



A prospective observational study of clinical characteristics and outcomes in patients with acute febrile illness

Dr. Sandeep Das

Department of Management, Telangana University, Telangana, India

Abstract

Acute febrile illness (AFI) is among the most frequent reasons for seeking care in tropical and subtropical settings, yet its causes overlap clinically and often remain unconfirmed. This paper synthesizes recent and foundational evidence on the clinical characteristics, etiological spectrum, and outcomes of AFI, with emphasis on prospective observational studies from India and meta-analyses from low- and middle-income countries. Sources were located through targeted searches and prioritized for 2023–2026 publications, supplemented by earlier hospital cohorts that report patient outcomes. Across the literature, dengue, scrub typhus, enteric fever, malaria, and leptospirosis recur as leading causes, but their relative weight shifts with region, season, and care setting. A substantial share of febrile patients, from roughly one-third to nearly two-thirds depending on setting, never receive a confirmed diagnosis. Indian hospital cohorts report mortality in the low single digits, with greater need for organ support in scrub typhus, leptospirosis, and malaria. Major barriers include limited diagnostic capacity, imperfect rapid tests, cross-reactivity, discretionary testing, and non-standardized study methods. The paper argues for locally informed diagnostic algorithms, confirmatory testing, standardized prospective protocols, and integrated surveillance.

Keywords: Acute febrile illness, undifferentiated fever, dengue, scrub typhus, prospective observational study, diagnostic uncertainty, India

Introduction

Fever is one of the commonest reasons people seek health care worldwide, and in tropical settings it poses a persistent diagnostic puzzle. Acute febrile illness (AFI) is best understood as a syndrome rather than a diagnosis: a rapid-onset fever, usually above 38 °C, lasting from a couple of days to about two weeks and accompanied by non-specific symptoms (Khanna *et al.*, 2026) ^[5]. Because headache, muscle pain, rash, and low platelet counts are shared by dengue, scrub typhus, typhoid, malaria, chikungunya, and leptospirosis, bedside assessment alone seldom identifies the cause (Wangdi *et al.*, 2019) ^[11]. Awareness of non-malarial causes has also grown over recent decades, adding to the number of conditions clinicians must consider (Wainaina *et al.*, 2022) ^[10].

Prospective observational designs suit this problem well. By enrolling patients at presentation and following them to discharge, they capture presenting features, test results, treatments, and outcomes under real clinical conditions. However, individual cohorts are typically single-centre and time-limited, so their findings are best read alongside pooled evidence. This paper therefore brings together recent meta-analyses and prospective hospital studies to describe what is known about the clinical characteristics and outcomes of AFI, where the evidence is thin, and what follows for practice and study design. It is a literature-grounded synthesis and does not report new patient data.

Review Approach

Sources were located through targeted searches of the open web and indexed bibliographic records, using combinations of terms such as acute febrile illness, acute undifferentiated fever, etiology, meta-analysis, India, and prospective. Preference was given to systematic reviews, meta-analyses, and prospective observational studies published between

2023 and 2026. Older hospital-based cohorts were retained when they reported clinical outcomes that recent papers did not, and they are identified by year in the text. Only information available in abstracts or open full texts was used, and figures are reported as the original authors presented them. This is a pragmatic narrative review rather than a registered systematic review; no formal risk-of-bias appraisal or flow diagram was produced.

Clinical Features, Etiology, and Outcomes of Acute Febrile Illness

Defining the syndrome and its presentation

Most patients with AFI arrive with a short febrile illness and non-specific complaints, and usually without an obvious focus of infection (Wangdi *et al.*, 2019) ^[11]. The pathogen list is long, spanning arboviruses, rickettsial and other bacterial infections, parasites, and enteric viruses. Consequently, clinical definitions rely on duration and temperature thresholds rather than on any characteristic sign, and confirmation depends on laboratory testing that is applied unevenly (Khanna *et al.*, 2026) ^[5].

Etiological spectrum across regions

A 2025 meta-analysis of studies from low- and middle-income countries estimated pooled prevalence among AFI cases of 20.2% for malaria, 15.0% for dengue, 8.0% for enteric fever, 5.7% for leptospirosis, and 3.5% for scrub typhus, while 36.9% of cases had no identified cause (Saady *et al.*, 2025) ^[9]. A review of 43 studies from South and Southeast Asia, covering 80,554 cases, found viral causes (18.5%) more common than bacterial ones (12.9%), with dengue leading overall at 11.8%. Leptospirosis was the main diagnosis among outpatients, whereas dengue dominated among admitted patients, and leptospirosis led in

Southeast Asia while dengue led in South Asia (Wangdi *et al.*, 2019) ^[11].

African evidence shows a similar picture of diversity and uncertainty. A meta-analysis of 133 studies including 391,835 patients from 25 countries reported many aetiological agents with large regional differences, and bacterial pathogens detected in blood accounted for the largest proportion (Wainaina *et al.*, 2022) ^[10]. A separate pooled estimate for East African adolescents and adults put fever of unidentified aetiology at 64%, though with extreme heterogeneity (Nooh *et al.*, 2023) ^[7]. A systematic review of zoonotic causes in malaria-endemic countries identified data on 30 zoonoses from 244 articles but only 53 of 110 countries, indicating large geographic gaps (Halliday *et al.*, 2020) ^[4].

Clinical characteristics and outcomes in Indian hospital cohorts

Prospective Indian cohorts add the patient-level detail that pooled reviews lack. In a tertiary hospital in South India enrolling 1,258 patients, scrub typhus (35.9%) and dengue (30.6%) were the leading diagnoses, followed by malaria (10.4%), enteric fever (3.7%), and leptospirosis (0.6%). Patients with enteric fever and scrub typhus presented later, at roughly ten and eight days respectively. Bleeding occurred in 7.7% overall and in 14% of dengue cases, and oxygen, ventilation, and inotrope requirements were higher in scrub typhus, leptospirosis, and malaria. Overall mortality was 3.3%, highest in scrub typhus (4.6%), then dengue (2.3%). Breathlessness, a white cell count above 10,000 per mm³, and low serum albumin each independently predicted scrub typhus (Abhilash *et al.*, 2016) ^[1].

Other cohorts show how rankings shift with place and period. A one-year study of 487 febrile patients in Kolar, Karnataka, found dengue the most frequent cause (52.1%), followed by scrub typhus, leptospirosis, chikungunya, enteric fever, and malaria, with most cases in the rainy and autumn seasons (Arvind *et al.*, 2018) ^[2]. In eastern India, scrub typhus led among 432 tested patients (26.3%) ahead of dengue (19.2%); an eschar was seen in only 6.1%, and no deaths were attributed to scrub typhus (Behera *et al.*, 2019) ^[3]. In a northern Indian hospital, 2,547 adults were evaluated; dengue accounted for 37.5%, enteric fever 16.5%, scrub typhus 14.4%, and bacterial sepsis 10.3%, while 11% remained undiagnosed (Mittal *et al.*, 2015) ^[6].

The most recent cohort, from Jalandhar in northern India (July 2023 to December 2024), evaluated 8,127 patients using rapid tests chosen by treating physicians. Dengue positivity was 9.75%, serologically positive typhoid 10.02%, hepatitis A 5.2%, hepatitis E 2.3%, and scrub typhus 3.4%, while malaria was rare. Dengue and typhoid peaked in the monsoon and post-monsoon months, and dengue positivity was higher in the 2023 outbreak period than later (Khanna *et al.*, 2026) ^[5].

Mixed infections and diagnostic ambiguity

Co-infection complicates interpretation. In the Jalandhar cohort, 4.32% of samples were classed as mixed infections, mainly dengue with typhoid, but the authors cautioned that cross-reactivity between dengue and typhoid IgM assays may have inflated this figure; only 15 of 646 serologically positive typhoid samples were culture-confirmed (Khanna *et al.*, 2026) ^[5]. The 2015 northern Indian series reported mixed infections in 1.9% of patients (Mittal *et al.*, 2015) ^[6].

Meta-regression across African studies likewise showed that the diagnostic method itself shaped the estimated share of typhoidal *Salmonella* and dengue (Wainaina *et al.*, 2022) ^[10].

Evidence on Effectiveness

The reviewed literature is overwhelmingly descriptive, so "effectiveness" here refers to how well current diagnostic and clinical approaches resolve the syndrome and to what outcomes follow. No trial evidence was located showing that a particular testing strategy changes mortality in AFI, and this gap should be stated plainly. What the cohorts do show is that structured evaluation yields usable information. Simple clinical and laboratory markers helped identify scrub typhus in the South Indian series (Abhilash *et al.*, 2016) ^[1], and the northern Indian authors concluded that careful clinical assessment supported by basic investigations can reach a reasonably certain diagnosis in most patients (Mittal *et al.*, 2015) ^[6].

Rapid tests extend this reach by returning results within hours, and the Jalandhar team found them useful for surveillance and outbreak detection, while acknowledging imperfect specificity for typhoid serology (Khanna *et al.*, 2026) ^[5]. Outcome data suggest where vigilance matters most: mortality of 3.3% and heightened organ-support needs in scrub typhus, leptospirosis, and malaria in one large cohort (Abhilash *et al.*, 2016) ^[1], against a series from eastern India with no scrub typhus deaths (Behera *et al.*, 2019) ^[3]. These differences may reflect case mix, timing of presentation, or treatment, which observational data cannot separate. The persistent share of undiagnosed cases, 36.9% in pooled LMIC data, shows that current approaches leave a large residual uncertainty (Saady *et al.*, 2025) ^[9].

Barriers and Challenges to Implementation

Diagnostic capacity is the foremost barrier. Primary care facilities and hospitals in many LMICs lack accessible tools and laboratory staff to identify multiple pathogens accurately (Nooh *et al.*, 2023) ^[7]. Where testing exists, it is often discretionary: in the Jalandhar cohort, tests were ordered at physicians' judgment, so denominators differed by pathogen and selection bias was possible, and most diagnoses rested on rapid serology without molecular confirmation (Khanna *et al.*, 2026) ^[5].

Research methods compound the problem. A scoping review of 190 full-text publications on AFI etiology highlighted wide variation in study design and laboratory methods and called for methodological standardization (Rhee *et al.*, 2019) ^[8]. African pooled analyses likewise urged standardized diagnostic procedures so that studies can be compared (Wainaina *et al.*, 2022) ^[10]. Heterogeneity is often extreme, as the I² of 99.6% in East African estimates illustrates (Nooh *et al.*, 2023) ^[7]. Finally, data on zoonotic and neglected causes remain sparse across much of the malaria-endemic world (Halliday *et al.*, 2020) ^[4], and scrub typhus is still described as under-recognized in some northern Indian settings (Khanna *et al.*, 2026) ^[5].

Discussion and Implications

Three themes emerge. First, no single pathogen dominates AFI everywhere. Even within India, the leading diagnosis varied between cohorts, so local, seasonal, and recent outbreak data should shape clinicians' pre-test probabilities more than national averages. Second, uncertainty is the

norm rather than the exception: undiagnosed fever, mixed infections, and test cross-reactivity mean that a single positive rapid result should be interpreted in context and, where feasible, confirmed. Third, outcome knowledge is thin. Most large series report etiology, whereas few follow patients systematically for complications, organ support, and death.

For practice, these findings favour locally informed diagnostic algorithms, awareness of early markers that flag severe or rickettsial disease, access to confirmatory culture or molecular testing for ambiguous results, and seasonal readiness during monsoon periods. For research, prospective protocols should define enrolment, a uniform test panel, follow-up, and outcome measures in advance, so that cohorts can be pooled. For public health, hospital-based laboratory surveillance can detect outbreaks early, as the Jalandhar team argued. The limitations of this paper should be kept in mind: it is a narrative synthesis, relies partly on abstracts, mixes studies of different eras and designs, and has not been appraised for risk of bias.

Conclusion

Acute febrile illness remains a diagnostically uncertain syndrome in which dengue, scrub typhus, enteric fever, malaria, leptospirosis, and hepatitis viruses compete for attention, and in which one-third or more of patients may leave without a confirmed cause. Prospective hospital cohorts from India show mortality in the low single digits and meaningful organ-support needs in selected infections, yet differences between studies are shaped as much by methods and setting as by biology. Progress depends on stronger diagnostics, standardized prospective study designs with systematic outcome follow-up, and sustained surveillance linking clinic, laboratory, and public health response.

References

1. Abhilash KPP, Jeevan JA, Mitra S, Paul N, Murugan TP, Rangaraj A, et al. Acute undifferentiated febrile illness in patients presenting to a tertiary care hospital in South India: Clinical spectrum and outcome. *Journal of Global Infectious Diseases*, 2016;8(4):147–154.
2. Arvind N, Prabhakar K, Savitha N, Mahendra M. Clinical and microbiological profile of patients with acute febrile illness attending a tertiary care hospital in South India. *Journal of Pure and Applied Microbiology*, 2018;12(2):757–763. <https://doi.org/10.22207/JPAM.12.2.36>
3. Behera B, Biswal M, Das RR, Dey A, Jena J, Dhal S, et al. Clinico-epidemiological analysis of scrub typhus in hospitalised patients presenting with acute undifferentiated febrile illness: A hospital-based study from Eastern India. *Indian Journal of Medical Microbiology*, 2019. https://doi.org/10.4103/ijmm.ijmm_19_147
4. Halliday JEB, Carugati M, Snavely ME, Allan KJ, Beamesderfer J, Ladbury GAF, et al. Zoonotic causes of febrile illness in malaria endemic countries: A systematic review. *The Lancet Infectious Diseases*, 2020, 20.
5. Khanna P, Gupta A, Sheemar S, Taperyal T, Taak S. Surveillance of infectious agents in acute febrile illnesses in a tertiary care hospital in northern India. *Infection Epidemiology and*

Microbiology, 2026;12(2):153–160.

<https://doi.org/10.52547/iem.12.2.153>

6. Mittal G, Ahmad S, Agarwal RK, Dhar M, Mittal M, Sharma S. Aetiologies of acute undifferentiated febrile illness in adult patients: An experience from a tertiary care hospital in northern India. *Journal of Clinical and Diagnostic Research*, 2015;9(12):DC22–DC24. <https://doi.org/10.7860/JCDR/2015/11168.6990>
7. Nooh F, Chernet A, Reither K, Okuma J, Brattig NW, Utzinger J, et al. Prevalence of fever of unidentified aetiology in East African adolescents and adults: A systematic review and meta-analysis. *Infectious Diseases of Poverty*, 2023, 12(1). <https://doi.org/10.1186/s40249-023-01105-z>
8. Rhee C, Kharod GA, Schaad N, Furukawa NW, Vora NM, Blaney DD, et al. Global knowledge gaps in acute febrile illness etiologic investigations: A scoping review. *PLoS Neglected Tropical Diseases*, 2019, 13.
9. Saady M, Ewaisha R, Azzazy HME. Regional burden of undifferentiated fever and leading infectious etiologies of acute febrile illness in low- and middle-income countries: A meta-analysis. *International Journal of Infectious Diseases*, 2025, 161. <https://doi.org/10.1016/j.ijid.2025.108152>
10. Wainaina M, Vey da Silva DA, Dohoo I, Mayer-Scholl A, Roesel K, Hofreuter D, et al. A systematic review and meta-analysis of the aetiological agents of non-malarial febrile illnesses in Africa. *PLoS Neglected Tropical Diseases*, 2022;16(1):e0010144. <https://doi.org/10.1371/journal.pntd.0010144>
11. Wangdi K, Kasturiaratchi K, Nery SV, Lau CL, Gray DJ, Clements ACA. Diversity of infectious aetiologies of acute undifferentiated febrile illnesses in south and Southeast Asia: A systematic review. *BMC Infectious Diseases*, 2019, 19.