A community-based surveillance to estimate the burden of typhoid fever in Bangladeshi children as a prelude to a typhoid vaccine trial

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Collaborating Institutions:
Johns Hopkins Bloomberg School of Public Health, Baltimore, USA  
ICDDR,B, Dhaka, Bangladesh  
Dhaka Shishu Hospital, Dhaka, Bangladesh  
Kumudini Hospital, Mirzapur, Bangladesh

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Background:

Despite significant decline in the incidence of typhoid fever with provision of safe drinking water and good sewage systems in Europe and North America over the decades, the disease is still considered one of the major public health threats on a global scale. It has been estimated that the global burden of typhoid fever is 21.6 million illnesses and 216,000 deaths annually [1]. Findings from most recent comparative analysis of the disease burden of typhoid fever across Asia are consistent with the geographical patterns of typhoid, with higher incidences in India, Pakistan, Bangladesh and Indonesia [2]. Recent hospital and population-based data from Bangladesh also support the notion that the infection rate is indeed high among south-east Asian communities [3,4]. With the advent of new vaccines for typhoid fever [5], there is a need for timely and accurate assessment of disease burden in typhoid endemic countries to guide policymakers to take decisions to incorporate typhoid vaccines in public health practice [6,7]. Indeed, the actual burden of the disease is poorly defined in most endemic countries. Reliable population-based data are sparse; studies that contribute to the new estimate are largely conducted in urban settings with higher burden of disease, and many of those have included placebo groups from typhoid vaccine trials [2,4,8-11]. The widespread prevalence of multidrug-resistant typhoid fever [12] also influences the true impact of disease in these regions.

Conventionally, typhoid fever has been reported as infrequent in children of pre-school age (<5 years). However, several recent regional reports indicate that typhoid fever in pre-school years may be under-appreciated and children of this age group may have among the highest infection rates [3,4,11,13]. Since the newer vaccines, particularly the Vi conjugate vaccine has shown promises in children [5,8], critical information on typhoid fever is needed to devise effective strategies to protect young children and also to set the optimum age of immunization.

We conducted this prospective, population-based surveillance in a rural community of Bangladesh to provide an assessment of the burden of typhoid fever and antimicrobial resistance pattern of *Salmonella* Typhi strains in children aged less than 5 years.

Methods:

The surveillance was set-up in Mirzapur, a rural sub-district of Bangladesh, located about 60 km north of the capital, Dhaka. Mirzapur has an estimated population of 400,000, distributed in 13 unions and 219 villages. The annual birth cohort is estimated to be about 11,000. The area is served by a 750-bed non-profit private hospital (Kumudini Hospital), and a 31-bed government Upazilla (sub-district) Health Complex, each with laboratory and X-ray facilities.

Typhoid fever surveillance was conducted in Mirzapur utilizing the general population and research infrastructure of an ongoing pneumococcal disease surveillance in under-5 children. Six of the 13 unions of Mirzapur were previously selected randomly for a neonatal health intervention study, and the same 6 unions also formed the population for this surveillance. The
study population was further divided into 72 clusters with about 2000 population (175-190 under-5 children) each. All children of 1-47 months of age residing in those clusters were enrolled in the surveillance. These enrolled children were planned to be followed-up till attainment of 59 months of age or the end of the study. This was an open cohort, with children born or in-migrating also being enrolled on a continuing basis. Informed consents were obtained from the parents at the enrollment of their children in the surveillance.

A trained village health worker (VHW) was assigned to each of the 72 clusters for active surveillance of enrolled children. The VHWs visited every household with an enrolled under-5 child once in a week and asked the mother (or caretaker) of the child whether the child was experiencing fever at the time of the visit. If the mother reported that the child had fever then the VHW recorded axillary temperature for three minutes and referred the child to Kumudini hospital if body temperature is recorded 38 C or higher irrespective of the duration of fever. All children from the surveillance area seeking care for illness from Kumudini hospital, including those referred by the VHWs, were included in this analysis. These children were examined by a study physician and a blood sample was collected for culture from patients with an axillary temperature of ≥38 C recorded in the hospital. Clinical information was obtained using standardized questionnaires.

We confirmed typhoid fever if we isolated Salmonella Typhi from blood during a febrile episode. Conventional blood culture bottles with trypticase soy broth supplemented with 0.025% SPS and 1% isovitalex were inoculated with 2-3 ml of blood, incubated at 37 C and subcultured on days 1, 3 and 5. Isolates were identified and tested for susceptibility to antibiotics following the standard procedures [3,14,15].

The surveillance sample size was based on data from India [11], assuming that the expected incidence of typhoid fever will be 25/1,000 child-years observed. Aiming for a precision of +/-33% and assuming 15% drop out or missing information, we needed to assemble 5,265 children aged 1-47 months old and prospectively follow them for a period of one year.

The study started from November 2005. Between Nov 2005 and March 2006, the surveillance was not fully in place resulting in blood cultures not being done for all eligible cases. This was largely a result of existing clinical practices at the Kumudini Hospital and because the surveillance was nested within an ongoing pneumococcal surveillance by ICDDR,B. From April 2006, changes were made in surveillance procedures, particularly by introducing blood cultures from possible enteric fever cases seen at the emergency. We propose that data between Nov 2005 and March 2006 be discarded. We are thus presenting the findings from the surveillance starting from April 2006.

Statistical analysis was performed using Stata version 8.0. A child started contributing to person time as soon as it gave consent. For calculating incidence rates, the number of isolates was divided by the child-years of observation.

The protocol was approved by the Ethical Review Committee of ICDDR,B.
Results:

Between April 2006 and October 2007, a total of 4,127 children contributed an estimated 5,165 child-years of observation. Village health workers assessed 9,472 episodes of reported illnesses due to fever in these children and referred 4,381 (46%) episodes to Kumudini Hospital. At the hospital, there were 4,455 sick-child visits at the outpatient and emergency departments from among the children enrolled in the surveillance. Among them, 4,207 were referred by village health workers and 248 children came to the hospital by themselves without any referral. Study physicians recorded axillary temperature of ≥38°C in 2,077 cases among all children reported to the hospital from our rural surveillance area.

A total of 1,922 (93%) blood samples were obtained from these febrile children at outpatient, emergency and inpatient departments. We recovered 21 organisms from blood (isolation rate: 1.09%). Blood culture grew *Salmonella Typhi* in 12 cases. More than half of the isolates were *Salmonella Typhi* (57%) and about a fourth were *Streptococcus pneumoniae* (24%). *Haemophilus influenzae* type b (Hib) accounted for 10% of the isolates. *Salmonella Typhi* infection was found entirely among the 1-4 years old children, particularly among >24 months. No cases was found among infants (<12 months of age).

Overall, typhoid fever incidence was 2.3 episodes/1,000 child-years of observation among pre-school children. We observed a highest incidence rate among 36-47 month old children at 4.7 per 1,000 child-years of follow-up.

Of the total culture-positive *S. Typhi* cases in the cohort, in vitro antimicrobial susceptibility testing showed a high prevalence of resistance to first line drugs, with 5 each to amoxicillin, chloramphenicol, and nalidixic acid (not the same children); ciprofloxacin resistance was found in isolate from one child. All the isolates were sensitive to ceftriaxone.
References:


