



“TO STUDY THE PREVALENCE OF AETIOLOGIES ACUTE UNDIFFERENTIATED FEBRILE ILLNESSES OF THE PATIENTS AT A TERTIARY CARE CENTRE IN UTTAR PRADESH, INDIA”.

Vikas Mishra¹, Deepika Shukla², Firoza Bano³, Sheela Sharma⁴, Sanjay Nigam⁵, Shrawan Kumar⁶, R Sujatha⁷, Nashra Afaq⁸, Madhu Yadav^{9*}, Gaurav Oberoi¹⁰, Qazi Rais Ahmed¹¹

¹Professor, Department of Microbiology G.S.V.M. Medical College, Kanpur, Uttar Pradesh, India

²Assistant Professor, Department of Microbiology Maharana Pratap Dental College and Hospital Kothi, Mandhana, Kanpur, Uttar Pradesh, India

³Associate Professor, Department of Community Medicine Al-Falah School of Medical Sciences and Research Centre, Faridabad, Haryana, India

⁴Professor and Head, Department of Obstetrics & Gynaecology Rama Medical College Hospital and Research Centre, Mandhana, Kanpur, Uttar Pradesh, India

⁵Professor, Department of Pathology Rama Medical College Hospital and Research Centre, Mandhana, Kanpur, Uttar Pradesh, India

⁶Professor and Head, Department of Medicine Rama Medical College Hospital and Research Centre, Mandhana, Kanpur, Uttar Pradesh, India

⁷Professor and Head, Department of Microbiology Rama Medical College Hospital and Research Centre, Mandhana, Kanpur, Uttar Pradesh, India

⁸Research Associate, Department of Microbiology and Central Research Laboratory Rama Medical College Hospital and Research Centre, Mandhana, Kanpur, Uttar Pradesh, India

^{9*}Associate Professor, Department of Microbiology G.S.V.M. Medical College, Kanpur, Uttar Pradesh, India

¹⁰Professor, Department of Pediatrics Bhargava Hospital, Kanpur, Uttar Pradesh, India.

¹¹Professor and Head, Department of Physiology Rama Medical College Hospital and Research Centre, Mandhana, Kanpur, Uttar Pradesh, India.

***Corresponding author:** Dr. Madhu Yadav

*Associate Professor, Department of Microbiology G.S.V.M. Medical College, Kanpur, Uttar Pradesh, India Email: madhu15dec@yahoo.com

Abstract

INTRODUCTION: The acute undifferentiated febrile illness (AUFI) connotes fever of <14 days duration without any evidence of organ or system specific aetiology. In the majority of hospitals, acute undifferentiated febrile illness (AUFI) is a prevalent clinical condition. If the cause of the fever is not identified and treated effectively as soon as possible, it could be fatal.

AIM AND OBJECTIVES: To study the Prevalence of Aetiologies acute undifferentiated febrile illnesses of the patients at a tertiary care centre in Uttar Pradesh, India.

MATERIAL AND METHODS: This was a Hospital based cross sectional study conducted in the Department of Microbiology at Rama Medical College Hospital & Research Centre, Mandhana, Kanpur. The study was carried out during the monsoon and post monsoon of the year 2022 for a period of 6 months from July 2022 to December 2022. A total of the 1520 clinical samples were recorded out of which there were 106 suspected cases. Sampling method was used and all-in-patients

fulfilling the AEFI definition were included. All in-patients with <14 days of fever with no localising source of infection were included in the study. The suspected cases were tested for various serological tests. Diagnosis was confirmed by suitable laboratory tests after exhaustive clinical examination.

RESULTS: In the present study the ratio of Male 60 (56.6%) was found to be more as compared to that of Female 46 (43.3%) with the maximum number of cases recorded in the age group of 20-40 years of age and least in the age group above 61 years of age. The most common cause of AEFI was the Dengue with the prevalence rate of 12.2% followed by Typhoid 7.5% , Enteric fever was found to be 7.5% Scrub typhus 1.88%, and least for Malaria 0.9%. It was also noted that there were no positive cases observed for Chikungunya and leptospira. It was also observed that the fever was the most common among all, followed by anaemia, hepatomegaly, splenomegaly with the maximum number of cases observed in the month of August to October.

CONCLUSION: When prioritising clinical and diagnostic workup and starting the appropriate empirical and supportive therapy, doctors are guided by their understanding of the local aetiology of AEFI. As the prevalence of multiple infections rises, complete clinical and diagnostic investigation for likely pathogens must be taken into account in AEFI patients who are not responding to treatment.

KEYWORDS: AEFI, Dengue, Leptospira, Chikungunya, Scrub typhus, Malaria, Typhoid

INTRODUCTION

Infectious diseases causes acute febrile illness, causing outpatient visits and hospital admissions, causing considerable morbidity and if not not treated can cause mortality[1-5].The term acute undifferentiated febrile illness (AEFI) is defined as fever of <14 days duration without any localised source of infection [6].There are a wide range of of infectious agents (bacteria, viruses, protozoa) causing AEFI, it is important to know about specific pathogens associated with each AEFI episode to address the public health challenge of AEFI [7–9].The common causes of AEFI's are dengue fever, chikungunya, scrub typhus, malaria, Enteric fever, Leptospirosis etc in the tropical countries [10].

Serological tests play a vital role in diagnosis of these febrile illnesses In resource limited settings fever may be treated empirically or self treated due to lack of access to diagnostic tests. Thus, knowledge of local prevalence of infections is critical in order to target clinical work up and treatment [11]. The present study was undertaken to find the aetiology of AEFI in patients attending a tertiary care centre in Uttar Pradesh.

MATERIALS & METHODS

The present study was a Hospital based cross sectional study conducted in the Department of Microbiology at Rama Medical College Hospital & Research Centre, Mandhana, Kanpur. The study was carried out during the monsoon and post monsoon of the year 2022 for a period of 6 months from July to December 2022 . Sampling method was used and all in-patients fulfilling the AEFI definition were included. All in-patients with <14 days of fever with no localising source of infection were included in the study. Patients on immunosuppressive therapy, cancer chemotherapy and HIV infection were excluded from the present study.

Laboratory tests

Patients with AEFI were tested for Dengue, Scrub typhus, Leptospira, Chikungunya, Enteric fever by serological tests during the study period. Peripheral blood smear was used to diagnose malaria. Dengue, Leptospira and Scrub typhus were tested by Dengue Duo, Leptospira IgG/Ig M and T sutsugamushi rapid tests respectively (SD Diagnostics)Widal Ag kit with titres of O \geq 80, H \geq 160 or four fold rise in titres (Febrile Antigen set, Span Diagnostics Ltd., Gujarat, India). Statistical analysis was performed in MS Excel 2010 to analyse the data.

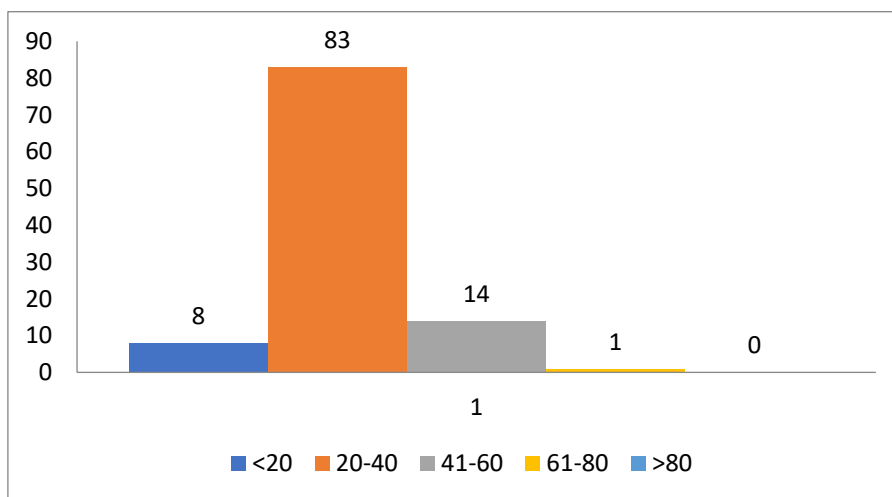
Ethical consideration: Ethical committee clearance was duly obtained from Institutional ethics committee and informed written and verbal consent was taken from all the patients.

RESULTS:

A total of the 1520 clinical samples were recorded out of which there were 106 suspected cases. The maximum number of cases were recorded in the age group of 20-40 years of age followed by 41-60 years and least in the age group above 61 years of age [Table No. 1]. The ratio of Male 60 (56.6%) was found to be more as compared to that of Female 46 (43.3%) [Table No. 2].

Age wise Distribution	No. of Isolates	Percentage
<20	8	7.54%
20-40	83	78.30%
41-60	14	13.20%
61-80	1	0.94%
>80	0	0%

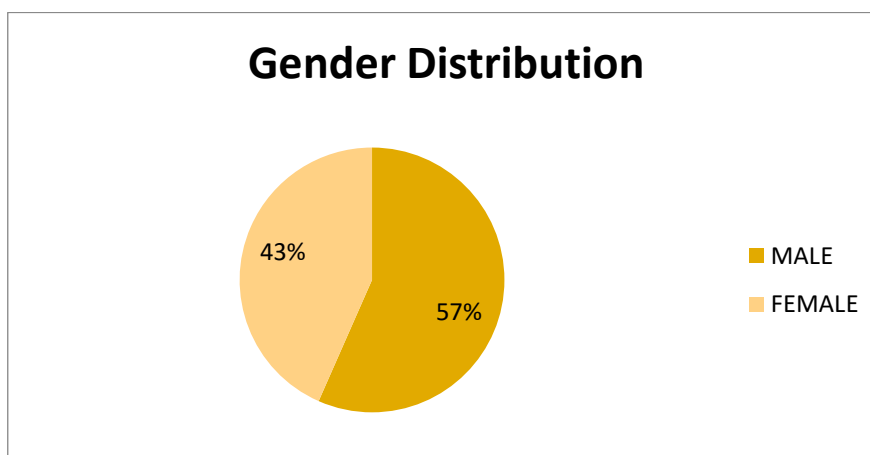
Table No. 1: Age wise Distribution of the cases



Graph No. 1: Graphical Representation of the Age wise distribution

Gender	No. of isolates	Percentage
MALE	60	56.60%
FEMALE	46	43.39%

Table No. 2: Gender wise Distribution of the cases



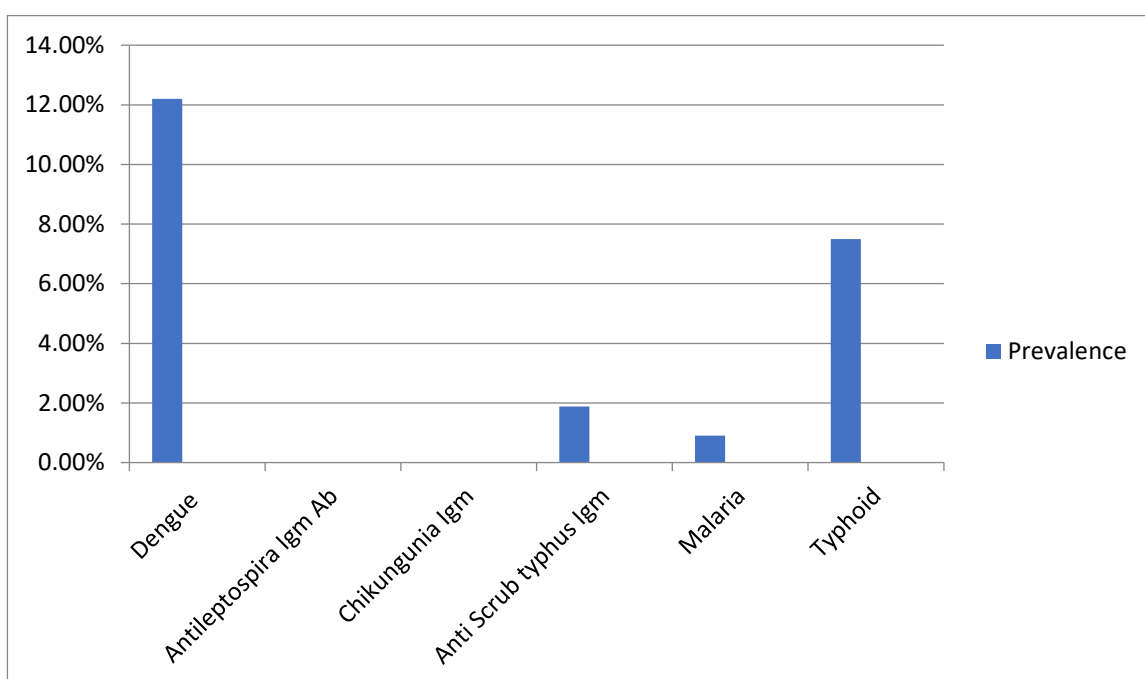
Graph No. 2: Graphical Representation of the Gender wise distribution

In the present study the most common cause of AUFI was the Dengue with the prevalence rate of 12.2% followed by Typhoid 7.5% and Scrub typhus 1.88% and least for Malaria 0.9%.

In the present study the prevalence of Enteric fever was found to be 7.5% and it was also noted that there were no positive cases observed for Chikungunia and leptospira.

Case	No. of Cases	Percentage (%)
Dengue	13	12.2%
Antileptospira Igm Ab	0	0%
Chikungunia Igm	0	0%
Anti Scrub typhus Igm	2	1.88%
Malaria	1	0.9%
Typhoid	8	7.5%

Table No. 3: Distribution of the AUFI cases



Graph No. 3: Graphical Representation of the AUFI cases

Month Wise Distribution	Dengue	Antileptospira Igm Ab	Chikungunia Igm	Anti Scrub typhus Igm	Malaria	Typhoid
July 2022	1	-	-	-	-	1
August 2022	2	-	-	-	-	2
September 2022	2	-	-	1	1	2
October 2022	5	-	-	1	-	2
November 2022	3	-	-	-	-	1
December 2022	-	-	-	-	-	-
Total	13 (12.2%)	-	-	2 (1.88%)	1 (0.94%)	8 (7.5%)

Table No.4: Month wise distribution of adult febrile patients along with their aetiologies of common causes of fever

From the Table No. 4 it was observed that the maximum number of cases observed were in the month of August to October.

Sign and Symptoms	Dengue 13 (12.2%)	Antileptospira Igm Ab	Chikungunia Igm	Anti Scrub typhus Igm2(1.88%)	Malaria 1 (0.94%)	Typhoid 8(7.5%)
Fever	10	-	-	2 (100)	1(100)	8 (100)
Rash	9	-	-	1	-	-
Bleeding	1	-	-	-	-	-
Icterus	-	-	-	1	1	2
Anaemia	-	-	-	1	1	5
Hepatomegaly	4	-	-	1	1	5
Splenomegaly	-	-	-	-	1	3

Table No.5: Clinical and laboratory parameters associated with common aetiological agents of

The fever was observed to be the most common AEFI among all the parameters.

DISCUSSION

Febrile illnesses are very common in the monsoon and post monsoon season in tropical countries. The term acute undifferentiated febrile illness (AEFI) is defined as fever of <14 days duration without any localised source of infection [12]. The common causes of AEFI's are dengue fever, chikungunya, scrub typhus, malaria, Enteric fever, Leptospirosis etc. in the tropical countries [13]. There are only a limited number of studies from Northern India reporting on the aetiology of fever and reliable surveillance data are not available [14]. The main objective of this study was to describe the aetiology of fever among patients in a tertiary care hospital in Northern India.

Acute febrile illnesses pose a diagnostic challenge due to their varied aetiology and limited diagnostic capabilities even in tertiary care hospitals. Most of them are caused by arthropod borne viral pathogens followed by bacteria and parasites. Serological tests are useful tools to diagnose these aetiological agents rapidly as they are relatively easy to perform and results can be delivered within a few hours of sample receipt in the laboratory.

In the present study out of the 1520 clinical samples there were 106 suspected cases. Out of the 106 suspected cases the ratio of Male 60 (56.6%) was found to be more as compared to that of Female 46 (43.3%). This study was parallel to the study performed by the author where the ratio of Males (58.4%) were more with compared to the Females (41.5%) [15] with the maximum age group of 20-40 years of age and least in the age group above 61 years of age. There were other studies in accordance to the present study [16]. Males were affected more as that of females. This may be due to their easy exposure to mosquitoes and mites because of their outdoor activities. [15, 16].

In the present study the most common cause of AEFI was the Dengue with the prevalence rate of 12.2% followed by Typhoid 7.5% and Scrub typhus 1.88% and least for Malaria 0.9%. This study was similar to the study performed by the Rammohan M.V.N.L. et al, 2019 [15] where the rate of Dengue was found to be the maximum. There were other study also performed where the rate of Dengue was found higher, stating the most common cause of AEFI in the present was Dengue followed by scrub typhus with prevalence rates of 21.6% and 9.5% respectively. Dengue, malaria, scrub typhus, enteric fever and leptospirosis have been identified as major causes of AEFI in Thailand, Malaysia and Nepal [17-21] and a few studies from South India [22,23]. There were other studies also in support to the present study where, Dengue was reported to be the major cause of febrile illness from two studies in Dehradun [24] and Rourkela [25]. There was another study which was in contrast to our study stating that Scrub typhus as a major cause of AEFI in South India with one study reporting nearly half of inpatient admissions due to scrub typhus among the AEFI's [26].

Two studies from a south Indian tertiary care hospital in 2007 and 2012-2013 have reported scrub typhus as predominant cause of AEFI-47.5% and 35.9% respectively [26]. Another study from Maharashtra in 2015-16 also found scrub typhus to be the predominant cause of AEFI [27]

In the present study the prevalence of Enteric fever was found to be 7.5% . This study was similar to the study performed by the other authors with 16.5% and 3.7% respectively [24,27]. In the present study it was also observed that the rate of Malaria was found to be 0.9%, 1.88% for Scrub typhus and it was also noted that there were no positive cases observed of Chikungunia and leptospira. This study was in support with the study performed by the other author [28]. There was another study where the prevalence of Chikungunia and leptospira was found to be the minimum [29]. The prevalence of malaria was also found to be low in our study. Relatively low prevalence of malaria was seen in the present study compared reported rates of 0.1% to 12 % from various studies [24,25,28,29,30]. Rise of non-malarial AUFI's in Asia and Africa has been attributed to the decline of malaria cases in these continents [29,31].

It was also observed that the fever was the most common among all, followed by anaemia, hepatomegaly, splenomegaly. In a cohort study by Abrahamsen et al., [32] from Southern India, bacterial infections (38%) and TB (19%) were the most common aetiological agents of fever. Another study from east India [33] reported that TB (53%), neoplasms (17%) and collagen vascular disorders (11%) were the dominant causes.

In the present study it was also observed that the maximum number of cases observed in the month of August to October. This study was similar to the study performed by other authors [15,16]. Another study in Vellore w reported maximum number of scrub and dengue cases in October [15,16,27].

For, mosquitoes and mites to breed and thrive, monsoon period is considered the best time. Drinking water is also contaminated during rainy season. All these factors lead to increase in above mentioned causes of fever in these particular months. Seasonal upsurge in fever is also a well known documentation in other studies [34,35].

The heavy burden of tropical infections such as dengue, enteric fever, scrub typhus and malaria. Beginning with the monsoon season, acute undifferentiated febrile illnesses (AUFI) are more common in tropical nations. The diagnosis and treatment of febrile disorders are made more difficult by several aetiologies, overlapping clinical manifestations, and mixed infections.

Physicians would be more effective if they were aware of the regional aetiology and seasonal occurrence of certain disorders.

Serological tests play a vital role in diagnosis of these febrile illnesses in resource limited settings. Data of the seasonal trend of AUFI's in a region would be useful in ordering relevant diagnostic tests and initiating early appropriate therapy.

Limitations of the study: Due to financial limitations and inadequate diagnostic resources, all infectious aetiology of febrile illnesses could not be determined in this investigation.

CONCLUSION

Our investigation successfully pinpointed the main causes of AUFI in this region of India. The most frequent cause of AUFI was dengue, which was followed by enteric fever, scrub typhus, and malaria. As clinical diagnosis is not always sufficient to detect all febrile patients, active fever surveillance is required. To fine-tune illness burden estimates of frequent causes of AUFI, laboratory confirmation is crucial. To anticipate pandemic readiness in terms of resources and healthcare delivery, we would advise creating accurate epidemiologic databases of various fever aetiologies in every location. Understanding the regional and seasonal patterns of acute undifferentiated fever is helpful when developing logical clinical, diagnostic, and therapeutic algorithms that guide doctors in selecting the best empirical antibiotics.

REFERENCES

1. FIND. Acute febrile syndrome. *FIND Acute Febrile SyndrStrateg*. 2012; 3: 1–31.
2. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: An updated systematic analysis for 2010 with time trends since 2000. *Lancet*. 2012; 379:2151–2161.
3. Moreira J, Bressan CS, Brasil P, Siqueira AM. Epidemiology of acute febrile illness in Latin America. *Clinical Microbiology and Infection*. *ClinMicrobiol Infect*; 2018. pp. 827–835.
4. Gasem MH, Kosasih H, Tjitra E, Alisjahbana B, Karyana M, Lokida D, et al. An observational prospective cohort study of the epidemiology of hospitalized patients with acute febrile illness in Indonesia. *PLoS Negl Trop Dis*. 2020; 14: 1–17.
5. Faruque LI, Zaman RU, Gurley ES, Massung RF, Alamgir ASM, Galloway RL, et al. Prevalence and clinical presentation of Rickettsia, Coxiella, Leptospira, Bartonella and chikungunya virus infections among hospital-based febrile patients from December 2008 to November 2009 in Bangladesh. *BMC Infect Dis*. 2017; 17: 141.
6. Joshi R, Colford JM, Reingold A. Nonmalarial acute undifferentiated fever in a rural hospital in central India – Diagnostic uncertainty and overtreatment with anti malarial agents. *Am J Trop Med Hyg*. 2008;78(3):393-99.
7. 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 Negl Trop Dis*. 2019; 13: e0007792.
8. Shrestha P, Dahal P, Ogbonnaa-Njoku C, Das D, Stepniewska K, Thomas N V, et al. Non-malarial febrile illness: a systematic review of published aetiological studies and case reports from Southern Asia and South-eastern Asia, 1980–2015. *BMC Med*. 2020; 18.
9. Elven J, Dahal P, Ashley EA, Thomas N V, Shrestha P, Stepniewska K, et al. Non-malarial febrile illness: a systematic review of published aetiological studies and case reports from Africa, 1980–2015. *BMC Med*. 2020; 18.
10. Chrispal A, Boorugu H, Gopinath KG, Chandy S, Prakash JA, Thomas EM, et al. Acute undifferentiated febrile illness in adult hospitalized patients- The disease spectrum and diagnostic predictors- An experience from a tertiary care hospital in South India. *Trop Doct*. 2010;40(4)230–234. doi: 10.1258/td.2010.100132
11. Chaturvedi HK, Mahanta J, Pandey A. Treatment-seeking for febrile illness in north-east India: an epidemiological study in the malaria endemic zone. *Malar J*. 2009;8(1):301.
12. Joshi R, Colford JM, Reingold A. Nonmalarial acute undifferentiated fever in a rural hospital in central India – Diagnostic uncertainty and overtreatment with anti malarial agents. *Am J Trop Med Hyg*. 2008;78(3)393-399.
13. Chrispal A, Boorugu H, Gopinath KG, Chandy S, Prakash JA, Thomas EM, et al. Acute undifferentiated febrile illness in adult hospitalized patients- The disease spectrum and diagnostic predictors- An experience from a tertiary care hospital in South India. *Trop Doct*. 2010; 40(4)230– 234.
14. John TJ, Dandona L, Sharma VP, Kakkar M. Continuing challenge of infectious diseases in India. *Lancet*. 2011;377(9761):252–69
15. Rammohan M.V.N.L. et al. Prevalence of acute undifferentiated febrile illnesses in a tertiary care centre in Telangana, South India. *Tropical Journal of Pathology and Microbiology*. 2019;5(8)
16. Mueller TC, Siv S, Khim N, Kim S, Fleischmann E, Ariey F, et al. Acute undifferentiated febrile illness in rural Cambodia: A 3-year prospective observational study. *PLoS One*. 2014; 9(4):e95868.
17. Jena B, Prasad MNV, Murthy S. Demand pattern of medical emergency services for infectious diseases in Andhra Pradesh – A geo-spatial temporal analysis of fever cases. *Indian Emerg J*. 2010; 1(5):821.

18. Murdoch DR, Woods CW, Zimmerman MD, Dull PM, Belbase RH, Keenan AJ, et al. The aetiology of febrile illness in adults presenting to Patan Hospital in Kathmandu, Nepal. *Am J Trop Med Hyg.* 2004; 70(6):670–5.
19. Sripanidkulchai R, Lumbiganon P. Aetiology of obscure fever in children at a university hospital in northeast Thailand. *Southeast Asian J Trop Med Public Health.* 2005;36(5):1243–1246.
20. Leelarasamee A, Chupaprawan C, Chenchittikul M, Udompanthurat S. Aetiologies of acute undifferentiated febrile illness in Thailand. *J Med Assoc Thai.* 2004; 87(5):464–472.
21. Ellis RD, Fukuda MM, McDaniel P, Welch K, Nisalak A, Murray CK, et al. Causes of fever in adults on the Thai-Myanmar border. *Am J Trop Med Hyg.* 2006; 74(1):108-113.
22. Gopalakrishnan S, Arumugam B, Kandasamy S, Rajendran S, Krishnan B. Acute undifferentiated febrile illness among adults - A hospital based observational study. *J Evol Med Dent Sci.*2013;2(14):2305-2319.
23. Kashinkunti MD, Gundikeri SK, Dhananjaya M. Acute undifferentiated febrile illness- clinical spectrum and outcome from a tertiary care teaching hospital of north Karnataka. *Int J Biol Med Res.*2013;4(2):3399-3402.
24. 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. *J Clin Diagn Res.* 2015; 9(12):DC22–DC24.
25. Rao PN, van Eijk AM, Choubey S, Ali SZ, Dash A, Barla P, et al. Dengue, chikungunya, and scrub typhus are important etiologies of non-malarial febrile illness in Rourkela, Odisha, India. *BMC Infect Dis.* 2019; 19(1):572. doi: 10.1186/s12879-019- 4161-6
26. Zeller H, Van Bortel W, Sudre B. Chikungunyais history in Africa and Asia and its spread to newregions in 2013-2014. *J Infect Dis.* 2016; 214(suppl 5):S436–S440.
27. Abhilash KP, 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. *J Glob Infect Dis.* 2016; 8(4):147-154.
28. Shelke YP, Deotale VS, Maraskolhe DL. Spectrum of infections in acute febrile illness in central India. *Indian J Med Microbiol.* 2017;35(4):480-484.
29. 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 Infect Dis.* 2019;19(1):577.
30. Morch K, Manoharan A, Chandy S, Chacko N, Alvarez-Uria G, Patil S, Henry A, Nesaraj J, Kuriakose C, Singh A, et al. Acute undifferentiated fever in India: a multi centre study of aetiology and diagnostic accuracy. *BMC Infect Dis.* 2017; 17(1):665
31. Prasad N, Murdoch DR, Reyburn H, Crump JA. Etiology of severe febrile illness in low-and middle income countries: a systematic review. *PLoS One.* 2015;10(6): e0127962.
32. Abrahamsen SK, Haugen CN, Rupali P, Mathai D, Langeland N, Eide GE, et al. Fever in the tropics: aetiology and case fatality – a prospective observational study in a tertiary care hospital in south India. *BMC Infectious Diseases.* 2013;13:355.
33. Kejariwal D, Sarkar N, Chakraborti SK, Agarwal V, Roy S. Pyrexia of unknown origin: a prospective study of 100 cases. *J Postgrad Med.* 2001; 47(2):104-07.
34. Jena B, Prasad MNV, Murthy S. Demand pattern of medical emergency services for infectious diseases in Andhra Pradesh – A geo-spatial temporal analysis of fever cases. *Indian Emergency Journal.* 2010; 1(5):821.
35. Murdoch DR, Woods CW, Zimmerman MD, Dull PM, Belbase RH, Keenan AJ, et al. The aetiology of febrile illness in adults presenting to Patan Hospital in Kathmandu, Nepal. *Am J Trop Med Hyg.* 2004; 70(6):670–75