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

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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.

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Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

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.[1] Although 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.[2]

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.[3–5] 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.[7] Indeed, population-based estimates of blood culture-confirmed typhoid are sparse. 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

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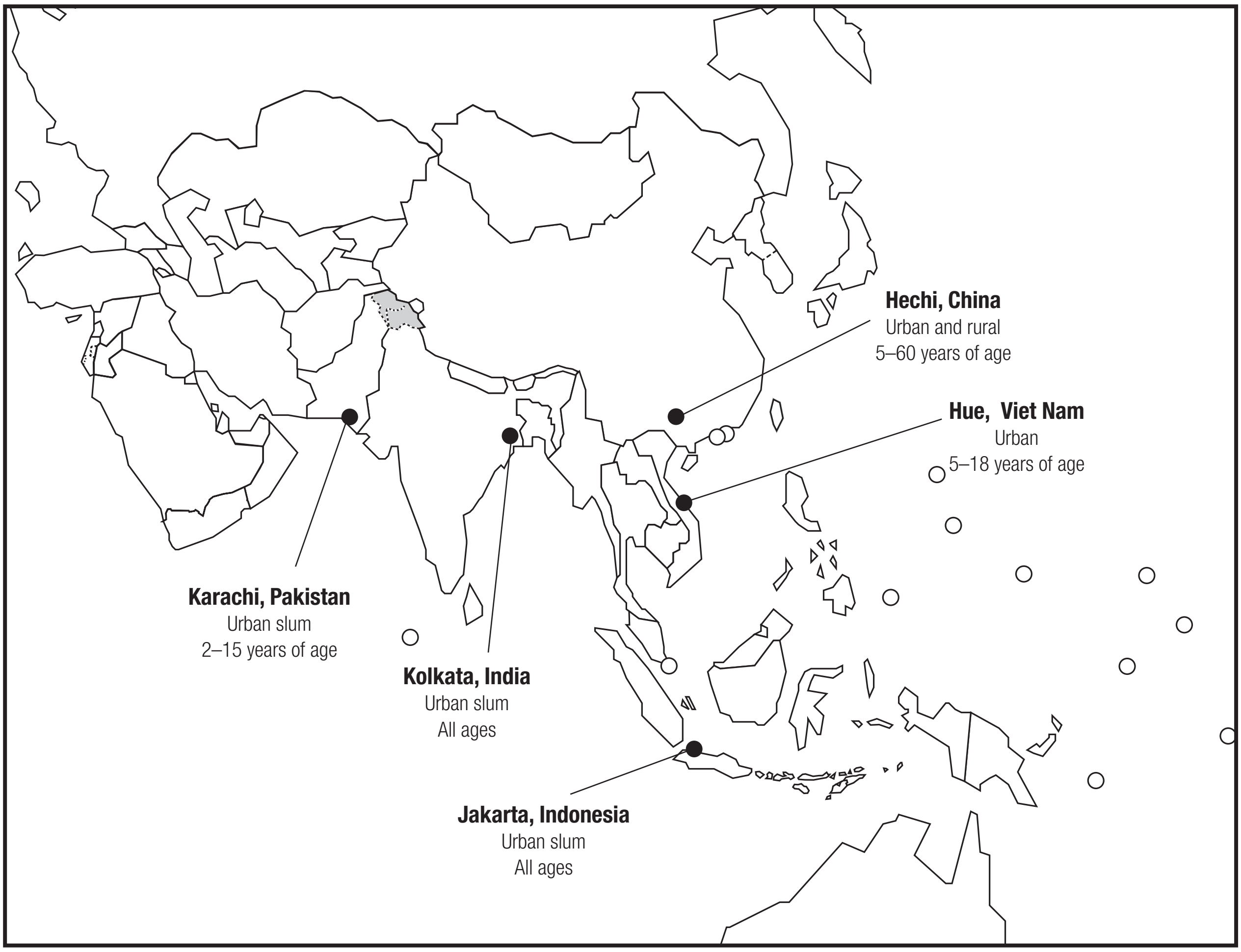
Fig. 1. **The typhoid fever surveillance study sites**



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, Sultanabad, and Bilal Colony): a total of 101 937 persons were recorded in the baseline censuses in 2001 for Hijrat Colony and Sultanabad 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**

Site	Hechi, China	Kolkata, India	North Jakarta, Indonesia	Karachi, Pakistan	Hue, Viet Nam	Total	*P*-value[a]
Site setting	Urban / rural	Urban slums	Urban slums	Urban slums	Urban	–	–
Total population from the study census [year of census]	112 889 [2001]	56 946 [2003]	160 261 [2002]	101 937 [2001, 2003][b]	281 781 [2002]	713 814	–
Surveillance period	1 Aug 2001 to 31 Jul 2002	1 Nov 2003 to 30 Oct 2004	1 Aug 2002 to 31 Jul 2003	1 Aug 2002 to 31 Jul 2004[c]	1 Jun 2002 to 30 Jun 2003	–	–
Surveillance target population (age in years)	5–60	All ages	All ages	2–15	5–18	–	–
Target population (persons)[d]	**97 928**	**56 946**	**160 261**	**41 845**	**84 455**	**441 435**	–
By age							
0–1 years	NA	1 121	3 506	NA	NA	4 627	–
2–4 years	NA	2 940	9 418	10 118	NA	22 476	–
5–15 years	17 084	12 767	32 164	31 727	66 114	159 856	–
≥ 16 years	80 844	40 118	115 173	NA	18 341	254 476	–
Mean age of target population (years)	31.2	28.6	26.7	8.5	12.1	23.4	< 0.0001
Febrile episodes analysed	**1 215**	**4 378**	**4 867**	**7 736**	**3 678**	**21 874**	–
By age							
0–1 years	NA	156	1 103	NA	NA	1 259	–
2–4 years	NA	354	509	2 455	NA	3 318	–
5–15 years	391	1 211	989	5 281	3 461	11 333	–
≥ 16 years	824	2 657	2 266	NA	217	5 964	–
Mean age of febrile cases (years)	27.4	24.9	17.3	7.4	10.4	14.7	–
Incidence of febrile episode (per 1000/year)	**12.4**	**76.9**	**30.4**	**184.9**	**43.6**	**49.6**	< 0.0001
By age							
0–1 years	NA	139.2	314.6	NA	NA	272.1	< 0.0001
2–4 years	NA	120.4	54.1	242.6	NA	147.6	< 0.0001
5–15 years	22.9	94.9	30.8	166.5	52.4	70.9	< 0.0001
≥ 16 years	10.2	66.2	19.7	NA	11.8	23.4	< 0.0001
Febrile episodes with blood culture taken	**1 215**	**4 342**	**3 954**	**7 415**	**3 611**	**20 537**	–
By age							
0–1 years	NA	145	404	NA	NA	549	–
2–4 years	NA	344	397	2 293	NA	3 034	–
5–15 years	391	1 201	945	5 122	3 400	11 059	–
≥ 16 years	824	2 652	2 208	NA	211	5 895	–
Mean age of febrile episodes with blood cultures taken (years)	27.4	25.0	20.5	7.5	10.4	15.4	–
Typhoid cases	**15**	**122**	**131**	**189**	**18**	**475**	–
By age							
0–1 years	NA	1	0	NA	NA	1	–
2–4 years	NA	10	14	58	NA	82	–
5–15 years	5	63	58	131	16	273	–
≥ 16 years	10	48	59	NA	2	119	–
Mean age of typhoid cases (years)	24.9	15.5	16.6	7.0	11.3	12.5	–
Typhoid Incidence (per 100 000/year)	**15.3**	**214.2**	**81.7**	**451.7**	**21.3**	**107.6**	< 0.0001
By age							
0–1 years	NA	89.2	0.0	NA	NA	21.6	0.0777
2–4 years	NA	340.1	148.7	573.2	NA	364.8	< 0.0001
5–15 years	29.3	493.5	180.3	412.9	24.2	170.8	< 0.0001
≥ 16 years	12.4	119.7	51.2	NA	10.9	46.8	< 0.0001

(Table 1, cont.)

Site	Hechi, China	Kolkata, India	North Jakarta, Indonesia	Karachi, Pakistan	Hue, Viet Nam	Total	*P*-value[a]
Typhoid prevalence (per 1000 febrile episodes with blood cultures taken)	**12.3**	**28.1**	**33.1**	**25.5**	**5.0**	**23.1**	< 0.0001
By age							
0–1 years	NA	6.9	0.0	NA	NA	1.8	0.0986
2–4 years	NA	29.1	35.3	25.3	NA	27.0	0.5432
5–15 years	12.8	52.5	61.4	25.6	4.7	24.7	< 0.0001
≥ 16 years	12.1	18.1	26.7	NA	9.5	20.2	0.0243

NA, not available.

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

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

[c] Baseline censuses were conducted in Hijrat and Sultanabad in 2001, and in Bilal Colony in 2003.

[d] 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 seeing febrile patients from the study area were included (China: 5 hospitals, 23 government clinics, 99 private clinics; Viet Nam: 4 hospitals, 32 government clinics, 55 private clinics). In the Indonesian site, all 8 government public health centres and 2 government hospitals serving the study area participated in the surveillance. In the Indian site, surveillance involved outpatient and inpatient areas of the 2 government hospitals serving the study population and also 5 study clinics that the project set up in the area. In the Pakistani site, 3 project health-care facilities served 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.[21] Categorical variables were compared using the χ^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

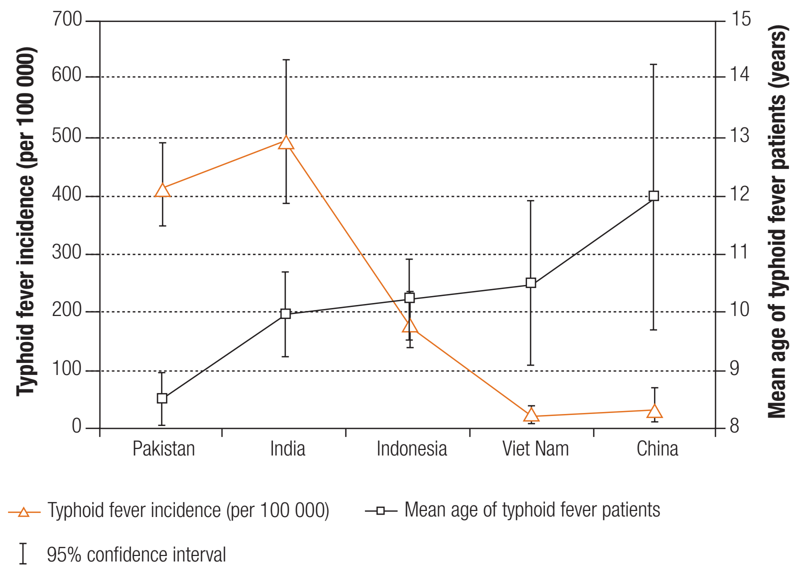
The local ethics committees of each participating site, the WHO Secretariat Committee on Research Involving Human Subjects, and the International Vaccine Institute's Institutional Review Board approved the protocols. Verbal informed consent was obtained before participants were interviewed or blood samples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

Fig. 2. **Incidence of typhoid fever and mean age of patients**[a]



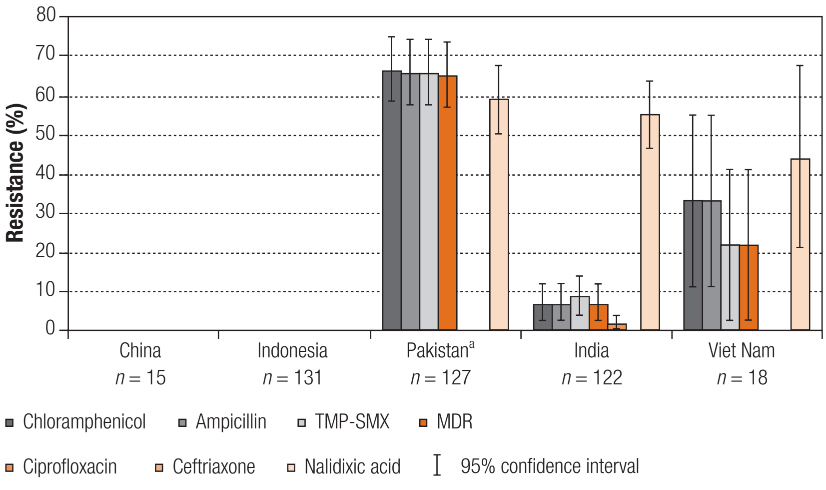
[a] Age group: 5–15 years.

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 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.

Fig. 3. **Antimicrobial agent resistance pattern of *S. enterica* serotype Typhi isolates by study site**



MDR, multidrug resistant (i.e to chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole); TMP-SMX, trimethoprim-sulfamethoxazole.

[a] Isolates from Pakistan were not tested for susceptibility to ciprofloxacin with the disc method, but were tested for minimum inhibitory concentration with nalidixic acid resistant strains and none were found resistant; out of 189 isolates detected during the surveillance period 127 isolates were subjected to all six susceptibility tests.

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,[1] 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.[10]

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 pre-school 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,[8,26] 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,[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 inexpensive antibiotics obsolete and make it necessary to use expensive newer antibiotics, though such antibiotics may be unavailable and unaffordable to many poor populations.[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.[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.[13] Moreover, decisions about vaccine use in Viet Nam, where the rate of typhoid was not high, are complicated by worrisome trends of antimicrobial resistance.[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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Competing interests: None declared.

Résumé

Etude 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 %) 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, atteignait jusqu'à 180,3 pour le site indonésien et se situait entre 412,9 et 493,5 pour les sites pakistanais et indiens. Dans leur ensemble, 23 % (96/413) des isolements étaient multirésistants (chloramphénicol, ampicilline et triméthoprime-sulfaméthoxazole).

Conclusion L'incidence de la fièvre typhoïde variait fortement d'un site à l'autre, avec des valeurs élevées en Inde et au Pakistan, intermédiaires en Indonésie et faibles en Chine et au Viet Nam. Ces résultats font ressortir l'ampleur de la charge de morbidité liée à la typhoïde, mais aussi son hétérogénéité géographique, dans les pays d'endémie asiatiques et soulignent l'importance des données de morbidité sur la prise de décisions politiques concernant les interventions pour lutter contre cette maladie.

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 Pakistán y Viet Nam 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 Viet Nam, 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 Viet Nam. 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.

ملخص

دراسة الحمى التيفية في خمسة بلدان: عبء المرض وآثار المكافحة

الهدف: تزويد أصحاب القرار السياسي بالمعلومات حول إدخال تدخلات وقائية من التيفود، وتشمل التلقيح (التطعيم).

الطريقة: استخدم تصميم للترصُّد المستقبلي المرتكز على السكان في المواقع التي تعتبر السلطات المحلية فيها التيفود مشكلة في كل من الصين والهند وإندونيسيا وباكستان وفييت نام. واستخدمت طرق سريرية ومختبرية وترصدية معيارية لاستقصاء حالات الحمى التي تتواصل لأكثر من 3 أيام على مدى فترة عام واحد. وقد شمل الترصُّد 435 441 شخصاً تتراوح أعمار 856 159 منهم بين 5 و15 عاماً.

الموجودات: اكتشفت 874 21 نوبة حمى، وعزلت السالمونيلات التيفية من 475 (2%) من مزارع الدم، وكان 57% منها (273 حالة من أصل 475 حالة) لدى من هم في عمر 5 –15 عاماً. وكان المعدل السنوي لكل مئة ألف شخص سنة لحدوث التيفود بين هذه المجموعة العمرية يتراوح بين 24.2 في مواقع في فييت نام، و29.3 سنة في مواقع في الصين، و180.3 في مواقع في أندونيسيا، و412.9 في مواقع في باكستان و493.5 في مواقع في الهند. وقد كان 23% من مجموع المستفردات (96 من أصل 413) مقاومة لأدوية متعدِّدة (الكلورامفنيكول والأمبيسلين والتريميثوبريم – سلفاميثوكسازول).

الاستنتاج: إن معدل حدوث التيفود يختلف اختلافاً كبيراً بين المواقع، ويبلغ أشده في الهند وباكستان، ومتوسط في إندونيسيا ومنخفض في الصين وفييت نام. وتوضح هذه الموجودات العبء الهام ولكنه غير متجانس جغرافياً للحمى التيفية في المناطق الموطونة في آسيا، كما يؤكد على أهمية البيِّنات حول عبء المرض في اتخاذ القرارات المتعلِّقة بسياسات التدخُّل الخاصة بمكافحة هذا المرض.

References

1. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. *Bull World Health Organ* 2004;82:346-53. PMID:15298225
2. *Background document: The diagnosis, treatment and prevention of typhoid fever*. Geneva: WHO; 2003.
3. Acharya IL, Lowe CU, Thapa R, Gurubacharva VL, Shrestra MB, Cadoz M, et al. Prevention of typhoid fever in Nepal with the VI capsular polysaccharide of Salmonella typhi. A preliminary report. *N Engl J Med* 1987;317:1101-4. PMID:3657877
4. Acosta CJ, Galindo CM, Ochiai RL, Danovaro-Holliday MC, Page AL, et al. The role of epidemiology in the introduction of VI polysaccharide typhoid fever vaccines in Asia. *J Health Popul Nutr* 2004;22:240-5. PMID:15609776
5. Simanjuntak CH, Paleologo FP, Punjabi NH, Darmowigoto R, Soeprawoto, Totosudirjo H, et al. Oral immunisation against typhoid fever in Indonesia with Ty21a vaccine. *Lancet* 1991;338:1055-9. PMID:1681365 doi:10.1016/0140-6736(91)91910-M
6. Bahl R, Sinha A, Poulos C, Whittington D, Sazawal S, Kumar R, et al. Costs of illness due to typhoid fever in an Indian urban slum community: implications for vaccination policy. *J Health Popul Nutr* 2004;22:304-10. PMID:15609783
7. DeRoeck D, Clemens JD, Nyamete A, Mahoney RT. Policymakers' views regarding the introduction of new-generation vaccines against typhoid fever, shigellosis and cholera in Asia. *Vaccine* 2005;23:2762-74. PMID:15780724 doi:10.1016/j.vaccine.2004.11.044
8. Lin FY, Ho VA, Kheim HB, Trach DD, Bay PV, Thanh TC, et al. The efficacy of a Salmonella typhi Vi conjugate vaccine in two-to-five-year-old children. *N Engl J Med* 2001;344:1263-9. PMID:11320385 doi:10.1056/NEJM200104263441701
9. Lin FY, Vo AH, Phan VB, Nguyen TT, Bryla D, Tran CT, et al. The epidemiology of typhoid fever in the Dong Thap Province, Mekong Delta region of Vietnam. *Am J Trop Med Hyg* 2000;62:644-8. PMID:11289678

10. Sinha A, Sazawal S, Kumar R, Sood S, Reddaiah VP, Singh B, et al. Typhoid fever in children aged less than 5 years. *Lancet* 1999;354:734-7. PMID:10475185 doi:10.1016/S0140-6736(98)09001-1
11. Yang HH, Wu CG, Xie GZ, Gu QW, Wang BR, Wang LY, et al. Efficacy trial of Vi polysaccharide vaccine against typhoid fever in south-western China. *Bull World Health Organ* 2001;79:625-31. PMID:11477965
12. Chuttani CS, Prakash K, Gupta P, Grover V, Kumar A. Controlled field trial of a high-dose oral killed typhoid vaccine in India. *Bull World Health Organ* 1977;55:643-4. PMID:338191
13. Brooks WA, Hossain A, Goswami D, Nahar K, Alam K, Ahmed N. Bacteremic typhoid fever in children in an urban slum, Bangladesh. *Emerg Infect Dis* 2005;11:326-9. PMID:15752457
14. Bhan MK, et al. Typhoid and paratyphoid fever. *Lancet* 2005;366:749-62. PMID:16125594 doi:10.1016/S0140-6736(05)67181-4
15. Acosta CJ, Galindo CM, Ali M, Elyazeed RA, Ochiai RL, Danovaro-Holliday MC, et al. A multi-country cluster randomized controlled effectiveness evaluation to accelerate the introduction of Vi polysaccharide typhoid vaccine in developing countries in Asia: rationale and design. *Trop Med Int Health* 2005;10:1219-28. PMID:16359401
16. Siddiqui FJ, Rabbani F, Hasan R, Nizami SQ, Bhutta ZA. Typhoid fever in children: some epidemiological considerations from Karachi, Pakistan. *Int J Infect Dis* 2006;10:215-22. PMID:16431148 doi:10.1016/j.ijid.2005.03.010
17. Khan MI, Sahito SM, Khan MJ, Wassan SM, Shaikh AW, Maheshwari AK, et al. Enhanced disease surveillance through private health care sector cooperation in Karachi, Pakistan: experience from a vaccine trial. *Bull World Health Organ* 2006;84:72-7. PMID:16501718 doi:10.2471/BLT.05.023630
18. Purohit BC. Private initiatives and policy options: recent health system experience in India. *Health Policy Plan* 2001;16:87-97. PMID:11238435 doi:10.1093/heapol/16.1.87
19. Sur D, Manna B, Deb AK, Deen JL, Danovaro-Holliday MC, von Seidlein L, et al. Factors associated with reported diarrhoea episodes and treatment-seeking in an urban slum of Kolkata, India. *J Health Popul Nutr* 2004;22:130-8. PMID:15473516
20. Bopp CB, Wells JG, Strockbine NA. Escherichia, Shigella and Salmonella. In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, eds. *Manual of clinical microbiology*, 7th edn. Washington, DC: ASM Press; 1999, pp. 459-474.
21. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med* 1998;17:873-90. PMID:9595617 doi:10.1002/(SICI)1097-0258(19980430)17:8<873::AID-SIM779>3.0.CO;2-I
22. Wain J, Pham VB, Ha V, Nguyen NM, To SD, Walsh AL, et al. Quantitation of bacteria in bone marrow from patients with typhoid fever: relationship between counts and clinical features. *J Clin Microbiol* 2001;39:1571-6. PMID:11283089 doi:10.1128/JCM.39.4.1571-1576.2001
23. Hoffman SL, Edman DC, Punjabi NH, Lesmana M, Cholid A, Sundah S, et al. Bone marrow aspirate culture superior to streptokinase clot culture and 8 ml 1:10 blood-to-broth ratio blood culture for diagnosis of typhoid fever. *Am J Trop Med Hyg* 1986;35:836-9. PMID:3089041
24. Farooqui BJ, Khurshid M, Ashfaq MK, Khan MA. Comparative yield of Salmonella typhi from blood and bone marrow cultures in patients with fever of unknown origin. *J Clin Pathol* 1991;44:258-9. PMID:2013632 doi:10.1136/jcp.44.3.258
25. Gilman RH, Terminel M, Levine MM, Hernandez-Mendoza P, Hornick RB. Relative efficacy of blood, urine, rectal swab, bone-marrow, and rose-spot cultures for recovery of Salmonella typhi in typhoid fever. *Lancet* 1975; 1:1211-3. PMID:48834 doi:10.1016/S0140-6736(75)92194-7
26. Robbins JB, Schneerson R, Anderson P, Smith DH. The 1996 Albert Lasker Medical Research Awards. Prevention of systemic infections, especially meningitis, caused by Haemophilus influenzae type b. Impact on public health and implications for other polysaccharide-based vaccines. *JAMA* 1996; 276:1181-5. PMID:8827975 doi:10.1001/jama.276.14.1181
27. Wain J, Hoa NT, Chinh NT, Vinh H, Everett MJ, Diep TS, et al. Quinolone-resistant Salmonella typhi in Viet Nam: molecular basis of resistance and clinical response to treatment. *Clin Infect Dis* 1997;25:1404-10. PMID:9431387 doi:10.1086/516128
28. Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid fever. *N Engl J Med* 2002;347:1770-82. PMID:12456854 doi:10.1056/NEJMra020201
29. Parry C, Wain J, Chinh NT, Vinh H, Farrar JJ. Quinolone-resistant Salmonella typhi in Vietnam. *Lancet* 1998;351:1289. PMID:9643778 doi:10.1016/S0140-6736(05)79356-9
30. Parry CM. The treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever in Viet Nam. *Trans R Soc Trop Med Hyg* 2004;98:413-22. PMID:15138078 doi:10.1016/j.trstmh.2003.10.014