

Costs of Illness Due to Typhoid Fever in an Indian Urban Slum Community: Implications for Vaccination Policy

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ABSTRACT

Data on the burden of disease, costs of illness, and cost-effectiveness of vaccines are needed to facilitate the use of available anti-typhoid vaccines in developing countries. This one-year prospective surveillance was carried out in an urban slum community in Delhi, India, to estimate the costs of illness for cases of typhoid fever. Ninety-eight culture-positive typhoid, 31 culture-positive paratyphoid, and 94 culture-negative cases with clinical typhoid syndrome were identified during the surveillance. Estimates of costs of illness were based on data collected through weekly interviews conducted at home for three months following diagnosis. Private costs included the sum of direct medical, direct non-medical, and indirect costs. Non-patient (public) costs included costs of outpatient visits, hospitalizations, laboratory tests, and medicines provided free of charge to the families. The mean cost per episode of blood culture-confirmed typhoid fever was 3,597 Indian Rupees (US\$ 1=INR 35.5) (SD 5,833); hospitalization increased the costs by several folds (INR 18,131, SD 11,218, $p<0.0001$). The private and non-patient costs of illness were similar (INR 1,732, SD 1,589, and INR 1,865, SD 5,154 respectively, $p=0.8095$). The total private and non-patient *ex-ante* costs, i.e. expected annual losses for each individual, were higher for children aged 2-5 years (INR 154) than for those aged 5-19 years (INR 32), 0-2 year(s) (INR 25), and 19-40 years (INR 2). The study highlights the need for affordable typhoid vaccines efficacious at 2-5 years of age. Currently-available Vi vaccine is affordable but is unlikely to be efficacious in the first two years of life. Ways must be found to make Vi-conjugate vaccine, which is efficacious at this age, available to children of developing-countries.

Key words: Typhoid fever; Vaccination; Typhoid and paratyphoid vaccines; Cost of illness; Costs and cost analysis; Cost-benefit analysis; Slums; Prospective studies; India

INTRODUCTION

Typhoid fever is a common cause of morbidity in adults and children in India and in many other developing

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countries (1). Available vaccines for typhoid fever are not being widely used despite widespread concern about *in-vitro* and clinical resistance to antibiotics (1). Currently, no data are available on the costs associated with typhoid fever at the community level in developing countries. Such data would facilitate cost-benefit analyses of different preventive and curative strategies for typhoid fever. Knowledge of costs of illness to individuals and to the health sector by age categories

could also help select an appropriate vaccine for public-health programmes among available candidates, which differ in efficacy at different ages.

A cohort of all 0-40-year old residents in an urban slum community in Govindpuri, Delhi, India, was followed from November 1995 to February 1997 to determine the incidence of typhoid fever. As reported earlier, the incidence of blood culture-confirmed typhoid fever among residents aged 0-40 year(s) during one calendar year (November 1995–October 1996) was 9.7 per 1,000 and that in pre-school children was 27.3 cases per 1,000 persons at risk per year (2). This paper presents the private and public costs of illness associated with typhoid fever in all cases detected in the cohort, by age and by response to antibiotic therapy. Implications for immunization policy are discussed.

MATERIALS AND METHODS

Study population

The study area is a densely-populated urban slum of low socioeconomic status located in Kalkaji, New Delhi. In 1995, a census of the population of the study area showed that 19,585 residents were living in 4,361 dwellings (Table 1). Members of a typical household lived in a one-room dwelling. The household members collected water from a public or private hand-pump. Children defaecated in open drains outside homes, and adults walked to open areas or two public latrines outside the slum area. All households had electricity, and the majority owned a television set.

Research design and fieldwork

All households in the study area were assigned a unique identification number. The population was divided into clusters with 70 households in each, and 26 such clusters were randomly selected for active twice-weekly surveillance for the detection of cases with typhoid fever (2). The remaining household clusters were kept only under passive surveillance at health facilities and neighbouring practitioners for the detection of fever cases. In active surveillance areas, cases could also be detected through passive surveillance.

Blood specimens for culture were obtained from all children aged less than five years, identified through either active or passive surveillance, who had fever (temperature $>38^{\circ}\text{C}$). Older children and adults had to have continuous fever for at least three days for a

blood specimen to be obtained. These methods have earlier been described in detail (2). Blood-collection centres were established at the chambers of all local medical practitioners and health facilities.

In total, 98 cases of culture-positive typhoid fever and 31 cases of culture-positive paratyphoid were identified. Ninety-four culture-negative cases exhibiting a syndrome of clinical symptoms of typhoid were also treated as typhoid fever. This 'clinical typhoid' syndrome was defined as high-grade continuous fever for seven days or more with no other obvious cause and no response to three days of anti-malarial therapy. A diagnosis of 'clinical typhoid' was made earlier, i.e. after five days of fever, if the patient additionally had bradycardia or splenomegaly. The costs of illness were estimated and are presented separately for blood culture-positive *Salmonella enterica* serotype Typhi, blood culture-positive *S. enterica* serotype Paratyphi and 'clinical typhoid' cases.

Measurement and calculation of costs of illness

Data to calculate the private costs of illness were collected through weekly in-person interviews conducted in the patients' homes. In the first interview, which took place once diagnosis was made through either blood culture or clinical diagnosis, the enumerator recorded treatment-seeking behaviour and expenditure from the onset of fever. The patient (if an adult) and the primary caregiver were interviewed to collect information on costs of illness. Subsequently, a detailed account of expenditure and behaviour was collected in weekly visits continuing for 90 days after diagnosis. At weekly interviews, the respondents reported the number of visits made to private care providers, hospital outpatient departments, public hospitals, local healers, and/or pharmacies and daily expenditure on consultation fees, laboratory tests, medicines, transportation, and other items, including special foods and drinks for the patient. Information on household members who missed work due to the patient's illness was also recorded. Only costs relating to the episode or the consequences of typhoid fever were included. If a person suffered from another illness or injury in the 90-day period, only the expense that preceded new morbidity was included for analysis.

The private costs of illness included the sum of direct medical, direct non-medical, and indirect costs. Direct medical costs included out-of-pocket expenditure on consultation fees, laboratory tests, and medicines. All efforts were made to record the expenditure made by

the family on drugs and laboratory tests even when the patient was admitted to a hospital. Non-medical direct costs included out-of-pocket expenditure on transportation, special foods and drinks, and other items. Indirect costs were calculated as the product of days of work missed by all household members and a monetary value of lost productivity, proxied by the average daily wage rate of INR 70 (US\$ 1.97). [Over the course of the study period from November 1995 to October 1996, the exchange rate between Indian rupee and the US dollar fluctuated between INR 34.32 and 36.59 per US\$. For the costs of illness presented in this study, we have assumed an average exchange rate, over the period, of US\$ 1=INR 35.5. All costs are expressed in 1996 Indian rupees.] The daily productivity losses of sick children were assumed to equal one-quarter of the average daily wage between the ages of 5 and 12 years and one-half for ages 12 to 19 years.

The non-patient costs of illness were those borne by institutions or the public sector. The non-patient costs were the sum of costs of outpatient visits or hospitalization in government hospitals, laboratory tests, and medicines provided free of charge to the patient. The estimates of non-patient costs associated with an outpatient visit (INR 200) and daily costs of hospitalization (INR 2000) were based on calculations used in a Masters thesis in Hospital Administration conducted at our institute (5). These included all costs to the institution, including infrastructure, staff salaries, and other operational costs. The estimated costs of free laboratory tests conducted in government hospitals or provided free of charge by the research team were based on the lowest rates charged by the local laboratories serving the study community. The research team treated each case with ciprofloxacin, the cost of which was about INR 8 per day for pre-school children and INR 15 per

Table 1. Socioeconomic and health characteristics of the Govindpuri study area, Kalkaji, Delhi, 1995

Characteristics	Findings
General	
1995 population	19,585 in 4,361 households
Average household size	4.5 persons per household
Infrastructure	
Source of water	Hand-pumps (public and private)–62% Public taps connected to municipal piped distribution system–27% Private connections–11%
Sanitation	Open space, public latrines, private pit-latrines
Electricity	99%
Household socioeconomic characteristics	
% of households with television	69
% of adults illiterate	36
Religion	Mixed Hindu, Muslim, others
Predominant dwelling type	1 room, attached, one-storey 28%–cement-floor and permanent roof 68%–either roof or floor not permanent 4%–neither roof nor floor permanent
% of households owning structure	90
% with motorcycle	2
Health indicators	
Average number of episodes of diarrhoea per child per year	8
% of children aged less than 5 years who are stunted	45
% of children aged less than 5 years who are wasted	18
Estimated infant mortality	60 per 1,000
Incidence of typhoid among individuals aged less than 5 years	27.3 per 1,000 per year
Incidence of typhoid among individuals aged 5-18 years	11.7 per 1,000 per year
Incidence of typhoid among individuals aged ≥ 19 years	1.1 per 1,000 per year

day for older children and adults. Twelve cases that did not respond to ciprofloxacin within 10 days were considered as treatment failures, and most of them were hospitalized and treated with third-generation cephalosporins (drug cost INR 200 per day).

Calculation of *ex-ante* costs of illness

The costs-of-illness calculations described above are *ex-post* estimates as they are based on information on direct and indirect costs incurred by the patient and society after an individual contracted typhoid fever. It is useful to look at the meaning of these estimates from the perspective of a member of the study population *before* he or she becomes infected, i.e. the *ex-ante* costs. By multiplying the estimated costs of illness of a case of typhoid fever by the incidence of the disease, we obtained *ex-ante* costs of illness, which are an estimate of the annual expected value of the cost of typhoid fever to an individual in the community.

Sensitivity analysis

A sensitivity analysis was conducted by varying three assumptions—the assumptions on daily wages, the non-patient costs of outpatient visits, and the daily hospitalization costs. To compute conservative (i.e. low) estimates of costs, each value was assumed to be one-half of the base case. To compute the upper end of the range of costs, each value was assumed to be one and one-half times the base case.

Statistical analysis

Data were analyzed using Stata version 7 (Stata Corporation, College Station, TX, USA). Costs were compared using Student's *t*-test assuming unequal variances if data were normally distributed and using Wilcoxon rank sum test if the data did not fulfill parametric assumptions.

RESULTS

Costs of *S. Typhi* blood culture-positive typhoid fever

The most reliable costs-of-illness data were obtained from culture-positive typhoid fever cases. The total mean costs (private costs plus public/institutional costs) of illnesses for cases detected by active surveillance (INR 3,273, SD 5,646) were somewhat lower than those detected only by passive surveillance (INR 4,287, SD 6,337, $p=0.1$). This may be because the patients detected through active surveillance received

early and optimal antibiotic treatment. The overall incidence of culture-positive typhoid fever was 9.7 per 1,000 (95% CI 7.5-12.5) by active surveillance and only 2.9 per 1,000 (95% CI 1.9-4.1) by passive surveillance. Due to the relatively few typhoid cases detected by passive surveillance, in Table 2 we have combined the cases detected either by active surveillance or by passive surveillance to estimate the total mean costs of blood culture-confirmed typhoid fever (INR 3,597, SD 5,833). The costs of an episode of typhoid increased several folds if the patient was hospitalized ($p<0.0001$).

Table 3 presents the composition of the private and non-patient (public or institutional) costs. The total private and total non-patient costs of illness were similar in magnitude ($p=0.8$). The private indirect costs accounted for about half of the private costs of illness. Hospitalization contributed about 70% of the average non-patient costs. The costs of clinic visits, laboratory tests, and medicines were all relatively small.

Table 4 shows the private and non-patient (public or institutional) costs by age for culture-confirmed typhoid fever. The age cohorts of 2-5, 5-19, and >19 years had comparable mean costs of illness. However, the composition of the costs was quite different for the three age cohorts. The private costs were much higher for adults than for children aged 2-5 years ($p<0.05$) and 5-19 years ($p=0.06$), largely because of their high indirect costs from loss of work. The non-patient costs for adult patients were low because they were rarely hospitalized. Pre-school children with typhoid fever were more often hospitalized, resulting in a much higher cost to the public sector.

High costs in many typhoid episodes were due to slow response to treatment, i.e. continued fever after 10 days of ciprofloxacin treatment requiring hospitalization and intravenous third-generation cephalosporins.

The mean total costs for clinically slow responders were INR 10,739 (SD 11,604) compared to INR 2,867 (SD 13,030) for early responders ($p<0.05$).

The annual *ex-ante* private expected losses to an individual in the study area were quite small (INR 18; Table 5). The calculations are based on the population-based incidence and costs of blood culture-confirmed typhoid fever cases detected through active surveillance. These *ex-ante* private costs were the highest for pre-school children aged 2-5 years (INR 37), followed by school-age children (INR 21). However, if one looks

at the expected annual losses from the perspective of both individual and society (private plus non-patient costs), the *ex-ante* costs of illness for pre-school children (INR 154) were much larger. This is because the total costs for cases among pre-school children were comparable with the costs of illness of the older children and

Table 2. Mean (SD) duration of fever, hospitalization rate, and mean total costs of illness by diagnosis (1996 INR)

Feature	Blood culture-confirmed typhoid (n=98)	Blood culture-confirmed paratyphoid (n=31)	'Clinical typhoid'* (n=94)
Total duration (days) of fever	14.2 (8.7)	10.4 (5.4)	15.6 (7.5)
% of cases hospitalized	11.1	3.1	14.8
Mean total cost	3,597 (5,833)	1,785 (1,331)	4,547 (7,890)
Mean total cost if hospitalized	18,131 (11,218)	–†	24,201 (11,923)
Mean total cost if not hospitalized	2,111 (1,375)	1,785 (1,331)	2,336 (2,449)

*This category includes patients who had clinical features of typhoid but were blood culture-negative
†Only 1 of 31 cases hospitalized

Table 3. Mean (SD) costs-of-illness components by components of private and non-patient costs (1996 INR)

Cost-of-illness component	Blood culture-confirmed typhoid (n=98)	Blood culture-confirmed paratyphoid (n=31)	'Clinical typhoid'* (n=94)
Private costs			
Medical direct	277 (459)	174 (225)	432 (785)
Non-medical direct	648 (725)	423 (489)	528 (661)
Indirect	806 (925)	795 (897)	1,134 (1,521)
Total private costs	1,732 (1,589)	1,393 (1,246)	2,072 (2,420)
Non-patient costs			
Clinic visits	269 (394)	116 (192)	328 (506)
Hospitalizations	1,316 (4,903)	0 (0)	1,883 (6,467)
Laboratory tests	157 (31)	161 (44)	157 (27)
Medicines	125 (86)	126 (90)	118 (163)
Total non-patient costs	1,865 (5,154)	391 (217)	2,475 (6,836)

*This category includes patients who had clinical features of typhoid but were blood culture-negative

Table 4. Mean (SD) costs of illness and hospitalization rate by age for blood culture-positive typhoid fever (1996 INR)

Age (years) cohort	Private cost of illness	Non-patient cost of illness	Total cost of illness	Percentage of cases hospitalized
0-2 (n=3)	1,144 (300)	663 (530)	1,807 (672)	0.0
2-5 (n=33)	1,191 (1,230)	2,764 (6,317)	3,955 (7,101)	21.4
5-19 (n=51)	1,894 (1,733)	1,622 (4,933)	3,516 (5,691)	8.6
19 and above (n=9)	2,999 (1,462)	318 (210)	3,317 (1,489)	5.3

Table 5. Overall and age-specific (1996 INR) *ex-ante* costs of illness using incidence estimates and mean costs from cases identified through active surveillance

Age (years) cohort	Including blood culture-positive typhoid cases only			Including both blood culture-positive and 'clinical typhoid' cases		
	Private cost	Non-patient cost	Total cost	Private cost	Non-patient cost	Total cost
0-2	16	9	25	28	16	44
2-5	37	118	154	56	179	235
5-19	21	11	32	35	17	53
19 and above	2	0	2	11	1	12
All ages	15	17	32	26	31	57

adults but the incidence of typhoid fever among pre-school children was much higher. Also, the majority of the costs for the 2-5-year cohort were non-patient costs due to their higher hospitalization rates.

Costs of blood culture-positive paratyphoid fever

The average *ex-post* cost of illness of a paratyphoid case was about half that of blood culture-confirmed typhoid cases ($p=0.06$; Table 2). This was expected because none of the paratyphoid patients was hospitalized due to the milder nature of the disease (6). The total private costs of illness were only marginally lower for blood culture-positive paratyphoid cases than for blood culture-confirmed typhoid patients ($p=0.3$; Table 3).

Costs of blood culture-negative 'clinical typhoid fever'

Diagnosis of typhoid by blood culture is highly specific but the sensitivity is only 40-45% when compared with a combination of bone-marrow aspirate, blood, and stool culture (7-9). The incidence of blood culture-confirmed typhoid fever is, thus, a significant under-estimate of the true incidence of typhoid fever. Cost data for culture-negative 'clinical typhoid' are presented separately in Tables 2 and 3.

The mean total costs of illnesses of 'clinical typhoid' cases were somewhat higher than that of blood culture-positive typhoid fever cases, but this difference was not significant ($p=0.9$; Table 2). The relative sizes of the cost components were comparable between these two types of cases (Table 3).

The *ex-ante* costs of illness increased substantially if both culture-positive and clinical typhoid cases were considered as true cases of typhoid fever (private costs INR 45 and total costs to society INR 92) rather than blood culture-positive cases only (private costs INR 18 and total costs to society INR 37). This increase in the *ex-ante* costs of illness was proportionately much greater for adults than for younger persons. Before this adjustment for clinical typhoid cases, the *ex-ante* costs of illness for an adult was INR 5 versus INR 30 after this adjustment.

Sensitivity analysis

The total mean costs of illness were INR 2,398 using the most conservative assumption about costs and INR 4,792 using the least conservative assumption compared to the base case mean of INR 3,597. Similarly, the *ex-ante* costs for culture-proven typhoid fever varied from INR 24 to INR 74 compared to the base case value of INR 37, and those based on an incidence estimate

that included both culture-proven typhoid and 'clinical typhoid' varied from INR 60 to INR 124 compared to the base case value of INR 92.

The *ex-ante* costs of illness, shown in Table 5, might be considered to be lower-end estimates because they are based on costs from cases identified through active surveillance. We, therefore, estimated the upper-end *ex-ante* costs of illness by multiplying the incidence of typhoid fever obtained through active surveillance by the costs from cases identified through passive surveillance. This analysis showed that the *ex-ante* costs for culture-proven typhoid were INR 43 (sensitivity analysis range 28-58) and those for both culture-proven typhoid and 'clinical typhoid' were INR 77 (range 50-103). The highest *ex-ante* costs were for the 2-5-year age cohort: INR 200 (range 124-276) for culture-proven typhoid and INR 305 (range 189-420) for both culture-proven typhoid and 'clinical typhoid'.

DISCUSSION

The main findings of this study are that there were substantial costs associated with an episode of typhoid fever and that the private costs of illness were comparable with non-patient costs even in a low-income study population where most medical services are provided either free of charge or at heavily subsidized prices. Further, the costs were several-fold higher for those who needed hospitalization or who did not respond adequately to antibiotic therapy. Finally, our analysis demonstrated that the costs of illness in pre-school children were as high as those in older children and adults.

The costs of illness shown in this paper are based on direct measurement of reported expenses and on some assumptions regarding daily wages, hospitalizations, and outpatient visit costs; sensitivity analysis indicated that these costs could vary by +33% from the mean estimates presented in this paper. The findings of the present study indicate that as clinical or *in-vitro* antibiotic resistance increases, the costs of illness are likely to increase substantially because of increased hospitalizations. Strategies to prevent the development of antibiotic resistance, therefore, deserve a high priority from an economic and humanitarian perspective. In high-incidence areas, physicians tend to treat empirically with anti-typhoid agents, usually fluoroquinolones. The use of vaccines could reduce the probability of such an illness being typhoid fever, restrict antibiotic use, and thereby limit the development of antibiotic resistance.

The *ex-ante* costs of illness were the highest for pre-school children. The currently-marketed Vi and Ty21a vaccines have been tested for efficacy only in school-age children and adults, although it would seem likely, at least for Vi vaccine, that efficacy extends down to two years of age. Given the high *ex-ante* costs of illness in pre-school children aged 2-5 years, in whom the Vi vaccine is theoretically applicable, data that demonstrate the efficacy of Vi vaccine at this age are urgently required. Newer vaccines, such as Vi-conjugate, may be capable of protecting infants, but their affordability in developing countries is uncertain.

An important issue in *ex-ante* cost calculations and in subsequent cost-benefit calculations is the low sensitivity of blood culture for diagnosis of typhoid fever (7-9). Because the average duration of fever and hospitalization for 'clinical typhoid' was similar to culture-positive cases and was much greater than those expected in acute febrile viral illnesses, a high proportion of the 'clinical typhoid' cases in this study may have been true typhoid cases.

Our calculated costs of illness as a measure of benefits of reduction in the incidence of a disease have limitations as these did not include the costs relating to pain and suffering incurred by the patient, the costs associated with the small mortality risk from typhoid, and behavioural changes that households may make to avoid contracting the disease, such as boiling water. There are also the opportunity costs of a typhoid patient taking a hospital bed from a potentially more severely-ill patient. These costs-of-illness estimates are, thus, conservative. However, the willingness to pay for the vaccine depends on the individual's perception of risk. A slum dweller, for instance, may be willing to pay very little to avoid typhoid fever, but might be willing to pay a considerable sum if he or a member of his family gets typhoid fever. Information on willingness to pay for the vaccine was not collected in this study.

We believe that these are the first estimates of costs of illness due to typhoid fever in a specific community in India and among the most detailed estimates available for any developing country. These estimates should facilitate cost-benefit analyses of various preventive strategies, including mass and selective immunizations. The high disease burden and several-fold higher non-patient costs of typhoid fever in pre-school children compared to older children and adults imply that greater

attention should be given to the development and use of vaccines that are efficacious in pre-school children.

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