क्षेत्रीय आयुर्विज्ञान संस्थान, इंफालः मणिपुर
REGIONAL INSTITUTE OF MEDICAL SCIENCES, IMPHAL, MANIPUR
(स्वास्थ्य और परिवार कल्याण मंत्रालय,भारत सरकार के अंतर्गत एक स्वायत्त संस्थान)
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CIRCULAR

Imphal, the 13th April, 2026

No. 66/RIMS-MRU/2026: It is to notify that, the **11th Research Masterclasses 2026**, of the Department of Health Research, Ministry of Health and Family Welfare, Government of India, will be conducted virtually, **on 24th April, 2026 (Friday)**.

2. All the faculties (RIMS, Dental College, and College of Nursing), members of EC, LRAC of MRU, Principal Investigators undertaking MRU funding projects (including under process projects) and residents are invited to attend the session at **Banting Hall, RIMS, Imphal**.

Date: 24.04.2026 (Friday)
Time: 3:00 PM onwards
Venue: Banting Hall, RIMS, Imphal **(Designated Site for Participation for RIMS)**
Event name: Research Masterclass under DHR-ICMR Research Grand Rounds
Speaker Name: Dr. Jacob John, Professor, Department of Community Health, Christian Medical College, Vellore, Tamil Nadu.

3. The **research paper** to be discussed during the Masterclass will be uploaded on the **RIMS website** and circulated to the concerned Departments/Colleges through official email.

13/4/2026

(Prof. Ng. Gunindro Singh)
Nodal Officer (i/c)
Multi-Disciplinary Research Unit,
RIMS, Imphal

Copy to:

1. The P.S. to Director, RIMS, for kind information of Director
2. The P.A. to Medical Superintendent, RIMSH, for kind information
3. The Dean (Academic), RIMS, for kind information.
4. All Heads of Departments, RIMS, Imphal
5. The Principal, Dental College, RIMS
6. The Principal, College of Nursing, RIMS
7. The Chairperson/Co-Chairperson/Member, LRAC, MRU, RIMS..
8. The Member, EC, MRU, RIMS, Imphal ....
9. The Principal Investigator, MRU, RIMS ....
10. The IT Cell, RIMS – with a request for uploading the notice in the website & technical support on **24.04.26**
11. Asst. Engineer (Elect. /Civil), RIMS - with a request for ensuring uninterrupted power supply & optimum AC functioning.
12. The Care Taker, Banting Hall, RIMS, Imphal - for proper upkeep of the venue & accompanying facilities.
13. Guard file.

No. R.11016/03/2025-HR
भारत सरकार/Government of India
स्वास्थ्य एवं परिवार कल्याण मंत्रालय/Ministry of Health & Family Welfare
स्वास्थ्य अनुसंधान विभाग/Department of Health Research

2nd Floor, IRCS Building
Sansad Marg, New Delhi – 110001
Dated 06.04.2026

To
The Dean/ Principal/ Director of Medical Colleges/ Institutes

Subject: Request to attend Research Masterclasses for MRU network– reg.

Sir/Madam,

DHR-ICMR has initiated a dedicated platform to conduct Research Grand Rounds to strengthen the National research ecosystem through sustained collaboration and knowledge exchange. The objectives of the Research Grand Rounds are as follows:

I. To deliberate on research methodologies, analytical tools, and emerging scientific approaches
II. To strengthen the methodological understanding amongst researchers needed to implement different kinds of research.
III. To foster collaboration and connectivity across research institutions

2. These Research Grand Rounds will be organized as monthly webinars entitled 'Research Masterclass' proposed around the last Friday of each month. The speakers for these Research Masterclasses will be eminent research scientists in the country who will be discussing their original research work in details from methodological point of view.

3. The next Research Masterclass is scheduled for **24.04.2026 (Friday)** at **3:00 PM**. The invited speaker is **Dr. Jacob John, Professor, Department of Community Health,** Christian Medical College, Vellore, Tamil Nadu. The research paper to be discussed during the research masterclass is enclosed. The link for the research masterclass will be shared shortly.

4. Accordingly, it is requested to kindly disseminate the information in your institution and ensure maximum participation in Research Masterclass. Your institute is requested to share at least two questions related to research paper attached on the following email: **dhr-mru@gov.in** latest by 20.04.2026. These questions will be discussed with the speaker during masterclass.

Yours faithfully,

(Dharkat R. Luikang)
Deputy Secretary to the Govt. of India

Copy to: The Nodal Officer of Multi-Disciplinary Research Units (MRUs)

ORIGINAL ARTICLE

Burden of Typhoid and Paratyphoid Fever in India

J. John, A. Bavdekar, T. Rongsen-Chandola, S. Dutta, M. Gupta, S. Kanungo, B. Sinha, M. Srinivasan, A. Shrivastava, A. Bansal, A. Singh, R.M. Koshy, D.R. Jinka, M.S. Thomas, A.P. Alexander, S. Thankaraj, S.E. Ebenezer, A.S. Karthikeyan, D. Kumar, S.K. Njarekkattuvalappil, R. Raju, N. Sahai, B. Veeraraghavan, M.V. Murhekar, V.R. Mohan, S.K. Natarajan, K. Ramanujam, P. Samuel, N.C. Lo, J. Andrews, N.C. Grassly, and G. Kang, for the NSSEFI Study Team*

ABSTRACT

BACKGROUND

In 2017, more than half the cases of typhoid fever worldwide were projected to have occurred in India. In the absence of contemporary population-based data, it is unclear whether declining trends of hospitalization for typhoid in India reflect increased antibiotic treatment or a true reduction in infection.

METHODS

From 2017 through 2020, we conducted weekly surveillance for acute febrile illness and measured the incidence of typhoid fever (as confirmed on blood culture) in a prospective cohort of children between the ages of 6 months and 14 years at three urban sites and one rural site in India. At an additional urban site and five rural sites, we combined blood-culture testing of hospitalized patients who had a fever with survey data regarding health care use to estimate incidence in the community.

RESULTS

A total of 24,062 children who were enrolled in four cohorts contributed 46,959 child-years of observation. Among these children, 299 culture-confirmed typhoid cases were recorded, with an incidence per 100,000 child-years of 576 to 1173 cases in urban sites and 35 in rural Pune. The estimated incidence of typhoid fever from hospital surveillance ranged from 12 to 1622 cases per 100,000 child-years among children between the ages of 6 months and 14 years and from 108 to 970 cases per 100,000 person-years among those who were 15 years of age or older. *Salmonella enterica* serovar Paratyphi was isolated from 33 children, for an overall incidence of 68 cases per 100,000 child-years after adjustment for age.

CONCLUSIONS

The incidence of typhoid fever in urban India remains high, with generally lower estimates of incidence in most rural areas. (Funded by the Bill and Melinda Gates Foundation; NSSEFI Clinical Trials Registry of India number, CTRI/2017/09/009719; ISRCTN registry number, ISRCTN72938224.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Kang can be contacted at gkang@cmcvellore.ac.in or at the Division of Gastrointestinal Sciences, Christian Medical College, Vellore, Tamil Nadu, India 632004.

*A list of members of the NSSEFI Study Team is provided in the Supplementary Appendix, available at NEJM.org.

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An estimated 14.3 million cases of enteric fever caused by *Salmonella enterica* serovar Typhi and Paratyphi (often called S. typhi and S. paratyphi) occurred globally in 2017, with S. typhi responsible for 11 million cases of typhoid fever and 120,000 deaths.[1] More than half the deaths were in children under 15 years of age. Since 2008, the World Health Organization (WHO) has recommended typhoid vaccination, but uptake has been limited because the available vaccines could not be used in young children.[2] The administration of Vi polysaccharide-based typhoid conjugate vaccines that are now available was recommended again in 2018 by the WHO, with priority given to countries with the highest burden.[3-6]

Despite the substantial burden of these infections, systematic surveillance in most countries has been limited, and marked variation in incidence within and among countries has been reported.[7] Furthermore, the true incidence of these infections may be masked by the widespread use of antibiotics.[8] Resistance to azithromycin, which has become widely used after the emergence of fluoroquinolone resistance, and resistance to third-generation cephalosporins are emerging concerns.[9,10]

In India, which has more than half the estimated global burden of typhoid, the implementation of public vaccination has remained low, in part because of the lack of data regarding the contemporary disease burden. We established Surveillance for Enteric Fever in India (SEFI) to address evidence gaps that had been identified by the National Technical Advisory Group on Immunization. From 2017 through 2020 in the National Surveillance System for Enteric Fever in India (NSSEFI) study, we conducted weekly surveillance for acute febrile illness and measured the incidence of typhoid and paratyphoid fever in four community cohorts (tier 1) and in six sites that combined hospital surveillance with surveys on local health care use (tier 2).

METHODS

TIER 1 SURVEILLANCE

From October 2017 through February 2018, we enrolled approximately 6000 eligible children between the ages of 6 months and 13 years at four prospective sites — three urban centers in Delhi, Kolkata, and Vellore and one rural center in Pune — in tier 1 community-based active surveillance. We followed each child for 24 months or until their 15th birthday. These study sites were chosen for their broad urban or rural populations and geographic representation across the country, along with the availability of medical personnel to perform high-quality community-based research.

The study procedures and informed consent forms were approved by the institutional review board of Christian Medical College and by ethics committees at each site. All the children in the defined catchment area were eligible; written informed consent was obtained from the primary caregiver. A detailed study protocol, including sample-size calculations, was published previously[11] and is available with the full text of this article at NEJM.org.

Weekly surveillance for fever was conducted either by a home visit or telephone interview, with one mandatory home visit each month. A digital thermometer and fever diary were provided to report any acute febrile illness. An initial report of fever triggered a home visit or a visit to a clinic or hospital to assess the child. Daily visits continued until the resolution of fever, which was defined as 3 consecutive days without fever. Physician-assigned diagnosis, clinical investigations, and treatment, including antibiotics, were recorded.

For children with potential enteric fever, which was defined as fever lasting for 3 or more consecutive days, an age-appropriate blood volume was inoculated into a BacT/ALERT or BACTEC bottle. The previous receipt of antibiotics was not considered to be a contraindication. S. typhi and S. paratyphi were isolated according to standard laboratory methods,[11,12] and antimicrobial susceptibility was determined according to the guidelines of the Clinical and Laboratory Standards Institute.[13]

We calculated the incidences of acute febrile illness, potential enteric fever, typhoid fever, and paratyphoid fever per child-year of observation using survival analysis with interval censoring of periods when valid recall was unavailable. The overall incidence was adjusted for the age structure at each site. We investigated the association between typhoid incidence and baseline household characteristics and location using the Andersen–Gill proportional-hazards model.[14] We estimated incidence with and without adjustment for the sensitivity of blood culture (60%).[8] Details regarding the statistical analysis plan are provided in the Supplementary Appendix, available at NEJM.org.

TIER 2 SURVEILLANCE

From February 2018 through March 2020, we initiated tier 2 of the study, which consisted of hospital-based surveillance combined with surveys regarding health care utilization. At six hospitals, we screened hospitalized patients who were at least 6 months of age for fever. After written consent had been obtained, we performed blood cultures using BACTEC. These study sites were chosen to represent geographic heterogeneity, urban and rural locations, and risk settings across India. The sites were often in regions with poor health and research infrastructure from which data are rarely obtained, and the selected hospitals provided care for a substantial proportion of the studied population. An independent agency conducted health care utilization surveys in the catchment area for each hospital to estimate the percentage of the population that used the surveillance hospitals for fever-related hospitalization.[14] Details regarding the study sites are available in the Supplementary Appendix.

We calculated the estimated incidence of hospitalized typhoid and paratyphoid fever among children between the ages of 6 months and 14 years and older persons (≥15 years of age) in the catchment population by dividing the number of culture-confirmed cases by the population size after adjustment for the age-specific proportion of febrile illnesses seen at the surveillance hospital from the health care utilization surveys (Fig. S1 in the Supplementary Appendix). The catchment population was defined as those living in the contiguous area from which 80% of hospitalizations in the previous 2 years had been recorded. Incidence was also adjusted for the proportion of eligible episodes in which blood culture was not performed because of nonconsent and for the sensitivity of blood culture. To estimate the incidence of typhoid of all clinical severity, we divided the estimates of patients who were hospitalized with typhoid fever by the percentage of those who had been hospitalized during tier 1 surveillance,[12] an adjustment approach for hybrid surveillance for enteric fever that has been reported in other studies.[15-17] To account for uncertainty in the adjusted estimates, we used Monte Carlo simulation that samples a range of values for each multiplier that was used in the health care utilization surveys (using a beta distribution) and report the 95% confidence interval (Tables S7 and S8). We performed sensitivity analyses on the blood-culture sensitivity when accounting for previous antibiotic exposure.

RESULTS

TIER 1

Characteristics of the Surveillance Cohort

A total of 24,062 children were enrolled at four sites, with 21,470 (89.2%) completing 24 months of follow-up; of the remaining children, 1436 (6.0%) had data censored at 15 years, and 1156 (4.8%) were either lost to follow-up or had withdrawal of consent (Fig. 1). Because of the differences between the three urban, densely populated city catchments and a rural agrarian community across several villages (Table S1), drinking water sources and toilet facilities varied substantially among the sites; 603 households (4.3%) had access only to unimproved water,[18] 3189 (22.6%) used bottled water (mainly in Pune), and the remainder had access to piped water or a public tap. Water treatment was inadequate for 10,425 children (73.7%). The majority of households (84.2%) had access to toilets, although 37.2% shared toilets with other families.

Incidence of Acute Febrile Illnesses

We recorded 76,027 cases of acute febrile illness during 46,959 child-years of observation across the four cohorts, with the highest incidence among children between the ages of 6 months and 4 years (2.45 episodes per child-year) (Table S2). The overall incidence among children between the ages of 6 months and 14 years was 1.73 episodes per child-year. The criteria for potential enteric fever were met in 20,911 cases (27.5%), and the incidence ranged from 24.2 to 29.2% among sites. Of these children, febrile illness continued in 70.1% (range, 67.0 to 75.8), so these children were eligible for blood culture.

Among the children with potential enteric fever, blood culture was performed in 86.6% (range, 79.1 to 93.6); blood culture was not performed in the remaining children because of lack of consent from the caregiver (7.3%) or other reasons (6.1%). The prespecified blood volume was obtained in 91.0% of cultures. Antibiotics were ad-

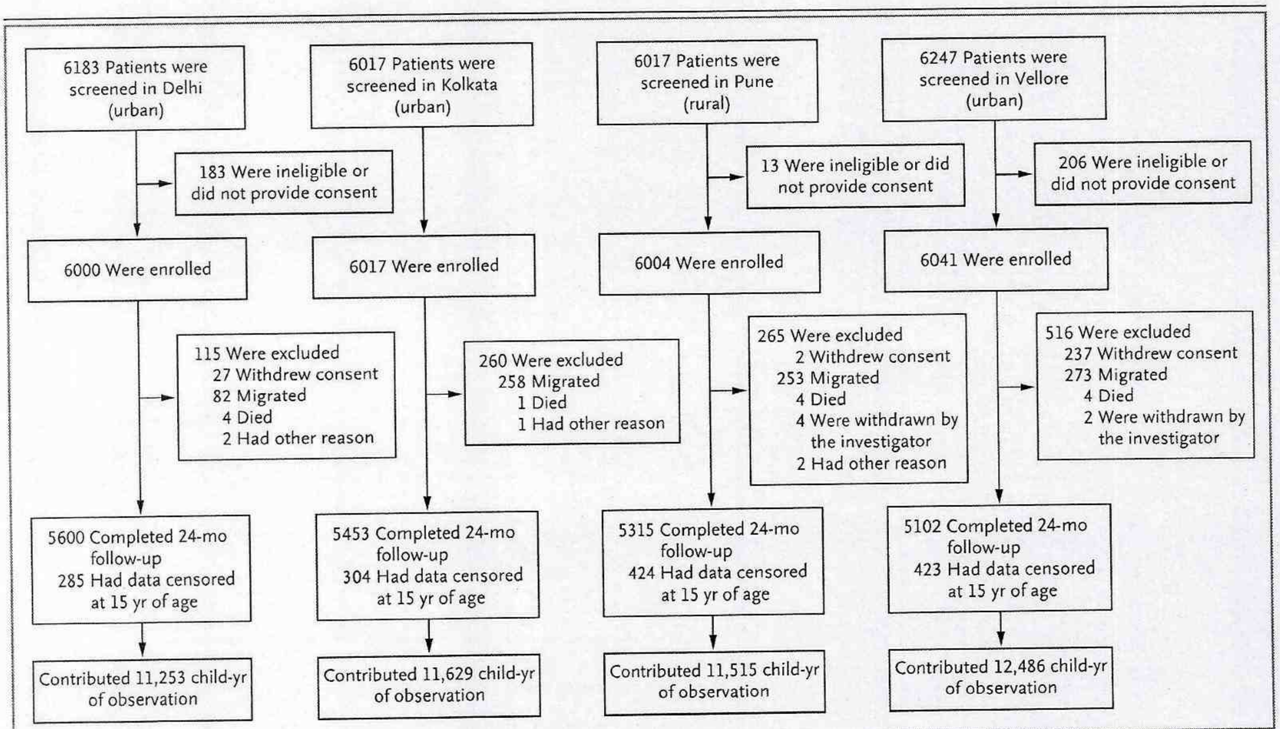

Figure 1. Enrollment and Outcomes in Tier 1 Surveillance Study.

From October 2017 through February 2018, a total of 24,062 children between the ages of 6 months and 13 years were recruited at four sites, with 21,470 (89.2%) completing 24 months of follow-up. Data were censored for 1436 children when they reached the age of 15 years, and 1156 children were excluded from the analysis for reasons that are indicated.

ministered in 67.7% of cases of potential enteric fever; in 38.8% of cases (range, 22.4 to 64.8), antibiotic administration occurred before blood culture. Blood cultures were performed on day 4 of fever in 67.6% of cases, on day 5 in 18.8%, and on day 6 to 16 for the remainder (13.6%). The clinical diagnoses in these cases are provided in Table S3.

Incidence of Culture-Confirmed Typhoid and Paratyphoid Fever

Cases of typhoid were confirmed by culture in 299 children, ranging from 4 in Pune to 146 in Vellore (Table 1). After adjustment for the age distribution in the local population, the overall incidence per 100,000 child-years among children between the ages of 6 months and 14 years was 576 (95% confidence interval [CI], 445 to 734) in Delhi, 714 (95% CI, 568 to 885) in Kolkata, 35 (95% CI, 9 to 89) in Pune, and 1173 (95% CI, 991 to 379) in Vellore (Fig. 2). The incidence was highest among children between the ages of 5 and 9 years in Vellore, Kolkata, and Pune and between the ages of 10 and 14 years in Delhi (Fig. S2). S. paratyphi was isolated from 33 children, for an overall incidence of 68 (95% CI, 47 to 96) per 100,000 child-years after adjustment for age.

The incidence of typhoid varied over time but did not show seasonality or an association with wetter monsoon months (hazard ratio, 0.95; 95% CI, 0.69 to 1.32) at any site. In the final multivariable model, the risk of typhoid was greater for children from households of greater-than-average size, with fewer assets, and without a sanitary toilet (Table S4). The typhoid incidence was 648 (95% CI, 568 to 739) per 100,000 child-years among children without access to safe water as compared with 611 (95% CI, 489 to 763) per 100,000 child-years in those with access to safe water. The incidence of typhoid was lower among the few children who had been vaccinated (hazard ratio, 0.60; 95% CI, 0.28 to 1.27).

Table 1. Incidence of Culture-Confirmed Typhoid and Paratyphoid Fever among Children in Tier 1.*

Variable	Vellore	Kolkata	Delhi	Pune	All Sites
Type of febrile illness					
Febrile illness — no. of children	23,548	17,741	14,439	20,299	76,027
Potential enteric fever — no. of children	6,878	4,285	4,198	5,550	20,911
Blood culture reported					
No. of children	4,156	2,293	2,533	3,701	12,683
No. of positive findings — no. (%)					
S. typhi	146 (3.5)	81 (3.5)	68 (2.7)	4 (0.1)	299 (2.4)
S. paratyphi	1 (<0.1)	13 (0.6)	12 (0.5)	7 (0.2)	33 (0.3)
Typhoid fever					
Age of 6 mo to 14 yr†					
No. of children	146	81	68	4	299
Rate per 100,000 child-yr (95% CI)	1173 (991–1379)	714 (568–885)	576 (445–734)	35 (9–89)	637 (567–713)
Age of 6 mo to 4 yr					
No. of children	30	20	13	0	63
Rate per 100,000 child-yr (95% CI)	974 (681–1392)	662 (427–1027)	459 (267–791)	0 (0–89)	536 (419–687)
Age of 5 to 9 yr					
No. of children	68	39	29	3	139
Rate per 100,000 child-yr (95% CI)	1341 (1057–1700)	958 (700–1311)	618 (429–889)	71 (23–220)	770 (652–909)
Age of 10 to 14 yr					
No. of children	48	22	26	1	97
Rate per 100,000 child-yr (95% CI)	1096 (826–1454)	485 (319–736)	693 (472–1017)	22 (3–158)	566 (464–690)
Paratyphoid fever					
Age of 6 mo to 14 yr†					
No. of children	1	13	12	7	33
Rate per 100,000 child-yr (95% CI)	8 (1–44)	112 (60–191)	98 (49–174)	61 (24–125)	68 (47–96)
Age of 6 mo to 4 yr					
No. of children	0	3	2	2	7
Rate per 100,000 child-yr (95% CI)	0 (0–82)	99 (32–308)	71 (18–282)	71 (18–284)	60 (28–125)
Age of 5 to 9 yr					
No. of children	0	7	2	2	11
Rate per 100,000 child-yr (95% CI)	0 (0–50)	172 (82–361)	43 (11–170)	47 (12–189)	61 (34–110)
Age of 10 to 14 yr					
No. of children	1	3	8	3	15
Rate per 100,000 child-yr (95% CI)	23 (3–162)	66 (21–205)	213 (107–426)	67 (22–208)	87 (53–145)

* During the tier 1 community-based surveillance, approximately 6000 eligible children between the ages of 6 months and 13 years were enrolled at each of four prospective sites — three in urban centers in Vellore, Kolkata, and Delhi and one in a rural center in Pune — and were followed for 24 months or until their 15th birthday. CI denotes confidence interval.

† In this category, values have been adjusted to match those in the age distribution (e.g., health care–seeking behavior, missed blood collection owing to nonconsent, the proportion of typhoid cases that resulted in hospitalization, and blood-culture sensitivity).

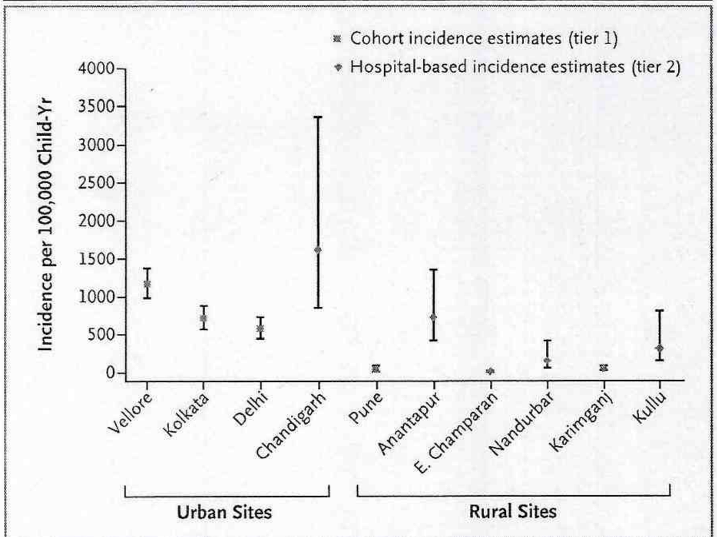

Figure 2. Adjusted Incidence of Typhoid Fever among Children in Tiers 1 and 2.

Shown are cohort incidence estimates (red data points) without adjustments and hospital-based incidence estimates (blue data points) for typhoid fever among children between the ages of 6 months and 14 years in tiers 1 and 2 of the study. The hospital-based incidence estimates were adjusted for health care–seeking behavior in the corresponding age group, missed blood collection owing to nonconsent, the proportion of typhoid cases that resulted in hospitalization, and blood-culture sensitivity. I bars indicate 95% confidence intervals that were calculated for the two analyses on the basis of the Poisson distribution or Monte Carlo simulation, respectively.

Clinical Characteristics of Typhoid Cases

The median duration of culture-confirmed typhoid fever was 9 days (interquartile range, 7 to 11), and the median highest temperature was 102.8°F (Table S5). Other than fever, common symptoms that were reported in 299 children were cough (in 48.5%), nausea or vomiting (in 46.5%), abdominal pain (in 45.8%), and headache (in 38.5%) (Fig. S3). Clinical characteristics of paratyphoid were similar to those of typhoid. No children with typhoid or paratyphoid died, although 46 of 299 (15.4%) and 7 of 33 (21%), respectively, were hospitalized.

Antibiotic Use and Sensitivity

Nearly all the children with confirmed typhoid received antibiotics (296 of 299), including 76.9% who received azithromycin and 48.5% who received a cephalosporin, with a majority of children (53.5%) receiving multiple antibiotics. Nearly all S. typhi isolates (98.3%) were not susceptible to ciprofloxacin.

TIER 2

Surveillance of Hospital Admissions

From February 27, 2018, to March 31, 2020, a total of 15,736 of 20,022 patients who had been admitted to the hospital for febrile conditions (78.6%) were recruited to the study at six hospitals. Of these patients, 8253 (52.4%) were male and 6120 (38.9%) were under the age of 15 years (Table S6).

Blood cultures were obtained from 13,264 patients (84.3%), with a mean blood volume of 8.9 ml in adults and 3.5 ml in children. The most common pathogen was S. typhi (in 221 [1.7%]), followed by staphylococcus species (in 197 [1.5%]) and *Escherichia coli* (in 178 [1.3%]). S. paratyphi A was recovered from 54 samples (0.4%), with one case of S. paratyphi C. Of these samples, 185 containing S. typhi and 52 containing S. paratyphi A were from patients within the catchment population. In 7.8% of the patients, blood culture was performed after antibiotic initiation.

Incidence of Culture-Confirmed Typhoid and Paratyphoid Fever

The incidence of typhoid fever in children per 100,000 child-years ranged from 12 cases (95% CI, 7 to 20) in East Champaran to 1622 cases (95% CI, 858 to 3359) in Chandigarh, after adjustment for surveillance coverage, study adherence, disease severity, and blood-culture sensitivity (Table 2 and Table S7). The incidence of paratyphoid fever per 100,000 child-years ranged from 0 at multiple rural sites to 696 (95% CI, 368 to 1439) at the urban Chandigarh site (Table S8). Among the patients who were 15 years of age or older, the adjusted incidence of typhoid fever per 100,000 person-years varied from 108 cases (95% CI, 69 to 177) in Karimganj to 970 cases (95% CI, 683 to 1420) in Chandigarh; the corresponding incidence for paratyphoid fever ranged from 8 cases (95% CI, 5 to 14) in Karimganj to 437 cases (95% CI, 308 to 641) in Chandigarh. The results of sensitivity analyses after adjustment for blood-culture sensitivity among patients with previous antibiotic exposure are presented in Tables S9 and S10.

The median durations of fever and hospitalization in patients with typhoid fever were 9 days and 5 days, respectively. The median highest temperature recorded was 102.4°F. The median age of the patients who were hospitalized with typhoid fever was 19.4 years (interquartile range, 10.1 to 24.7), with 54.3% of the patients between the

Table 2. **Estimated Incidence of Typhoid and Paratyphoid Fever in Hospital-Based Tier 2 Surveillance.***

Age Group and Study Site	**Setting**	**Geographic Region**	**Typhoid Fever**			**Paratyphoid Fever**	
			Hospitalized Patients	Person-Yr of Observation†	Estimated Incidence (95% CI)	Hospitalized Patients	Estimated Incidence (95% CI)
			no.		*no./100,00 person-yr*	*no.*	*no./100,00 person-yr*
Patients <15 yr of age							
Chandigarh	Urban	Northern	21	71,595	1622 (858–3359)	9	696 (368–1439)
Anantapur	Rural	Southern	19	194,244	730 (419–1356)	3	115 (66–214)
E. Champaran	Rural	Northern Gangetic	1	392,098	12 (7–21)	0	—
Nandurbar	Rural	Western	2	129,095	151 (61–415)	0	—
Karimganj	Rural	Northeastern	6	260,043	48 (31–88)	0	—
Kullu	Rural	Himalayan	5	51,210	308 (155–815)	0	—
Patients ≥15 yr of age							
Chandigarh	Urban	Northern	71	193,571	970 (683–1420)	32	437 (308–641)
Anantapur	Rural	Southern	8	776,975	119 (73–202)	0	—
E. Champaran	Rural	Northern Gangetic	15	667,627	130 (81–218)	4	34 (22–58)
Nandurbar	Rural	Western	7	485,642	174 (98–317)	1	25 (14–45)
Karimganj	Rural	Northeastern	13	504,789	108 (69–177)	1	8 (5–14)
Kullu	Rural	Himalayan	17	192,650	275 (172–469)	2	32 (20–55)

* In tier 2 of the study, six sites in both urban and rural areas were used for a combination of hospital surveillance and surveys on local health care utilization. Additional details regarding the characteristics of the tier 2 surveillance sites are available in the Supplementary Appendix.

† The number of person-years of observation was the same for typhoid and paratyphoid.

ages of 15 and 30 years. Of the 221 patients with typhoid fever, 202 recovered without complications, 14 were referred to another hospital, 4 left the hospital against medical advice, and 1 died.

DISCUSSION

During 2 years of active surveillance, the incidence of culture-confirmed typhoid in three urban Indian cohorts of children exceeded published thresholds above which routine administration of typhoid conjugate vaccines becomes highly cost-effective.[19,20] The incidence was substantially higher than burden estimates that were based on mathematical models that had been fit to hospital-reported cases[21] and was similar to the reported incidence from cohort studies conducted between 1995 and 2006.[22-24] The estimated incidence among children was even higher after adjustment for the low sensitivity of blood culture, with the adjusted incidence ranging from 960 per 100,000 child-years (95% CI, 742 to 1223) in Delhi to 1955 per 100,000 child-years (95% CI, 1652 to 2298) in Vellore. These estimates are also consistent with the estimates in children in urban Chandigarh from the tier 2 hospital-based surveillance.

The high incidence of typhoid in urban India suggests that declines in reported cases from hospitals have been driven by changes in health care–seeking behavior and widespread antibiotic treatment rather than by a reduction in transmission. Antibiotics are commonly available without a prescription, and the number of defined daily doses used in India increased from 3.2 billion to 6.5 billion per year between 2000 and 2015.[25]

The apparent masking of typhoid disease by widespread use of effective antibiotics highlights the major risk posed by emerging strains of extensively drug-resistant S. typhi, a factor that strengthens the argument for the expanded administration of typhoid conjugate vaccines.[10] In our study, although disease incidence peaked among children between the ages of 5 and 9 years, the disease burden was substantial starting at the age of 1 year. Routine immunization with a single dose of a typhoid conjugate vaccine at 9 months of age according to WHO recommendations would offer early protection, with a one-time catch-up immunization of children up to 15 years of age providing protection in a larger vulnerable age range.[5]

Among children, the estimated incidence of typhoid fever in rural areas was lower than that in urban areas. Although urban vaccination alone may reduce incidence, rural areas continue to have moderate levels of disease, and urban migration of younger people will threaten gains achieved through an urban-only vaccination strategy. More than half the patients who were hospitalized with typhoid fever in rural settings were 15 years of age or older, which indicates a substantial burden in adults that may reflect lower exposure during childhood and consequent vulnerability if they migrate to higher-risk settings.

This geographic heterogeneity adds complexity for immunization programs and is also an important issue elsewhere, with many studies in Africa and Asia showing a low incidence of S. typhi[26,27] in rural areas but others showing a relatively high incidence in rural or periurban sites.[28] The uncertainty of our typhoid estimates in rural areas is larger than that in urban areas because the majority of rural data came from tier 2 of the study.

The most administered antibiotics for potential enteric fever were azithromycin and cephalosporins (cefixime or ceftriaxone). The predominant genotype of S. typhi that was circulating in India (4.3.1, also called H58) remains susceptible to these antibiotics, and all isolates were susceptible to ceftriaxone. Strains of extensively drug-resistant S. typhi with resistance to third-generation cephalosporins that have been reported in Pakistan have not yet been isolated in India.[10] However, six S. typhi isolates and eight S. paratyphi A isolates showed evidence of resistance to azithromycin. This finding was consistent with the emergence of azithromycin resistance elsewhere.[9] The spread of S. typhi strains that are resistant to azithromycin and other first-line antibiotics would change typhoid treatment from the use of oral antibiotics to the use of parenteral antibiotics in an inpatient setting, which would be associated with higher mortality and put a further strain on health systems. The burden of paratyphoid was variable and lower in tier 1 sites than in tier 2 sites. The variable incidence and the observed antimicrobial resistance in S. paratyphi are of particular importance because typhoid conjugate vaccines do not protect against S. paratyphi.

Our study has several limitations. In the active surveillance cohorts, early treatment with antibiotics may have resulted in the resolution of fever in some children, which would have meant that they were ineligible for blood culture, a factor that could have contributed to an underestimation of the true incidence. We aimed to minimize this bias through weekly fever surveillance and early referral for blood culture. Nonetheless, 30% of the patients with potential enteric fever were ineligible for blood culture because of defervescence; of these patients, 28% had received antibiotics for at least 48 hours. Previous analyses from this study on the relationship between the use of antibiotics and culture positivity did not show an association.[29] We were also unable to perform a blood culture in 13% of eligible cases of potential enteric fever, and in 9% of such cases we did not obtain a sufficient blood volume, which means that we may have missed some episodes. The 10 study sites (4 in tier 1 and 6 in tier 2) were not randomly selected and thus were not entirely representative of India, so we did not calculate a national incidence estimate. These sites were chosen to broadly reflect the geographic heterogeneity, urban or rural locations, and risk settings available in India, but achieving full representativeness was not possible, given the size of the country and the intensive resources needed to conduct such studies.

In addition, the tier 2 estimates with respect to enteric fever are more uncertain than those in tier 1. Estimates of typhoid incidence from hospital-based surveillance depend on accurate multipliers used to account for such variables as health care–seeking behavior, disease severity, blood-culture administration, and blood-culture sensitivity, each of which retains substantial individual uncertainty. The overall magnitude of the product of these multipliers leads to considerable uncertainty in the estimation of the incidences of typhoid and paratyphoid fever on the basis of hospital admissions data. To address this limitation, we derived confidence intervals using Monte Carlo simulation and based our estimates of health care utilization on surveys from 5000 households at each site, which show appropriately wide intervals suggesting uncertainty.[30] This hybrid surveillance method has been applied in infectious disease surveillance across multiple pathogens.[15-17] Finally, the tier 2 surveillance did not perform sample-size calculations to inform study design.

Despite improvements in water and sanitation and declining trends regarding typhoid cases reported from hospitals, the burden of typhoid in urban India remains high, particularly among the poorest households. The expansion in the use of typhoid conjugate vaccines — in parallel with continued emphasis on safer water, sanitation, and food — offers the potential for a reduction of an underestimated and often overlooked disease in a country that carries the highest burden of typhoid.

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Disclosure forms provided by the authors are available at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix for

Burden of typhoid and paratyphoid fever in India

Table of contents

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Supplementary Methods

Tier 1 statistical analysis

Baseline household characteristics were compared between sites using the chi-squared test. The incidence rates of fever, PEF, and typhoid and paratyphoid fever were calculated per child year of observation (CYO) using survival analysis with interval censoring of periods where valid recall was unavailable. Repeated occurrence of events was permitted in the analysis. Age-group specific incidence was estimated using the 'stsplit' function in STATA and the overall incidence calculated as an average across age-groups, weighted to reflect the age structure of the underlying population at each site. Confidence intervals were calculated using the quadratic approximation to the Poisson log-likelihood for the log-rate parameter. We investigated the association of typhoid incidence with baseline household characteristics and location using Andersen-Gill's proportional hazards model.[1] We built the model incorporating prespecified household (overcrowding, type of family, family size, separate kitchen, and low assets score), environmental (type of house, safe water, treatment of water, sanitary practice of child, sanitary practice of household, and sharing of toilet) and individual (gender, vaccination) level variables and selected the final model based on the Akaikie Information Criteria (AIC). The analysis was performed using STATA 14.2 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.) and R programming language (R version 3.6.1).

Tier 1 notification

We did not explicitly measure the duration of time between notification and visit in the cohort study. However, since most of the weekly surveillance visits were in-person, the bulk of the notifications for cases were at the time of the first visit. When notifications were identified during the telephonic contact, visits were initiated within one day. We found that the mean interval between the onset of fever and the first visit was 1.89 days (sd 1.31days).

Tier 2 Hospital based surveillance sites

The surveillance sites were chosen to represent different geographic and risk settings such as climate and population density. We considered the site's ability to conduct research and the proportion of the catchment population accessing healthcare at the study hospital. Since all sites were required to conduct blood cultures on all febrile admissions, this necessitated the establishment of culture facilities at some facilities, with quality control procedures including proficiency testing at all facilities. All sites provided data on febrile hospitalizations during 2016 and 2017, and geographically contiguous administrative areas from which 80% of the hospitalized febrile patients came to the study facility constituted the catchment for each site.

A brief description of surveillance sites follows.

1) The Anantapur site in the southern state of Andhra Pradesh had a catchment population of 487,000 served by the 350-bed Rural Development Trust Hospital (RDT) at Bathallapali
2) The Nandurbar site in the western state of Maharashtra had a population of 311,000 with a predominantly tribal population was served by Chinchpada Christian Hospital, a 50-bed charitable hospital.

3) The East Champaran site in Bihar is one of the most backward districts of the country. This site has a catchment population of 530,000 in the Raxaul and Ramgarhwa blocks and is served by the Duncan Hospital, Raxaul, a 200-bedded surveillance facility.

4) The Karimganj site in the north-eastern state of Assam is located at the tri-junction of Assam, Tripura, and Mizoram. The Makunda Christian Leprosy and General Hospital is a 160-bed charitable facility that serves Lowairpoa and Patharkandi blocks with a population of 384,000.

5) The Kullu site in the Himalayan ranges of Himachal Pradesh, with a catchment population of 123,000, is served by the 55-bed Lady Willingdon Hospital in Manali.

6) Chandigarh, the only urban site, identified a population of 143,000 in Sectors 45 and 52 as its catchment population. The Civil Hospital at Sector 45 Chandigarh, a 50-bedded government hospital, was the primary inpatient healthcare facility for this population.

Establishment of the hospital surveillance system

Physicians recruited patients older than six months hospitalized at each study facility with presenting complaint of fever, irrespective of the duration or recorded temperature. At admission, study personnel took informed consent and collected age-appropriate blood samples for blood culture. The patients were managed using site-specific treatment protocols. The study protocol required no intervention other than blood culture and data collection. We collected sociodemographic information, history of prior treatment, clinical and laboratory data on electronic case report forms (CRF). The data was stored on a secured, cloud-based, custom-built data management system. Patients with blood-culture confirmed enteric fever were monitored daily to document temperature trends, antibiotic therapy, and complications if any.

Quality control of data and monitoring

The study protocol was harmonised by the coordination unit at the Christian Medical College, Vellore (CMCV), in consultation with the Scientific Advisory Process for Optimal Research on Typhoid (SAPORT), an advisory group established by the Bill and Melinda Gates Foundation, with participation from the World Health Organisation. The coordination unit monitored sites through frequent site visits and data validation checks. Deviations from the protocol were addressed by joint review and re-training. Laboratories participated in an external quality assurance system.

Laboratory methods

At admission, age-appropriate blood volumes (3 ml for infants; 5 ml for those between 1 and 15 years; 8 -10 ml for those older than 15 years) were collected and cultured using an automated system (BD BACTEC™ blood culture system). All the *S.* Typhi and *S.* Paratyphi isolates were reconfirmed and characterised for antimicrobial susceptibility at the central laboratory at CMCV.

Healthcare utilization survey

Two rounds of healthcare utilization surveys were conducted in 2018 and 2019 to identify the proportion of all febrile hospitalizations from the catchment population at the study hospital. A two-stage cluster sampling strategy was used for the selection of households. In the first stage, a random sample of 100 geographical clusters was selected in each site using probability proportional to size method. In the second stage, 50 households were selected from each cluster by systematic random sampling. The methods of the healthcare utilization survey are detailed elsewhere.[2]

Incidence calculation and statistical methods

Crude incidence of severe (hospitalized) enteric fever was calculated by dividing the number of culture-confirmed typhoid and paratyphoid fevers by the catchment population and adjusting for the period of surveillance. The catchment area population was estimated based on projections for the year 2019 from the 2011 census. Only culture-positive enteric fever cases at the study facility from the catchment area contributed to the numerator.

Given the many factors that affect enteric fever incidence measurement through hospital-based surveillance, we performed adjustments (Supplementary Figure S1). Since only a subset of all febrile hospitalizations occurred at the surveillance facility, we adjusted for the proportion of illness with similar presentations treated elsewhere based on the healthcare utilization survey (A2). This ranged from 0.10 in Nandurbar to 0.38 in Chandigarh and Karimganj.[2] A subset of participants admitted with fever failed to receive a blood culture either because of non-consent or operational reasons (ranging from 0-40% among sites), and they were assumed to have a risk of typhoid like those who received a blood culture at the same age and site (A3). We adjusted for the poor sensitivity of blood culture using an adjustment based on blood volume inoculated in culture. (A4). The correction for blood culture sensitivity was assumed to be 60% with an uncertainty range from 50-70%.[3] These adjustments were incorporated in a probabilistic multiplier model. A Monte Carlo approach using a beta distribution generated 1,000 randomly sampled iterations to account for uncertainty in the multiplication parameters. We used the simulation results to obtain the median and 95% uncertainty intervals for the number of total cases of febrile hospitalizations in the catchment area (Supplementary Table S7, S8).

As an additional analysis to permit comparison with studies that estimate the incidence of enteric fever of all severity, we adjusted our estimates of severe enteric fever for the proportion of enteric fevers that require hospitalization (0.154) in cohort studies that formed the tier 1 surveillance (A1). We performed a sensitivity analysis using a lower blood culture sensitivity of 40% (varied 30-50%) for the site- and age-specific fraction of study participants who received antibiotics prior to blood culture collection. Statistical analysis was performed using STATA 15.0 and R 3.6.1

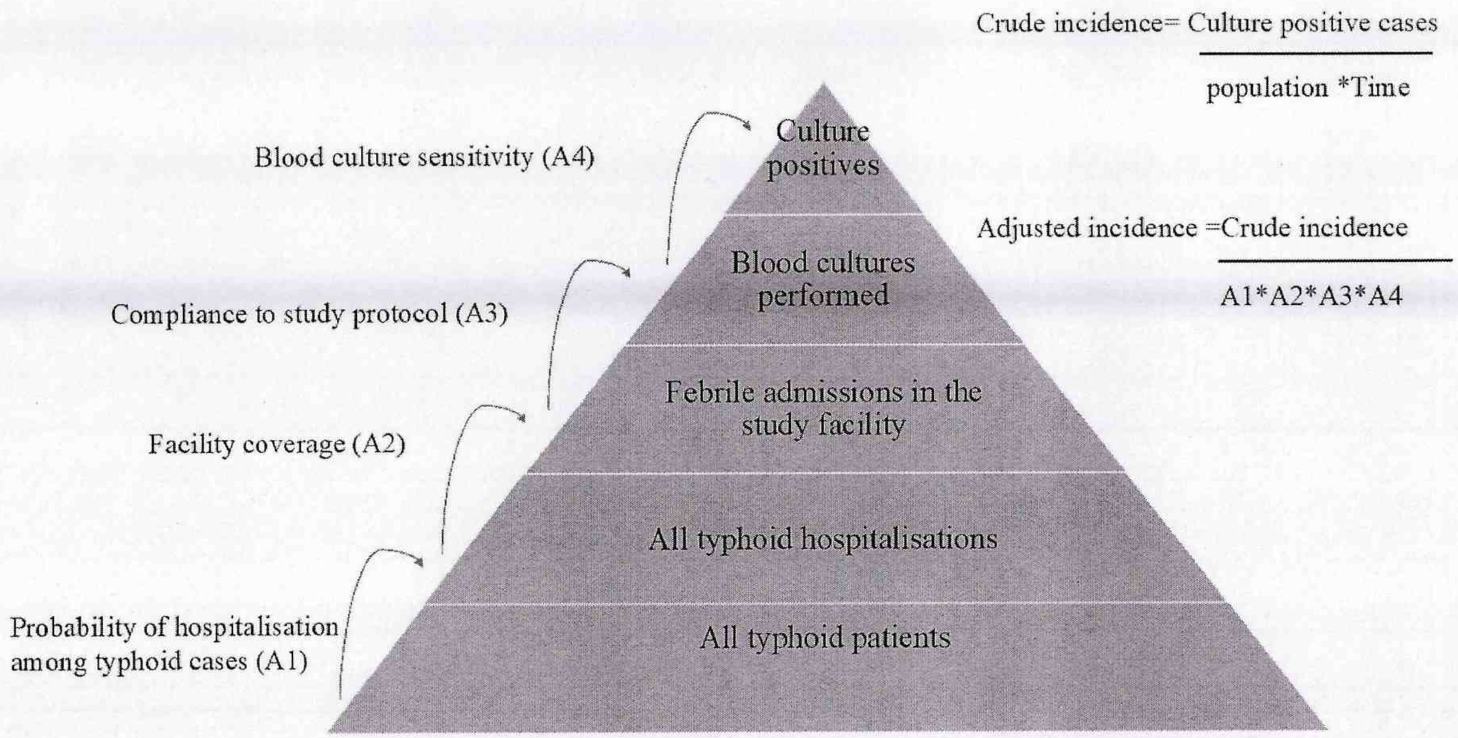

Figure S1: Typhoid disease hybrid surveillance pyramid. The apex represents culture-confirmed typhoid hospitalizations identified in the study hospital. The base of the triangle represents the true burden of typhoid fever in the community. To estimate the true incidence in the community, the crude incidence rate obtained from the hospital-based surveillance is adjusted for A1 (severity of typhoid requiring hospitalization), A2 (proportion seeking healthcare at study facility), A3 (Proportion of hospitalized fevers receiving blood culture), & A4 (sensitivity of blood culture).

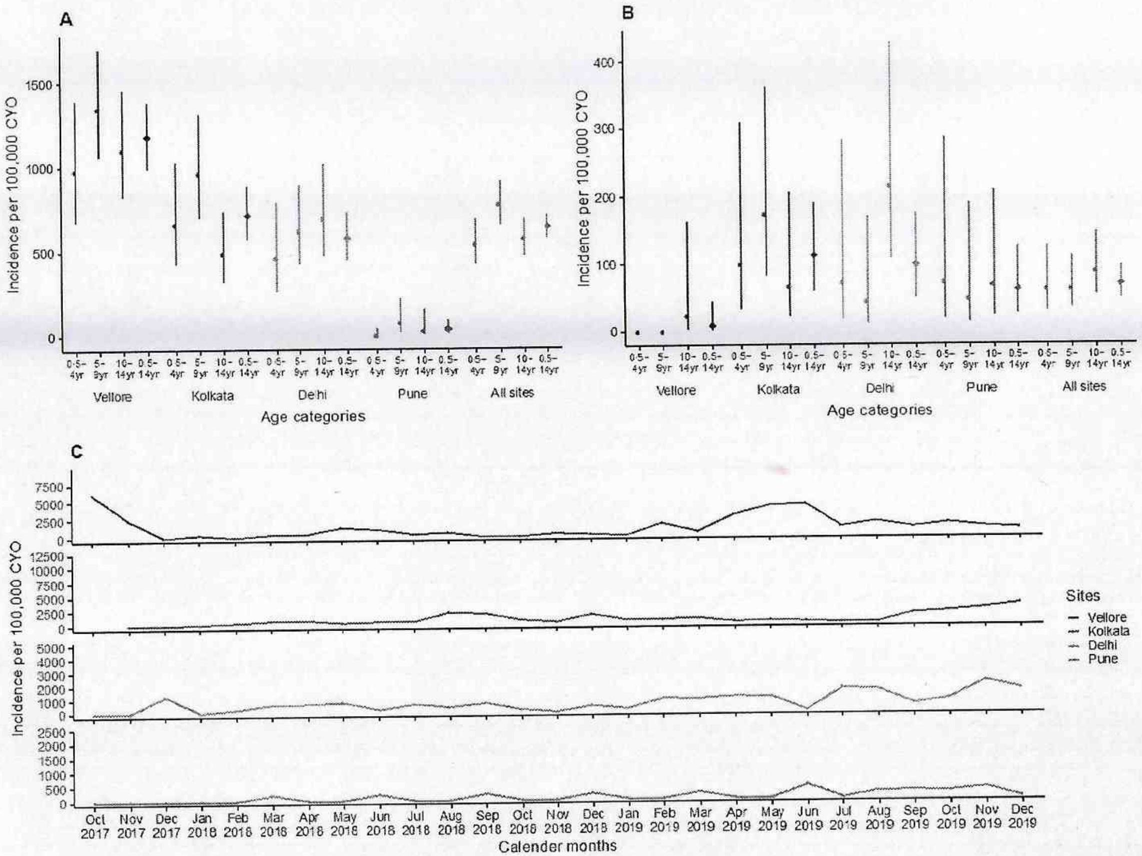

Figure S2: Incidence of culture-confirmed typhoid and paratyphoid fever by Tier 1 cohort site, age, and time.

A) Incidence of typhoid fever and B) incidence of paratyphoid fever by study site and age group. Error bars indicate 95% confidence intervals. C) Monthly incidence (unadjusted) of typhoid and paratyphoid fever at each site with 95% confidence intervals given by the shaded region and periods of high rainfall (monsoon) indicated by the grey rectangles. Incidence in the 0.5-14 years age group is adjusted to match the underlying age-distribution in panel A and B.

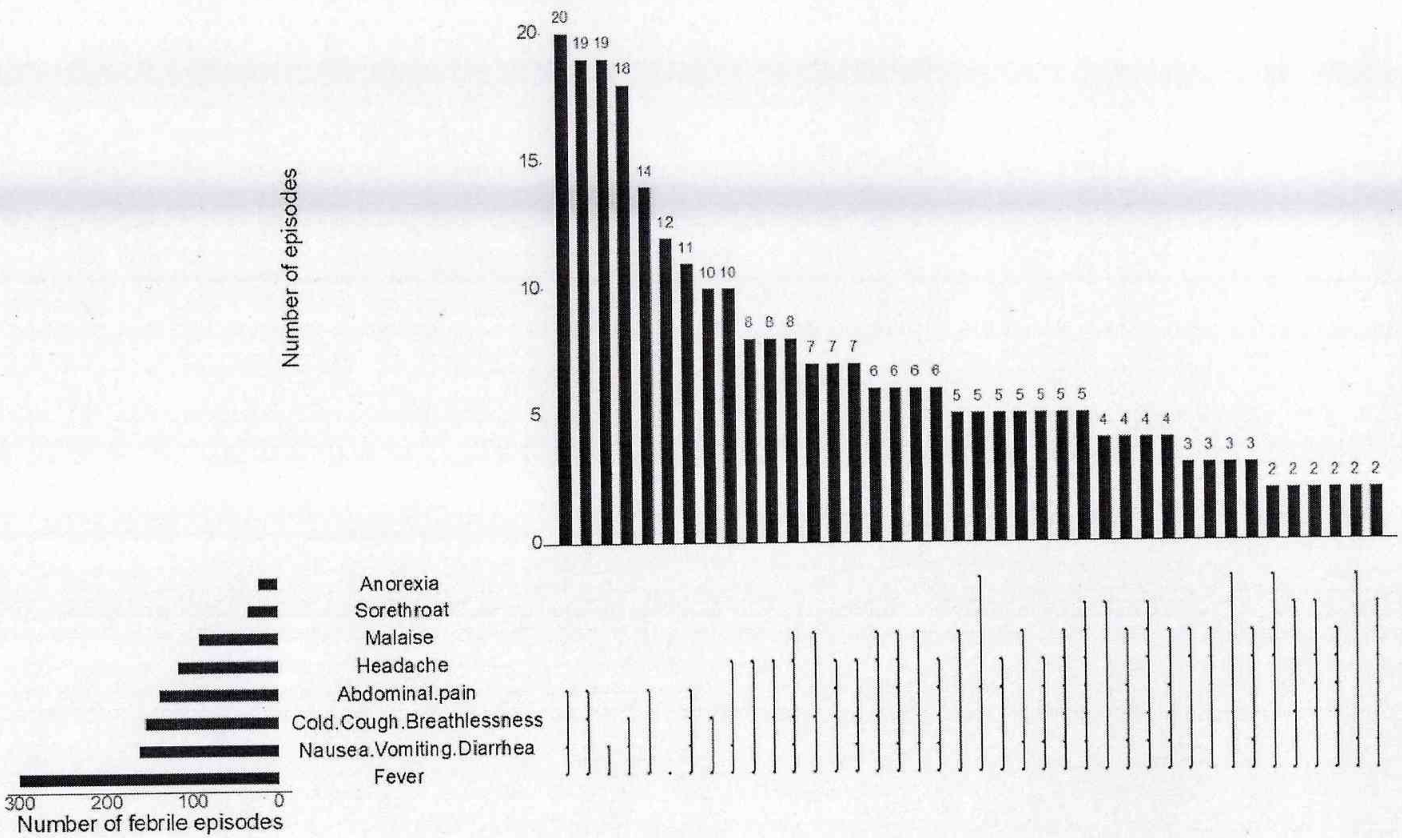

Figure S3: Clinical characteristics of culture-confirmed typhoid cases showing co-occurrence of symptoms, ordered by their frequency across the Tier 1 cohort sites.

Supplementary Tables

Table S1: Cohort study setting and baseline household characteristics for tier 1 surveillance

Site	Vellore	Kolkata	Delhi	Pune	Overall
Type of setting	urban	urban	urban	rural	-
Study area (km^2)	2.2	4.15	0.42	79	
Total number children enrolled	6041	6017	6000	6004	24062
Sex					
Male	3079 (51.0)	3085 (51.3)	3067 (51.1)	3230 (53.8)	12 461 (51.8)
Female	2962 (49.0)	2932 (48.7)	2933 (48.9)	2774 (46.2)	11 601 (48.2)
Age at enrolment					
0.5-4 years	2466 (40.8)	2017 (33.5)	1926 (32.1)	2000 (33.3)	8409 (34.9)
5-9 years	2320 (38.4)	2000 (33.2)	2547 (42.5)	2004 (33.4)	8871 (36.9)
10-14 years	1255 (20.8)	2000 (33.2)	1527 (25.5)	2000 (33.3)	6782 (28.2)
Reported typhoid vaccination*	488 (8.1)	103 (1.7)	62 (1.0)	92 (1.5)	745 (3.1)
Total number of households	3214	4106	3123	3696	14 139
Mean household size (SD)	5.3 (1.9)	4.9 (1.6)	5.3 (1.9)	5.0 (2.0)	5.1 (1.9)
Median monthly family income (IQR) (INR 1000s)	8 (6-10)	9 (8-12)	12 (10-15)	15 (12-25)	10 (8-15)
Separate kitchen available for cooking	2450 (76.2)	1388 (33.8)	2316 (74.2)	2574 (69.6)	8728 (61.7)
Low assets score (< 10)	1490 (46.4)	3032 (73.8)	1333 (42.7)	954 (25.8)	6809 (48.2)
Main source of drinking water					
Piped water into dwelling	577 (18.0)	431 (10.5)	1961 (62.8)	47 (1.3)	3016 (21.3)
Other 'improved' water sources†	2440 (75.9)	3366 (82.0)	815 (26.1)	710 (19.2)	7331 (51.9)
Bottled water	173 (5.4)	96 (2.3)	305 (9.8)	2615 (70.8)	3189 (22.6)
'Unimproved' water sources	24 (0.8)	213 (5.2)	42 (1.3)	324 (8.8)	603 (4.3)
Water treated adequately**	1133 (35.3)	395 (9.6)	1271 (40.7)	915 (24.8)	3714 (26.3)
Type of toilet facility used					
Closed sewer system	0 (..)	1711 (41.7)	40 (1.3)	577 (15.6)	2328 (16.5)
Other sewer system‡	1932 (60.1)	116 (2.8)	14 (0.5)	181 (4.9)	2243 (15.9)
Independent sewer system§	1053 (32.8)	2274 (55.4)	3069 (98.3)	2884 (78.0)	9280 (65.6)
Other unsanitary defecation practices‖	229 (7.1)	5 (0.1)	0 (..)	54 (1.5)	288 (2.0)
Shared toilet facility with other households	536 (16.7)	3181 (77.5)	785 (25.1)	752 (20.4)	5254 (37.2)
Improved sanitation facility available	1061 (33.0)	4094 (99.7)	3118 (99.8)	3634 (98.3)	11 907 (84.2)
Sanitary disposal of child's faeces practised	2411 (75.0)	3757 (91.5)	3026 (96.9)	3397 (91.9)	12 591 (89.1)

Data are n (%) except where indicated. SD=standard deviation. IQR=inter-quartile range. INR=Indian rupees.*Typhoid vaccination reported at the time of screening † include piped water into the yard, public tap/ standpipe, tubewell/borewell, protected well, & springs **Boiling, chlorination, filtration, solar disinfection, and using electronic purifiers were considered as adequate water treatment ‡ include pit latrine, flush/pour flushes to elsewhere. §include septic tank and pit latrine with slab. ‖include pit latrine without slab, open pit/composting/hanging toilet, bush/field/no facility

Table S2: Incidence of fever and potential enteric fever across the four cohorts

	Vellore	Kolkata	Delhi	Pune	Overall
Incidence of fever (number, rate per CYO (95% confidence interval))					
0.5-4 years	9505, 3.08 (3.02-3.15)	6175, 2.05 (2.00-2.10)	5612, 1.98 (1.93-2.03)	7503, 2.67 (2.61-2.73)	28 795, 2.45 (2.43-2.48)
5-9 years	8710, 1.72 (1.68-1.75)	6071, 1.49 (1.45-1.53)	5412, 1.15 (1.22-1.18)	7441, 1.76 (1.72-1.80)	27 634, 1.53 (1.51-1.55)
10-14 years	5333, 1.22 (1.19-1.25)	5495, 1.21 (1.18-1.24)	3415, 0.91 (0.88-0.94)	5355, 1.20 (1.16-1.23)	19 598, 1.14 (1.13-1.16)
Total*	23 548, 1.95 (1.92-1.97)	17 741, 1.60 (1.57-1.62)	14 439, 1.41 (1.39-1.43)	20 299, 1.95 (1.92-1.97)	76 027, 1.73 (1.72-1.74)
Median duration of fever, days (IQR)	2 (1- 3)	2 (1- 3)	2 (1- 4)	2 (1- 3)	2 (1- 3)
Incidence of potential enteric fever‡ (number, rate per 100 CYO (95% confidence inter					
0.5-4 years	2893, 93.9 (90.5- 97.4)	1671, 55.3 (52.8-58.1)	1592, 56.2 (53.5-59.1)	2032,72.2 (69.2-75.5)	8188, 69.7 (68.3- 71.2)
5-9 years	2580, 50.9 (48.9-52.9)	1483, 36.4 (34.6-38.3)	1634, 34.8 (33.2-36.5)	2138, 50.6 (48.5-52.8)	7835, 43.4 (42.4-44.4)
10-14 years	1405, 32.1 (30.5-33.8)	1131, 24.9 (23.5-26.4)	972, 25.9 (24.3- 27.6)	1380, 30.8 (29.2-32.5)	4888, 28.5 (27.7-29.3)
Total*	6878, 57.1 (55.7-58.4)	4285, 39.4 (38.2-40.5)	4198, 40.6 (39.4- 41.8)	5550, 53.3 (52.0-54.7)	20911, 47.8 (47.2-48.4)
Proportion all fever that were potential enteric fever (PEF) (%)	29	24	29	27	28
Number of PEFs eligible for blood culture$ (%)	4610 (67.0)	2900 (67.7)	3183 (75.8)	3955 (71.3)	14648 (70.1)
Proportion of PEFs receiving antibiotics	4354 (63.3)	2956 (69.0)	2813 (67.4)	4014 (72.3)	14155 (67.7)
Time to initiation of antibiotic from fever onset among PEFs					
First day	419 (9.6)	410 (13.9)	513 (18.1)	1262 (31.4)	2604 (18.4)
Second day	598 (13.7)	501 (17.0)	444 (15.7)	1475 (36.8)	3018 (21.3)
Third day	560 (12.9)	353 (11.9)	476 (16.8)	771 (19.2)	2160 (15.3)
Fourth day	1758 (40.4)	1190 (40.3)	782 (27.6)	329 (8.2)	4059 (28.7)
Fifth day	606 (13.9)	356 (12.0)	309 (10.9)	109 (2.7)	1380 (9.9)
Six or more days	413 (9.5)	146 (4.9)	307 (10.8)	68 (1.7)	934 (6.6)
Number of blood cultures performed among eligible PEFΣ (%)	4156 (90.2)	2293 (79.1)	2533 (79.6)	3701 (93.6)	12683 (86.6)
Blood culture not performed for eligible PEF	454 (9.8)	607 (20.9)	650 (20.4)	254 (6.4)	1965 (13.4)

Reasons for not performing blood culture for eligible PEF					
Refusal	247 (5.4)	160 (5.5)	539 (16.9)	129 (3.2)	1075 (7.3)
Others	207 (4.5)	447 (15.4)	111 (3.5)	125 (3.1)	890 (6.1)
Antibiotics used before blood culture (%)	929 (22.4)	753 (32.8)	835 (33.0)	2398 (64.8)	4915 (38.8)
Duration between antibiotic initiation and blood culture					
Two days	277 (29.8)	144 (19.1)	156 (18.7)	447 (18.6)	1024 (20.8)
Three days	311 (33.5)	258 (34.3)	251 (30.1)	949 (39.6)	1769 (36.0)
Four days	220 (23.7)	235 (31.2)	263 (31.5)	811 (33.8)	1529 (31.1)
Five days	75 (8.1)	78 (10.4)	84 (10.1)	126 (5.3)	363 (7.4)
Six or more days	46 (5.0)	38 (5.1)	81 (9.7)	65 (2.7)	230 (4.7)

Data are n (%) except where indicated. *Adjusted to match the underlying age distribution of the populations. ¶An episode of fever was counted as a fever from day one to the last day with elevated temperature that was followed by three fever-free days ‡A child with a fever episode of three or more consecutive days was categorized as potential enteric fever (PEF). ∑Children with PEF were eligible for blood culture. $A child who satisfied the PEF criteria but was afebrile over the last 12 hours prior to the time of performing the blood culture. CYO=child-years of observation. IQR=inter-quartile range.

Table S3: Final clinical diagnosis for potential enteric fevers in the surveillance for enteric fever in India (SEFI) cohorts

Site	Vellore	Kolkata	Delhi	Pune	Overall
Probable bacterial infection					
Appendicitis	3 (0.04%)	0 (..)	0 (..)	0 (..)	3 (0.02%)
Bacterial infection	14 (0.2%)	19 (0.48%)	1 (0.03%)	0 (..)	34 (0.19%)
Ear infection	31 (0.45%)	18 (0.46%)	1 (0.03%)	11 (0.3%)	61 (0.35%)
Enteric fever*	174 (2.53%)	105 (2.68%)	71 (2.28%)	13 (0.35%)	363 (2.06%)
Lower respiratory tract infection	546 (7.94%)	1,077 (27.46%)	18 (0.58%)	345 (9.32%)	1,986 (11.27%)
Scrub	2 (0.03%)	1 (0.03%)	0 (..)	0 (..)	3 (0.02%)
Skin & soft tissue infection	22 (0.32%)	20 (0.51%)	1 (0.03%)	5 (0.14%)	48 (0.27%)
Tuberculosis	2 (0.03%)	0 (0.00%)	3 (0.1%)	0 (0.00%)	5 (0.03%)
Urinary tract infection	72 (1.05%)	5 (0.13%)	2 (0.06%)	5 (0.14%)	84 (0.48%)
Possible bacterial infection					
Acute gastroenteritis	177 (2.57%)	154 (3.93%)	17 (0.55%)	149 (4.02%)	497 (2.82%)
Eye infections	18 (0.26%)	5 (0.13%)	0 (..)	0 (..)	23 (0.13%)
Fever with rash	79 (1.15%)	6 (0.15%)	0 (..)	0 (..)	85 (0.48%)
Other infections	51 (0.74%)	10 (0.25%)	2 (0.06%)	2 (0.05%)	65 (0.37%)
Pharyngitis	160 (2.33%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	161 (0.91%)
Tonsillitis	163 (2.37%)	45 (1.15%)	6 (0.19%)	10 (0.27%)	224 (1.27%)
Unlikely bacterial infection					
Dengue	129 (1.88%)	10 (0.25%)	0 (..)	0 (..)	139 (0.79%)
Jaundice	43 (0.63%)	7 (0.18%)	2 (0.06%)	1 (0.03%)	53 (0.3%)
Measles	2 (0.03%)	6 (0.15%)	0 (..)	1 (0.03%)	9 (0.05%)
Mumps	36 (0.52%)	7 (0.18%)	0 (..)	26 (0.7%)	69 (0.39%)
Upper respiratory tract infection	3,180 (46.23%)	1,396 (35.59%)	377 (12.11%)	501 (13.53%)	5,454 (30.96%)
Varicella	34 (0.49%)	15 (0.38%)	3 (0.1%)	32 (0.86%)	84 (0.48%)
Acute undifferentiated fever	1,940 (28.22%)	1016 (25.91%)	2,610 (83.82%)	2,601 (70.24%)	8,167 (46.36%)
Total	6,878	3,922	3,114	3,703	17,617

* Enteric fever includes clinical diagnosis without blood culture

Table S4: Factors associated with the risk of typhoid in the final multivariable proportional hazards model

Risk factor	Univariable hazard ratio	Multivariable hazard ratio
Rural vs urban study site	0.04 (0.02-0.11)	0.05 (0.02-0.15)
Age in years	0.98 (0.95-1.00)	0.98 (0.96-1.01)
Received typhoid vaccine	0.71 (0.54-1.50)	0.60 (0.28-1.27)
Family size less than six	0.68 (0.54-0.86)	0.71 (0.56-0.90)
Low asset score (<10)	1.57 (1.24-1.98)	1.23 (0.97-1.55)
Improved sanitary facility	0.37 (0.29-0.47)	0.50 (0.39-0.63)

Table S5: Clinical characteristics and treatment of typhoid fever cases in the cohorts

	Typhoid n=299	Paratyphoid n=33
Symptoms other than fever		
Diarrhea	58 (19.4)	4 (12.1)
Nausea/vomiting	139 (46.5)	11 (33.3)
Abdominal pain	137 (45.8)	17 (51.5)
Loss of appetite	22 (7.4)	1 (3.0)
Cough	145 (48.5)	17 (51.5)
Headache	115 (38.5)	9 (27.3)
Sore throat	33 (11.0)	3 (9.1)
Body pain	18 (6.0)	0 (..)
Duration of fever (days), median (IQR)	9 (7-11)	8 (7-10)
Highest documented temperature (□F), median (IQR)	102.8 (101.6-103.7)	102.2 (100.9-103.7)
Hospitalized	46 (15.4)	7 (21.2)
Antibiotics taken	296 (99.0)	33(100)
Azithromycin	230 (76.9)	18 (54.6)
Cephalosporin	145 (48.5)	25 (75.8)
Penicillin	47 (15.7)	8 (24.2)
Others	92 (30.8)	13 (39.4)
Monotherapy	136 (45.9)	13 (39.4)
Multiple	160 (54.1)	20 (60.6)
Proportion susceptible to different antibiotics*	n tested = 294	n tested=33
Ampicillin	293† (99.7)	33 (100)
Chloramphenicol	293† (99.7	32 (97.0)
Co-trimoxazole	293 (99.7	32 (97.0)
Ceftriaxone	294 (100)	33 (100)
Azithromycin	288 (98.0)	25 (75.8)
Ciprofloxacin	5 (1.7)	1 (3.0)

*Antibiotic susceptibility testing results were not available for 4 children; †same isolate was non-susceptible to chloramphenicol and co-trimoxazole

Table S6: Recruitment details and socio-demographic profile of patients from the Tier 2 hospital-based surveillance

		Chandigarh	Anantapur	East Champaran	Nandurbar	Karimganj	Kullu	Overall
Recruitment details- n	Total admissions	20632	36629	24016	6812	26631	7353	122073
	Total AFI admissions	5036	4917	2030	2244	4264	1531	20022
	Total AFI patients enrolled	1650 (32.8)	4508 (91.7)	1,743 (85.9)	2234 (99.5)	4249 (99.6)	1352 (88.3)	15736 (78.6)
	Total blood cultures done n (%)	1600 (97.0)	2884 (64.0)	1592(91.3)	2208 (98.8)	3653 (86.0)	1327 (98.2)	13264 (84.3)
Among all enrolled	*S.* Typhi	92 (5.8)	53 (1.8)	16 (1.0)	12 (0.5)	25 (0.7)	23 (1.7)	221 (1.7)
(% positive)	*S.* Paratyphi	41 (2.6)	5 (0.2)	4 (0.2)	1 (0.1)	2 (0.1)	2 (0.1)	55 (0.4)
From catchment area	*S.* Typhi	92 (5.8)	27 (0.9)	16 (1.0)	9 (0.4)	19 (0.5)	22 (1.7)	185 (1.4)
(% positive)	*S.* Paratyphi	41 (2.6)	3 (0.1)	4 (0.3)	1 (0)	1 (0)	2 (0.2)	52 (0.4)
Sex- n (%)	Male	918 (55.6)	2507 (55.6)	889 (51.0)	1194 (53.5)	2038 (48.0)	707 (52.3)	8253 (52.5)
Age- n (%)	6m-5 years	89 (5.4)	1699 (37.7)	233 (13.4)	149 (6. 7)	1024 (24.1)	316 (23.4)	3510 (22.3)
	6-10 years	80 (4.9)	817 (18.1)	97 (5.6)	111 (5.0)	344 (8.1)	127 (9.4)	1576 (10.0)
	11-15 years	104 (6.3)	444 (9.9)	82 (4.7)	123 (5.5)	218 (5.1)	63 (4.7)	1034 (6.6)
	>=15 years	1377 (83.5)	1548 (34.3)	1331 (76.4)	1851 (82.9)	2663 (62.7)	846 (62.6)	9616 (61.1)
Highest education Mean (SD)	No of years	10.9 (3.8)	9.3 (4.8)	10.9 (4.7)	9.4 (4.9)	9.3 (3.2)	11.7 (3.9)	9.8 (4.3)
Highest occupation n (%)	Student	0 (..)	0 (..)	0 (..)	0 (..)	0 (..)	0 (..)	0 (..)
	Unemployed	4 (0.2)	5 (0.1)	10 (0.6)	3 (0.1)	3 (0.1)	3 (0.2)	28 (0.2)
	Daily wage	371 (22.5)	4054 (89.9)	410 (23.5)	1893 (84.7)	3189 (75.1)	152 (11.2)	10069 (64.0)
	Salaried	961 (58.2)	423 (9.4)	621 (35.6)	266 (11.9)	762 (17.9)	327 (24.2)	3360 (21.4)
	Business	304 (18.4)	24 (0.5)	387 (22.2)	72 (3.2)	294 (6.9)	870 (64.6)	1951 (12.4)
	Household work	10 (0.6)	2 (0.04)	315 (18.1)	0 (..)	1 (0.02)	0 (..)	328 (2.1)
Type of house- n (%)	Hut	4 (0.2)	1524 (33.8)	18 (1.0)	1 (0.04)	99 (2.3)	1 (0.1)	1647 (10.5)
	Kutcha	30 (1.8)	611 (13.6)	598 (34.3)	1776 (79.5)	2682 (63.1)	338 (25.0)	6035 (38.4)
	Pucca	1596 (96.7)	2370 (52.6)	1012 (58.1)	441 (19.7)	991 (23.3)	766 (56.7)	7176 (45.6)
	Mansion	0 (..)	0 (..)	20 (1.2)	0 (..)	3 (0.1)	82 (6.1)	105 (0.7)
	Mixed	20 (1.2)	3 (0.1)	95 (5.5)	16 (0.7)	474 (11.2)	165 (12.2)	773 (4.9)

Table S7: Incidence of hospitalized typhoid fever per 100,000 person years of observation from the Tier 2 hospital-based surveillance

Site	Age group	Person years	Culture confirmed	Crude incidence*	Proportion severe (95% range) (A1)	Study facility utilization (95% range) (A2)	Compliance to the protocol (A3)	Blood culture Sensitivity (95% range) (A4)	Adjusted incidence *	95% Uncertainty Interval #
Chandigarh	Paediatric	71595	21	29.3	0.15 (0.12, 0.20)	0.23 (0.12, 0.39)	0.89	0.6 (0.5, 0.7)	1622.4	858.2 – 3358.8
	Adult	193571	71	36.7	0.15 (0.12, 0.20)	0.42 (0.35, 0.50)	0.98	0.6 (0.5, 0.7)	969.9	683 – 1420
	Overall	265164	92	34.7	0.15 (0.12, 0.20)	0.38 (0.32, 0.45)	0.97	0.6 (0.5, 0.7)	1024	723.2 – 1493
Anantapur	Paediatric	194244	19	9.8	0.15 (0.12, 0.20)	0.23 (0.13, 0.36)	0.65	0.6 (0.5, 0.7)	730.2	419.4 – 1356.2
	Adult	776975	8	1.0	0.15 (0.12, 0.20)	0.16 (0.10, 0.22)	0.62	0.6 (0.5, 0.7)	119.3	72.7 - 201.9
	Overall	971220	27	2.8	0.15 (0.12, 0.20)	0.18 (0.13, 0.24)	0.64	0.6 (0.5, 0.7)	273.8	178.2 - 433.1
East Champaran	Paediatric	392098	1	0.3	0.15 (0.12, 0.20)	0.36 (0.23, 0.51)	0.66	0.6 (0.5, 0.7)	11.9	7.4 - 20.5
	Adult	667627	15	2.3	0.15 (0.12, 0.20)	0.19 (0.13, 0.28)	0.99	0.6 (0.5, 0.7)	130.3	80.8 - 217.8
	Overall	1059725	16	1.5	0.15 (0.12, 0.20)	0.24 (0.18, 0.31)	0.91	0.6 (0.5, 0.7)	76.5	50.8 - 118.7
Nandurbar	Paediatric	129095	2	1.6	0.15 (0.12, 0.20)	0.13 (0.04, 0.27)	0.98	0.6 (0.5, 0.7)	151.4	60.9 - 415.3
	Adult	485642	7	1.4	0.15 (0.12, 0.20)	0.09 (0.06, 0.15)	0.99	0.6 (0.5, 0.7)	173.5	97.7 - 317.1
	Overall	614737	9	1.5	0.15 (0.12, 0.20)	0.10 (0.06, 0.15)	0.99	0.6 (0.5, 0.7)	168.6	99.7 - 292.7
Karimganj	Paediatric	260043	6	2.3	0.15 (0.12, 0.20)	0.63 (0.38, 0.84)	0.83	0.6 (0.5, 0.7)	48.1	31.2 - 87.8
	Adult	504789	13	2.6	0.15 (0.12, 0.20)	0.30 (0.2, 0.41)	0.88	0.6 (0.5, 0.7)	108.4	69.3 - 177.4
	Overall	764834	19	2.5	0.15 (0.12, 0.20)	0.35 (0.26, 0.46)	0.86	0.6 (0.5, 0.7)	90	60.2 - 140
Kullu	Paediatric	51211	5	9.8	0.15 (0.12, 0.20)	0.37 (0.14, 0.66)	0.96	0.6 (0.5, 0.7)	307.8	154.7 - 815.1
	Adult	192650	17	8.8	0.15 (0.12, 0.20)	0.36 (0.23, 0.50)	0.99	0.6 (0.5, 0.7)	274.9	171.9 - 468.9
	Overall	243860	22	9.0	0.15 (0.12, 0.20)	0.36 (0.24, 0.49)	0.98	0.6 (0.5, 0.7)	283	181.6 - 464.7
All sites	Paediatric	1098286	54	4.9	0.15 (0.12, 0.20)	0.29 (0.23, 0.35)	0.76	0.6 (0.5, 0.7)	250.5	173.1 - 373
	Adult	2821254	131	4.6	0.15 (0.12, 0.20)	0.24 (0.21, 0.27)	0.90	0.6 (0.5, 0.7)	239	172.1 - 341.5
	Overall	3919540	185	4.7	0.15 (0.12, 0.20)	0.25 (0.22, 0.28)	0.84	0.6 (0.5, 0.7)	247.3	179.5 - 351.1

* per 100,000 Person Years. # Estimated using Monte Carlo simulation

The 95% range for the A1 and A4 adjustment factors were sampled from beta distributions with shape parameters (A1: 46, 253) and (A4: 57, 38), respectively, based on certainty of these estimates. The 95% range for the A2 adjustment factor was sampled from a normal distribution with a logistic transformation.

Table S8: Incidence of hospitalized paratyphoid fever per 100,000 person years of observation from the Tier 2 hospital-based surveillance

Site	Age group	Person years	Culture confirmed	Crude incidence*	Proportion severe (95% range) (A1)	Study facility utilization (95% range) (A2)	Compliance to the protocol (A3)	Blood culture Sensitivity (95% range) (A4)	Adjusted incidence*	95% Uncertainty Interval #
Chandigarh	Paediatric	71595	9	12.6	0.15 (0.12, 0.20)	0.23 (0.12, 0.39)	0.89	0.6 (0.5, 0.7)	696.2	368.3 – 1439.3
	Adult	193571	32	16.5	0.15 (0.12, 0.20)	0.42 (0.35, 0.50)	0.98	0.6 (0.5, 0.7)	437.1	308 - 640.5
	Overall	265164	41	15.5	0.15 (0.12, 0.20)	0.38 (0.32, 0.45)	0.97	0.6 (0.5, 0.7)	456.3	322.3 - 665.7
Anantapur	Paediatric	194244	3	1.5	0.15 (0.12, 0.20)	0.23 (0.13, 0.36)	0.65	0.6 (0.5, 0.7)	115.3	66.3 - 213.7
	Adult	776975	0	0	0.15 (0.12, 0.20)	0.16 (0.10, 0.22)	0.62	0.6 (0.5, 0.7)	0	-
	Overall	971220	3	0.3	0.15 (0.12, 0.20)	0.18 (0.13, 0.24)	0.64	0.6 (0.5, 0.7)	30.4	19.8 - 48.1
East Champaran	Paediatric	392098	0	0	0.15 (0.12, 0.20)	0.36 (0.23, 0.51)	0.66	0.6 (0.5, 0.7)	0	-
	Adult	667627	4	0.6	0.15 (0.12, 0.20)	0.19 (0.13, 0.28)	0.99	0.6 (0.5, 0.7)	34.8	21.5 - 58.1
	Overall	1059725	4	0.4	0.15 (0.12, 0.20)	0.24 (0.18, 0.31)	0.91	0.6 (0.5, 0.7)	19.1	12.7 - 29.7
Nandurbar	Paediatric	129095	0	0	0.15 (0.12, 0.20)	0.13 (0.04, 0.27)	0.98	0.6 (0.5, 0.7)	0	-
	Adult	485642	1	0.2	0.15 (0.12, 0.20)	0.09 (0.06, 0.15)	0.99	0.6 (0.5, 0.7)	24.8	14 - 45.3
	Overall	614737	1	0.2	0.15 (0.12, 0.20)	0.10 (0.06, 0.15)	0.99	0.6 (0.5, 0.7)	18.7	11.1 - 32.6
Karimganj	Paediatric	260043	0	0	0.15 (0.12, 0.20)	0.63 (0.38, 0.84)	0.83	0.6 (0.5, 0.7)	0	-
	Adult	504789	1	0.2	0.15 (0.12, 0.20)	0.30 (0.2, 0.41)	0.88	0.6 (0.5, 0.7)	8.3	5.3 - 13.6
	Overall	764834	1	0.1	0.15 (0.12, 0.20)	0.35 (0.26, 0.46)	0.86	0.6 (0.5, 0.7)	4.7	3.2 - 7.4
Kullu	Paediatric	51211	0	0	0.15 (0.12, 0.20)	0.37 (0.14, 0.66)	0.96	0.6 (0.5, 0.7)	0	-
	Adult	192650	2	1.0	0.15 (0.12, 0.20)	0.36 (0.23, 0.50)	0.99	0.6 (0.5, 0.7)	32.4	20.2 - 55.2
	Overall	243860	2	0.8	0.15 (0.12, 0.20)	0.36 (0.24, 0.49)	0.98	0.6 (0.5, 0.7)	25.7	16.5 - 42.3
All sites	Paediatric	1098286	12	1.1	0.15 (0.12, 0.20)	0.29 (0.23, 0.35)	0.76	0.6 (0.5, 0.7)	55.7	38.5 - 82.7
	Adult	2821254	40	1.4	0.15 (0.12, 0.20)	0.24 (0.21, 0.27)	0.90	0.6 (0.5, 0.7)	73	52.5 - 104.4
	Overall	3919540	52	1.3	0.15 (0.12, 0.20)	0.25 (0.22, 0.28)	0.84	0.6 (0.5, 0.7)	69.5	50.5 - 98.6

* per 100,000 Person Years. # Estimated using Monte Carlo simulation

The 95% range for the A1 and A4 adjustment factors were sampled from beta distributions with shape parameters (A1: 46, 253) and (A4: 57, 38), respectively, based on certainty of these estimates. The 95% range for the A2 adjustment factor was sampled from a normal distribution with a logistic transformation.

Table S9: Sensitivity analysis on blood culture sensitivity with preceding antibiotics usage on incidence of typhoid fever

Site	Age group	Culture confirmed	Blood culture sensitivity (95% range)	Adjusted incidence*	95% Uncertainty Interval #
Chandigarh	Paediatric	21	0.56 (0.47, 0.66)	1728.2	911 - 3578.2
	Adult	71	0.58 (0.48, 0.67)	1012.2	710.5 - 1486.3
	Overall	92	0.57 (0.47, 0.67)	1071.6	754.1 - 1569.5
Anantapur	Paediatric	19	0.59 (0.49, 0.68)	784.4	429.2 - 1387.6
	Adult	8	0.58 (0.48, 0.67)	123.9	75.4 - 210.1
	Overall	27	0.58 (0.48, 0.68)	282	182.8 - 446.7
East Champaran	Paediatric	1	0.57 (0.47, 0.67)	12.5	7.7 - 21.6
	Adult	15	0.58 (0.48, 0.67)	136	84.1 - 227.6
	Overall	16	0.57 (0.47, 0.67)	80	53 - 124.4
Nandurbar	Paediatric	2	0.6 (0.5, 0.7)	151.4	61 - 417.8
	Adult	7	0.6 (0.5, 0.69)	174.3	98 - 318
	Overall	9	0.6 (0.5, 0.69)	169.5	99.9 - 294.5
Karimganj	Paediatric	6	0.59 (0.49, 0.69)	48.5	31.5 - 88.8
	Adult	13	0.58 (0.48, 0.68)	111.3	71 - 182.3
	Overall	19	0.59 (0.49, 0.68)	92	61.3 - 143.1
Kullu	Paediatric	5	0.57 (0.47, 0.66)	325.7	163.2 - 861.2
	Adult	17	0.57 (0.47, 0.66)	290.6	180.8 - 496.8
	Overall	22	0.57 (0.47, 0.66)	299.1	191.1 - 493.6
All sites	Paediatric	54	0.59 (0.49, 0.68)	256.8	177.3 - 382.9
	Adult	131	0.58 (0.48, 0.68)	246.3	177.1 - 352.9
	Overall	185	0.58 (0.48, 0.68)	254.4	184.3 - 362.2

* per 100,000 Person Years. # Estimated using Monte Carlo simulation

This sensitivity analysis used data on the proportion of participants with antibiotics prior to blood culture collection by age group and site, incorporating a lower sensitivity estimate (40%) for blood cultures taken from these study participants.

Table S10: Sensitivity analysis on blood culture sensitivity with preceding antibiotics usage on incidence of paratyphoid fever

Site	Age group	Culture confirmed	Blood culture sensitivity (95% UI) #	Adjusted incidence*	95% Uncertainty Interval #
Chandigarh	Paediatric	9	0.56 (0.47, 0.66)	740.5	391.1 - 1538.4
	Adult	32	0.58 (0.48, 0.67)	456.1	320.5 - 670
	Overall	41	0.57 (0.47, 0.67)	477.4	336 - 699.3
Anantapur	Paediatric	3	0.59 (0.49, 0.68)	118.2	67.7 - 219.4
	Adult	0	0.58 (0.49, 0.68)	0	-
	Overall	3	0.58 (0.48, 0.68)	31.3	20.3 - 49.6
East Champaran	Paediatric	0	0.57 (0.47, 0.67)	0	-
	Adult	4	0.58 (0.48, 0.67)	36.2	22.4 - 60.6
	Overall	4	0.57 (0.47, 0.67)	20	13.2 - 31.1
Nandurbar	Paediatric	0	0.6 (0.5, 0.7)	0	-
	Adult	1	0.6 (0.5, 0.69)	24.9	14 - 45.5
	Overall	1	0.6 (0.5, 0.69)	18.8	11.1 - 32.7
Karimganj	Paediatric	0	0.59 (0.49, 0.69)	0	-
	Adult	1	0.58 (0.49, 0.68)	8.6	5.5 - 14
	Overall	1	0.59 (0.49, 0.68)	4.8	3.2 - 7.5
Kullu	Paediatric	0	0.57 (0.47, 0.66)	0	-
	Adult	2	0.57 (0.47, 0.66)	34.2	21.3 - 58.5
	Overall	2	0.57 (0.47, 0.66)	27.2	17.4 - 44.8
All sites	Paediatric	12	0.59 (0.49, 0.68)	57.1	39.4 - 85.1
	Adult	40	0.58 (0.48, 0.68)	75.2	54.1 - 107.8
	Overall	52	0.58 (0.48, 0.68)	71.5	51.8 - 101.8

* per 100,000 Person Years. # Estimated using Monte Carlo simulation

This sensitivity analysis used data on the proportion of participants with antibiotics prior to blood culture collection by age group and site, incorporating a lower sensitivity estimate (40%) for blood cultures taken from these study participants.

Supplementary Methods References

1. Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. Ann Statist 1982;10:1100-20.

2. Raju R, Kezia Angelin J, Karthikeyan AS, et al. Healthcare Utilization Survey in the Hybrid Model of the Surveillance for Enteric Fever in India (SEFI) Study: Processes, Monitoring, Results, and Challenges. J Infect Dis 2021;224:S529-s39.

3. Antillon M, Saad NJ, Baker S, Pollard AJ, Pitzer VE. The relationship between blood sample volume and diagnostic sensitivity of blood culture for typhoid and paratyphoid fever: a systematic review and meta-analysis. J Infect Dis 2018;218:S255-s67.