciprofloxacin/ofloxacin. Both the *Salmonella* Paratyphi A isolates were susceptible to ciprofloxacin/ofloxacin. All 19 isolates were susceptible to ceftriaxone and cefixime. The single *S.* Paratyphi B isolate was susceptible to all classes of drugs tested.

DISCUSSION

The incidence of *S.* Typhi bacteremia in children < 2 years of age in this region of coastal southern Pakistan is 443 cases per 100,000 child-years. Moreover, among the 7 cases of *S.* Typhi bacteremia in this age group, 4 were observed in infants < 12 months of age and 3 in toddlers. These findings add to the limited evidence available about the burden of typhoid in children < 2 years old, and underscore the need for a vaccine that could be used in routine childhood immunization programs targeting children under 2 years in endemic countries and confer long-term immunity. (11,13,14)

We observed lower severity of illness among children who had typhoid fever, compared with that observed in India (Table 2).(14) In our cohort, the majority of the cases had had fever for less than 3 days before they presented at the community health center and received appropriate care, but the mean temperature in the typhoid bacteremia group was significantly higher compared with the non-bacteremia group ($p = 0.004$). Similarly, a greater proportion of the typhoid cases had fever ≥ 39° C, compared with the other bacteremia and non-bacteremia cases ($p = 0.01$). There were no difference in the nutritional status of cases between groups, with almost half the children in each group suffering from moderate and/or severe wasting (WAZ < −2).

We also observed a trend of lower severity of illness among the typhoid bacteremia cases < 24 months old compared to cases > 2 years old. Children < 24 months old had a lower mean temperature and more than 70% of the children in this age group had improved at 1-week follow-up compared with only a third of the children in 2–5 years age group. We cannot comment as to whether the clinical syndrome in the younger children was a self-limiting *S.* Typhi bacteremia as every child diagnosed with clinical pneumonia or prolonged febrile illness received oralantibiotics.(21)

The reduced morbidity among the typhoid fever cases in our cohort may be explained by the intense active surveillance that was part of the study, with CHW assessing each child weekly, and referring sick children to the community health centers for timely case management. The community clinics also provided free care to all area children. This may have resulted in appropriate care being sought by families of sick children much earlier than is usually the case, reducing the burden of morbidity attributed to typhoid fever. However, at 1 week follow-up, only half the children with typhoid bacteremia reported improvement in clinical symptoms, compared with children with other bacteremia and no bacteremia ($p = 0.005$).

Our study is unique in documenting a high incidence of typhoid bacteremia in infants < 12 months of age. Ours is the first prospective, systematic population-based study to show this. Although there have been other surveillance studies for *S.* Typhi bacteremia among larger populations compared to ours, none showed a high disease burden in this age group.(9,11,12,14) In the study of Sinha et al,(14) utilizing active household surveillance in a Delhi slum, no cases of typhoid bacteremia were isolated from infants < 12 months old. Brooks et al,(11) working in a slum of Dhaka, found 26 cases of *S.* Typhi bacteremia among children < 5 years old based on active household surveillance, but only 1 child among these 26 was < 12 months old. Both these studies collected blood for culture from all febrile children < 5 years old, irrespective of febrile episode duration. Therefore, the trigger for collecting a culture was as sensitive as ours.

Lin et al,(12) working in the Mekong delta of Vietnam, found no cases of typhoid bacteremia in infants < 24 months old. However, the surveillance was passive, hospital-based surveillance, and required that the patients have fever for at least 3 days, which may have decreased the sensitivity of the surveillance system in detecting mild disease. As part of large-scale, systematic surveillance for typhoid fever conducted in five Asian countries, India and Indonesia conducted passive, facility-based surveillance for typhoid bacteremia among all ages, requiring that the patients have a fever lasting at least 3 days.(9) In addition, India augmented the passive surveillance with monthly household visits. The incidence of bacteremic *S.* Typhi disease in children < 12 months old was found to be 89.0 per 100,000 child-years in India and 0 per 100,000 child-years in Indonesia.

Our observed incidence of 506 cases per 100,000 child-years in infants < 1 year of age is much higher than reported elsewhere. The reasons for this are unclear. One possibility is that the low rates of exclusive breastfeeding reported in Pakistan, and also in these communities, lead to earlier exposure to enteric pathogens compared with other settings. The overall high incidence of typhoid fever observed in the less than 5 years old population is attributed to lack of adequate clean water and sanitation facilities in low-income, peri-urban areas of Karachi. The majority of the homes in these areas do not have piped water. Instead, residents use community taps, or have water brought in through tankers for consumption after long-term storage in homes. Furthermore, many of these communities have grown from squatter settlements, with no urban planning. The result is a crude sewage disposal system, which overflows into the streets frequently, and contaminates the community's water supply.

The two currently licensed typhoid vaccines, oral Ty21a and parenteral Vi, are not recommended for use in young children. Therefore, if infants are to be considered possible candidates for immunization, it will have to be with future vaccines. The conjugate vaccine, Vi-rEPA, administered in 2 doses to 2–5 year-olds during vaccine-efficacy trials in Vietnam showed an overall vaccine efficacy of 89% for approximately 4 years of follow-up, but has not been commercialized.(15,16) Preliminary evidence from immunogenicity studies show promising results for the Indian typhoid conjugate vaccine (Vi conjugated with tetanus

toxoid as carrier protein).(22) Currently, there are no efficacy data from the use of typhoid conjugate vaccines in infants. There are also live oral vaccines, proposed to be used as single-dose, currently under clinical development.

Surprisingly, 80% of *Salmonella* Typhi and Paratyphi were susceptible to first line antimicrobial agents, a finding which is in contrast to data from other regional studies.(9,11) On the other hand, the number of serovar Typhi isolates with reduced susceptibility to fluoroquinolones was high, a problem also noted in other Asian countries.(23–27)

The majority of the culture confirmed cases of typhoid were given a clinical diagnosis of pneumonia. This could be partially attributed to the focus on pneumonia in this study. However, others have also reported an atypical presentation of typhoid in young children, including pneumonia.(2–4,6,8)

Our study has some limitations. First, this study was not designed to measure typhoid fever or disease impact. The surveillance program was designed to identify and capture invasive pneumococcal disease. Second, blood culture sensitivity for detection of *Salmonella* Typhi and Paratyphi is relatively low, estimated at 25%--50%.(28) Third, the prevalence of previous antimicrobial use of approximately 10% was self reported, and we were unable to validate these reports. If antibiotic use is actually higher than reported, the number of *Salmonella* Typhi and Paratyphi isolates recovered from peripheral blood could have been reduced. Fourth, only a third of all febrile episodes could be cultured. Ours is thus a conservative estimate of incidence.

Our study reports high rates of typhoid fever in per-urban settings. Incidence rates in urban squatter settlements may be even higher due to increased population density. There is also evidence of typhoid fever being prevalent in rural areas of highly endemic countries. Outbreaks of *Salmonella* Typhi have been reported in rural communities of Thailand and India.(29–31) In Vietnam, a population-based surveillance study conducted in three rural communities detected typhoid attack rate of 358 per 100,000 person per year in children 2–4 years old.(12)

Enough evidence exists for the burden of typhoid in very young children living in urban and peri-urban areas of highly endemic countries to make the case for the introduction of the newer typhoid vaccines, effective in children younger than 1 year of age, in routine Expanded Programme of Immunizations (EPI) schedules. More information from rural areas will be needed for countries to make informed policy decisions about whether to vaccinate selected populations at higher risk, or the entire birth cohort of the country.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Incidence of *Salmonella* Typhi bacteremia among children under 5 years older

Age specific incidence	N	Incidence* (95% CI)
< 12 months	4	506.4 (160.9–1,222.0)
12–23 months	3	379.8 (96.6–1,034.0)
24–59 months	9	379.8 (185.2–697.0)
Overall (< 59 months)	16	405.1 (239.8–643.9)

* Incidence is calculated per 100,000 child-years

Table 2

Clinical characteristics of culture confirmed typhoid cases, other bacteremia isolates and non-bacteremia cases detected in active surveillance during a 15-month period in peri-urban Karachi

	Typhoid bacteremia (n = 16)	Other bacteremia (n = 20)	No bacteremia (n = 1352)	p-value
Age in months [a]	24(10–56)	13.5(1–55)	18(1–59)	0.18
Temp in °C [a]	38.5(37.4–40.5)	38.1(36.5–39.9)	38(35.6–41.0)	0.009*
Temp ≥ 39 °C [b]	6(37.5%)	6(30%)	206(15.2%)	0.01
Duration of fever in days [a]	2(1–7)	3(0–7)	3(0–34)	0.89
Weight (kg) [a]	9.7(5–14)	7.3(2.5–13.4)	8.3(2.1–18)	0.18
Weight-for-age [a]	−1.98(−5.2—0.12)	−2.98(−4.9–(−0.84))	−2.02(−5.8—4.9)	0.66
Wasting [b]				
Moderate(WHZ −2 to −3)	4(25%)	6(33.3%)	331(26.7%)	0.81
Severe(WHZ <−3)	4(25%)	5(27.8%)	296(33.9%)	0.92
Respiratory rate [a]	45(40–65)	49(38–90)	48(20–105)	0.54
Heart rate [a]	132(90–168)	132(90–160)	124(88–160)	0.39
Danger signs: Lethargy [b]	---	1(5%)	6(0.4%)	0.02
Danger signs: Unable to drink [b]	---	1(5%)	6(0.4%)	0.02
Danger signs: Cyanosis [b]	--	--	2(0.1%)	
Danger signs: Convulsions [b]	--	--	2(0.1%)	
Danger signs: Chest indrawing [b]	--	2(10%)	29(2.1%)	0.20
Tonsillitis/Pharyngitis/Sinusitis[b]	2(12.5%)	---	61(4.5%)	0.19
Diarrhea [b]	1(6.3%)	2(10%)	78(5.8%)	0.73
Previous antibiotic therapy [b]	2(12.5%)	1(5.0%)	45(3.3%)	0.13
Status at 1 week follow-up [b]				
Improved/Well #	8(50.0%)	14(73.7%)	1075(81.4%)	0.005
Died	--	3(15%)	1(0.07%)	<0.001

[a] Median(range)

[b] Count(%)

* Typhoid bacteremia is different from no bacteremia (p-value 0.004)

8, 3, and 276 children were still sick at 1-week follow-up in the 3 groups of children, respectively.