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Spatial epidemiology and multilevel determinants of enteric fever in the India-Bangladesh-Myanmar border region

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Abstract

Background

India is estimated to account for more than 50% of the global burden of enteric fever. Despite the burden, accurate diagnosis remains challenging, particularly in resource-limited settings, hiding the true burden of disease. Even though several surveillance studies have estimated enteric fever incidence in selected regions of India, population-level data at the village level across districts, especially from resource-limited settings in northeast India, would greatly help in understanding the true burden and the multilevel determinants affecting the spread of the disease.

Methods

The passive surveillance data of enteric fever cases (2022–2025) from the northeast state of Mizoram that shares its international borders with Myanmar and Bangladesh was used for the secondary data analysis. District-wise incidence rates of enteric fever cases (n = 47656) were calculated per 100 000-person-years. Individual-level risk factors of hospitalization were assessed using multivariable logistic regression. Village-level determinants for enteric fever incidence and hospitalization were examined using mixed-effects zero-inflated negative binomial and negative binomial regression models, respectively, integrating demographic, infrastructural, healthcare access, and WASH indicators from the Government of India Antyodaya dataset. Spatial analyses were performed using ArcGIS.

Results

The average annual incidence of enteric fever reports in Mizoram was 920 per 100 000 person-years. The incidence rate among children < 15 years was 914 per 100 000 person-years. Enteric fever cases were most frequently reported in urban centers; Aizawl, the capital city of Mizoram accounted for 26.2% of the total enteric fever burden. Hospitalization rates were higher in private hospitals than in public hospitals (OR 9.68, 95% CI 6.58–14.26). Villages with poor WASH indicators, such as open drainage, lack of household latrines, and poor waste management, along with indicators of improved urban infrastructure, had increased reporting of enteric fever.

Conclusion

The huge burden of enteric fever across rural and urban districts of Mizoram underscores the need to strengthen laboratory infrastructure and surveillance, antimicrobial resistance monitoring, and the rational use of antibiotics. It also supports targeted implementation of typhoid conjugate vaccination to high-risk groups alongside sustained investments in WASH and public health surveillance systems.

Introduction

Enteric fever caused by *Salmonella enterica* serotypes Typhi (typhoid) and Paratyphi (paratyphoid) [1] remains endemic in low- and middle-income countries facing overcrowding, inadequate access to water, sanitation, and hygiene (WASH) infrastructure, and a constrained health system [2]. In 2021, the global burden of enteric fever was estimated to be ~ 9.32 million cases and 107.5 thousand deaths; India accounted for more than half (~ 58%) of the global enteric fever cases with the highest age-standardized enteric fever incidence (411.5 cases per 100 000 person-years) and 51.5 thousand deaths [3]. Clinically, enteric fever is characterized by the gradual onset of fever, accompanied by abdominal symptoms [1]. In severe cases, it leads to internal bleeding and perforation of the digestive system [4], accounting for a 2.49–4.45% case fatality rate (CFR) among hospitalized patients [5].

Accurate diagnosis of enteric fever is a critical challenge, particularly in remote areas [6]. Blood culture, with a sensitivity of 40–60%, requires continuous electric supply, robust laboratory infrastructure, costly reagents, and long incubation time, limiting its use in resource-constrained peripheral health settings [6]. Therefore, clinicians rely on the Widal agglutination test and immunochromatography test (ICT)—both of which are easy to use, rapid, and cheap but have low diagnostic accuracy. However, their widespread use can lead to under- or over-diagnosis, hiding the true burden of the disease, complicating treatment, and potentially increasing antimicrobial resistance.

A National Surveillance System for Enteric Fever in India (NSSEFI) study from 2017-18 in children between 6 months and 14 years based on four cohorts has identified typhoid incidence estimates ranging from 35 to 1173 cases per 100 000 child-years [7]. Another NSSEFI study based on hospitalized patients, in six hybrid surveillance sites from 2018-20, has reported incidence from 12 to 1622 [7], underscoring the data heterogeneity in different sites. Regional differences were also reported in earlier studies carried out in Delhi (976 cases per 100,000 person-years) in 1995-96 [8] and Kolkata (265 cases per 100,000 person-years) in 2006 [9]. Past studies have largely focused on the disease burden of metropolitan or selected urban centers, leaving peripheral and border regions under-studied. A fine-scale multidimensional study that focuses on clinical, environmental, epidemiological, and social factors affecting disease prevalence, including WASH practices, is necessary to inform targeted control.

Enteric fever is a notifiable disease under the Integrated Disease Surveillance Program (IDSP) [10], which requires continuous digital reporting of suspected enteric fever cases (P-form) and laboratory-confirmed typhoid and paratyphoid cases (L-form). The recent establishment of the Integrated Health Information Platform (IHIP) has further strengthened disease surveillance by introducing digital recording of individual cases across all health facilities nationwide [11]. This provides systemic population-level passive surveillance data to understand the epidemiology of enteric fever and identify outbreaks. The Northeast (NE) Indian state of Mizoram, located in the Indo-Myanmar region, has been endemic to malaria for decades [12]. In the last decade, dengue [13], scrub typhus [14], and typhoid [15] have also emerged as serious public health threats. The hilly terrain, high annual rainfall, dependence on surface water sources, limited

hygiene, and poor sanitation create favorable conditions for the transmission of enteric fever [16–18]. Low socio-economic conditions, inaccessibility to better healthcare settings, and non-specific febrile symptoms could further increase the risk [19].

The population-based estimates of incidence and spatial distribution to understand individual and community-level risk factors are lacking in Mizoram and in NE India. To our knowledge, this is the first study to characterize the geographic pattern of enteric fever burden in Mizoram and examine its risk factors at multiple levels of the administrative and ecological hierarchy. Mizoram has an efficient health system, even with limited resources, they perform rigorously in carrying out differential diagnosis and reporting endemic infectious diseases. Health centers routinely screen for malaria, scrub typhus, dengue, typhoid, and other febrile illnesses in health sub-centers, primary health centers, and hospitals. Although most suspected enteric fever cases in this setting are diagnosed using Widal or ICT rather than the gold-standard blood culture, the resulting data provide comprehensive statewide coverage of enteric fever reports and enable systematic analysis of spatiotemporal trends.

In this study, we used passive surveillance data reported through the IHIP platform, collated by the Health & Family Welfare Department, Government of Mizoram, to describe the incidence and distribution of enteric fever reports across the state and to examine risk factors at the individual and community levels. By adopting a social–ecological and multi-level epidemiological framework, we aim to go beyond simple incidence estimates to understand how socio-economic conditions, water governance, sanitation practices, and broader structural factors shape patterns of reported enteric fever in the remote border state of Mizoram.

Methods

Study setting and population

Mizoram, a hilly state in the northeastern region of India, shares international boundaries with Bangladesh to its west and Myanmar to its east [12]. The state is administratively divided into 11 districts: Aizawl, Lunglei, Champhai, Serchhip, Kolasib, Lawngtlai, Siaha, Mamit, Hnahthial, Khawzawl, and Saitual [20]. According to Census 2011, the total population is ~ 1.1 million, with about one-third living in the capital Aizawl, which is the most urbanized district [21]; the latest population estimate based on Wang et.al is 457119 [22]. The state is predominantly composed of Schedule Tribes living in both urban and rural areas, and its literacy rate is 91.33%, the third highest in India [21]. The climate of Mizoram is subtropical, with heavy monsoon rainfall, which facilitates the transmission of infectious diseases [23].

Study design

Ecological study design using retrospective passive surveillance data of enteric fever reports.

Data source

Retrospective anonymized line-listing data of enteric fever cases reported from all the health centers during 2022 to 2025 (n = 47,656) were obtained from the Integrated Disease Surveillance Program (IDSP), Directorate of Health Services, Govt. of Mizoram. The cases were reported from primary health centers, community health centers, subdistrict hospitals, district hospitals, medical colleges, and private hospitals. The cases were diagnosed using the Widal test, immunochromatographic test (Typhidot), enzyme-linked immunosorbent assay (ELISA), nucleic acid amplification test (NAAT), and blood culture. Individual-level records were geocoded to 853 villages classified in the 2011 Census; enteric fever case counts and inpatient department (IPD) case counts were aggregated for each village across all four surveillance years. Sociodemographic, infrastructure, WASH, and healthcare-related variables for all villages were sourced from the Antyodaya dataset, a Government of India initiative for recording administrative data at respective panchayats, to monitor development and service delivery indicators across rural areas [24].

Incidence calculation

The year-wise incidence rates were calculated per 100,000 person-years for under 15 years and 15 years and above, for all districts, using projected 2020 population estimates [24–26]

. The projected population for the Saitual district (separated from Aizawl in 2019) was estimated by applying Aizawl's growth rate from 2011 to 2021 [28].

Spatial analysis

The line listing data were consolidated into 853 villages across Mizoram's 11 districts obtained from Census 2011 and assigned unique spatial identifiers for the preparation of a spatial database using ArcGIS 10.4 software (https://desktop.arcgis.com). The year-wise distribution of enteric fever cases from 2022 to 2024 (up to September) was mapped using choropleth maps, with the intensity of color proportional to case numbers.

Individual-level analysis

The chi-square test was performed to assess the association between socio-demographic and clinical variables with hospitalization, using IBM SPSS software (version 29.0). The variables significant at a p-value < 0.05 were selected for multivariate logistic regression analysis using STATA version 13. Standard errors were adjusted for 11 clusters representing the 11 districts of the state to account for potential intra-cluster correlation in hospitalization

outcomes due to shared environmental factors and healthcare access within the districts. Adjusted odds ratios (aOR) with a confidence interval (CI) of 95% were calculated; a p-value < 0.05 is considered significant.

Village-level panel data construction and analysis

The village-wise enteric fever reports from 2022 to 2025 were constructed into a longitudinal panel dataset by restructuring village-level data from wide to long format, i.e., one record per village per year. Villages with missing data (outcome or predictors) were excluded, and a total of 2,200 observations were obtained from 550 villages. The year 2022 was used as a centred year variable (year_c) in all models to capture secular temporal trends. Seventeen predictors were selected to cover socioeconomic conditions, WASH infrastructure, and healthcare access of the villages (**Supplementary Table 01**). All continuous and ordinal predictors were z-standardised prior to modelling.

A two-step collinearity screening test was applied: Pairwise Spearman rank correlation was applied to all predictors, and variables expressing high collinearity ($|r| \geq 0.70$) were removed while retaining one theoretically relevant variable (**Supplementary Fig. 1**). Then, VIF was assessed on all selected variables to test multicollinearity, and variables with values below 3.0 were retained (**Supplementary Fig. 2**). Poisson regression was not a good fit, as the null model for village-level enteric fever case counts showed overdispersion (dispersion ratio = 4.97, Pearson χ^2 = 12,010.1, $p < 0.001$); 34.7% of village-year observations reported zero enteric fever cases. Therefore, both the negative binomial (NB) and the zero-inflated negative binomial (ZINB) models were compared using null models with a district-level random intercept. ZINB showed lower AIC ($\Delta AIC > 2$) and was selected as the final model for the reported enteric fever case. However, there was no overdispersion (dispersion ratio = 0.62, $p = 1.00$) for IPD case counts. Still, the NB mixed model was preferred over Poisson due to the skewed distribution of IPD cases. However, the likelihood ratio between Poisson and NB null models favored the NB regression (χ^2 = 625.07, df = 1, $p < 0.001$; $\Delta AIC = 623.1$), and the NB mixed model was selected as the final model for IPD case counts.

Both outcomes were modelled using mixed-effects count regression with district specified as a random intercept, using the glmmTMB package in R [29]. The natural logarithm of village population was included as an offset so that estimated associations reflect incidence rates rather than case counts. All 17 z-standardised village-level predictors and the centred year variable were included as fixed effects. Exponentiated coefficients are reported as incidence rate ratios (IRR) with 95% confidence intervals. Residual adequacy was evaluated using the DHARMa package in R [29]. which generates scaled randomised quantile residuals through simulation (500 iterations) and tests for deviations from the expected uniform distribution. Statistical significance was defined at $p < 0.05$ throughout.

Ethics statement

The IRB that waived informed consent for the secondary data analysis was the Institutional Human Ethics Committee (IHEC), Central University of Kerala (CUK/IHEC/2024/D/07). We confirm that all methods performed in this study were in accordance with the protocol reviewed and approved by the IHEC.

Results

Socio-demographic and clinical characteristics of enteric fever cases and their association with hospitalization

A total of 47,656 enteric fever cases were reported during 2022 (n = 4499), 2023 (n = 15193), 2024 (n = 13923) and 2025 (n = 14041). Aizawl reported the highest enteric fever cases, contributing to 26.2% (n = 12493) of the total cases, followed by Lunglei (17.9%, 8545), and Serchhip (10.3%, 4890). Summer (May to August) accounted for the highest proportion of cases in the year (43%, 20828). The 15–44-year age group was most frequently affected (42.2%, n = 20124), followed by the 45 + age group (23.7%, n = 11,280). 47.8% (n = 22,765) of the infected cases presented with acute fever (< 7 days) and were predominantly tested by ICT-based RDTs (54.7%, 26,070). Higher reporting of enteric fever cases was observed in public hospitals (77.6%, 36,999). Overall hospitalization rate of reported enteric fever cases during the study period was 0.06 (n = 3,003) (Table 01).

Table 01
Socio-demographic and clinical profile of reported enteric fever cases

Count	Frequency	Percentage
Total Cases	**47656**	
District		
Aizawl	12493	*26.2%*
Champhai	4408	*9.2%*
Hnahthial	2135	*4.5%*
Khawzawl	1880	*3.9%*
Kolasib	2099	*4.4%*
Lawngtlai	4076	*8.6%*
Lunglei	8545	*17.9%*
Mamit	2790	*5.9%*
Saiha	1754	*3.7%*
Saitual	2586	*5.4%*
Serchhip	4890	*10.3%*
Year		
2022	4499	*9.4%*
2023	15193	*31.9%*
2024	13923	*29.2%*
2025	14041	*29.5%*
Season		
Winter *(November to January)*	8650	*18.2%*
Spring *(February to April)*	7976	*16.7%*
Summer *(May to August)*	20828	*43.7%*
Autumn *(September to October)*	10202	*21.4%*
Sex (N = 47647)		
Male	22355	*46.9%*
Female	25292	*53.1%*
Age group		
below 2 years	2051	*4.3%*
2–4 years	4169	*8.7%*
5–14 years	10032	*21.1%*
15–44 years	20124	*42.2%*
45 years and above	11280	*23.7%*
Symptoms		
Acute fever (< 7 days)	22765	*47.8%*
Prolonged fever (≥ 7 days)	8140	*17.1%*
Typhoid symptoms˜	16751	*35.1%*
Test performed (N = 47655)		
Widal	20199	*42.4%*
ICT (Typhoid)	26070	*54.7%*

Note: The transgenders in the dataset were excluded due to their negligible count (n = 9); ˜ Typhoid symptoms – Fever, headache, diarrhoea, and rashes in some cases; † Others- Culture, NAAT, IgM ELISA

Count	Frequency	Percentage
Total Cases	**47656**	
District		
Others†	1386	*2.9%*
Hospital type		
Public	36999	*77.6%*
Private	10657	*22.4%*
Hospitalization		
Inpatient (IPD)	3003	6.3%
Outpatient (OPD)	44653	93.7%
Note: The transgenders in the dataset were excluded due to their negligible count (n = 9); ˜ Typhoid symptoms – Fever, headache, diarrhoea, and rashes in some cases; † Others- Culture, NAAT, IgM ELISA		

[Table 01]

Spatiotemporal distribution of enteric fever cases in Mizoram from 2022–2025:

Enteric fever cases were reported across all districts, indicating endemic transmission throughout the state. Urban centers of Aizawl, Kolasib, Champhai, and Lunglei recorded the highest case concentrations (501 and above), while rural and remote villages also showed considerable burden in the 6–100 case range **(**Fig. 01**).** The year-wise distribution of reported enteric fever cases is shown in **Supplementary Fig. 03**. Compared to 336 in 2022, the case locations increased to 516, 500, and 515 in 2023, 2024, and 2025, respectively. In 2022, cases were moderate, concentrated primarily around Aizawl, which later spread to Serchhip, Champhai, and Hnahthial and other districts from 2023 onwards. However, in 2024 and 2025, enteric fever reports decreased in the peripheral districts, showing reduced intensity, but Aizawl and surrounding areas remained the consistent epicenter.

[Figure 01]

Enteric fever cases showed a clear seasonal pattern, increasing in summers from May and peaking during July–August, followed by a decline towards December.

Across all months, females consistently report slightly higher case counts than males, with both sexes exhibiting similar seasonal trends (**Supplementary Fig. 04)**.

Incidence of enteric fever case reports in Mizoram from 2022–2025

Children under 15 years reported higher enteric fever incidence compared to those aged 15 years and above (**Supplementary Fig. 05**). The annual incidence of enteric fever per 100,000 person-years in Mizoram from January 2022 to December 2025 was 348, 1174, 1075, and 1085, respectively (Table 01). The average annual incidence of enteric fever in Mizoram was 920 per 100,000 person-years, with a higher incidence among children < 15 years (914 per 100,000 person-years) than among the ≥ 15 years age group (546 per 100,000 person-years). Marked inter-district heterogeneity was observed in the distribution of disease—the Serchhip district recorded the highest average annual incidence (1,920 per 100,000 person-years), followed by Lunglei (1,545) and Hnahthial (1,493). Aizawl, the capital city of Mizoram, which contributed 26.2% of total enteric fever cases in the state had the least incidence (683 per 100,000 person-years) along with Kolasib (483 per 100,000 person-years).

[Table 02]

Table 02
Incidence of age-wise enteric fever reports among the districts in Mizoram from 2022–2025 (n = 47656)

Cases/ 100 000 person-years		2022			2023			2024			2025			Av (2
		Below 15	15 and above	Total	Below 15	15 and above	Total	Below 15	15 and above	Total	Below 15	15 and above	Total	Be 15
Aizawl	Cases	457	926	1383	1371	3004	4375	897	2596	3493	670	2572	3242	33
	Incidence	424 [386–464]	265 [248–283]	303 [287–319]	1271 [1204–1340]	860 [830–891]	957 [929–986]	831 [778–888]	743 [715–772]	764 [739–790]	621 [575–670]	736 [708–765]	709 [685–734]	78 [7 81
Champhai	Cases	260	205	465	502	584	1086	503	942	1445	515	897	1412	17
	Incidence	1064 [938–1201]	259 [225–297]	449 [409–492]	2054 [1878–2242]	738 [679–801]	1049 [987–1113]	2058 [1882–2246]	1191 [1116–1269]	1395 [1324–1469]	2107 [1929–2297]	1134 [1061–1210]	1364 [1293–1437]	18 [1 19
Hnahthial	Cases	135	312	447	185	450	635	120	439	559	112	382	494	55
	Incidence	1600 [1341–1893]	1142 [1019–1276]	1250 [1137–1371]	2192 [1888–2532]	1647 [1498–1807]	1776 [1640–1919]	1422 [1179–1700]	1607 [1460–1764]	1563 [1436–1698]	1327 [1093–1597]	1398 [1262–1546]	1381 [1262–1509]	16 [1 17
Khawzawl	Cases	23	42	65	196	193	389	126	300	426	321	679	1000	66
	Incidence	262 [166–392]	148 [106–199]	174 [135–222]	2229 [1928–2564]	678 [586–781]	1044 [943–1153]	1433 [1194–1706]	1054 [938–1180]	1143 [1037–1257]	3650 [3262–4072]	2385 [2209–2572]	2684 [2520–2855]	18 [1 20
Kolasib	Cases	100	119	219	327	450	777	134	295	429	213	461	674	77
	Incidence	390 [317–474]	143 [119–172]	202 [176–230]	1276 [1141–1422]	542 [493–595]	715 [666–767]	523 [438–619]	355 [316–398]	395 [358–434]	831 [723–950]	555 [506–609]	620 [575–669]	75 [7 81
Lawngtlai	Cases	112	113	225	494	645	1139	348	590	938	671	1103	1774	16
	Incidence	321 [264–386]	100 [82–120]	152 [133–173]	1415 [1293–1546]	571 [528–617]	770 [726–816]	997 [895–1107]	522 [481–566]	634 [594–676]	1922 [1780–2074]	976 [919–1036]	1199 [1144–1257]	11 [1 12
Lunglei	Cases	243	383	626	1277	1712	2989	1094	1768	2862	749	1319	2068	33
	Incidence	745 [654–844]	363 [327–401]	453 [418–490]	3913 [3701–4134]	1620 [1545–1699]	2161 [2085–2240]	3352 [3156–3557]	1673 [1596–1753]	2070 [1994–2147]	2295 [2134–2465]	1248 [1182–1318]	1495 [1432–1561]	25 [2 26
Mamit	Cases	83	190	273	418	706	1124	236	473	709	239	445	684	97
	Incidence	359 [286–445]	254 [219–293]	453 [418–490]	3913 [3701–4134]	1620 [1545–1699]	2161 [2085–2240]	3352 [3156–3557]	1673 [1596–1753]	2070 [1994–2147]	2295 [2134–2465]	1248 [1182–1318]	1495 [1432–1561]	10 [9 11
Siaha	Cases	45	96	141	284	388	672	186	345	531	118	292	410	63
	Incidence	404 [295–541]	266 [216–325]	299 [252–352]	2550 [2262–2865]	1076 [972–1189]	1424 [1319–1536]	1670 [1439–1928]	957 [859–1064]	1125 [1032–1225]	1060 [877–1269]	810 [720–908]	869 [787–957]	14 [1 15
Saitual	Cases	43	59	102	339	368	707	287	559	846	353	578	931	10
	Incidence	318 [230–429]	135 [103–174]	178 [145–216]	2511 [2250–2793]	842 [758–932]	1236 [1146–1330]	2125 [1887–2386]	1279 [1175–1389]	1479 [1381–1582]	2614 [2349–2902]	1322 [1217–1435]	1627 [1524–1735]	18 [1 20
Serchhip	Cases	212	341	553	413	887	1300	421	1264	1685	420	932	1352	14
	Incidence	1411 [1227–1614]	701 [628–779]	868 [797–944]	2748 [2489–3026]	1823 [1705–1947]	2041 [1932–2155]	2801 [2540–3082]	2598 [2456–2745]	2646 [2521–2775]	2794 [2534–3075]	1915 [1794–2042]	2123 [2011–2239]	24 [2 25
Mizoram	Cases	1713	2786	4499	5806	9387	15193	4352	9571	13923	4381	9660	14041	16
	Incidence	561 [534–588]	282 [271–292]	348 [337–358]	1900 [1852–1950]	949 [930–968]	1174 [1155–1192]	1424 [1382–1467]	968 [948–987]	1075 [1058–1094]	1434 [1392–1477]	977 [957–996]	1085 [1067–1103]	91 [9 92

Note: The population was taken from Harvard population estimates for 2022 except for Saitual.

The population for Saitual was calculated from the percentage increase in Aizawl and the 2011 census population of Saitual.

The age-wise population was obtained using the proportion of the < 15-year-old population from the 2011 census for Mizoram.

Incidence was calculated as cases per 100000 child-years for < 15 years age group and cases per 100000 person-years for ≥ 15 years age group.

Individual predictors of hospitalization among reported enteric fever cases in Mizoram

Summer (39.7%, 1192), females (50.8%, 1527), private hospitals (60.7%, 1822), urban residence (55%), provisional diagnosis of fever < 7 days (54.3%, 1631), Widal test (51.2%, 1335), age group 15–44 years (40.4%, 1213), and year 2024 (33.5%, 1005) accounted for increased hospitalization rates of enteric fever reports. All the variables were significantly associated with hospitalization ($p < 0.05$) (**Supplementary Table 2**).

Multivariate logistic regression shows significantly lower odds of hospitalization among cases reported in autumn compared with winter (OR 0.845, 95% CI 0.744–0.959, $p = 0.009$), whereas spring and summer were not significant. Females had lower odds of hospitalization than males (OR 0.882, 95% CI 0.804–0.967, $p = 0.007$). Compared to infants under 2 years, children aged 2–4 years (OR 0.661, $p < 0.001$) and 5–14 years (OR 0.507, $p < 0.001$) had significantly lower odds of hospitalization, while the adult and elderly populations did not show any significant differences. Symptoms did not significantly influence hospitalization odds. Among diagnostic tests, cases diagnosed using ICT-based rapid diagnostic tests had significantly lower odds of hospitalization compared to culture- or molecular-based cases (OR 0.389, $p < 0.001$). Enteric fever cases reporting to private facilities were almost ten times more likely to be hospitalized compared to those attending public hospitals (OR 9.683, 95% CI 6.575–14.261, $p < 0.001$) **(**Table 03**)**.

Table 03
Factors associated with hospitalization among enteric fever cases, Mizoram, India, 2022–2025. (N = 47,646 cases)

Variable / Category	OR (95% CI)	p-value
Surveillance year		
2022 (ref)		
2023	1.186 (0.960–1.466)	0.114
2024	**1.631** (1.204–2.209)	**0.002***
2025	**1.363** (1.123–1.654)	**0.002***
Season		
Winter *(November to January)*		
Spring *(February to April)*	1.052 (0.903–1.225)	0.516
Summer *(May to August)*	0.941 (0.832–1.064)	0.330
Autumn *(September to October)*	**0.845** (0.744–0.959)	**0.009***
Sex		
Male (ref)		
Female	**0.882** (0.804–0.967)	**0.007***
Age group (years)		
< 2 (ref)		
2–4	**0.661** (0.525–0.832)	**< 0.001****
5–14	**0.507** (0.380–0.676)	**< 0.001****
15–44	0.784 (0.539–1.139)	0.202
≥ 45	1.296 (0.878–1.913)	0.191
Presenting symptoms		
Acute Fever only (ref)		
Chronic Fever	1.153 (0.830–1.603)	0.397
Fever + gastrointestinal	0.689 (0.420–1.129)	0.139
Diagnostic test performed		
Culture/other (ref)		
Widal test (positive)	1.448 (0.942–2.226)	0.091
ICT-based RDT (positive)	**0.389** (0.250–0.606)	**< 0.001****
Hospital type		
Public (ref)		
Private	**9.683** (6.575–14.261)	**< 0.001****

Dependent variable: Inpatient hospitalization (outcome group), OPD (reference); AOR= Adjusted CI= Confidence Interval, ref= Reference; mean VIF of regression model = 2.45;
Model: Logistic regression with cluster-robust standard errors (Huber–White sandwich estimator; 11 clusters at district level).

Area under ROC curve = 0.7708

Model fit: Log pseudolikelihood = −9,526.23; McFadden pseudo-R^2 = 0.150.

Significance thresholds: *p < 0.05; **p < 0.001.

[Table 03]

Village-level predictors of enteric fever burden

Community-level predictors of reported enteric fever cases and hospitalization are presented in Table 04. A multilevel zero-inflated negative binomial (ZINB) model was fitted for overall enteric fever case reports, and a negative binomial mixed model was used for hospitalized cases, with district as a random intercept and population as an offset.

Table 04
Village-level predictors affecting enteric fever case reports and hospitalization

Predictor	EF cases – ZINB	EF IPD cases – NB model
Population	**-0.319 (0.007)****	0.029 (0.791)
Pucca households	**0.429 (< 0.001)*****	0.036 (0.701)
Waste disposal	-0.045 (0.362)	**-0.224 (0.005)****
Open drainage	**0.146 (0.002)****	0.004 (0.954)
Distance to SC	-0.045 (0.303)	0.002 (0.976)
No latrine	**0.241 (< 0.001)*****	**0.116 (0.054).**
Good Anganwadi	**0.161 (< 0.001)*****	0.020 (0.783)
Distance to public transport	**-0.249 (< 0.001)*****	**-0.258 (< 0.001)*****
Pucca road	-0.082 (0.089).	0.100 (0.162)
Villages declared ODF	0.014 (0.768)	0.116 (0.130)
WASH committee	**0.219 (0.001)****	0.063 (0.499)
Solid waste collection	0.078 (0.076).	0.130 (0.042)*
Water chlorination	**0.120 (0.005)****	0.079 (0.202)
Water testing	-0.015 (0.719)	0.001 (0.993)
Piped water	-0.011 (0.777)	-0.062 (0.288)
Electricity hours	**0.217 (< 0.001)*****	**0.207 (0.002)****
Households receiving food grains from fair price shop	0.065 (0.057).	0.055 (0.290)
Year	**0.307 (< 0.001)*****	**0.273 (< 0.001)*****
Note: Values are incidence rate ratios (IRR) obtained by exponentiating model coefficients.		
IRR > 1 indicates increased incidence; IRR < 1 indicates decreased incidence.		
Models include a district-level random intercept.		
Population included as log-offset.		
EF cases model uses zero-inflated negative binomial; EF IPD uses negative binomial.		
Zero-inflation results are presented as odds ratios (OR).		
Significance: *** p < 0.001, ** p < 0.01, * p < 0.05,. p < 0.1		
Wide confidence intervals in zero-inflation suggest model instability / weak separation.		
Zero-inflation component: No predictors were statistically significant; estimates were unstable (large SEs), suggesting weak evidence for structural zeros.		

From the ZINB model, a higher proportion of pucca (permanent) households (β = 0.43; p < 0.001), presence of open drainage (β = 0.15; p = 0.002), households without latrines (β = 0.24; p < 0.001), coverage of good Anganwadi services (β = 0.16; p < 0.001), presence of WASH committees (β = 0.22; p = 0.001), water chlorination coverage (β = 0.12; p = 0.005), and electricity supply hours (β = 0.22; p < 0.001) were positively associated with higher reporting of EF cases. On the contrary, larger population size (β = −0.32; p = 0.007) and longer distance to public transport (β = −0.25; p < 0.001) were associated with lower reporting of enteric fever cases. There was a strong positive temporal trend in enteric fever cases during the study period (β = 0.31; p < 0.001). None of the predictors in the zero-inflation component were statistically significant.

In the NB model for hospitalized enteric fever cases, good waste disposal practices (β = −0.22; p = 0.005) and longer distance to public transport (β = −0.26; p < 0.001) were negatively associated with IPD cases, while solid waste collection (β = 0.13; p = 0.042) and longer electricity supply hours (β = 0.21; p = 0.002) were positively associated with IPD case counts. There was a significant increasing trend in IPD cases over the study period (β = 0.27; p < 0.001). The area under curve as 0.77

[Table 04]

Supplementary Figs. 6 and 7 show the results of diagnostic testing of the DHARMa package—QQ-plot, Kolmogorov-Smirnov test, outlier test, and dispersion test. For the enteric fever case reports count model, both the dispersion test (p = 0.960) and the zero-inflation test (p = 0.068) were non-significant, suggesting overdispersion and excess zeros in the outcome. The Kolmogorov–Smirnov test (0.070) showed a negligible deviation, but the model was considered a good fit as dispersion and zero-inflation checks were optimal. For the NB IPD model, all the DHARMa diagnostics were non-significant (KS: D = 0.016, p = 0.609; dispersion: p = 0.872; zero-inflation: p = 0.716), indicating good overall fit.

Discussion

This study provides the first systematic, population-based, multilevel social-epidemiological characterization of passive enteric fever reports in Mizoram. The average annual incidence of reported enteric fever cases in Mizoram was 920 per 100,000 person-years, which is more than double the geospatial model-based estimate of 444 cases per 100,000 person-years derived by Cao et al. [30]. It reflects the limitation of ecological modeling in capturing heterogeneity at the subnational level and the ability of a strong healthcare infrastructure in disease surveillance, as the state has systematically integrated screening and line listing for multiple infectious diseases across all health settings. The Widal test and Typhidot test, despite their low diagnostic specificity [31, 32], are commonly used in most of the healthcare units in Mizoram due to poor infrastructure and lack of training to use blood/bone marrow culture, which could have resulted in the overestimation of cases. Enteric fever diagnosis by clinical presentation, traditional Widal tests, and rapid diagnostic tests (RDTs) is most common in rural and peri-urban centres of low- and middle-income countries; however, due to their low predictive value, these methods overestimate true burden of disease and lead to frequent misdiagnoses and inappropriate treatment [33–35]. Typhidot has been shown to yield false-positive results in patients with dengue fever due to serological cross-reactivity, which is concerning, particularly in Mizoram, which is endemic to multiple diseases [36]. However, Mizoram has the highest documented enteric fever cases in India and must be considered as a signal of endemicity rather than an artifact of ascertainment. The disease followed a seasonal pattern with increased cases in summer, followed by decline during autumn. The rise in cases reported coincides with the monsoon (summer monsoon) in Mizoram, likely due to contamination of surface water, which is the primary source of drinking water in Mizoram. Environmental analysis using a global dataset showed enteric fever cases are positively associated with preceding rainfall in regions located between 35°–11° N [37], where our study site falls. While summer witnessed high case reporting, higher odds of hospitalization were noted in winter, despite the low prevalence, which could be due to seasonal low immunity in winters of coinfection with other flu. Males had higher odds of hospitalization, likely due to occupational exposure. Enteric fever cases reported in private hospitals were almost ten times more likely to be hospitalized than in public health facilities; this is likely explained by differences in healthcare-seeking behavior, better infrastructure, and standards of care in the private sector [38]. However, hospitalization in private facilities substantially increases the economic burden of the disease. Previous estimates indicate the mean direct cost of severe enteric fever ranges from US$119.1 (95% CI, US$85.8–152.4) in smaller hospitals in urban slums/rural/tribal settings and US$405.7 (95% CI, US$366.9–444.4) in urban referral hospitals [39]. This underscores the need for strengthening public healthcare infrastructure in diagnosis and treatment of febrile cases and expanding preventive strategies such as implementing typhoid conjugate vaccination (TCV), particularly in high-endemic settings.

As of 2024, WHO has prequalified the use of three typhoid conjugate vaccines due to their effectiveness, safety, single use, protection for age group > 4 years, and suitability to children > 6 months of age [40]. Regions with > 100 typhoid cases per 100 000 person-years are categorized as high-burden [41]. Mizoram, with children < 15 years being predominantly affected with 914 enteric fever reports per 100,000 child-years and high hospitalization rates of children < 2 years, would greatly benefit from vaccination with TCV. Introducing TCV can prevent typhoid cases and deaths up to 17–36% in urban areas and 19–36% in rural areas [42]. Vaccination with TCV is suggested to be cost-effective in countries with 300 or more typhoid cases per 100 000 person-years [43]. Within the first 10 years of implementing a nationwide community-based catch-up campaign targeting children aged 1–15 years alongside routine vaccination in India, TCV could avert 21–39 million cases and save $1.6–$2.2 billion [44].

Our spatial analysis showed a heterogeneous distribution across the state, with higher enteric fever reporting in urban areas of Mizoram; Aizawl accounted for one-fourth (26.2%) of the total enteric fever burden. The spatial heterogeneity could be due to increased urbanization, higher population density, and unimproved sanitation infrastructure. Higher reporting of enteric fever was observed in villages with open drainage, lack of household latrines, and poor solid-waste practices, which are key drivers of enteric fever transmission. Contamination of open drains with sewage waste from open defecation and unimproved latrine facilities in the locality, and open drain flooding during rainfall, increase the odds of enteric fever, particularly among the younger population [45]. Poor solid waste management attracts stray animals and flies, increasing the risk of disease occurrence and severity despite individual hygiene practices. Chaelin et al. show that unsafe waste management, untreated water, limited hygiene practices, and exposure to contaminated surface water substantially increase the odds of typhoid fever [18]. The presence of a water chlorination system and a WASH committee in villages is associated with higher reports of enteric fever, likely indicating a targeted public health response—areas with higher enteric fever reports or recognized water quality issues may have a WASH committee and prioritized chlorination as a reactive measure. Good Anganwadi infrastructure enables referral of children with febrile and diarrheal illnesses to health workers or the nearest health centers, thereby increasing the reporting of enteric fever. Villages situated at a longer distance to public transport facilities have lesser odds of enteric fever reporting and hospitalization, likely due to limited access to healthcare. Villages with a higher proportion of pucca houses and longer hours of electricity supply indicate better infrastructure and improved living standards, enabling better healthcare access and care-seeking behavior, thereby increasing enteric fever reports and hospitalization. Another explanation—although we couldn't capture it in the study—is that these urbanized settings are likely to have overcrowded places with availability of street food, which could also explain the increased case reports.

Mizoram also has a huge burden of scrub typhus and other rickettsial infections [14], the incidence rates are the highest in India. The overlapping clinical presentations of scrub typhus, enteric fever, dengue, and other acute undifferentiated febrile illnesses often lead to empirical antibiotic treatment, particularly in peripheral healthcare settings where confirmatory diagnostics remain limited. Consequently, antibiotics such as azithromycin, doxycycline, ceftriaxone, and fluoroquinolones are extensively used across Mizoram for the management of scrub typhus and enteric fever; sustained antibiotic use could lead or have led to the emergence of drug-resistant *S*. Typhi and *S*. Paratyphi strains. Mizoram shares its international borders with typhoid-endemic countries of Bangladesh [46] and Myanmar [15, 47]. Azithromycin resistance to *S*. Typhi and *S*. Paratyphi has been reported in Bangladesh, with the first case identified as early in 2013 [48]. While no data on enteric fever AMR is available from Myanmar, AMR to first-line antibiotics for other bacterial infections is prevalent [49]. In recent years, Mizoram has seen an influx of refugees from Bangladesh and Myanmar [47–49]; genomic analysis could give important insights into the population structure of the circulating enteric fever strains and drug resistance. Even though extensively drug-resistant *S*. Typhi has not been reported in India, the recent reports of resistance to azithromycin [53] and third-generation cephalosporins are worrying.

The study has some notable limitations. Firstly, 97% of clinically suspected typhoid cases were diagnosed using the Widal test or the Typhidot RDT, which has lower diagnostic accuracy than the gold standard, blood/bone marrow culture. The present analysis considered all clinically suspected and serologically positive cases collectively as enteric fever, without species-level stratification between *S.* Typhi and *S.* Paratyphi. The study relied on passive surveillance data obtained from healthcare facilities across Mizoram; these reports could be likely influenced by healthcare-seeking behavior, healthcare accessibility, clinician testing practices, and availability of diagnostic facilities, resulting in under-ascertainment of cases in remote, resource-limited settings. It is passive surveillance data, so we miss the cases that are underreported due to the health-seeking behavior of people. We could not calculate the CFR attributable to typhoid and paratyphoid due to the absence of mortality data. The duration of hospitalization is considered a proxy indicator of the severity; the duration of hospitalization in paratyphoid is shorter [58]. As we lacked data on the duration of hospitalization, we could not compare the recovery time in typhoid and paratyphoid. As enteric fever cases are reported from health units across Mizoram, the decision of the handling physician to perform enteric fever diagnosis could affect the final data from individual health units.

For decades, malaria has been the major public health concern in Mizoram [59]. In recent years, the state has also been witnessing a huge burden of scrub typhus [14] and enteric fever [15]. The high incidence of infectious diseases in Mizoram is due to the integration of specialized diagnostics into its healthcare units, which enables early diagnosis. However, the health centres rely on suboptimal diagnostic tools for screening enteric fever, resulting in misdiagnosis of febrile cases and inappropriate antibiotic prescriptions. Improving diagnostic facilities for screening febrile cases in peripheral healthcare settings enables understanding the true burden and transmission dynamics of typhoid and paratyphoid fever and reduces misdiagnosis and inappropriate antibiotic use. Establishment of sentinel surveillance sites for culture-confirmed enteric fever and antimicrobial resistance monitoring is needed in Aizawl and other urban areas with high enteric fever reporting. This can provide critical evidence on circulating *S.* Typhi and *S.* Paratyphi strains and emerging drug resistance patterns. With efficient diagnostics and accurate reporting, a similar burden of enteric fever might also be seen in several parts of India, thus underlining a strong case for including TCV vaccination in the immunization schedule.

Conclusion

Mizoram reports more enteric fever cases than national estimates, and these cases are disproportionately concentrated in urban areas. The high incidence rates of enteric fever across Mizoram and increased hospitalization of children < 2 years of age in the study present compelling evidence for the urgent implementation of TCV in Mizoram. The steep increase in enteric fever incidence over the years warrants immediate assessment of species-specific culture-confirmed cases and the status of antibiotic resistance among circulating strains of S. Typhi and S. Paratyphi. The findings of this study could also have important public health implications for enteric fever control in the districts of Bangladesh and Myanmar that border Mizoram.

Declarations

Ethics approval and consent to participate

The IRB that waived informed consent for the secondary data analysis was the Institutional Human Ethics Committee (IHEC), Central University of Kerala (CUK/IHEC/2024/D/07). We confirm that all methods performed in this study were in accordance with the protocol reviewed and approved by the IHEC.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the Integrated Disease Surveillance Program of Mizoram's Health and Family Welfare Department and are not publicly available. The request for de-identified datasets should be made to Dr. Lalfakzuala Pautu, State Vector Borne Disease Control Programme, Health & Family Welfare Department, Mizoram, Email ID: fakaento@gmail.com. Data for village-level predictors were obtained from the Mission Antyodaya 2022-23 website (https://missionantyodaya.dord.gov.in/).

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

LP, PTP, and PBN conceptualized, designed, and wrote the first draft of the manuscript. SS, CV, and PTW contributed to the literature search. VC, VL, EZ, PKB, SKB, and KB contributed to the review and editing of the manuscript. PKB and PTP analysed the data, and KB made the figure. All authors have read and agreed to the final version of the manuscript.

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Figures

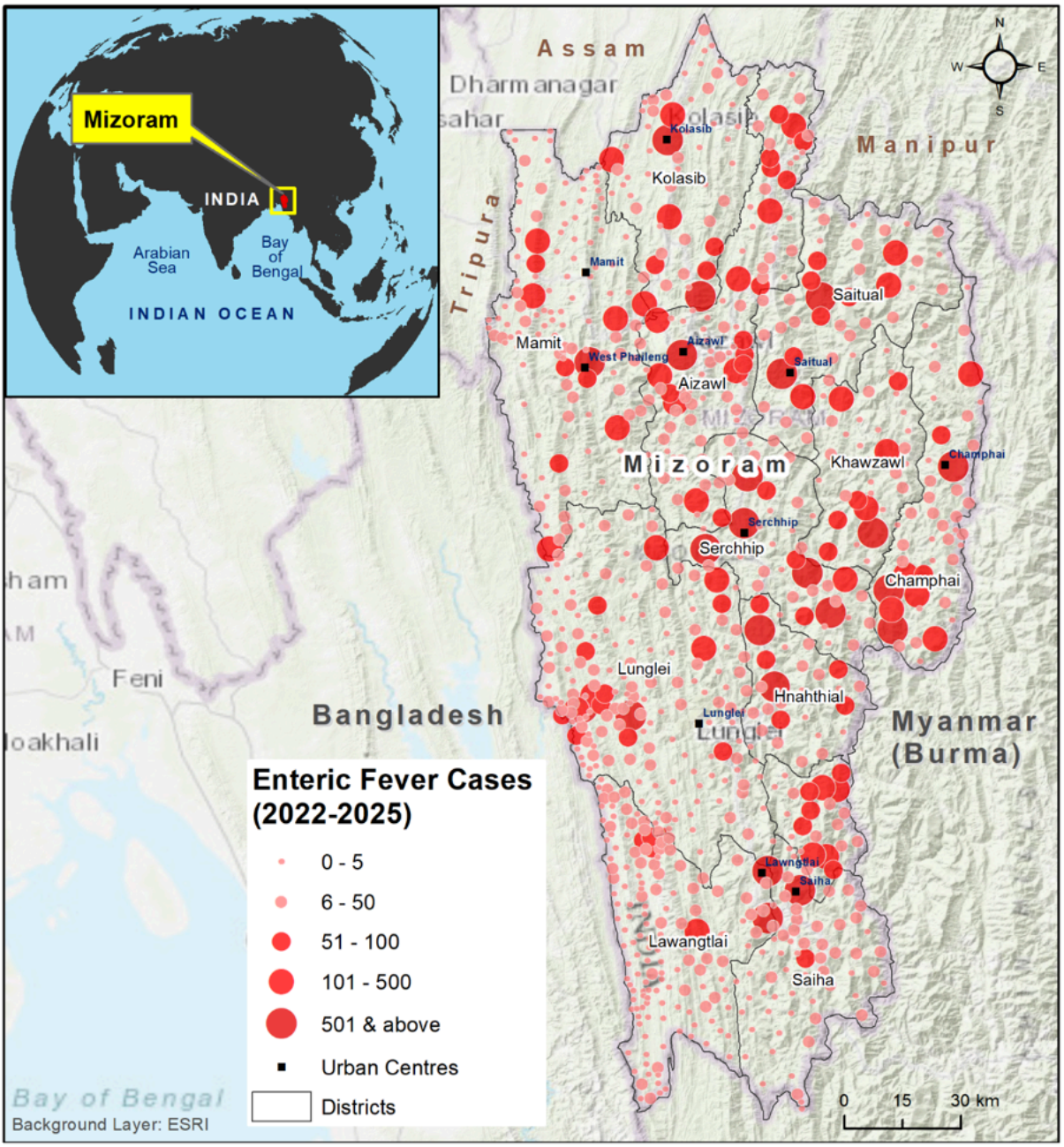


Figure 1

Spatial distribution of enteric fever reports across Mizoram during 2022-2025

The size of the red circles represents the cumulative number of enteric fever cases reported at each village/town through the Integrated Health Information Platform (IHIP). Black squares denote urban centres, and grey polygons represent district boundaries. The inset map shows the geographic location of Mizoram in Northeast India.

Supplementary Files

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