A study of typhoid fever in five Asian countries: disease burden and implications for controls

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Introduction

Typhoid fever is a systemic infection caused by Salmonella enterica serotype Typhi (S. typhi). The disease remains an important public health problem in developing countries. In 2000, it was estimated that over 2.16 million episodes of typhoid occurred worldwide, resulting in 216 000 deaths, and that more than 90% of this morbidity and mortality occurred in Asia. Despite improved water quality and sanitation constitute ultimate solutions to this problem, vaccination in high-risk areas is a potential control strategy recommended by WHO for the short-to-intermediate term. 6 Two safe and efficacious typhoid vaccines, the injectable Vi polysaccharide and the oral Ty21a, have been licensed; and new, improved candidate vaccines are currently being tested. 7 8 However, typhoid vaccination has not been implemented as a routine public health measure in most typhoid-endemic countries despite the low price of the vaccine (Vi polysaccharide costs ca. US$ 0.50 per dose) and the high cost of treating the disease. 6 Policy-makers in several developing countries have indicated that updated data on the incidence of typhoid in their countries are essential before they introduce the vaccines into programmes. 9 Indeed, population-based estimates of blood culture-confirmed typhoid are scarce. In Asia, disease burden estimates have usually relied on routinely reported, clinically diagnosed cases of typhoid fever compiled by governments or hospitals, usually with uncertain denominators. Clinical diagnosis of typhoid is not specific

Objective

To inform policy-makers about introduction of preventive interventions against typhoid, including vaccination.

Methods

A population-based prospective surveillance design was used. Study sites where typhoid was considered a problem by local authorities were established in China, India, Indonesia, Pakistan and Viet Nam. Standardized clinical, laboratory, and surveillance methods were used to investigate cases of fever of ≧ 3 days’ duration for a one-year period. A total of 441 435 persons were under surveillance, 159 856 of whom were aged 5–15 years.

Findings

A total of 21 874 episodes of fever were detected. Salmonella typhi was isolated from 475 (2%) blood cultures, 57% (273/475) of which were from 5–15 year-olds. The annual typhoid incidence (per 100 000 person years) among this age group varied from 24.2 and 29.3 in sites in Viet Nam and China, respectively, to 180.3 in the site in Indonesia; and to 412.9 and 493.5 in sites in Pakistan and India, respectively. Altogether, 23% (96/413) of isolates were multidrug resistant (chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole).

Conclusion

The incidence of typhoid varied substantially between sites, being high in India and Pakistan, intermediate in Indonesia, and low in China and Viet Nam. These findings highlight the considerable, but geographically heterogeneous, burden of typhoid fever in endemic areas of Asia, and underscore the importance of evidence on disease burden in making policy decisions about interventions to control this disease.

because the presenting signs and symptoms are diverse and similar to those of other common febrile illnesses, such as malaria and dengue fever. A specific diagnosis of typhoid requires access to a competent laboratory that can process blood cultures; such laboratories are uncommon in resource-poor regions. Population-based studies of the incidence of culture-confirmed typhoid have therefore usually come from the control arms of typhoid vaccine trials.3,5,8–14

We conducted prospective population-based surveillance in five Asian countries using standardized surveillance techniques, as well as standardized clinical and microbiological methods, to provide an updated assessment of the burden of typhoid in Asia. The studies were also performed in preparation for a series of effectiveness trials of Vi polysaccharide vaccine.4,15 In this paper, we present the disease burden estimates from a 12-month pre-vaccination surveillance period in each site in these five countries.

**Methods**

**Study sites**

Sites in five Asian countries, which are considered to be endemic for typhoid; China, India, Indonesia, Pakistan, and Viet Nam, participated in the programme. As a result of discussions with local collaborators, we selected study populations that satisfied the following criteria: a high perceived burden of typhoid fever, absence of control programmes against the disease, willingness of the community to participate, and feasibility of a vaccination trial (Fig. 1). With the exception of the site in Pakistan, no reliable estimates of the incidence of blood-culture proven typhoid were available.16 Prior to the onset of surveillance, a census was conducted at each site to enumerate the entire population. Each household and each individual resident in the study areas were assigned unique study numbers and recorded in the project data management system.

The study site in China, Hechi, in Guangxi Zhuang Autonomous Region, included urban (Jin-Cheng Jiang) and rural (Dong Jiang) townships: 112,889 residents were registered in the baseline census in 2001. In India, wards 29 and 30 of Kolkata, West Bengal, which consist of legally recognized urban slums, were selected as the study site (population, 56,946 in the baseline census in 2003). Two impoverished municipal districts in North Jakarta, Tanjung Priok and Koja, constituted the study site in Indonesia: 160,261 persons were registered in the baseline census in 2002. For Pakistan, surveillance was conducted in three squatter settlements in Karachi (Hijrat Colony, Sultanaabad, and Bilal Colony): a total of 101,937 persons were recorded in the baseline censuses in 2001 for Hijrat Colony and Sultanaabad and in 2003 for Bilal Colony. The central coastal city of Hue was selected as the study site in Viet Nam: there were 281,781 persons in the baseline census in 2002.
Table 1. Characteristics and incidence of typhoid fever from the study sites

<table>
<thead>
<tr>
<th>Site</th>
<th>Hechi, China</th>
<th>Kolkata, India</th>
<th>North Jakarta, Indonesia</th>
<th>Karachi, Pakistan</th>
<th>Hue, Viet Nam</th>
<th>Total</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site setting</td>
<td>Urban / rural</td>
<td>Urban slums</td>
<td>Urban slums</td>
<td>Urban</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surveillance target population (age in years)</td>
<td>5–60</td>
<td>All ages</td>
<td>All ages</td>
<td>2–15</td>
<td>5–18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Target population (persons) | 97,928 | 56,946 | 160,261 | 41,845 | 84,455 | 441,435 |         |

<table>
<thead>
<tr>
<th>By age</th>
<th>0–1 years</th>
<th>2–4 years</th>
<th>5–15 years</th>
<th>≥ 16 years</th>
<th>Mean age of target population (years)</th>
<th>&lt; 0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile episodes analysed</td>
<td>1,215</td>
<td>4,378</td>
<td>4,867</td>
<td>7,736</td>
<td>3,678</td>
<td>21,874</td>
</tr>
<tr>
<td>By age</td>
<td>0–1 years</td>
<td>2–4 years</td>
<td>5–15 years</td>
<td>≥ 16 years</td>
<td>Mean age of febrile cases (years)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Incidence of febrile episode (per 1000/year)</td>
<td>12.4</td>
<td>76.9</td>
<td>30.4</td>
<td>184.9</td>
<td>43.6</td>
<td>49.6</td>
</tr>
<tr>
<td>By age</td>
<td>0–1 years</td>
<td>2–4 years</td>
<td>5–15 years</td>
<td>≥ 16 years</td>
<td>Mean age of febrile episodes with blood cultures taken (years)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Febrile episodes with blood culture taken</td>
<td>1,215</td>
<td>4,342</td>
<td>3,954</td>
<td>7,415</td>
<td>3,611</td>
<td>20,537</td>
</tr>
<tr>
<td>By age</td>
<td>0–1 years</td>
<td>2–4 years</td>
<td>5–15 years</td>
<td>≥ 16 years</td>
<td>Mean age of typhoid cases (years)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Typhoid cases</td>
<td>15</td>
<td>122</td>
<td>131</td>
<td>189</td>
<td>18</td>
<td>475</td>
</tr>
<tr>
<td>By age</td>
<td>0–1 years</td>
<td>2–4 years</td>
<td>5–15 years</td>
<td>≥ 16 years</td>
<td>Mean age of typhoid cases (years)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Typhoid Incidence (per 100,000/year)</td>
<td>15.3</td>
<td>214.2</td>
<td>81.7</td>
<td>451.7</td>
<td>21.3</td>
<td>107.6</td>
</tr>
<tr>
<td>By age</td>
<td>0–1 years</td>
<td>2–4 years</td>
<td>5–15 years</td>
<td>≥ 16 years</td>
<td>Mean age of typhoid cases (years)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
Typhoid fever burden in Asia

Research

Table 1, cont.

<table>
<thead>
<tr>
<th>Site</th>
<th>Hechi, China</th>
<th>Kolkata, India</th>
<th>North Jakarta, Indonesia</th>
<th>Karachi, Pakistan</th>
<th>Hue, Viet Nam</th>
<th>Total</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typhoid prevalence (per 1000 febrile episodes with blood cultures taken)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1 years</td>
<td>NA</td>
<td>6.9</td>
<td>0.0</td>
<td>NA</td>
<td>NA</td>
<td>1.8</td>
<td>0.0986</td>
</tr>
<tr>
<td>2–4 years</td>
<td>NA</td>
<td>29.1</td>
<td>35.3</td>
<td>25.3</td>
<td>NA</td>
<td>27.0</td>
<td>0.5432</td>
</tr>
<tr>
<td>5–15 years</td>
<td>12.8</td>
<td>52.5</td>
<td>61.4</td>
<td>25.6</td>
<td>4.7</td>
<td>24.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>≥ 16 years</td>
<td>12.1</td>
<td>18.1</td>
<td>26.7</td>
<td>NA</td>
<td>9.5</td>
<td>20.2</td>
<td>0.0243</td>
</tr>
</tbody>
</table>

NA, not available.

* P-value for the five site comparison, estimated with 4 degrees of freedom.

† Surveillance conducted from 1 Aug 2002 to 31 Jul 2003 in Hijrat and Sultanabad, and from 1 Aug 2003 to 31 Jul 2004 in Bilal Colony.

‡ Baseline censuses were conducted in Hijrat and Sultanabad in 2001, and in Bilal Colony in 2003.

§ For Hue, Viet Nam, the age is up to 18 years; for Hechi, China, the age is up to 60 years.

Surveillance

The age groups under surveillance were selected as those judged by local officials to be the most appropriate targets for typhoid vaccination: 5–60 year-olds in the Chinese site; all ages in the Indian and Indonesian sites; 2–15 year-olds in the Pakistani site; and school-aged children and adolescents (5–18 years) in the Vietnamese site (Table 1).

Patients residing in the catchment areas and presenting to a treatment facility with fever lasting ≥ 3 days were eligible to participate in the study. The surveillance included individuals treated as outpatients as well as inpatients. Surveillance included both systematic collection of clinical information, recorded on standardized forms, and collection of a single blood culture by venepuncture. Approximately 5–8 ml of blood was collected from adults and used to inoculate Bactec Plus Aerobic culture bottles (Becton Dickinson, New Jersey, United States of America); for children, about 3–5 ml of blood was inoculated into Bactec Peds Plus culture bottles.

In the Chinese and Vietnamese sites, all health-care facilities serving as clinics and referral points for the patients. In the Indian and Pakistani sites, in addition to passive surveillance, each household was visited by community health workers on a monthly (India) or weekly (Pakistan) basis to encourage febrile patients to attend participating health-care facilities; also, private practitioners were encouraged to refer patients for free typhoid diagnosis and treatment at these facilities, since the surveillance sites were considered insufficient to capture all cases from the communities.17–19

Microbiology

Laboratories for microbiological evaluations of blood cultures were established at each site. Blood culture bottles were transported to the laboratory on the day of blood collection, incubated, and observed for growth. If bacterial growth was confirmed, the contents of the bottle were subcultured on MacConkey agar plates. In the absence of visible growth, the contents of the bottle were subcultured on MacConkey agar on days 1, 2, 4 and 7. The bottles were incubated for a minimum of 10 days before being discarded. Lactose nonfermenting colonies were screened using Kligler’s iron agar. Colonies indicative of S. typhi (acid butt, alkaline slant, trace amount of hydrogen sulfide) were tested for slide agglutination with Vi antiserum, Salmonella D1 group-specific antiserum, Salmonella O factor 9 antiserum, and Salmonella H factor d antiserum as appropriate (Becton Dickinson Laboratories, New Jersey, USA).20 S. typhi isolates were sent to a reference laboratory (Wellcome Trust Research Unit, Ho Chi Minh City, Viet Nam) for confirmation. Antimicrobial susceptibility testing was performed using the Kirby-Bauer disc diffusion method on Mueller-Hinton agar with standard antimicrobial discs (Becton Dickinson Laboratories, New Jersey, USA). Resistance to six antimicrobial agents [chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole (TMP-SMX), nalidixic acid, ciprofloxacin, and ceftriaxone] was assessed at all sites except Pakistan, where ciprofloxacin was tested by a minimum inhibitory concentration method if nalidixic acid resistance was observed with the disc diffusion method.

Study definitions, data management and analysis

A patient from the target population presenting to a participating treatment centre with a history of fever lasting ≥ 3 days was considered as having a febrile episode. A typhoid episode was defined as an episode of febrile illness during which S. typhi was isolated from a blood culture. Census and surveillance data were double-entered into a custom data entry program (FoxPro, Microsoft, Washington, USA) with error and consistency check programs. Typhoid patients and not “episodes” were considered in the analysis; thus, each individual could be included only once in the numerator for calculation of incidence. We assumed that each person residing in the study area at the time of the census contributed 12 months to the denominator. Incidence per 100 000 person-years was calculated using age-specific denominators from the baseline census. The numerator was the number of age-specific disease episodes. We calculated 95% confidence intervals for incidence using the Wilson
score method. Categorical variables were compared using the \( \chi^2 \) test and dimensional variables were compared using analysis of variance. Typhoid rates by site were compared using Poisson regression models or Barnard’s test. Pairwise comparisons of countries or of groups of countries for specific variables were undertaken only after first confirming that there was statistically significant heterogeneity among all five sites with respect to the variable under analysis, using an appropriate test with four degrees of freedom. The correlation between typhoid incidence and the mean age was analysed using Spearman’s rank test. A value of \( P < 0.05 \) (two-tailed) was considered statistically significant. Stata/SE 8.0 (Stata Corporation, Texas, USA) was used for the analysis.

**Ethical clearance**

The local ethics committees of each participating site, the WHO Secretariat Committee on Research Involving Human Subjects, and the International Vaccine Institute’s Institutional Review Board approved the protocols. Verbal informed consent was obtained before participants were interviewed or blood samples collected from them.

**Results**

A total of 441,435 persons in the targeted age groups were under surveillance for one year (Table 1), during which 21,874 fever episodes lasting ≥ 3 days were detected and 475 persons had blood culture-confirmed *S. typhi*. The overall incidence of fever lasting ≥ 3 days for the five sites combined was 49.6 per 1000 person-years, ranging from 12.4 to 184.9 for the sites in China and Pakistan, respectively. The incidence of typhoid ranged from 15.3 cases per 100,000 person-years among those aged 5–60 years in China to 451.7 cases per 100,000 person-years among 2–15 year-olds in Pakistan. Overall, the *S. typhi* isolation rate (prevalence) was 23.1% per 1000 cultured febrile episodes and ranged from 5.0 (Vietnamese site) to 33.1 per 1000 (Indonesian site).

Because the age groups under study varied by site, we compared the incidence in 5–15 year-olds, as this age group was surveyed in each site (Table 1). Among the 159,856 such persons under surveillance in the five sites, 273 typhoid cases were detected. The overall incidence was 170.8 cases per 100,000 person-years, ranging from 24.2 to 493.5 for the sites in Viet Nam and India, respectively (\( P < 0.0001 \) for the overall difference of incidence among the five sites). The rates were significantly higher (\( P < 0.0001 \)) in the south Asian sites (Pakistan and India) than in the south-east and north-east Asian sites (Viet Nam, Indonesia and China). Within this age group, the mean age at onset of typhoid was 8.5 years for the site in Pakistan, 10.0 years in India, 10.2 years in Indonesia, 10.5 years in Viet Nam and 12.0 years in China (\( P < 0.0001 \) for differences among the five sites). The mean age of onset of typhoid was significantly lower in the south Asian sites that in the south-east and north-east Asian sites (\( P = 0.003 \)) and suggested that there was an inverse correlation between typhoid incidence and the mean age of typhoid cases in the five sites (Spearman \( \rho = -0.8; P = 0.1 \); Fig. 2). The prevalence of typhoid-positive blood cultures among 5–15 year-olds was 24.7% per 1000 febrile episodes, and ranged from 4.7 to 61.4 per 1000 (\( P < 0.0001 \)). The prevalence of positive cultures was significantly (\( P < 0.0001 \)) higher in the three sites with the highest incidence (India, Indonesia, and Pakistan) than in the other two sites.

The incidence of typhoid among children aged 2–5 years was 573.2, 340.1 and 148.7 per 100,000 person-years in the sites in Pakistan, India and Indonesia, respectively, and was similar to that in school-aged children and adolescents at these sites.

A total of 42 typhoid cases required hospitalization: 6 (40% of all cases) in China, 2 (2%) in India, 26 (20%) in Indonesia, 3 (2%) in Pakistan, and 5 (28%) in Viet Nam (\( P < 0.0001 \) for overall heterogeneity of these proportions in the five sites). Altogether, 15 hospitalized cases (36% of all hospitalized cases, 5% of all cases from the age group) were in children aged 5–15 years: 2 in the sites in China, 1 in India, 7 in Indonesia, 2 in Pakistan, and 3 in Viet Nam. With the exception of the Chinese and Indonesian sites, the majority of the inpatient cases involved children aged 5–15 years. All detected cases recovered and no death due to typhoid was reported.

The antimicrobial susceptibility of *S. typhi* isolates varied between sites (Fig. 3). All *S. typhi* isolates were tested for antimicrobial susceptibility, except for those from the Pakistani site where 127 out of 189 isolates (67%) detected during the surveillance period were tested using all six susceptibility tests. Nearly 60% of these 127 isolates were resistant to chloramphenicol, ampicillin, TMP-SMX and nalidixic acid. In contrast, all isolates from sites in China and Indonesia were susceptible to all antimicrobial agents. Multidrug resistance (resistance to chloramphenicol, ampicillin and TMP-SMX) was observed in 83 (65%) isolates from the site in Pakistan, 4 (22%) from the site in India and 7 (32%) from the site in Indonesia, respectively, and was similar to that in school-aged children and adolescents at these sites.
in Viet Nam, and 9 (7%) from the site in India, but not in isolates from the Chinese or Indonesian sites ($P < 0.0001$ for overall heterogeneity of these proportions among the five sites). Nalidixic acid resistance was found in 75 (59%) isolates from the site in Pakistan, 69 (57%) from that in India, and 8 (44%) from that in Viet Nam, but from no isolates in the Chinese or Indonesian sites ($P < 0.0001$ for overall heterogeneity of these proportions among the five sites). Two isolates (1.6%) from the Indian site were resistant to ciprofloxacin.

**Discussion**

This study, the first prospective, multicentre study to compare the disease burden of typhoid fever across Asia using standardized clinical and microbiological methods and surveillance procedures, provides important contemporary information about the disease. Our results are consistent with the geographical patterns of typhoid cited in a recent review, with higher incidences in the study sites in India, Indonesia and Pakistan, and lower incidences in the sites in Viet Nam and China. Our data also indicate that, in the higher-incidence study sites, the incidence of typhoid fever in pre-school children aged 2–5 years was of the same order of magnitude as that for school-aged children aged 5–15 years. These findings are consistent with earlier work showing that, in high-incidence areas, the incidence of typhoid in pre-school children can approximate that for school-aged children.

**Potential limitations**

Although the study procedures were standardized across the five sites, recruitment strategies for patients had to be adapted to the local conditions at each site. The most notable difference was that in the Indian and Pakistani sites the surveillance was supplemented by periodic home visits to encourage the study population to seek care for fever at the study treatment centres. However, two considerations suggest that the differences in recruitment procedures do not fully explain the variations in typhoid incidences among the five sites. First, the age at onset of typhoid in children aged 5–15 years, the common age group for all sites, suggested an inverse correlation with the observed incidence of typhoid, which would be expected if the higher observed incidences corresponded to a higher force of $S. typhi$ infection. Second, in the 5–15 year age group there was a higher prevalence of $S. typhi$ in blood cultures in the three highest-risk sites (India, Indonesia and Pakistan) than in the two lowest-incidence sites (China and Viet Nam). If the variation in typhoid incidence had merely been a manifestation of more intensive surveillance, one would have expected that the higher-incidence sites would have had similar or lower prevalences than the lower-incidence sites.

In addition, the characteristics of the sites were different (urban, rural and urban slum), though they were all selected on the basis of impressions by local public health officials that they had a high incidence of typhoid. This feature adds a note of caution about the ability to generalize our findings to the countries where the sites were located. With the exception of the site in Pakistan, no site had antecedent, population-based surveillance for blood culture-proven typhoid upon which to base judgments about typhoid incidence.

Furthermore, because of our reliance upon a single blood culture for diagnoses, the observed incidence of typhoid fever was undoubtedly an underestimate. Although blood cultures remain a gold standard for diagnosis, the poor sensitivity of this method has been acknowledged.$^{22–25}$ Adding to this poor inherent sensitivity was the availability of over-the-counter antimicrobials at each site and the likely possibility that self-medication before presentation for care further reduced the sensitivity of blood cultures.

Lastly, only 127 of the 189 $S. typhi$ isolates were tested for antimicrobial sensitivity to the complete panel of six antibiotics from the site in Pakistan. However, we are unaware of any bias in the selection of these isolates for testing and the high rate of antibiotic resistance is consistent with findings from routine testing of typhoid isolates from the Aga Khan University Hospital in Karachi (Z Bhutta, unpublished data, 2005).

**Implications of our findings**

It is remarkable that, among the five sites considered by local public health officials to have appreciable burdens of typhoid, both the incidence and prevalence of blood culture-confirmed typhoid varied considerably. This geographical variability underscores the importance of determining the burden of typhoid at the country level in making decisions about vaccinating against the disease.

The high disease burden in preschool children in certain sites highlights the importance of vaccines and delivery systems that can reach this age group, as
well as older children and adolescents, in populations with a high disease burden of typhoid fever among young children. Since neither of the currently commercially available vaccines (Vi polysaccharide and Ty21a) is licensed for under-two year-olds, development of vaccines, such as Vi-protein conjugate vaccine,\textsuperscript{[26]} that can potentially be given in the expanded programme on immunization (EPI) schedule of infant immunizations is a high priority.

As with disease incidence, antimicrobial agent susceptibility patterns varied markedly among our study sites. The site in Pakistan had the most significant problem with antimicrobial agent resistance, with nearly two-thirds of the isolates being multidrug resistant. Nalidixic acid resistance, which is associated with a poorer treatment outcome for fluoroquinolone therapy,\textsuperscript{[27]} was observed in high proportions of isolates from the sites in India, Pakistan and Viet Nam. Increasing rates of antibiotic resistance may ultimately render expensive antibiotics obsolete and make it necessary to use expensive newer antibiotics, though such antibiotics may be unavailable and unaffordable to many poor populations.\textsuperscript{[28]} Antimicrobial resistance patterns may also differ within a country, and our results cannot necessarily be generalized to the entire country where our studies were conducted. Nevertheless, the observed patterns of resistance that we found may be a harbinger of increasing antimicrobial resistance, emphasizing the need to monitor patterns of resistance and to consider typhoid vaccines as disease control tools.

Information on typhoid case fatality rate is limited, especially in population-based studies.\textsuperscript{[1]} Our study did not detect any typhoid-related deaths, probably because of the early diagnosis and the prompt referral for appropriate antibiotic treatment of our patients. Though this level of medical care for typhoid is not routinely available in the developing world, the absence of typhoid mortality suggests that, in addition to disease prevention, early diagnosis and appropriate treatment can prevent typhoid mortality and possibly reduce the severity of the disease, even in areas with limited resources.

**Conclusion**

The findings that we have reported in this paper can assist in making decisions on which geographical areas to target and age groups to vaccinate in Asia against typhoid fever. Although improvements in sanitation and water systems are the ultimate solutions to the control of the disease, vaccination should be considered in the near-to-intermediate term. Recognizing the limitations in generalizing our site-specific data, we propose that our findings are consistent with the notion that countries in south Asia and possibly south-east Asia have a high burden of typhoid fever. Recent data from Bangladesh also suggest a very high burden of the disease.\textsuperscript{[29]} Moreover, decisions about vaccine use in Viet Nam, where the rate of typhoid was not high, are complicated by worrisome trends of antimicrobial resistance.\textsuperscript{[29,30]} Our findings highlight the complex geographical variation in the disease incidence, age groups affected, and level of antimicrobial resistance, all of which need to be considered in deliberations about the deployment of typhoid vaccines as tools to assist in the control of typhoid fever.

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**Résumé**

**Étude de la fièvre typhoïde dans cinq pays asiatiques : charge de morbidité et implications pour la lutte contre cette maladie**

**Objectif** Informer les décideurs à propos de l’introduction de mesures préventives contre la typhoïde, notamment la vaccination.

**Méthodes** Une étude de surveillance en population de type prospective a été menée. Des sites d’étude ont été mis en place en Chine, Inde et Indonésie, ainsi qu’au Pakistan et au Viet Nam dans les endroits où les autorités locales considéraient que la typhoïde posait problème. Des méthodes standardisées d’étude clinique, d’analyse biologique et de surveillance ont été appliquées pour investiguer sur une période de un an les cas de fièvre durant 3 jours et plus. Au total, 441 435 personnes ont été placées sous surveillance, parmi lesquelles 159 856 étaient âgées de 5 à 15 ans.

**Résultats** 21 874 épisodes fébriles ont été détectés au total. La bactérie *Salmonella typhi* a été isolée sur 475 (2,7 %) cultures sanguines, parmi lesquelles 57 % (273/475) provenaient d’enfants de 5 à 15 ans. L’incidence annuelle de la typhoïde (pour 100 000 personnes et par an) variait dans cette tranche d’âge entre 24,2 et 29,3 pour les sites vietnamiens et chinois, atteignant jusqu’à 180,3 pour le site indonésien et se situait entre 412,9 et 493,5 pour les sites pakistaniens et indiens. Dans leur ensemble, 23 % (96/413) des isolaments étaient multirésistants (chloramphénicol, ampicilline et triméthoprime-sulfaméthoxazole).

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**Competing interests:** None declared.
Resumen

Estudio sobre la fiebre tifoidea en cinco países asiáticos: carga de morbilidad e implicaciones para el control de la enfermedad

Objetivo Informar a los planificadores de políticas sobre la introducción de intervenciones preventivas contra la fiebre tifoidea, entre ellas la vacunación.

Métodos Se realizó un estudio de vigilancia prospectiva poblacional en sitios donde las autoridades locales de China, la India, Indonesia, el Pakistan y Vietnam consideraron que la fiebre tifoidea constituía un problema. Se utilizaron métodos clínicos, de laboratorio y de vigilancia normalizados para investigar durante un año los casos de fiebre de duración > 3 días. En total, se sometió a vigilancia a 441 435 personas, de las cuales 159 856 tenían entre 5 y 15 años.

Resultados Se detectaron 21 874 episodios febriles. Se aisló *Salmonella typhi* en 475 (2%) hemocultivos, un 57% (273/475) de los cuales correspondían a pacientes de 5 a 15 años. En este grupo de edad, la incidencia anual de fiebre tifoidea (por 100 000 personas-año) fue de 24,2 en el sitio de Vietnam, 29,3 en China, 180,3 en Indonesia, 412,9 en el Pakistán, y 493,5 en la India. El 23% (96/413) de los aislados fueron multirresistentes (cloranfenicol, ampicilina y trimetoprim-sulfametoxazol).

Conclusión La incidencia de fiebre tifoidea varió considerablemente de un sitio a otro, siendo más elevada en la India y el Pakistán, intermedia en Indonesia, y baja en China y Vietnam. Estos resultados revelan que la carga de morbilidad por fiebre tifoidea es considerable, pero geográficamente heterogénea, en zonas endémicas de Asia, y subrayan lo importante que es disponer de datos científicos sobre la carga de morbilidad a la hora de tomar decisiones políticas sobre las intervenciones de control de esta enfermedad.

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References


