Indian J Med Res 140, August 2014, pp 310-313

Correspondence

Trends of typhoid fever seropositivity over ten years in north India

Sir,

Typhoid fever is a noted cause of morbidity worldwide with an estimated 21.7 million cases, the bulk of the burden being borne by India, South and Central America and subSaharan Africa, all with growing population and poor sanitary conditions[1,2]. There is a dearth of available epidemiological data to project the actual situation in India, though a few hospital and large population based studies have demonstrated substantial changes in the incidence of typhoid fever[3-5].

In this context, over 100 years since its introduction, the Widal test has been and is still being widely used for the diagnosis of typhoid fever, simply owing to the fact that no other serodiagnostic test of sufficient sensitivity and specificity along with cost-effectiveness has been developed especially in typhoid endemic regions[6]. Several commercial rapid diagnostic tests namely Typhidot and Tubex have also shown sensitivity and specificity of 70 and 80 per cent, respectively in most of the surveillance studies worldwide, apart from being costlier than the agglutination tests[7]. In actual practice, most of the infections by *Salmonella enterica* serotype Typhi are diagnosed clinically without proper laboratory evidence and consequently treated presumptively with antibiotics[8]. The real concern is that though the gold standard technique of culture isolation of *Salmonella* Typhi (*S*. Typhi) provides a definitive diagnosis in 73-97 per cent cases prior to medications, excessive antibiotic use has reduced this isolation rate to 40-60 per cent[9]. At the same time, as against developed countries with low prevalence of typhoid where Widal test can be abandoned, developing endemic regions where culture facilities are far from reality, the slide and tube agglutination test against the O and H antigens of *S*. Typhi is perhaps the only laboratory method despite controversies regarding its use in diagnosis of typhoid fever. In the present study, the trend of antibody titres to O and H antigens of *S*. Typhi in patients of different age groups with typhoid fever from north India was analyzed over a period of ten years (1998-2002 and 2007-2011).

All consecutive patients attending the outpatient and inpatient services of the various departments of Institute of Medical Sciences, a tertiary care hospital, at Varanasi, north India, with chief complaint of fever during the two study periods, were screened by semiquantitative slide agglutination with *S. enterica* serotype Typhi O and H antigens [prepared in-house from the standard strains *S.*Typhi 901 obtained from Microbial Type Culture Collection (MTCC), Chandigarh]. Only those cases were included in the study who presented with fever for at least one week duration and without any diagnosis made for the cause of fever. Patients with underlying respiratory infections, malaria, dengue, hepatitis, haematological or other systemic disorders were excluded. History of previous attacks of typhoid fever could not be elucidated from the cases due to their poor awareness status and insufficient medical records. However, history of previous typhoid vaccination was collected from the seropositive cases. Blood samples (5 ml) collected from these patients were received in the department of microbiology and serum was separated. Positive serum samples showing visible agglutination were confirmed by serial dilutions as per standard method[10]. Titres of $\geq$ 160 for either O or H or both were considered as significant titres[11]. The seropositive titres were analyzed and compared retrospectively by Student's paired t test over two five year periods (January 1998-December 2002 and January 2007-December 2011) using SPSS version 15 (SPSS Inc., Chicago, USA), based on prevalence of seropositive titres in different age groups (0-$\leq$15 and >15- $\leq$30 yr) and seasonality.

Although an external quality control was not used, errors in performance of the test were minimized due to repeated internal quality control tests and inclusion of those results which were performed by the same laboratory technician under similar conditions in the entire study. The study protocol was approved by the Institute's ethical committee.

A total of 13148 serum samples were tested seropositive of the total 22725 sample tested. None of the cases were previously vaccinated against typhoid fever. There was a significant increase (P<0.05) in the overall seropositivity rates over the years in the study period from 29.98 ± 11.16 per cent in 1998-2002 to 65.54 ± 6.22 per cent in 2007-2011 (Fig. 1). Seropositivity rates in age group 0- ≤15 yr increased from 32.66 ± 13.79 to 50.04 ± 9.61 per cent and from 28.42 ± 13.38 to 62.08 ± 4.82 per cent in the >15- ≤30 yr age group. Total number of samples tested in the >30 yr age group was small and, therefore, not included in the study. There was a shift in predominance of seropositivity in the early adult age group (>15- ≤30 yr), from the paediatric age group (0- ≤15yr).

Despite an increase in seropositivity rates, there was a decline in the annual increase rate of seropositivity in both the age groups over the years (Fig. 2). This decline was consistent in the second half of the study period (2007-2011) as compared to the first (1998-2002). A seasonal variation in the trend of seropositive titres with two peaks corresponding to the months of February- April and July- October was seen in both the study periods (Fig. 3).

Typhoid fever continues to be a public health problem especially in the tropics. The present study

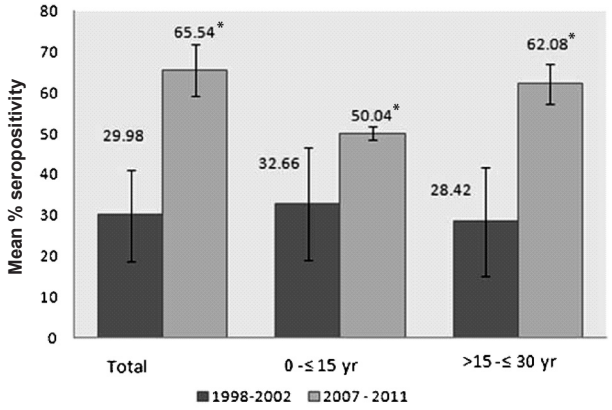

Fig. 1. Prevalence of seropositive titres in patients with different age groups. *P<0.05 compared to 1998-2002 period.

showed a significant rise in seropositivity over the study period. Other than typhoid fever in many situations the increase in seropositivity rates can be explained by rising prevalence of non typhoidal *Salmonella* (NTS) infections in the community[3,9]. The prior sensitization due to continuous exposure in an endemic set up as a cause of rise in seropositivity has been considered to justify the testing of a single serum for typhoid fever, especially in situations where paired serum sample is unavailable and initiation of treatment is urgently required[12]. Prevalence of non typhoidal salmonellosis has been on rise especially with increasing HIV infections, although such problems have not yet been documented in Indian studies[3]. A study from Thailand has shown a different scenario[13].

Inspite of rise in seropositivity rates, the study demonstrated a decline in the annual increase rate of seropositivity over the years. This could have been due to the typhoid vaccination approach. Controlled trials have proven the efficacy of Vi antigen vaccine especially in the under 5 yr age group, which is highly vulnerable to typhoid fever in the endemic regions. Along with this, Vi vaccination has also been seen to provide herd protection in the community[14]. Proportion of paratyphoid fever mainly due to Paratyphi A infections has been on rise[15]. This has been explained by the use of TA vaccine instead of a bivalent one thus providing monovalent protection against *S*.Typhi at the cost of *S*.Paratyphi A infections[16]. Studies have shown that with economic development and improved sanitation measures directed at control of other waterborne diseases have effectively reduced the incidence of typhoid cases in South America[17]. The commonest age group susceptible to typhoid fever is the 5-19 yr age group, with gradual decline due to probable acquisition of immunity from previous infections or exposure to subclinical infections[16]. In this study, a shift in predominance of seropositivity was seen. Majority of the seropositive cases belonged to the early adult (>15- ≤30 yr) age group rather than the <15 yr age group in the second five year interval. Similar findings have been reported earlier. Hence, the fact that typhoid fever is primarily a disease of childhood and early adolescents[17] may not hold true against a background of its changing epidemiology due to childhood vaccination policies.

Similar to most of the tropical diseases of infectious origin, seasonal pattern in distribution of seropositive titres were noted in our study, with maximum cases during early summer and monsoons.

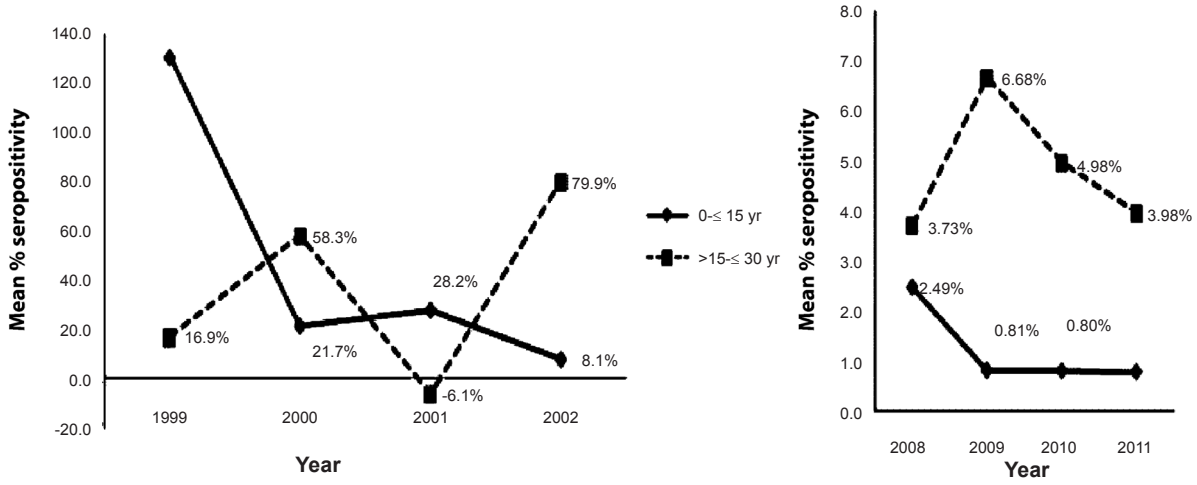

Fig. 2. Per cent annual change in seropositivity in the two five year periods.

Studies from other parts of the country have reported increased cases of typhoid fever during these periods of the year corresponding to increased contamination of water[3,16,18].

One of the limitations of this study was that we could not include blood culture technique for all the samples and therefore, could only predict the epidemiological trends rather than the exact incidence of the disease. Further, a prospective approach rather than a retrospective one could have yielded a better insight. In conclusion, the present study revealed the changing trends of typhoid fever as obtained by an inexpensive accessible, easily performed screening test During a 10 yr period in north India. The findings indicate towards a need to review the vaccination policy for typhoid fever in an endemic set up.

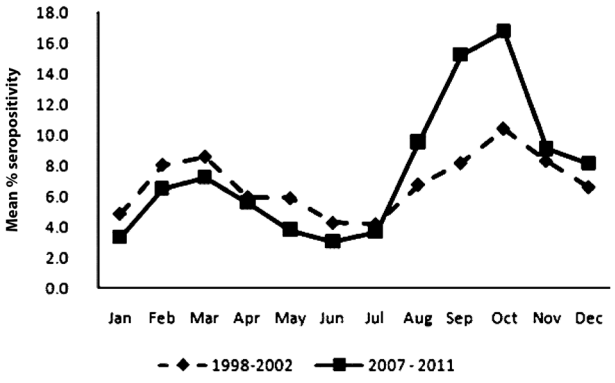

Fig. 3. Seasonal variation in seropositivity rates during the study periods.

Acknowledgment

Authors thank Dr T.B. Singh, Department of Community Medicine, IMS, BHU, Varanasi, for providing guidance for statistical analysis.

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