

Dengue, Scrub Typhus, And Leptospirosis Among Patients with Acute Febrile Illness in Western Uttar Pradesh, India

Neha K. Mani¹, Priyanka Singh², Ankur Goyal³, Vikas Kumar⁴, Vinay Verma⁵

¹Research Scholar, Department of Microbiology, NIMS University Rajasthan, Jaipur

²Associate Professor, Department of Biotechnology, NIMS University Rajasthan, Jaipur

³Professor, SNMC, Department of Microbiology, Uttar Pradesh, Agra

⁴Associate Professor, SNMC, Department of Microbiology, Uttar Pradesh, Agra

⁵Research Scholar, Department of Microbiology, NIMS University Rajasthan, Jaipur

Abstract

Background: Acute undifferentiated febrile illnesses (AFIs) present a significant diagnostic challenge in India, particularly during the monsoon and post-monsoon seasons when multiple endemic pathogens circulate simultaneously. The concurrent circulation of Dengue virus, *Orientia tsutsugamushi*, and *Leptospira* spp. complicates clinical management, as these pathogens often share overlapping symptomatic profiles, particularly AFI, that obscure differential diagnosis between arboviral and non-arboviral diseases. This diagnostic ambiguity is further exacerbated by the increasing prevalence of coinfection, which often manifests with more severe clinical markers than single-pathogen infections.

Methods: This retrospective, hospital-based investigation analyzed the serological findings from patients presenting with AFI at a tertiary care centre in Western Uttar Pradesh. Diagnostic laboratory procedures utilized IgM ELISA testing for *Leptospira* and *O. tsutsugamushi*, alongside ELISA for Dengue NS1 antigen and IgM antibodies.

Results: The analysis revealed that 56.8% of the study cohort exhibited serological evidence of at least one or more than one infection, with dengue being the most frequent mono-infection presentation (40.9%). Alongside, combination of dengue and scrub typhus (6.8%) representing the concurrent infection made an important observation.

Conclusions: The study highlights that other than coinfection of arboviral infections, non-arboviral infections, particularly among patients presenting with acute undifferentiated fever, is often an overlooked concern. This silently complicates clinical management and thus necessitates integrating comprehensive diagnostic panels into routine clinical practice to mitigate the morbidity associated with these emerging zoonotic and vector-borne synergistic infections.

Keywords: Dengue, Scrub typhus, Leptospirosis, Co-infection, Acute febrile illness (AFI), Western Uttar Pradesh, Serology.

Introduction

Acute febrile illness (AFI) is one of the most common clinical syndromes encountered in tropical and subtropical countries and remains a major contributor to morbidity and healthcare utilization. Defined as the acute onset of fever of short duration without an obvious localized source of infection, AFI encompasses a wide range of infectious diseases, including viral, bacterial, parasitic, and rickettsial illnesses. The increasing incidence of acute undifferentiated febrile illnesses in India during monsoon and post-monsoon seasons has highlighted a rising burden in vector-borne and zoonotic infections, including dengue, scrub typhus, and leptospirosis which frequently complicate clinical management^{1,2}

Scrub typhus and leptospirosis are important re-emerging zoonotic infections that contribute substantially to the burden of acute febrile illness in India, particularly during the monsoon and post-monsoon seasons. Scrub typhus, caused by *Orientia tsutsugamushi* and transmitted through the bite of infected chigger mites, has been increasingly recognized across diverse geographical regions of the country. Leptospirosis, caused by pathogenic *Leptospira* species, is primarily acquired through exposure to water or soil contaminated with the urine of infected animals and is commonly associated with heavy rainfall, flooding, and occupational or environmental exposure. Both infections are endemic in many parts of India and have shown an increasing number of reported cases over the past decade. Specifically, the recent surge of dengue in Western Uttar Pradesh has been frequently compounded by the concurrent presence of scrub typhus and leptospirosis, driven by shared environmental and seasonal risks. This overlapping transmission dynamic poses significant diagnostic dilemmas, as the clinical presentation of these pathogens often mimics mono-infections, potentially obscuring the presence of multi-etiological febrile illnesses^{3,4}. The clinical manifestations of scrub typhus and leptospirosis frequently overlap with those of dengue, presenting with nonspecific symptoms such as acute fever, headache, myalgia, arthralgia, nausea, vomiting, and

thrombocytopenia. In severe cases, all three infections may progress to multiorgan dysfunction, hepatic and renal impairment, bleeding manifestations, or shock, making clinical differentiation particularly challenging in the absence of laboratory confirmation. Consequently, failure to systematically screen for these concurrent zoonotic and vector-borne agents during peak seasonal windows can result in delayed targeted antimicrobial administration and heightened morbidity.⁵ Because these vector-borne and zoonotic pathogens share similar clinical manifestations and seasonal peaks,⁶ empirical monotherapies often fails to address the full spectrum of infecting agents, underscoring the urgent need for routine multi-pathogen screening during recurrent seasonal outbreaks⁷. Consequently, there is an urgent clinical requirement for diagnostic protocols that simultaneously screen for these disparate pathogens to prevent delayed targeted therapies.^{8,9}

Given that these pathogens often exhibit overlapping clinical features, identifying co-infections is essential to mitigate the risk of multi-organ dysfunction and mortality in endemic regions.¹⁰ Recent surveillance data from tertiary care centers in Uttar Pradesh underscore this trend, revealing that a significant proportion of acute febrile cases harbor multiple concurrent infections.^{11,12} Consequently, reliance on clinical features alone may lead to misdiagnosis or delayed diagnosis, potentially resulting in inappropriate patient management. This diagnostic challenge is especially significant during dengue season, when heightened clinical suspicion for dengue may overshadow the consideration of other treatable endemic infections.

During the post-monsoon dengue season, the high incidence of laboratory-confirmed and clinically suspected dengue cases often leads clinicians to prioritize dengue as the primary diagnosis in patients presenting with acute febrile illness. However, this heightened focus may inadvertently reduce consideration of other endemic infections such as scrub typhus and leptospirosis, which frequently circulate during the same season and present with similar clinical manifestations. Consequently, reliance on clinical assessment alone may result in missed or delayed diagnosis of these coexisting infections. Unlike dengue, for which management is primarily supportive, scrub typhus and leptospirosis are bacterial zoonotic infections that respond well to early antimicrobial therapy. Failure to recognize these infections may delay appropriate treatment, increasing the risk of severe complications, including acute kidney injury, hepatic dysfunction, acute respiratory distress syndrome, meningoencephalitis, multiorgan failure, and death. Therefore, comprehensive diagnostic evaluation for multiple endemic pathogens is essential to ensure timely diagnosis, guide appropriate therapy, and improve patient outcomes.

Although several studies from different parts of India have reported the occurrence of dengue, scrub typhus, and leptospirosis individually or as dual infections. But the evidence regarding scrub typhus and leptospirosis distribution and co-infection with dengue in Western Uttar Pradesh remains scarce. This lack of regional data hampers accurate assessment of the local disease burden and may contribute to under-recognition of treatable zoonotic infections among patients presenting with acute febrile illness.

Therefore, this study aimed to investigate the distribution of dengue, scrub typhus, and leptospirosis among patients presenting with acute febrile illness during post-monsoon season when dengue is prominently circulating in several parts of Western Uttar Pradesh, India, and to evaluate the frequency and patterns of non- arboviral co-infections among these pathogens.

Materials and Methods

Study Design and Setting

This cross-sectional, laboratory-based observational study was undertaken during peak dengue endemic season, in a tertiary care centre of Western Uttar Pradesh, India. Blood samples were taken as part of the investigation from patients who were admitted to the center's In-patient Department (IPD) or presenting with an acute febrile illness in the Out-patient Department (OPD). These patients were then referred to the tertiary care center's Virology Laboratory for laboratory testing of dengue and other clinically significant endemic pathogens, such as scrub typhus and leptospirosis.

Study Population

A total of 88 consecutive patients presenting with acute febrile illness (AFI) during the investigation were included in the study. AFI was defined as the acute onset of fever of less than 14 days' duration without an apparent localized

source of infection. All eligible patients from whom blood samples were received during the post-monsoon period were included irrespective of age or sex.

Inclusion Criteria

- Patients presenting with acute febrile illness (fever of <14 days' duration) during the peak dengue season.
- Patients with no differential symptoms other than AFI
- Patients of all age groups and both sexes.

Exclusion Criteria

- Patients with an established non-infectious cause of fever at presentation.
- Samples with insufficient serum volume for laboratory analysis.
- Duplicate samples obtained from the same patient during the study period.

Sample Collection and Processing

Venous blood samples were collected from enrolled patients following standard aseptic procedures. The samples were transported under appropriate cold-chain conditions to the Virology Laboratory, Department of Microbiology, Government Medical College, Agra. The blood samples were centrifuged for serum separation as soon as received at the laboratory. The separated serum samples were either processed for serological testing or stored under recommended laboratory conditions until further analysis, in accordance with the laboratory's standard operating procedures.

Laboratory Investigations

All serum samples were tested for dengue virus, scrub typhus, and leptospirosis using commercially available ELISA assay kits according to the respective manufacturers' instructions.

Dengue Diagnosis

Serological testing for dengue infection was conducted utilizing enzyme-linked immunosorbent assay (ELISA) methodologies. Patients who presented within the initial five days of fever onset underwent testing for the dengue NS1 antigen using the NS1 Ag MICROLISA kit, produced by J. Mitra & Co. Pvt. Ltd. Samples collected after five days of illness were screened for anti-dengue IgM antibodies employing IgM antibody capture ELISA kits developed by the National Institute of Virology. Additionally, all samples were tested for anti-chikungunya IgM antibodies using NIV IgM capture ELISA kits. All assays adhered to the manufacturer's instructions, with appropriate positive and negative controls included in each run to ensure quality assurance. The kit sensitivity and specificity for the NIV dengue IgM capture ELISA kit were 98.53% and 98.84%, respectively; for the NS1 Ag MICROLISA, they were 99.69% and 100%; and for the chikungunya IgM capture ELISA, they were 95.0% and 98.0%, respectively.

Scrub Typhus & Leptospirosis Diagnosis

All serum samples underwent screening for IgM antibodies against *Orientia tsutsugamushi* utilizing a commercially available IgM ELISA kit for Scrub typhus (J. Mitra & Co. Pvt. Ltd., New Delhi, India). The assay was conducted and interpreted in accordance with the manufacturer's instructions. Additionally, leptospiral infection was assessed using the *Leptospira* IgM ELISA (J. Mitra & Co. Pvt. Ltd., New Delhi, India). This assay was executed following the manufacturer's protocol, with reactive IgM results indicating a recent leptospiral infection.

The kit sensitivity and specificity for IgM ELISA kit for Scrub typhus (J. Mitra & Co. Pvt. Ltd., New Delhi, India) were 100% and 98.58%, respectively; for the *Leptospira* IgM ELISA (J. Mitra & Co. Pvt. Ltd., New Delhi, India), they were 99.62% and 99.92% respectively.

Case Definitions

Laboratory-confirmed dengue, scrub typhus, and leptospirosis cases were defined as patients demonstrating reactive results in the respective serological assays. Co-infection was defined as simultaneous laboratory evidence of infection with two or more pathogens among dengue virus, *Orientia tsutsugamushi*, and *Leptospira* species in the same patient.

Data Collection

Demographic and clinical information, including age, sex, presenting clinical features, etc., were obtained from the patient. Laboratory results were compiled to determine the distribution of individual infections (arboviral/non-arboviral) and investigate the presence of co-infections among the study population.

Ethical Considerations

The study utilized anonymized serum samples collected as part of a routine laboratory testing of patients presenting with acute febrile illness at a tertiary care centre in North India. All patient identifiers were removed prior to data analysis, and confidentiality was maintained throughout the study in accordance with the ethical principles of the Declaration of Helsinki.

Results

Among the 88 clinical samples tested, 50 (56.8%) were laboratory-confirmed for at least one pathogen. Dengue monoinfection was the most frequent diagnosis, identified in 36 samples (40.9%), followed by dengue–scrub typhus coinfection in 6 samples (6.8%). Scrub typhus and leptospirosis monoinfections were each detected in 4 samples (4.5%). The remaining 38 samples (43.2%) were negative for dengue virus, scrub typhus, and leptospirosis.

The demographic characteristics of patients with laboratory-confirmed infections has been summarized in Table 1. Out of the 36 patients with dengue monoinfection, 24 (66.7%) were female and 12 (33.3%) were male. Scrub typhus and leptospirosis monoinfections each showed an equal sex distribution, with 2 females (50.0%) and 2 males (50.0%) in each group. Among the patients with dengue–scrub typhus coinfection, 4 (66.7%) were female and 2 (33.3%) were male. There was no statistically significant association between diagnostic category and sex (Pearson's $\chi^2=0.810$, $df=3$, $p=0.847$).

The age distribution varied descriptively across diagnostic categories. Among the dengue monoinfection cases, 16 (44.4%) occurred in patients aged 0–18 years, 14 (38.9%) in those aged 19–30 years, and 6 (16.7%) in those aged 31–60 years. All leptospirosis monoinfection cases occurred in the 0–18-year age group (4/4, 100.0%). Scrub typhus monoinfection cases were equally distributed between the 0–18-year and 19–30-year groups, with 2 cases (50.0%) in each group. Dengue–scrub typhus coinfection cases were evenly distributed across the 0–18-year, 19–30-year, and 31–60-year groups, with 2 cases (33.3%) in each group. No laboratory-confirmed infections were observed among individuals aged >60 years.

As no confirmed cases were recorded in the >60-year age group, this category was excluded from the inferential analysis. Comparison of the remaining age groups (0–18, 19–30, and 31–60 years) across the four diagnostic categories showed no statistically significant association between age group and diagnosis (Pearson's $\chi^2=8.449$, $df=6$, $p=0.208$).

The post-monsoon period predominantly featured dengue infections, aligning with the established seasonal transmission pattern in the region. Dengue was the most frequently confirmed infection in laboratory tests, followed by scrub typhus and leptospirosis. A subset of patients exhibited coinfection with both dengue and scrub typhus. While the distribution of infections indicated a higher prevalence among females and younger individuals across various diagnostic categories, these differences did not reach statistical significance in the initial categorical analyses.

Table 1. Demographic variables of laboratory-confirmed disease categories

Demographic variable	Dengue, n (%)	Scrub typhus, n (%)	Leptospirosis, n (%)	Coinfection n (%) Dengue and scrub typhus
Total cases	36 (40%)	4 (4.54%)	4 (4.54%)	6 (6.81%)
Sex				
Male	12 (33.3)	2 (50.0)	2 (50.0)	2 (33.3)
Female	24 (66.7)	2 (50.0)	2 (50.0)	4 (66.7)
Age group (years)				
0–18	16 (44.4)	2 (50.0)	4 (100.0)	2 (33.3)
19–30	14 (38.9)	2 (50.0)	0 (0.0)	2 (33.3)
31–60	6 (16.7)	0 (0.0)	0 (0.0)	2 (33.3)

>60	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
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Overall, dengue was the predominant infection detected during the study period. However, the identification of additional infections among patients assessed during the season suggests that overlapping causes of acute febrile illness were present in the affected population. The detection of dual positivity for dengue and scrub typhus further indicates that dengue and other febrile infections may occur simultaneously during such periods.

Discussion

The predominance of dengue aligns with its established role as a primary driver of acute febrile illness in tropical settings¹³. This elevated prevalence, often observed during post-monsoon periods, highlights how environmental factors facilitate the rapid circulation of dengue virus within specific geographical regions. Furthermore, the concurrent identification of dengue, scrub typhus, and leptospirosis emphasizes the diagnostic complexity inherent in acute undifferentiated febrile illnesses, where clinical manifestations often lack sufficient specificity for accurate pathogen differentiation^{14,15}.

As these zoonotic and vector-borne diseases continue to re-emerge, the challenge of overlapping etiological patterns necessitates a heightened clinical awareness to address the diagnostic pitfalls inherent in managing acute undifferentiated febrile illnesses¹⁶. Clinical management is further complicated by the high sensitivity of diagnostic assays like IgM ELISA for leptospirosis, which necessitates early screening to differentiate between these clinically similar, yet therapeutically distinct, infectious agents¹⁷. By integrating advanced diagnostic strategies, clinicians can effectively navigate the diagnostic confusion caused by the shared clinical manifestations and potential for serological cross-reactivity inherent in these endemic tropical diseases¹⁸. Regarding coinfection patterns, laboratory analysis revealed a 6.81% occurrence of dual pathogen positivity, with dengue and scrub typhus representing the most frequent overlap. Although a low coinfection burden of dengue and scrub typhus is observed here, but it underscores the critical necessity of comprehensive differential diagnosis during acute febrile illness, as simultaneous infections may significantly complicate clinical trajectories¹⁹.

Furthermore, while pediatric populations (0–18 years) exhibited the highest susceptibility to dengue and leptospiral infections, adult cohorts demonstrated a broader, more uniform distribution across all three infections similar to other studies as well.^{20,21} The substantial burden observed in this younger demographic mirrors broader regional trends where school-aged children and adolescents exhibit the highest vulnerability to infection, underscoring the critical need for pediatric-focused prevention strategies^{22,23}. This increased susceptibility in younger individuals is often linked to both immunological naivety and behavioral patterns that elevate exposure to diverse transmission vectors²⁴. Additionally, the demographic distribution indicates a higher vulnerability among female participants across all categories, except leptospirosis where the burden is equal. This variance in sex-based vulnerability suggests that exposure risks may be influenced by occupation or activity-specific patterns within the investigated endemic region as suggested in other studies²⁵.

During rainy or post-monsoon periods, the concurrent circulation of dengue, scrub typhus, and leptospirosis may increase the likelihood of mixed infections and requires integrated surveillance and simultaneous testing to distinguish true coinfections from serological cross-reactivity³. Such diagnostic complexities underscore the necessity of prioritizing differential diagnostic panels, as these pathogens often present with indistinguishable clinical manifestations in resource-constrained primary healthcare settings^{26,27}.

Effective clinical management in these regions requires maintaining a high index of suspicion for multiple pathogens simultaneously to reduce morbidity and mortality associated with delayed therapeutic interventions²⁸. Consequently, future public health initiatives should emphasize the implementation of multiplex diagnostic assays to enhance the resolution of etiological identification in patients presenting with undifferentiated fever²⁹. Furthermore, the high morbidity and mortality associated with these zoonotic pathogens necessitate the systematic adoption of multiplex diagnostic platforms to enhance the resolution of etiological identification in patients presenting with undifferentiated fever^{21,29-30}.

Limitations Of The Study

Since the analysis relies on single-point serological results, dual positivity should be interpreted as concurrent seropositivity rather than definitive active coinfection, with confirmation through a fourfold rise in convalescent antibody titres or pathogen-specific PCR improving etiological certainty.

Conclusion

The findings demonstrate that dengue and other acute febrile illnesses exhibit overlapping clinical symptoms, complicating clinical differentiation. This underscores the need for screening and accurate diagnosis of multiple infections with similar clinical manifestations, including arboviral, non-arboviral, and zoonotic infections, when evaluating patients. Thus, relying solely on single-etiology diagnostics in endemic regions may result in significant underreporting of secondary pathogens.³

To address the complex etiology of acute undifferentiated febrile illnesses and prevent suboptimal patient outcomes due to missed coinfections, it is essential to integrate comprehensive diagnostic panels into routine clinical protocols³¹ An expanded diagnostic framework is crucial for accurately characterizing the true burden of acute undifferentiated febrile illness, as co-infections are frequently identified in clinical settings where multiple pathogens circulate concurrently.³² Ultimately, transitioning towards multiplex molecular diagnostics in local health units will facilitate more precise clinical management and enhance the surveillance of complex febrile syndromes. Future research should focus on implementing modular, semi-quantitative molecular assays, which have demonstrated significant potential in improving diagnostic accuracy and surveillance efficiency in resource-constrained environments.

By systematically incorporating broader screening for both viral and bacterial agents, healthcare providers can better navigate the diagnostic challenges posed by seasonal pathogen overlaps and improve the overall accuracy of disease surveillance. This transition toward multi-pathogen surveillance is vital for capturing the full spectrum of circulating infectious agents that contribute to febrile morbidity. Ultimately, these diagnostic improvements must be coupled with robust clinical algorithms that account for the high likelihood of pathogen interactions, which can profoundly alter both disease severity and therapeutic requirements.

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All authors declare that this work has not got any financial assistance from funding agency and has not included any study related to humans and/or animals.

Ethical Responsibilities of Authors

All authors declare that this research article is original and has not been published elsewhere in any form or language (partially or in full).

Consent to Participate

Not applicable

Consent to Publish

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Declaration of Generative AI and AI-assisted technologies in the writing process:

During the preparation of this work, the authors had not used any AI-AI assisted technologies. We both authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Data transparency

All authors agree that all data, materials as well as software application has supported their published claims and complied with field standards.

Author contributions

Dr. Priyanka Singh, Dr. Ankur Goyal, and Dr. Vikas Kumar have contributed to the study conception and design for this research work. Material's preparation, data collection and analysis were performed by scholar, Ms. Neha K. Mani and Mr. Vinay Verma. The first draft of the manuscript was written by Neha K. Mani. Dr. Priyanka Singh, Dr. Ankur Goyal, and Dr. Vikas Kumar have thoroughly reviewed and approved the final manuscript.

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