

Original Research Article

Clinical and etiological profile of children hospitalized with acute undifferentiated febrile illness in South-Eastern Rajasthan, India: a prospective observational study

Anjali Tiwari¹, Rajendra Prasad Nagar¹, Poorva Tiwari^{2*}

¹Department of Pediatrics, Shrimati Heera Kunwar Baa Mahila Hospital, Jhalawar Medical College, Jhalawar, Rajasthan, India

²Department of Pediatrics, JK Lone Hospital, SMS Medical College, Jaipur, Rajasthan, India

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*Correspondence:

Poorva Tiwari,

E-mail: poorvatiwari09@gmail.com

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ABSTRACT

Background: Etiological data on acute undifferentiated febrile illness (AUFI) in India come mainly from adults in humid, high-endemicity regions; pediatric data from semi-arid north-west India are sparse. We determined the etiology, laboratory profile, outcomes and laboratory discriminators in hospitalized children in south-eastern Rajasthan.

Methods: Prospective observational study at a tertiary teaching hospital in Jhalawar, Rajasthan. Two hundred children aged 2 months–18 years with fever ≤ 7 days and no identifiable focus after baseline assessment underwent a standardized diagnostic panel. Proportions carry Wilson 95% confidence intervals (CIs). Sparse cell counts required Monte Carlo permutation testing (100 000 replicates) with Holm adjustment across 16 comparisons; threshold performance was assessed post hoc.

Results: No etiology was identified in 105 children (52.5%, 95% CI 45.6–59.3). Scrub typhus predominated (33, 16.5%, CI 12.0–22.3; 34.7% of resolved diagnoses), then urinary tract infection (25, 12.5%), dengue (22, 11.0%), malaria (10, 5.0%) and enteric fever (5, 2.5%). Enrollment peaked in August–October (88, 44.0%; $p < 0.001$). All laboratory parameters except creatinine differed by diagnosis (adjusted $p \leq 0.002$), as did length of stay, complications and defervescence time. Thresholds were specific but insensitive: hemoglobin < 80 g/l for scrub typhus (specificity 97.0%, sensitivity 45.5%, likelihood ratio 15.2), platelets $< 100 \times 10^9/l$ for dengue (86.0%, 68.2%, 4.9). Complications affected 39 children (19.5%), intensive care 25 (12.5%); none died.

Conclusions: Scrub typhus, not dengue or malaria, led identifiable causes and accounted for most transfusions. Empirical doxycycline warrants evaluation in post-monsoon fever. Routine thresholds modify suspicion but cannot replace specific testing; the unresolved half defines the gap molecular diagnostics must close.

Keywords: Acute undifferentiated febrile illness, Scrub typhus, *Orientia tsutsugamushi*, Children, Rajasthan, Diagnostic accuracy, India

INTRODUCTION

Acute undifferentiated febrile illness (AUFI), fever without a localizing source after history, examination and baseline investigations, is among the commonest reasons for pediatric admission in tropical Asia.^{1,2} It is defined by

what clinicians cannot yet see rather than by any shared biology, and collects illnesses whose management diverges sharply: a child with scrub typhus needs doxycycline within days, a child with dengue needs fluid monitoring and no antibiotic, and most need neither. Because presentations overlap, empirical broad-spectrum

therapy is widespread, driving resistance and delaying specific treatment.^{3,4}

Indian studies report strikingly different diagnostic mixes. The largest multicenter series, of 1564 patients across six states, found malaria and dengue to predominate and documented low accuracy of the routine tests then in use.⁵ A Kerala study found dengue in 43.5% and no identifiable cause in 29.9%.⁶ Pooled national estimates place scrub typhus in roughly a quarter of hospitalized AUFI cases, with heterogeneity approaching 99%.^{7,8} National averages are therefore of limited bedside use: the prior probability a clinician should apply is a district-level quantity.

Three gaps motivated this study. Indian AUFI cohorts are predominantly adult or restricted to children under five. Most data come from the humid south, north-east and sub-Himalayan belt, whereas south-eastern Rajasthan is semi-arid and lies outside the traditionally recognized high-endemicity regions; scrub typhus was first reported from the state only in the last decade and pediatric series from arid north-west India remain few.^{3,9,10} Finally, published cohorts rarely quantify how much a routine laboratory result shifts the probability of a specific diagnosis, the quantity a clinician deciding on doxycycline needs.^{11,12} We therefore characterized the presentation, etiology, laboratory profile, seasonality and short-term outcomes of AUFI in children admitted to a tertiary teaching hospital in Jhalawar, Rajasthan, and quantified the discriminatory value of the laboratory thresholds available in such a setting.

METHODS

Ethical approval

The study was approved by the Institutional Ethics Committee of Jhalawar Medical College and Associated Group of Hospitals (reference S. No. 86; 24 July 2024). Written informed consent was obtained from a parent or guardian of every participant, with written assent from children aged 12 years and above.

Design, setting and participants

This prospective observational study was conducted in the Department of Pediatrics at Shrimati Heera Kunwar Baa Mahila Hospital, Jhalawar Medical College, a government tertiary teaching hospital serving a rural, agrarian catchment in the Hadoti region of south-eastern Rajasthan. All eligible children admitted between August 2024 and July 2025 were approached consecutively (Figure 1).

Children aged 2 months to 18 years were eligible if they had an axillary temperature above 38.0 °C documented at or before admission, fever of 7 days or less, and no identifiable focus after history, examination and baseline investigations. Exclusions were an organ-specific cause

evident at presentation (radiologically confirmed pneumonia, confirmed meningitis, or urinary tract infection established before enrollment); chronic systemic illness, chromosomal abnormality, congenital malformation or documented immunodeficiency; postoperative state; or suspected drug-induced fever. The target of 200 was fixed a priori to estimate a proportion of approximately 20% to within ± 6 percentage points.

Data collection and case definitions

A pre-structured case record form captured age, sex, residence, socioeconomic class (modified Kuppuswamy scale), immunization status, fever duration and pattern, symptoms, exposure history and systemic examination including a directed search for eschar in the axillae, groin, perineum and neck.

All participants underwent complete blood count, peripheral blood film, C-reactive protein (CRP), erythrocyte sedimentation rate, blood glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, blood culture, urine microscopy and culture on a catheter specimen in children up to 2 years and a midstream clean-catch specimen thereafter, malaria rapid antigen testing, dengue enzyme-linked immunosorbent assay (ELISA) and scrub typhus IgM ELISA. Widal testing and chest radiography were done when indicated.

Diagnoses were assigned as follows: scrub typhus anti-Orientia tsutsugamushi IgM above the positivity threshold defined below, in a compatible illness; dengue positive NS1 antigen or anti-dengue IgM ELISA; malaria asexual parasitemia on blood film or positive rapid antigen test; urinary tract infection growth above 5×10^4 colony-forming units (CFU)/mL in a catheter specimen or $\geq 10^5$ CFU/mL in a clean-catch specimen, with pyuria above 5 leucocytes per high-power field, in a child in whom urinary infection had not been established before enrollment; mixed or contaminated growth was not diagnostic; enteric fever isolation of *Salmonella Typhi* or *Paratyphi* on blood culture, or a Widal titre above 1:160 in a compatible illness. Children in whom no test was positive were classified as unresolved and were not reclassified as viral illness.¹³⁻¹⁶

Scrub typhus IgM was measured with the Scrub Typhus IgM Microlisa indirect ELISA (J. Mitra & Co. Pvt. Ltd, New Delhi, India). A cut-off was calculated for each run as the mean negative-control optical density plus 0.350, and IgM units derived as sample optical density divided by that cut-off, multiplied by ten. Samples above 11 units were positive, 9–11 units equivocal and below 9 negative; no sample was equivocal.

Outcomes

The primary outcome was the distribution of assigned etiologies. Secondary outcomes were length of stay,

intensive care unit (ICU) admission, any complication (shock, encephalopathy or seizures, bleeding, acute kidney injury, hepatic dysfunction, respiratory failure or myocarditis), time to sustained defervescence (axillary temperature below 37.5 °C for 24 consecutive hours without antipyretic), transfusion, in-hospital mortality and 30-day readmission.

Statistical analysis

Categorical data are presented as counts and percentages, with Wilson score 95% confidence intervals (CIs) for the principal proportions.¹⁷ Each variable was examined across the six diagnostic groups in a single omnibus test. In every cross-tabulation more than 20% of expected cell counts fell below five, a consequence of the small enteric fever (n=5) and malaria (n=10) strata, so the asymptotic Pearson chi-square approximation was invalid. Exact p values were obtained by Monte Carlo permutation of the Pearson statistic conditional on the observed margins, using 100 000 replicates.¹⁸ Sixteen pre-specified comparisons were adjusted by the Holm step-down procedure at 5%; Benjamini–Hochberg false discovery rates gave concordant conclusions.¹⁹ Row-specific p values were not computed. Seasonality was assessed by chi-square goodness-of-fit against a uniform distribution and by exact binomial test of the August-to-October share against the 25% expected under uniformity. Post hoc, we quantified the discriminatory value of each dichotomized threshold against its assigned diagnosis, computing sensitivity, specificity, predictive values and likelihood ratios with Wilson 95% CIs across the whole cohort. Analyses used Python 3.12 (SciPy 1.17, statsmodels 0.14). Two-sided p values below 0.05 were significant. No imputation was undertaken and no adjusted models fitted; there were no missing data.²⁰

RESULTS

Participants and clinical presentation

Of 986 children assessed for eligibility, 330 met inclusion criteria and 200 were enrolled (Figure 1). One hundred and seventeen (58.5%) were male. School-age children predominated: 65 (32.5%) were aged 10–15 years, 60 (30.0%) 5–<10 years and 50 (25.0%) 1–<5 years, while 15 (7.5%) were infants. One hundred and fifty (75.0%) belonged to the lower-middle or upper-lower socioeconomic strata and 165 (82.5%) were fully immunized for age (Table 1). Etiological distribution did not differ by age group or sex (both adjusted $p=1.00$).

Fever had been present for 3–4 days in 78 children (39.0%) and 5–6 days in 58 (29.0%); the pattern was continuous in 112 (56.0%). Admission temperature was 38.1–38.9 °C in 89 (44.5%) and 40.0°C or above in 35 (17.5%). Constitutional symptoms dominated: loss of appetite in 156 (78.0%) and fatigue in 134 (67.0%), with headache in 89 (44.5%) and myalgia in 78 (39.0%). Examination was unremarkable in 151 children (75.5%);

pallor (41, 20.5%), dehydration (32, 16.0%) and splenomegaly (27, 13.5%) were commonest (Table 2). No eschar was found in any child, including those subsequently diagnosed with scrub typhus.

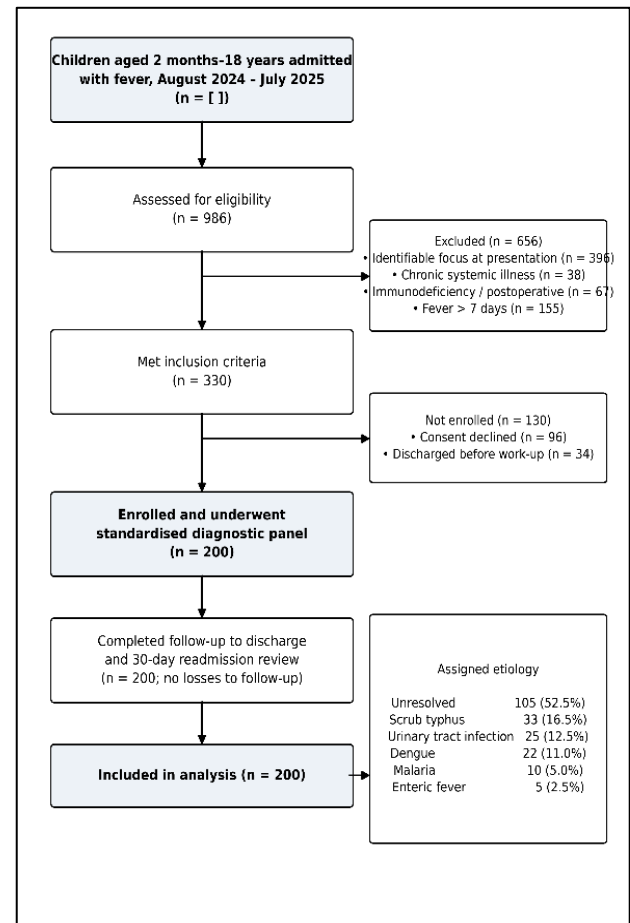


Figure 1: Flow of participants through the study. Numbers assessed for eligibility, excluded with reasons, meeting inclusion criteria, not enrolled with reasons, enrolled, followed up and analyzed, with the distribution of assigned diagnoses among the 200 children analyzed.

Flow diagram with five stacked boxes connected by downward arrows. From 986 children assessed for eligibility, 656 were excluded (396 identifiable focus at presentation, 38 chronic systemic illness, 67 immunodeficiency or postoperative, 155 fevers over 7 days), leaving 330 who met inclusion criteria. Of these, 130 were not enrolled (96 consent declined, 34 discharged before work-up), leaving 200 enrolled and analysed with no losses to follow-up. A side box lists assigned diagnoses: unresolved 105, scrub typhus 33, urinary tract infection 25, dengue 22, malaria 10, enteric fever 5.

Assigned etiology and seasonality

No etiology was assigned in 105 children (52.5%; 95% CI 45.6–59.3). Among the 95 with an established diagnosis, scrub typhus was commonest (33; 34.7% of resolved diagnoses; 16.5% of the cohort, 95% CI 12.0–22.3), followed by urinary tract infection (25; 12.5%), dengue (22; 11.0%), malaria (10; 5.0%) and enteric fever 5.

(5; 2.5%) (Table 3). No co-infections occurred. Enrollments were not uniformly distributed through the year ($\chi^2=54.8$, 11 df, $p<0.001$). Eighty-eight children (44.0%; 95% CI 37.3–50.9) were enrolled between August and October against 50 expected (exact binomial $p<0.001$), with a September–October plateau of 33 each month; 142 (71.0%) fell within the June-to-November monsoon window (Figure 2).

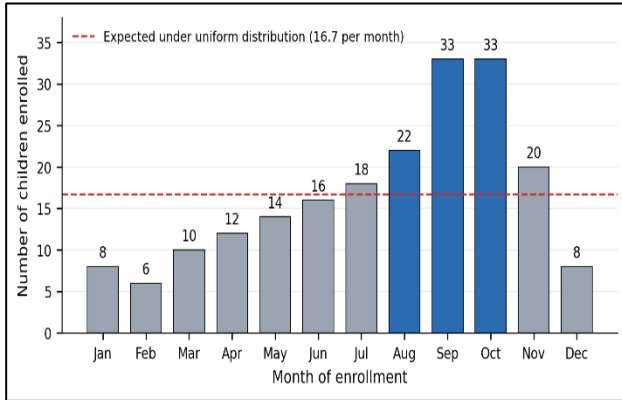


Figure 2: Monthly distribution of enrolled children with acute undifferentiated febrile illness (n=200). Bars for August to October are shaded to indicate the monsoon and post-monsoon peak; the dashed line marks the 16.7 enrollments per month expected under a uniform distribution. Enrollments were not uniformly distributed across the year ($\chi^2=54.8$, 11 df, $p<0.001$).

Vertical bar chart of enrollments by calendar month. Counts rise from 8 in January and 6 in February through the spring and early summer to a peak of 33 in both September and October, then fall to 20 in November and 8 in December. August, September and October bars are shaded darker. A horizontal dashed line at 16.7 marks the count expected if enrollments were evenly distributed.

Laboratory findings

Every hematological and biochemical parameter except creatinine differed across groups after Holm adjustment (Table 4). Anemia below 80 g/l was concentrated in scrub typhus (15/33, 45.5%). Dengue was characterized by leukopenia below $4.0 \times 10^9/l$ and thrombocytopenia below $100 \times 10^9/L$, each in 15 of 22 children (68.2%). Leukocytosis above $11.0 \times 10^9/l$ was largely confined to

urinary tract infection (17/25, 68.0%) and enteric fever (3/5). Transaminase elevation above 200 U/l was disproportionately a feature of malaria (ALT and AST each 4/10). Hyperbilirubinemia of 20 $\mu\text{mol/l}$ or more was commonest in scrub typhus (21/33, 63.6%), as were CRP above 10 mg/l (20/33, 60.6%) and erythrocyte sedimentation rate above 50 mm/h (19/33, 57.6%). Creatinine did not differ after adjustment (adjusted $p=1.00$), and no child exceeded 265 $\mu\text{mol/l}$.

Discriminatory value of laboratory thresholds

Individual thresholds were consistently specific and insensitive (Table 5). Hemoglobin below 80 g/l was the strongest discriminator, identifying scrub typhus with 97.0% specificity (95% CI 93–99) and a positive likelihood ratio of 15.2, but detecting fewer than half of cases (sensitivity 45.5%). ALT above 200 U/l identified malaria with 98.4% specificity and a likelihood ratio of 25.3, on only ten cases.

Thrombocytopenia and leukopenia each identified dengue with 68.2% sensitivity and specificity near 86–87%, yielding likelihood ratios of 4.9 and 5.3 and predictive values below 40%. Leukocytosis identified urinary tract infection with 68.0% sensitivity and 90.9% specificity. No threshold could be used alone, and negative likelihood ratios ranged from 0.35 to 0.61.

Hospital course and outcomes

One hundred and twenty-two children (61.0%) were discharged within three days and 8 (4.0%) stayed beyond a week. Twenty-five (12.5%) required intensive care and 39 (19.5%) had a complication; none died. Length of stay, complications and defervescence time differed by etiology after adjustment (adjusted $p=0.001$, <0.001 and 0.004), whereas ICU admission did not (adjusted $p=0.39$) (Table 6).

Complications were proportionally commonest in malaria (6/10) and scrub typhus (15/33, 45.5%) and rarest in unresolved illness (5/105, 4.8%). Five children (2.5%) received platelets, four with dengue, and 11 (5.5%) received packed cells, eight with scrub typhus. Eight (4.0%) were readmitted within 30 days, without significant variation by diagnosis.

Table 1: Baseline characteristics of children admitted with acute undifferentiated febrile illness (n=200).

Characteristics	Category	N (%)
Age group (years)	2 months –<1	15 (7.5)
	1–<5	50 (25.0)
	5–<10	60 (30.0)
	10–15	65 (32.5)
	>15–18	10 (5.0)
Sex	Male	117 (58.5)
	Female	83 (41.5)
Socioeconomic class ^a	Upper	12 (6.0)

Continued.

Characteristics	Category	N (%)
	Upper middle	28 (14.0)
	Lower middle	85 (42.5)
	Upper lower	65 (32.5)
	Lower	10 (5.0)
Immunization status	Fully immunized for age	165 (82.5)
	Partially immunized	28 (14.0)
	Unimmunized	7 (3.5)

^aModified Kuppuswamy scale.

Table 2: Clinical presentation at admission (n=200).^a

Features	N	%
Temperature at admission		
38.1–38.9°C	89	44.5
39.0–39.9°C	76	38.0
40.0–40.9°C	28	14.0
≥ 41.0 °C	7	3.5
Duration of fever at presentation		
1–2 days	45	22.5
3–4 days	78	39.0
5–6 days	58	29.0
7 days	19	9.5
Fever pattern		
Continuous	112	56.0
Intermittent	65	32.5
Remittent	23	11.5
Associated symptoms		
Loss of appetite	156	78.0
Weakness or fatigue	134	67.0
Headache	89	44.5
Myalgia	78	39.0
Nausea or vomiting	65	32.5
Abdominal pain	42	21.0
Cough	35	17.5
Diarrhoea	28	14.0
Joint pain	22	11.0
Rash (reported)	18	9.0
Examination findings		
Normal examination	151	75.5
Pallor	41	20.5
Dehydration	32	16.0
Splenomegaly	27	13.5
Lymphadenopathy	18	9.0
Petechiae	12	6.0
Hepatomegaly	10	5.0
Hepatosplenomegaly	8	4.0
Oedema	8	4.0
Rash (observed)	7	3.5
Icterus	6	3.0
Ecchymoses	3	1.5
Cyanosis	2	1.0
Eschar	0	0.0

^aSymptoms and signs are not mutually exclusive; a child could have more than one finding.

Table 3: Assigned etiology of acute undifferentiated febrile illness (n=200).^a

Diagnosis	N	% of cohort (95% CI)	% of resolved (n = 95)
Unresolved (no etiology assigned)	105	52.5 (45.6 – 59.3)	—
Scrub typhus	33	16.5 (12.0 – 22.3)	34.7
Urinary tract infection	25	12.5 (8.6 – 17.8)	26.3
Dengue	22	11.0 (7.4 – 16.1)	23.2
Malaria	10	5.0 (2.7 – 9.0)	10.5
Enteric fever	5	2.5 (1.1 – 5.7)	5.3

CI, confidence interval. ^aWilson score method. Categories are mutually exclusive; no co-infections occurred.

Table 4: Laboratory findings by assigned etiology (n=200).^a

Parameters	Dengue (22)	Scrub typhus (33)	Enteric fever (5)	Malaria (10)	UTI (25)	Unresolved (105)	Adj. p ^b
Hemoglobin, g/l							
<80	1 (4.5)	15 (45.5)	0 (0)	1 (10.0)	0 (0)	3 (2.9)	< 0.001
80–100	4 (18.2)	12 (36.4)	1 (20.0)	3 (30.0)	2 (8.0)	12 (11.4)	
>100	17 (77.3)	6 (18.2)	4 (80.0)	6 (60.0)	23 (92.0)	90 (85.7)	
Leucocyte count, ×10⁹/l							
<4.0	15 (68.2)	3 (9.1)	0 (0)	2 (20.0)	0 (0)	18 (17.1)	< 0.001
4.0–11.0	7 (31.8)	28 (84.8)	2 (40.0)	6 (60.0)	8 (32.0)	78 (74.3)	
>11.0	0 (0)	2 (6.1)	3 (60.0)	2 (20.0)	17 (68.0)	9 (8.6)	
Platelet count, ×10⁹/l							
<100	15 (68.2)	8 (24.2)	0 (0)	3 (30.0)	2 (8.0)	12 (11.4)	< 0.001
100–150	5 (22.7)	6 (18.2)	1 (20.0)	5 (50.0)	3 (12.0)	18 (17.1)	
>150	2 (9.1)	19 (57.6)	4 (80.0)	2 (20.0)	20 (80.0)	75 (71.4)	
Alanine aminotransferase, U/l							
<40	12 (54.5)	8 (24.2)	2 (40.0)	2 (20.0)	22 (88.0)	85 (81.0)	<0.001
40–80	6 (27.3)	18 (54.5)	2 (40.0)	1 (10.0)	3 (12.0)	15 (14.3)	
80–200	3 (13.6)	6 (18.2)	1 (20.0)	3 (30.0)	0 (0)	4 (3.8)	
> 200	1 (4.5)	1 (3.0)	0 (0)	4 (40.0)	0 (0)	1 (1.0)	
Aspartate aminotransferase, U/l							
<40	10 (45.5)	6 (18.2)	1 (20.0)	1 (10.0)	20 (80.0)	78 (74.3)	<0.001
40–80	7 (31.8)	16 (48.5)	3 (60.0)	2 (20.0)	4 (16.0)	20 (19.0)	
80–200	4 (18.2)	9 (27.3)	1 (20.0)	3 (30.0)	1 (4.0)	6 (5.7)	
>200	1 (4.5)	2 (6.1)	0 (0)	4 (40.0)	0 (0)	1 (1.0)	
Total bilirubin, μmol/l							
<20	18 (81.8)	12 (36.4)	4 (80.0)	6 (60.0)	23 (92.0)	92 (87.6)	0.002
20–51	4 (18.2)	18 (54.5)	1 (20.0)	3 (30.0)	2 (8.0)	12 (11.4)	
>51	0 (0)	3 (9.1)	0 (0)	1 (10.0)	0 (0)	1 (1.0)	
Creatinine, μmol/l							
<88	20 (90.9)	26 (78.8)	5 (100)	7 (70.0)	22 (88.0)	98 (93.3)	1.00
88–133	2 (9.1)	5 (15.2)	0 (0)	2 (20.0)	2 (8.0)	6 (5.7)	
133–265	0 (0)	2 (6.1)	0 (0)	1 (10.0)	1 (4.0)	1 (1.0)	
C-reactive protein, mg/l							
<3	12 (54.5)	5 (15.2)	1 (20.0)	3 (30.0)	8 (32.0)	68 (64.8)	<0.001
3–10	8 (36.4)	8 (24.2)	3 (60.0)	2 (20.0)	12 (48.0)	28 (26.7)	
10–50	2 (9.1)	12 (36.4)	1 (20.0)	3 (30.0)	5 (20.0)	8 (7.6)	
>50	0 (0)	8 (24.2)	0 (0)	2 (20.0)	0 (0)	1 (1.0)	
Erythrocyte sedimentation rate, mm/h							
<20	8 (36.4)	2 (6.1)	1 (20.0)	1 (10.0)	6 (24.0)	45 (42.9)	0.002
20–50	12 (54.5)	12 (36.4)	2 (40.0)	4 (40.0)	14 (56.0)	52 (49.5)	
50–100	2 (9.1)	15 (45.5)	2 (40.0)	4 (40.0)	5 (20.0)	7 (6.7)	
>100	0 (0)	4 (12.1)	0 (0)	1 (10.0)	0 (0)	1 (1.0)	

UTI, urinary tract infection. ^aValues are n (%) within each diagnostic group; thresholds are those recorded prospectively and are not age-adjusted. ^bMonte Carlo exact p value (100 000 permutations of the Pearson statistic conditional on the observed margins), Holm-adjusted across 16 pre-specified omnibus comparisons; one test per parameter across all six groups.

Table 5: Discriminatory performance of individual laboratory thresholds against the assigned diagnosis (n=200).^a

Threshold	Target diagnosis	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, %	LR+	LR–
Hemoglobin <80 g/l	Scrub typhus	45.5 (30.4 – 61.5)	97.0 (93.2 – 98.7)	75.0	15.2	0.56
Bilirubin ≥20 μmol/l	Scrub typhus	63.6 (46.6 – 77.8)	85.6 (79.5 – 90.1)	46.7	4.4	0.42
CRP >10 mg/l	Scrub typhus	60.6 (43.7 – 75.3)	86.8 (80.9 – 91.1)	47.6	4.6	0.45
ESR >50 mm/h	Scrub typhus	57.6 (40.8 – 72.8)	86.8 (80.9 – 91.1)	46.3	4.4	0.49
Platelets <100×10⁹/l	Dengue	68.2 (47.3 – 83.6)	86.0 (80.3 – 90.2)	37.5	4.9	0.37
Leucocytes <4.0×10⁹/l	Dengue	68.2 (47.3 – 83.6)	87.1 (81.5 – 91.2)	39.5	5.3	0.37
Leucocytes >11.0×10⁹/l	Urinary tract infection	68.0 (48.4 – 82.8)	90.9 (85.8 – 94.3)	51.5	7.4	0.35
ALT >200 U/l	Malaria	40.0 (16.8 – 68.7)	98.4 (95.5 – 99.5)	57.1	25.3	0.61
AST >200 U/l	Malaria	40.0 (16.8 – 68.7)	97.9 (94.7 – 99.2)	50.0	19.0	0.61

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval (Wilson score method); CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LR+, positive likelihood ratio; LR–, negative likelihood ratio; PPV, positive predictive value. ^aPost hoc analysis. Each threshold was evaluated against the whole cohort, with all children not assigned the target diagnosis treated as controls. Predictive values depend on the case mix of this cohort and are not transportable to settings with different prevalence; estimates are not externally validated.

Table 6: Hospital course and short-term outcomes by assigned etiology (n=200).^a

Outcomes	Dengue (22)	Scrub typhus (33)	Enteric fever (5)	Malaria (10)	UTI (25)	Unresolved (105)	Adj. p ^b
Length of hospital stay (days)							
1–3	8 (36.4)	12 (36.4)	0 (0)	2 (20.0)	18 (72.0)	82 (78.1)	0.001
4–7	12 (54.5)	18 (54.5)	4 (80.0)	6 (60.0)	7 (28.0)	23 (21.9)	
>7	2 (9.1)	3 (9.1)	1 (20.0)	2 (20.0)	0 (0)	0 (0)	
Time to sustained defervescence (hours)							
<24	2 (9.1)	8 (24.2)	0 (0)	1 (10.0)	15 (60.0)	38 (36.2)	0.004
24–48	12 (54.5)	18 (54.5)	1 (20.0)	4 (40.0)	9 (36.0)	48 (45.7)	
48–72	6 (27.3)	6 (18.2)	2 (40.0)	3 (30.0)	1 (4.0)	16 (15.2)	
>72	2 (9.1)	1 (3.0)	2 (40.0)	2 (20.0)	0 (0)	3 (2.9)	
Other outcomes							
ICU admission	3 (13.6)	4 (12.1)	2 (40.0)	3 (30.0)	5 (20.0)	8 (7.6)	0.39
Any complication	8 (36.4)	15 (45.5)	2 (40.0)	6 (60.0)	3 (12.0)	5 (4.8)	<0.001
Platelet transfusion	4 (18.2)	1 (3.0)	0 (0)	0 (0)	0 (0)	0 (0)	—
Packed-cell transfusion	0 (0)	8 (24.2)	0 (0)	1 (10.0)	0 (0)	2 (1.9)	—
Readmission ≤30 days	1 (4.5)	2 (6.1)	0 (0)	1 (10.0)	1 (4.0)	3 (2.9)	1.00
In-hospital death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	—

ICU, intensive care unit; UTI, urinary tract infection. ^aValues are n (%) within each diagnostic group; associations are unadjusted and may be confounded by age, time to presentation and referral pathway. ^bMonte Carlo exact p value (100 000 permutations), Holm-adjusted across 16 pre-specified omnibus comparisons. Transfusion rows were not formally tested because of near-total sparsity.

DISCUSSION

In this prospective cohort of 200 children admitted with undifferentiated fever to a tertiary hospital in semi-arid

south-eastern Rajasthan, scrub typhus was the leading identifiable cause, accounting for one in six admissions and more than a third of resolved diagnoses. Dengue and malaria, dominating most Indian AEFI series, together

accounted for fewer cases than scrub typhus alone. Just over half remained unresolved despite a standardized panel. Enrollments clustered in the post-monsoon months, complications occurred in a fifth of children, and none died.

Scrub typhus outside the classically recognized high-endemicity regions

The predominance of scrub typhus has the clearest implications for practice. Rajasthan is arid to semi-arid and sits outside the humid belt within which scrub typhus has conventionally been sought; the state was added to the list of affected regions only in the last decade.³ Our figure of 16.5% is lower than the pooled Indian estimate of approximately 25% among hospitalized AUFI patients and well below high-endemicity southern states, but substantially higher than the 6.2% reported in a retrospective pediatric review from arid north-west India.^{7-9,21} That series tested when clinicians suspected scrub typhus, whereas we tested every enrolled child. Ascertainment, not ecology, may explain much of the difference, which is itself the argument for protocolized testing.

Two features make suspicion-driven testing particularly unsafe here. No child had an eschar, consistent with Indian pediatric series in which it is absent in the large majority and with the north-west Indian series in which none of 21 confirmed cases had one.^{9,22} The characteristic clinical sign is therefore unavailable here. Second, presentation was overwhelmingly constitutional, with three quarters of children having an entirely normal examination, consistent with evidence that symptoms and signs discriminate poorly for serious infection in febrile children.¹² The clinical gestalt on which selective testing depends therefore carries little information.

The severity signal reinforces this. Scrub typhus accounted for 15 of 39 complications and 8 of 11 packed-cell transfusions, and children with scrub typhus had the highest rate of severe anemia. Since the infection responds rapidly to doxycycline or azithromycin and untreated infection carries a case fatality of approximately 7% nationally, rising sharply with organ involvement, the cost asymmetry between empirical treatment and missed diagnosis is stark.^{7,23} A prospective trial of protocolized empirical doxycycline in children with post-monsoon undifferentiated fever in this ecology, with pre-specified diagnostic and stewardship endpoints, is the logical next step; our data are hypothesis-generating rather than sufficient to change policy.

The unresolved half

That 52.5% remained unresolved reflects the limits of a serology-and-culture panel rather than an absence of pathogens, and it would be a category error to treat this fraction as a measure of viral disease. Colvin et al detected viruses in 76% of young children with fever

without apparent source, but also in many afebrile controls, so detection and causation cannot be equated; Tran and colleagues identified a pathogen by blood polymerase chain reaction in 53.9% of Vietnamese children under five.^{24,25}

Neither transfer directly to school-age Indian children. Our unresolved fraction quantifies the yield a district hospital here can currently expect, and therefore the gap a multiplex molecular platform must close to justify its cost.

Occult urinary tract infection

Urinary tract infection was the second commonest diagnosis, in 12.5% of children. This deserves emphasis precisely because urinary infection is an exclusion criterion: these were children in whom infection was not apparent at eligibility assessment and emerged only on culture. It is the commonest serious bacterial infection in young febrile children and is readily missed when the child cannot localize symptoms.^{15,16} Its frequency here, in a cohort screened primarily for tropical infections, argues that urine microscopy and culture belong in the first-line AUFI panel. Consistent with this, these children had the shortest defervescence time of any group, 60.0% afebrile within 24 hours.

Laboratory thresholds as modifiers, not rules

This analysis is uncommon in Indian pediatric AUFI cohorts, which typically report associations without quantifying bedside value.²⁶ The pattern is consistent: thresholds are specific but insensitive. Hemoglobin below 80 g/L multiplies the odds of scrub typhus roughly fifteen-fold and ALT above 200 U/l multiplies the odds of malaria roughly twenty-five-fold, so an abnormal result is a genuine reason to act. But every marker missed a third to two thirds of cases, and the best negative likelihood ratio was 0.35, nowhere near sufficient to exclude anything. These thresholds should raise the priority of specific testing, but must never be used to withhold it. Estimates are post hoc and require external validation.

Statistical considerations

A methodological point has wider relevance. Every cross-tabulation in this design contains sparse strata, and in our data the asymptotic chi-square test was invalid throughout. Substituting exact permutation testing with multiplicity control changed conclusions materially: the associations between etiology and age group, ICU admission and creatinine all lost significance, whereas an unadjusted per-row chi-square would have declared each significant. Given how routinely per-cell chi-square values are reported in AUFI series with strata of five or ten patients, some published associations are likely artefacts of an inappropriate test.

Limitations

This was a single-center inpatient study, so the case mix reflects tertiary referral and cannot be extrapolated to community fever; hospital proportions are not incidence. Of 330 eligible children, 130 were not enrolled, mainly because consent was declined, and systematic differences between these children and those enrolled could not be assessed. Monthly counts reflect enrolled children rather than all febrile admissions, so the seasonal pattern may partly reflect variation in enrollment. Scrub typhus was assigned on a single acute-phase IgM ELISA without immunofluorescence or polymerase chain reaction confirmation. The manufacturer's reported sensitivity of 100% derives from small in-house panels and is not independently validated; the insert designates the assay a screening test and documents cross-reaction with dengue virus, Epstein-Barr virus and Brucella material in a cohort including 22 children with dengue. Independent evaluations report lower accuracy than manufacturer panels, and a single acute-phase IgM may reflect residual antibody in an endemic population.²⁷⁻²⁹

Our scrub typhus figure should be read as seropositivity in a compatible illness rather than confirmed acute infection, and the same applies to dengue resting on IgM alone. Enteric fever assigned on Widal testing is especially uncertain, since Widal has poor specificity while blood culture detects only a minority of true cases, so 2.5% is likely an underestimate.^{30,31} Prior antibiotic exposure, not systematically recorded, further reduces yield. Leptospirosis, chikungunya and rickettsiae other than *O. tsutsugamushi* were not sought and will sit within the unresolved fraction. Thresholds were applied uniformly from 2 months to 18 years without age adjustment, which particularly affects hemoglobin and creatinine in infants. Diagnostic subgroups were small, so comparisons involving them are underpowered. Complications were a composite without severity grading, and readmission was ascertained only at the study hospital, so the 30-day figure is a lower bound. Differences between etiological groups are unadjusted and may be confounded by age, time to presentation, referral pathway and treatment.

CONCLUSION

Among children hospitalized with acute undifferentiated febrile illness in semi-arid south-eastern Rajasthan, scrub typhus was the leading identifiable cause, eschar was universally absent and examination was normal in three quarters, a combination that makes suspicion-driven testing unreliable and supports protocolized scrub typhus serology and urine culture for every child with post-monsoon undifferentiated fever here. Routine thresholds are specific enough to raise suspicion but too insensitive to exclude disease. More than half of admissions remained unresolved, defining the limit of present practice. A prospective evaluation of empirical

doxycycline, and multicenter replication across arid north-west India, are the priorities that follow.

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