

# Non-Covid causes of acute undifferentiated febrile illness during the Covid pandemic: an etiological analysis from Uttar Pradesh, India

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## Summary

**Background and Aims:** febrile illnesses are one of the leading causes of morbidity and mortality in India, which are very com-

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Key words: AUFI, Chikungunya, dengue, leptospira, malaria, scrub typhus, seasonal prevalence.

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mon in the monsoon and post-monsoon season in tropical countries. Acute Undifferentiated Febrile Illness (AUFI) is a term usually used to refer to such conditions until diagnosed. This study was conducted to understand the prevalence of mixed infections, and the etiology and seasonal distribution of AUFI cases during the Corona Virus Disease (COVID) pandemic.

**Materials and Methods:** this study was a hospital-based cross-sectional study of six months (August 2021 to January 2022). Samples were collected by random sampling method from SN Medical College, Agra, and Mathura District. The diagnosis was made by Rapid Diagnostic Test for Malaria, and ELISA for Dengue, Chikungunya, Leptospira, and Scrub typhus.

**Results:** a total of 9016 non-repetitive serum samples were collected, from males (4657) and females (4359), with a mean age of 42 years. The most common infections were: dengue (26.5%), malaria (0.85%), leptospira (0.54%), scrub typhus (0.32%), and Chikungunya (0.14%). The commonest co-infection was dengue with scrub typhus. Triple infections were also observed.

**Conclusions:** the diversity of clinical presentations and etiological agents with limited diagnostic facilities demonstrates the complexity of AUFI. The knowledge of the local and seasonal distribution of acute febrile illnesses is thus very useful to formulate clinical, diagnostic, and management algorithms for positive outcomes, reducing hospital costs, and burden on healthcare facilities. Further upliftment of health services at the root level is still a long way to go.

## Introduction

Febrile illnesses are amongst the leading causes of morbidity and mortality in India. These diseases are quite common within the monsoon and post-monsoon season in tropical countries like India, although malaria occurs throughout the year in many tropical countries. There are few studies on fever etiology in India, and surveillance is limited due to the lack of accessibility to health facilities. Acute Undifferentiated Fever Illness (AUFI) also called 'acute fever' or 'short febrile illness' is defined as a fever of fewer than two weeks of duration without any localized source of infection [9, 21]. Most AUFI are arthropod-borne infections, with severity ranging from mild or self-limiting infections to life-threatening states [2]. Malaria, dengue, Chikungunya, scrub typhus, leptospirosis, enteric fever are the common causes of AUFI [4, 7, 10]. AUFI occur commonly in tropical countries like India [9, 21]. Malaria and dengue are the foremost prevalent febrile illness-associated types in India [4].

Malaria is a mosquito-borne infection and is responsible for the majority of mortality and morbidity, and it occurs throughout the year in many tropical areas [16]. Dengue and Chikungunya are arboviral diseases transmitted by the bite of an infected *Aedes* mosquito. 'Dengue fever' also referred to as break bone fever is a mosquito-borne infectious tropical disease caused by the Dengue Virus (DENV). It occurs primarily within the equatorial regions of Africa, the Americas, Southeast Asia, and the Western Pacific [1]. DENV has an incubation period of 4-10 days and can cause asymptomatic to severe infections. Mild dengue fever infections are characterized by fever with or without rash, while more severe infections include high-grade fever, severe headache, arthralgia, retrobulbar pain, and rash. Few patients acquire more severe conditions, including Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) [8, 28, 27].

Chikungunya Virus is another important cause of febrile illness in the Indian sub-continent [26]. It is caused by a member of the family Togaviridae, genus Alphavirus and is transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes. The clinical picture is characterized by acute onset of fever, joint and muscle pain, headache, nausea, fatigue, and rash. Chikungunya shares many similarities with dengue, both in terms of epidemiology and clinical illness. Like the Dengue Virus, Chikungunya is usually misdiagnosed as dengue, and outbreaks of the two diseases can occur simultaneously [25]. Scrub typhus is a mite-borne infectious disease caused by the gram-negative obligate intracellular bacterium *Orientia tsutsugamushi* (*Rickettsia tsutsugamushi*). Disease manifestations vary from mild or asymptomatic infection to severe, potentially fatal illness, with clinical features of high fever, skin rash, headache, myalgia, lymphadenopathy, gastrointestinal symptoms, and cough. Scrub typhus is often underdiagnosed because of nonspecific clinical features and relatively lower prevalence of the characteristic eschar, making it difficult to differentiate from other febrile illnesses [24, 11].

Besides, Leptospirosis is a zoonotic bacterial disease caused by pathogenic serovars of *Leptospira*. In humans, it can cause a wide range of symptoms ranging from mild febrile illness to hepatic or renal failure. In acute undifferentiated fever, symptoms are non-specific, and if accurate diagnostic modalities are not available, treatment should be broad to avoid causality [6, 22].

Aims of this study were to determine the etiology of AUFIs, the prevalence of mixed infections and the seasonal distribution of AUFIs during the COVID pandemic.

**Table 1. Gender-wise distribution of total confirmed acute undifferentiated febrile illness (AUFIs) patients.**

Sex	No. of patients	Percentage (%)
Male	1320	52.3
Female	1204	47.7
Total	2524	100

**Table 2. Prevalence of acute undifferentiated febrile illness (AUFIs).**

Febrile illness	Number of cases	Percentage (%)
Dengue	2393	26.5
Malaria	77	0.85
Leptospirosis	49	0.54
Scrub typhus	29	0.32
Chikungunya	13	0.14

## Materials and Methods

It was a hospital-based cross-sectional study conducted in the Department of Microbiology, Sarojini Naidu Medical College, Agra (Uttar Pradesh), from August 2021 to January 2022, by random sampling method. Both IPD and OPD patients fulfilling the AUFIs criteria (with less than 14 days of fever without localized cause) with prior patient consent were enrolled. Patients with hematological malignancies, autoimmune disorders, and those on chemotherapy were excluded. The samples from Mathura district (Uttar Pradesh) were also included.

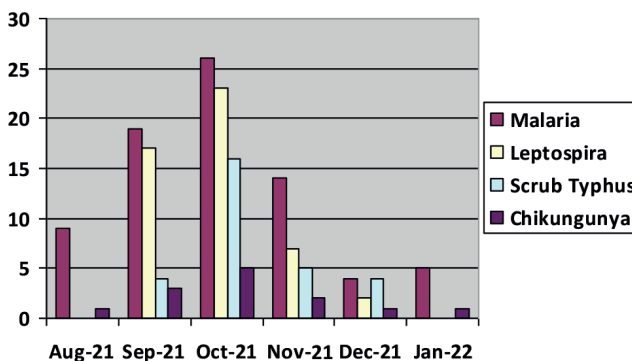
Malaria diseases were diagnosed by Rapid Card Test and Peripheral Blood Smear for Microscopy. Dengue, Chikungunya, leptospira, and scrub typhus were tested by qualitative ELISA by NS1/ IgM Dengue ELISA, IgM Chikungunya ELISA, IgM Scrub Typhus ELISA, and IgM Leptospira ELISA, according to manufacturer's instructions.

The data thus produced was recorded in IBM SPSS Ver.25 for statistical analysis.

## Results

A total of 9,016 non-repetitive samples were collected from patients suspected of AUFIs, with a mean age of 42 years (1 year to 85 years). Two thousand five hundred and twenty-four cases were diagnosed as cases of AUFIs, with a prevalence of 27.9%. In particular, 1320 males (52.2%) and 1204 females (47.7%) were diagnosed as cases of AUFIs, with the male-female ratio of 1.1:1 (Table 1).

Dengue was the most common infection (26.5%), followed by malaria (0.85%), leptospirosis (0.54%), scrub typhus (0.32%), and Chikungunya (0.14%) (Table 2). The highest number of AUFIs cases were observed in October, the lowest in January. Overall, 43 patients presented multiple infections. Precisely, 37 patients had dual infections while six patients were diagnosed with triple infections. Thirty-one of the 37 patients had a dual infection of dengue with scrub typhus, while six patients were diagnosed with a co-infection of Chikungunya and scrub typhus. In cases of triple infections, three cases were diagnosed with dengue, scrub typhus and Chikungunya; two patients were diagnosed with dengue, malaria and scrub typhus, while one patient had malaria, scrub typhus and Chikungunya. The trend of AUFIs in this region is shown in Figure 1, which describes the peak of cases reported in October, followed by November and



**Figure 1. Seasonal distribution of malaria, leptospira, scrub typhus, and Chikungunya.**

September. Only a few cases were reported in August and December 2021, and January 2022 (Figure 2).

## Discussion

Most of the febrile illnesses included in the AEFI are caused by arthropod-borne viral, parasites and bacteria pathogens. Globally, currently available serological tests are very useful in diagnosing these infections as they are relatively simple, easy to perform, and add up the advantage of early reporting. Most of the etiological agents responsible for the AEFI are zoonotic, which are prevalent in areas with heavy rainfall during the monsoon season.

In the present study, the male population (51.6%) is slightly more affected than the female (48.3%). This finding is consistent with many international and Indian studies, including the studies from Uttar Pradesh. The male predominance may be associated with the outdoor occupational exposure of males [12]. Dengue was the most common cause of AEFI in our study, followed by malaria, leptospirosis, scrub typhus, and Chikungunya. This finding is consistent with other similar studies [12, 15, 18].

Dengue infections vary in severity, ranging from influenza-like illness to life-threatening Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS).

Our study had a higher prevalence of severe dengue cases (60%) compared to that reported by Souza *et al.* (7.6%) [20]. A study conducted by Singh *et al.*, from the region of Uttarakhand, demonstrates dengue, malaria, and typhoid as the commonest etiological agents of acute febrile illness [13]. A study by Neelu Sree *et al.*, found dengue, malaria, scrub typhus and leptospirosis with the highest prevalence in acute febrile illness [17].

dengue and malaria, both arthropod-borne diseases, endemic in many parts of India, show a seasonal trend during the monsoon and winter seasons [4]. The majority of cases of scrub typhus and dengue were reported during the monsoon and post-monsoon seasons as per the reported patterns of disease transmission [14, 5].

A meta-analysis which included studies from 1998 to 2019 to evaluate etiologies of undifferentiated febrile illness in the South and Southeast Asia revealed dengue as the most common cause of AEFI, followed by scrub typhus, malaria, leptospirosis, and typhoid [23]. Mixed infection with more than one organism can result in illness with overlapping symptoms posing diagnostic and therapeutic challenges to the physician.

The management of AEFI is often limited by poor infrastructure and the absence of specificity in symptoms of various febrile

illnesses. The differential diagnosis, due to overlapping etiologies and non-specific clinical symptoms, and the non-availability of accurate diagnostic facilities, is very difficult. Rapid diagnostic tests are temperature sensitive and therefore lose their diagnostic efficiency when stored at room temperature [3].

## Conclusions

This study establishes that dengue, malaria, leptospirosis, and scrub typhus were the major causes of febrile illness during the Covid pandemic. The diversity of clinical presentations and etiological agents with limited diagnostic facilities demonstrated the complexity of the diagnosis and treatment of AEFI. Thus, the knowledge of the local and seasonal distribution of acute febrile illnesses proved very useful in formulating clinical, diagnostic, and management algorithms for positive outcomes, reducing hospital costs, and burden on healthcare facilities. The rising incidence of mixed infections emphasizes the urgent need for a comprehensive diagnostic workup.

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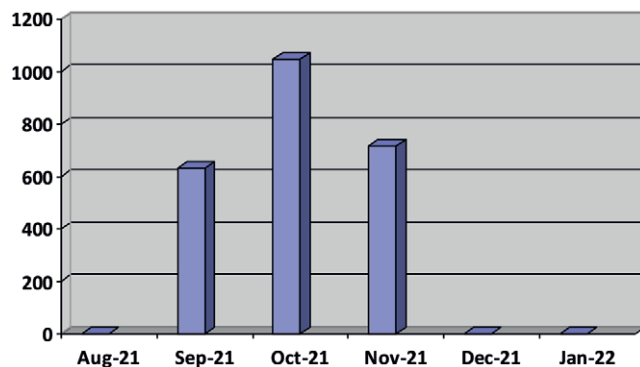


Figure 2. Seasonal distribution of dengue.

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