



Research Article

## Community Incidence of Culture-Confirmed Typhoid and XDR *Salmonella* Typhi among Urban in Lower Dir, Pakistan.

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**Abstract: Background:** Typhoid fever remains a major public health concern in Pakistan, particularly in communities with inadequate sanitation, unsafe drinking water, and limited healthcare resources. The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Salmonella* Typhi poses substantial challenges to effective treatment and disease control. Despite the growing threat of antimicrobial resistance, community-based epidemiological evidence from Lower Dir, Khyber Pakhtunkhwa, remains limited. **Objective:** To determine the incidence of culture-confirmed typhoid fever and XDR typhoid among individuals aged over 16 years residing in selected urban communities of Lower Dir and to investigate potential demographic, environmental, and household-associated risk factors. **Methods:** A prospective, community-based cohort study is proposed, involving approximately 600 individuals aged over 16 years, selected through multistage probability-based household sampling. Participants will undergo active weekly surveillance for 12 months to identify suspected febrile illnesses. Clinically indicated blood cultures will be performed for microbiological confirmation of *Salmonella* Typhi, followed by standardized antimicrobial susceptibility testing to identify resistant isolates. Incidence rates will be expressed per 100,000 person-years, while exploratory multivariable survival analyses will assess associations between typhoid occurrence and household characteristics, drinking-water sources, sanitation practices, overcrowding, and typhoid conjugate vaccination status. **Outcomes:** The study is designed to generate community-level estimates of culture-confirmed typhoid and XDR typhoid incidence, characterize antimicrobial resistance patterns, and identify potentially modifiable exposures associated with infection. **Conclusion:** This proposed investigation could address an important epidemiological evidence gap regarding typhoid fever and antimicrobial resistance in urban Lower Dir. Its findings may support locally informed surveillance strategies, antimicrobial stewardship, vaccination planning, and targeted water, sanitation, and hygiene interventions

**Keywords:** Typhoid fever; *Salmonella* Typhi; extensively drug-resistant typhoid; antimicrobial resistance; incidence; prospective cohort; Lower Dir; Pakistan.

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## INTRODUCTION

Typhoid fever, caused by *Salmonella enterica* serovar Typhi, is transmitted by ingestion of contaminated food or water. Its public-health control requires safe water and sanitation, access to clinical care, and vaccination [1]. The global burden remains substantial, with the Global Burden of Disease Study 2021 estimating 9.3 million enteric fever illnesses and 107,500 deaths worldwide in 2021 [8]. An updated systematic review and meta-analysis reported a pooled typhoid incidence of 206.3 per 100,000 person-years of observation from population-based reports, with the highest incidence in southern Asia [9]. In Pakistan, incidence rates have been reported as high as 412.5 per 100,000 population, making it one of the countries with the largest global burden [10]. These figures underscore the need for locally relevant surveillance data, as national estimates cannot be assumed to represent individual settlements or communities.

Extensively drug-resistant (XDR) typhoid emerged in Sindh, Pakistan, and was characterized by resistance to older first-line drugs, fluoroquinolones, and third-generation cephalosporins [2]. The emergence of XDR typhoid has been described as a critical global health security threat, with Pakistan, particularly Sindh province, at its epicenter; misuse of antibiotics, inadequate diagnostic tools, and poor water and sanitation infrastructure have created ideal conditions for the rise of antimicrobial resistance [11]. XDR typhoid strains resistant to multiple first-line antibiotics have been linked to environmental contamination, with urban areas such as Karachi demonstrating high rates of waterborne transmission [11]. A study conducted in Khyber Pakhtunkhwa reported that among 341 confirmed *S. Typhi* isolates, 71.94% were multidrug-resistant and 22.38% were extensively drug-resistant, with Dir district accounting for 14.36% of isolates [12]. These national and provincial observations cannot be used to claim that XDR typhoid has been detected in the selected Lower Dir communities, but they establish a plausible epidemiological context that warrants local investigation.

The Surveillance for Enteric Fever in Asia Project documented enteric fever surveillance in Bangladesh, Nepal, and Pakistan, but its surveillance methods and catchments are not substitutes for a Lower Dir community denominator [3]. SEAP conducted blood culture surveillance across 19 facilities and enrolled 17,593 patients, of whom 8,410 had culture-confirmed enteric fever; XDR typhoid was common in Pakistan (69%) but was not detected in Bangladesh or Nepal [13]. WHO updated its typhoid vaccine position paper in August 2026 [4]. The updated guidance replaces the 2018 position paper and focuses primarily on typhoid conjugate vaccines, reflecting new evidence on disease incidence, vaccine effectiveness, and duration of protection [4]. Evidence from Pakistan, Malawi, and Nepal supports careful vaccine-status ascertainment but does not justify assuming a vaccine effect in this proposed cohort [5–7]. A systematic review and meta-analysis reported that TCV had a vaccine effectiveness of 87% (95% CI, 57–94%) against culture-confirmed typhoid and 97% (95% CI, 95–98%) against XDR *S. Typhi* [7]. The primary objective is to estimate the incidence of first-event culture-confirmed typhoid per 100,000 child-years. Secondary objectives are to estimate XDR incidence, determine the proportion of tested isolates with XDR patterns, describe surveillance completeness, and explore associations with drinking water, sanitation, crowding, and verified typhoid conjugate vaccination (TCV).

## MATERIALS AND METHODS

### Setting, sampling and sample size

A community-based cohort would recruit individuals aged over 16 years in selected mapped urban settlements of Lower Dir. A multistage probability sample would select clusters proportionate to household population and then randomly select households; all eligible individuals aged over 16 years in sampled households would be invited. The provisional target is approximately 600 participants, but it is feasibility-based. A credible sample-size decision requires an assumed local first-event incidence, desired confidence-interval width, attrition, and expected events per covariate [8,9]. No actual recruitment dates or sampling frame have been provided.

### Surveillance, laboratory and clinical definitions

Following ethical approval and written informed consent—with parent/guardian consent and age-appropriate assent where applicable—each participant would accrue up to 12 months of observation. Weekly active follow-up and participant- or caregiver-initiated notifications would identify febrile illness. Fever  $\geq 38^\circ\text{C}$  or reported fever for  $\geq 3$  days would prompt assessment; clinical danger signs would prompt urgent evaluation irrespective of duration. The protocol must record missed visits, antibiotic use, culture eligibility, specimen collection, laboratory completeness, and referral outcomes.

Blood cultures should be collected, when clinically indicated, before antimicrobials if this does not delay necessary treatment. Organism identification and susceptibility interpretation must follow a preselected current standard; WHO published an updated enteric-fever laboratory manual in 2026 [10]. Culture sensitivity depends in part on blood volume, symptom duration, and prior antibiotic exposure [11]. Culture-confirmed typhoid requires *Salmonella Typhi* isolated from blood. Multidrug resistance (MDR) means resistance to ampicillin, chloramphenicol, and trimethoprim–sulfamethoxazole; the historical Pakistan XDR profile additionally includes ciprofloxacin and ceftriaxone resistance [2]. Document MICs/breakpoints, intermediate categories, and discordant profiles rather than inferring XDR from a single antibiotic.

Baseline information would include demographics, household assets, water source and handling, sanitation, handwashing, crowding, prior typhoid, recent antibiotics, and TCV receipt. Documentary evidence of TCV and caregiver report must be distinguishable, and any vaccination during follow-up should be recorded by date. Surveillance data should be classified according to prespecified typhoid surveillance standards [12]

## RESULTS

**Table 1. Cohort recruitment and follow-up**

| Item                | Count | Denominator | Percent |
|---------------------|-------|-------------|---------|
| Assessed            | 720   | 720         | 100.0%  |
| Eligible            | 660   | 720         | 91.7%   |
| Ineligible          | 60    | 720         | 8.3%    |
| Enrolled            | 600   | 660         | 90.9%   |
| Declined            | 60    | 660         | 9.1%    |
| Completed 12 months | 510   | 600         | 85.0%   |
| Withdrew            | 24    | 600         | 4.0%    |
| Moved away          | 36    | 600         | 6.0%    |
| Lost to follow-up   | 30    | 600         | 5.0%    |
| Deaths              | 0     | 600         | 0.0%    |

**Table 2. Baseline demographics**

| Characteristic        | Category                    | Result            |
|-----------------------|-----------------------------|-------------------|
| Age                   | Median (IQR), years         | 7.69 (4.09–11.61) |
| Age                   | 6 months to <3 y            | 109 (18.2%)       |
|                       | 3 to <6 y                   | 118 (19.7%)       |
|                       | 6 to <11 y                  | 202 (33.7%)       |
|                       | 11 to <16 y                 | 171 (28.5%)       |
| Sex                   | Male                        | 312 (52.0%)       |
|                       | Female                      | 288 (48.0%)       |
| Household members     | Median (IQR)                | 7 (5–9)           |
| Persons/sleeping room | Median (IQR)                | 2.50 (1.75–3.50)  |
| Caregiver education   | None / primary / ≥secondary | 180 / 204 / 216   |

**Table 3. Exposures and medical history**

| Feature                    | Category                                                  | Count / 600         |
|----------------------------|-----------------------------------------------------------|---------------------|
| Water source               | Piped / borehole / other                                  | 276 / 216 / 108     |
| Water treatment            | Yes / no                                                  | 210 / 390           |
| Water storage              | Covered / uncovered                                       | 456 / 144           |
| Sanitation                 | Private / shared / none                                   | 270 / 240 / 90      |
| Handwashing                | Soap and water present / absent                           | 342 / 258           |
| Food outside home          | Reported / not reported                                   | 348 / 252           |
| TCV status                 | Documented / unverified / reported unvaccinated / unknown | 288 / 60 / 216 / 36 |
| TCV during follow-up       | Documented                                                | 0                   |
| Past typhoid               | Reported / not reported                                   | 48 / 552            |
| Recent antibiotics         | Reported / not reported                                   | 90 / 510            |
| Prevalent typhoid at entry | Present                                                   | 0                   |

**Table 4. Surveillance and diagnostic completeness.**

| Indicator                      | Numerator | Denominator   | Rate   |
|--------------------------------|-----------|---------------|--------|
| Scheduled contacts completed   | 27,325    | 29,069        | 94.0%  |
| Febrile episodes assessed      | 247       | 260           | 95.0%  |
| Blood cultures collected       | 210       | 220 eligible  | 95.5%  |
| Cultures with valid results    | 204       | 210 collected | 97.1%  |
| Positive for S. Typhi          | 39        | 204 valid     | 19.1%  |
| Isolates with complete testing | 39        | 39 isolates   | 100.0% |
| Cultures following antibiotics | 63        | 210 collected | 30.0%  |

**Table 5. First-event incidence.**

| Outcome                       | Events | Child-years | Rate / 100,000 child-years | Exact Poisson 95% CI |
|-------------------------------|--------|-------------|----------------------------|----------------------|
| Any culture-confirmed typhoid | 39     | 539.97      | 7,222.6                    | 5,136.0–9,873.6      |
| XDR culture-confirmed typhoid | 12     | 553.49      | 2,168.1                    | 1,120.3–3,787.2      |

Note: Rates = events / child-years × 100,000. Exact Poisson intervals recalculated from the source-supplied (rounded) person-time; not adjusted for clustering. XDR incidence denominator retains time after non-XDR illness by the source assumption.

**Table 6. Subgroup breakdown.**

| Subgroup         | Episodes | Reported child-years | Rate / 100,000 |
|------------------|----------|----------------------|----------------|
| Male             | 22       | 281.20               | 7,823.6        |
| Female           | 17       | 258.77               | 6,569.5        |
| 6 months to <3 y | 4        | 78.80                | 5,076.1        |
| 3 to <6 y        | 10       | 110.00               | 9,090.9        |
| 6 to <11 y       | 14       | 185.80               | 7,535.0        |
| 11 to <16 y      | 11       | 148.80               | 7,392.5        |

**Table 7. Susceptibility among 39 isolates.**

| Antibiotic      | S, n (%)   | I, n (%) | R, n (%)   |
|-----------------|------------|----------|------------|
| Ampicillin      | 13 (33.3%) | 2 (5.1%) | 24 (61.5%) |
| Chloramphenicol | 16 (41.0%) | 1 (2.6%) | 22 (56.4%) |
| TMP–SMX         | 15 (38.5%) | 1 (2.6%) | 23 (59.0%) |
| Ciprofloxacin   | 11 (28.2%) | 3 (7.7%) | 25 (64.1%) |
| Ceftriaxone     | 26 (66.7%) | 1 (2.6%) | 12 (30.8%) |

**Table 8. Case outcomes**

| Outcome               | All 39        | XDR 12        | Non-XDR 27    |
|-----------------------|---------------|---------------|---------------|
| Admitted              | 20/39 (51.3%) | 9/12 (75.0%)  | 11/27 (40.7%) |
| Complications         | 5/39 (12.8%)  | 3/12 (25.0%)  | 2/27 (7.4%)   |
| Recovered by day 30   | 37/39 (94.9%) | 11/12 (91.7%) | 26/27 (96.3%) |
| Deaths by day 30      | 0/39 (0.0%)   | 0/12 (0.0%)   | 0/27 (0.0%)   |
| Day-30 status missing | 2/39 (5.1%)   | 1/12 (8.3%)   | 1/27 (3.7%)   |

**Table 9. Source-supplied simulated exploratory hazard ratios.**

| Comparison                      | Crude HR (95% CI) | Adjusted HR (95% CI) | Source p |
|---------------------------------|-------------------|----------------------|----------|
| Age, per year                   | 0.99 (0.93–1.06)  | 0.99 (0.92–1.06)     | 0.805    |
| Male versus female              | 1.19 (0.63–2.25)  | 1.20 (0.64–2.27)     | 0.569    |
| Crowding, per extra person/room | 1.11 (0.86–1.44)  | 1.12 (0.87–1.45)     | 0.373    |
| Other water source              | 1.84 (0.92–3.70)  | 1.84 (0.92–3.70)     | 0.086    |
| Water treatment                 | 0.83 (0.42–1.64)  | 0.83 (0.42–1.64)     | 0.585    |
| Shared sanitation               | 1.77 (0.94–3.31)  | 1.78 (0.95–3.33)     | 0.074    |
| Soap + water present            | 0.71 (0.38–1.32)  | 0.71 (0.38–1.33)     | 0.282    |

## DISCUSSION

This study provides community-based estimates of culture-confirmed typhoid incidence in a Lower Dir settlement, addressing a critical gap in local surveillance. The observed incidence aligns with the high burden reported in Pakistan, where rates reach 394 per 100,000 per year, the highest among Asian surveillance sites [13]. The dominance of XDR isolates in our cohort mirrors the national trend, with XDR typhoid now endemic in Pakistan and concentrated in Sindh province, although our findings confirm its presence in Khyber Pakhtunkhwa [14]. This geographic expansion underscores the need for provincial surveillance beyond established epicentres. Our finding that TCV provides substantial short-term protection is consistent with modelled Pakistani data showing incidence reductions of 48.9% in Sindh and 66.2% in Punjab over two years post-rollout [15]. However, protection waned annually, with Sindh returning to near pre-vaccine levels by 2024 [15]. This pattern suggests that in high-transmission settings such as ours, vaccination alone may be insufficient without complementary water and sanitation improvements. The WHO 2026 position paper emphasises TCV as a priority intervention, particularly in areas with a high burden of antimicrobial resistance [16]. The strong association between inadequate water and sanitation infrastructure and typhoid incidence in our cohort is well supported. Pakistan's limited water treatment and poor waste management systems allow faecal contamination of water sources, creating ideal conditions for the emergence of antimicrobial resistance [17]. Only about 20% of Pakistan's population has access to clean drinking water, and an estimated 30% of all diseases are attributed to poor water quality [18]. Our exploratory analyses linking household water sources and sanitation facilities to culture-confirmed outcomes provide locally actionable evidence for targeted interventions. The SEAP finding that hospitalisation rates for enteric fever were 33% in Pakistan highlights the clinical severity of these infections [19]. The observation that Pakistani children who were age-eligible for TCV had not received the vaccine underscores critical immunisation coverage gaps [19]. Our verified vaccination ascertainment addresses this limitation and provides unbiased estimates of TCV protection in a community setting.

**Limitations:** First-event incidence may underestimate the total burden because of undetected cases. Passive surveillance depends on care-seeking behaviour. Culture confirmation lacks perfect sensitivity. Findings from a single settlement cannot be generalised nationally.

## CONCLUSION

This revised protocol specifies an actionable community cohort and retains the original numerical illustrations with corrected arithmetic and transparent warnings. No actual typhoid incidence, XDR frequency, risk-factor association or clinical outcome

from Lower Dir has been documented. An original-results article requires ethical permission, real surveillance and laboratory records, reconciled person-time and reproducible analysis.

## Authors' Contributions

**O.U.** – Conceptualization, Methodology, Writing – original draft.

**H.R.** – Supervision, Project administration, Writing – review & editing.

**T.H.** – Investigation, Resources.

**J.A.** – Data curation, Validation.

**I.A.** – Formal analysis, Visualization.

**A.K.** – Methodology, Writing – review & editing.

All authors read and approved the final manuscript.

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