IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 21, Issue 2 Ser.16 (February. 2022), PP 29-33
www.iosrjournals.org

Serodiagnosis of Mosquito Borne Infections in Acute Febrile Illness Cases

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Abstract:
Background: *Acute febrile illness (AFI) is a common cause of patient visits to healthcare centres of India. Among AFIs the mosquito borne infections have gained concern in the recent years due to their shared endemicity, seasonal variation and recurring outbreaks. Co-infections complicate the diagnosis and course of treatment.This study was aimed to diagnose mosquito borne infections- dengue, malaria, chikungunya and their co-infections in acute febrile illness cases attending a tertiary care hospital.****Materials and Methods:****A Cross sectional study including 324 serum samples from acute fever cases of both sexes and all age groups giving consent during January 2021 to October 2021 at a tertiary care hospital. Diagnosis of dengue was done using NS1 Ag and IgMAb ELISA.Chikungunya was diagnosed by IgMAb ELISA. For diagnosis of malaria microscopic examination of peripheral smear and rapid antigen detection kits were used.*
Results:*Among the 324 samples, 131 (38.3%) were positive of which mono-infection was found in 106 (80.9%) samples and co-infections were seen in 25 (19.1%) samples. The commonest aetiology among mono-infections was dengue 81 (61.8%) followed by malaria 21 (16%), chikungunya 4 (3.1%).A male to female ratio of 2.04 was observed. Maximum cases (24/131) were seen in month of July followed by September.*
Conclusion:*Continuous surveillance by simultaneous testing for these mosquito borne infections in AFI cases and informing the clinicians and public health officials in endemic regions will guide in clinical management and taking up of preventive measures.*
Key words:*Acute febrile illness, Chikungunya, coinfections, Dengue, ELISA, Malaria*

Date of Submission: 13-02-2022 Date of Acceptance: 28-02-2022

I. Introduction

Acute febrile illness (AFI) is a common cause of patient visits to healthcare centres of Southeast Asia, including India.[1] Acute febrile illness is characterized by malaise, myalgia and a raised temperature for less than 3 weeks duration, lacking any localized organ-specific signs or symptoms.[2] Febrile illness in Southeast Asia was reported to be caused principally by dengue, malaria, typhoid, scrub typhus, leptospirosis and chikungunya[3] among which the mosquito-borne illnesses have gained concern due to their shared endemicity, seasonal variation[4,5] and recurring outbreaks.[6] Simultaneous infections with >1 infectious agent complicates the diagnosis leading to misdiagnosis of dual infection as monoinfection.[7]

II. Materials and Methods

The present cross sectional study was carried out at Sir Ronald Ross Institute of Tropical and Communicable diseases, Osmania Medical College, Hyderabad, Telanganafrom January 2021 to October 2021 and institutional ethical committee approval was obtained. A total of 324 acute fever cases of both sexes and all age groups giving consent were included in the study.

Study Design: Prospective observational study

Study Location: This was a tertiary care teaching hospital based study done in Department of Microbiology, at Sir Ronald Ross Institute of Tropical and Communicable diseases, Osmania Medical College, Hyderabad, Telangana

Study Duration: January 2021 to October 2021.

Sample size: 324 blood samples.

Subjects and selection methods: Fever cases with <15 days duration of both sexes and all age groups admitted at Sir Ronald Ross Institute of Tropical and Communicable diseases and giving consent**Inclusion criteria:**

1. All age group patients attending the hospital with fever of <15 days suspected as dengue, chikungunya or malaria.
2. Patients giving informed consent

Exclusion criteria:

1. Patients with fever of >15 days
2. Patients not giving consent

Procedure methodology:

After obtaining informed consent,5ml and 2ml of blood in plain tube and EDTA tube respectively were collected from each patient. Blood without anticoagulant was centrifuged at 3000g for 10 minutes for separation of serum. MAC-ELISA kit supplied by NIV Pune is used for Dengue (DEN) and Chikungunya (CHK) IgM antibody (Ab) detection and BIO-RAD Platelia™ Dengue NS1 Ag ELISA kit was used for the detection of dengue specific NS1 antigen (NS1 Ag) as per the manufacturer's instructions. For diagnosis of malaria thick and thin smears for malaria parasite stained with Jaswant Singh Bhattacharji stain were done. Serodiagnosis of malaria was done using SD BIOLINE Malaria Ag P.f/P.v test kit. Complete blood picture results were noted.

III. Results

Among 342 samples from AFI cases, 131 (38.3%) were positive either for Dengue (81, 23.7%), Chikungunya (4,1.7%), Malaria (21,6.1%) or co-infections (25,7.3%). Of the 131 positive samples, mono-infection was found in 106 (80.9%) samples and co-infections were seen in 25 (19.1%) samples as shown in figure1.

Figure 1: Positivity among tested samples

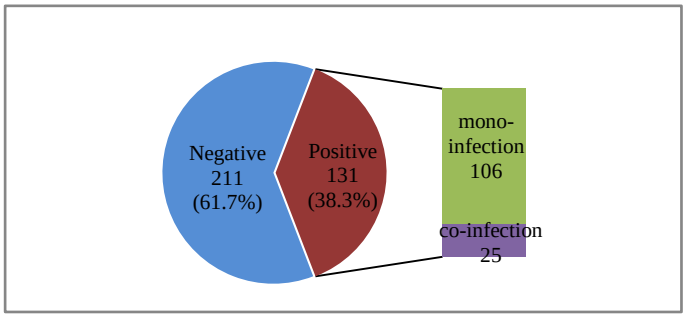
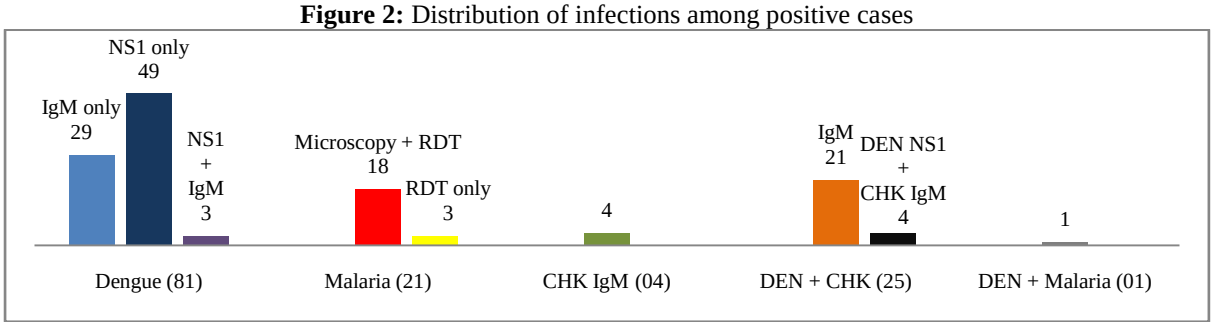


Figure 2 shows that the commonest aetiology among mono-infections in the present study was dengue 81 (61.8%) diagnosed by dengue NS1 Ag and IgMAb, followed by malaria 21 (16%),chikungunya 4 (3.1%). Among the 21 malaria positive samples, 18 (13.7%) were *Plasmodium vivax*and 03 (2.3%) were *Plasmodium falciparum*.

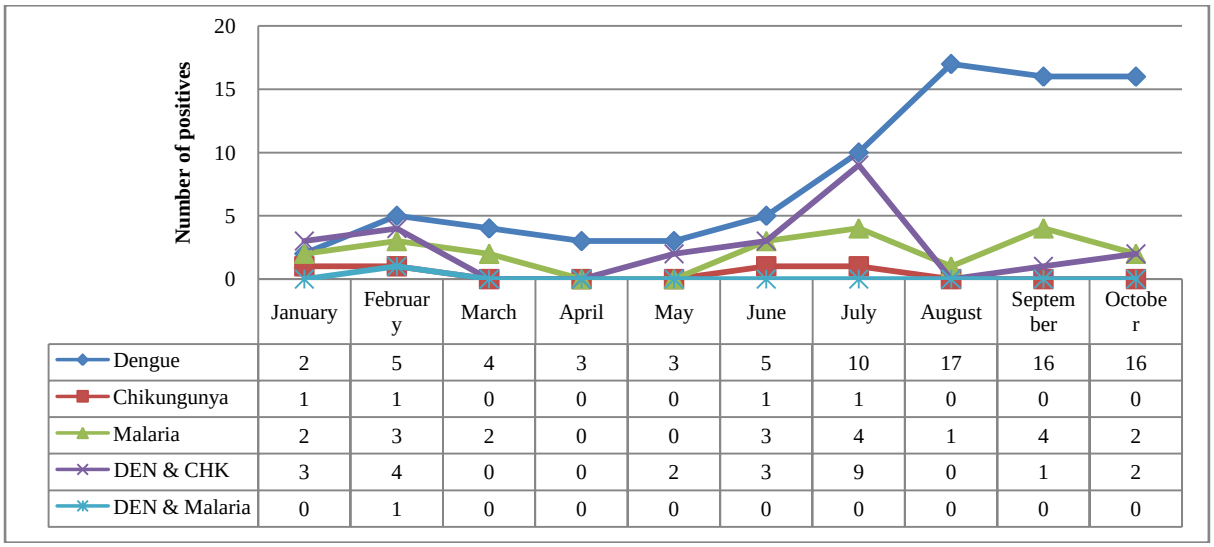
Figure 2: Distribution of infections among positive cases



Most common co-infection was dengue and chikungunya 24 (18.3%) followed by dengue and malaria 01 (0.8%) [Figure 2]. Plasmodium falciparum was found in the co-infection. Both DEN IgM and CHK IgM were positive in 20 samples and both DEN NS1 Ag and CHK IgM positive was seen in 04 samples among the DEN and CHK coinfections.

In the present study maximum positivity for mosquito-borne infections (24/131) was seen in month of July followed by September [Figure 3].

Figure 3: Month wise distribution of positive cases (n=131)



	January	February	March	April	May	June	July	August	September	October
Dengue	2	5	4	3	3	5	10	17	16	16
Chikungunya	1	1	0	0	0	1	1	0	0	0
Malaria	2	3	2	0	0	3	4	1	4	2
DEN & CHK	3	4	0	0	2	3	9	0	1	2
DEN & Malaria	0	1	0	0	0	0	0	0	0	0

As shown in table 1, among the positive cases, the most common age groups affected were 21-30 years (34.3%) and 11-20 years (32.8%) followed by 31-40 years (16%) age group. Out of the positive samples, 88(67.2%) were male and 43(32.8%) were female with male to female ratio of 2.04. Male preponderance was seen in dengue, malaria and co-infections but in chikungunya equal distribution was seen. The single Dengue and malaria co-infection in the present study was seen in a 19 year old male patient.

Table1: Age and gender wise distribution of positive cases

Age in years	*DEN		†CHK		Malaria		*DEN and †CHK		*DEN and Malaria		Total
	M	F	M	F	M	F	M	F	M	F	
0 – 10	05	0	0	01	0	0	0	01	0	0	07
11 – 20	25	06	0	0	03	0	05	03	01	0	43
21 – 30	15	12	02	01	07	01	04	03	0	0	45
31 – 40	06	04	0	0	03	02	06	0	0	0	21
41 – 50	01	04	0	0	03	01	0	01	0	0	10
> 50	01	02	0	0	01	0	0	01	0	0	05
Total	53	28	02	02	17	04	15	09	01	0	131

Complete blood picture of the positive samples revealed that 20.1% of the dengue positive samples had thrombocytopenia while both leucopenia along with thrombocytopenia was seen in 8.6% cases. Among chikungunya cases only leucopenia was seen in 25% samples whereas thrombocytopenia was not observed. Anemia was observed in 27% of the samples with malaria while leucopenia along with thrombocytopenia was seen in 14.3% of the samples positive for malaria whereas only thrombocytopenia was seen in co-infection of dengue and malaria [Table 2].

Table 2: Details of complete blood picture results of positive cases

AFI* (total no. of cases)	Leucopenia	Thrombocytopenia	Leucopenia + Thrombocytopenia
Dengue (81)	15 (18.5%)	17 (20.1%)	7 (8.6%)
Chikungunya (04)	01 (25%)	--	--
Malaria (21)	02 (9.5%)	02 (9.5%)	03 (14.3%)
†DEN + CHK‡ (24)	03 (12.5%)	04 (16.6%)	--
DEN + Malaria (01)	--	01 (100%)	--

IV. Discussion

Etiological diagnosis of acute febrile illness in the developing tropical countries presents with various challenges as these diseases share endemicity, vector transmission and overlapping nonspecific clinical features.

Among 324 samples, 131 (38.3%) showed positive results for dengue, chikungunya and Malaria with male preponderance (67.2%). A multicentric study by Morch et al. conducted across Assam, Bihar, Chattisgarh, Maharshtra, Andhra Pradesh and Tamilnadu during 2017 observed 57% were males and 40% were females among the positives.[8] Similar male preponderance was observed in 2018 studies by Andrews MA et al. (63.2% males and 36.7% females) done in Kerala[9] and Singh J et al. (63.6% males and 36.4% females) done in Uttar

Pradesh[10]. Positivity with 61.8% males and 34.6% females was reported by a 2019 study done in Delhi by Abhishek KS et al.[11]

Most common cause of mosquito borne acute febrile illness in the present study was dengue mono-infection (61.8%). The positivity of dengue infection among different studies varied depending on the place and the time of study. Shelke YP et al. in central India, 2017[12], Andrews MA et al. in Kerala, 2018[8] and a multicentric study done by Garg S et al. in 2017[13] reported 17.6%, 43.5% and 59.6% dengue positivity, respectively.

Of the 81 dengue positive samples IgM positivity was seen in 32 (39.5%) and NS1 positivity was seen in 52 (64.2%) samples. Dengue IgM and NS1 antigen positivity rates observed among various studies are shown in Table 3.

Table 3: NS1 and IgM positivity in dengue positive cases among various studies

Study and number of dengue positives	*NS1 Ag (%)	IgM (%)
Shelke YP et al.[12] (Central India, 2017), n= 47	72.34	27.65
Shanmugan et al.[14] (Tamilnadu, 2016), n= 474	45.6	76.8
Abhishek KS et al.[11] (Delhi, 2019), n=34	35.2	94.1
Present study, n=81	64.1	39.5

In the present study of the 131 positive samples, 16% cases were positive for malaria infection which is in concordance with previous studies conducted in 2017 by shelke YP et al. (12.2%) in central India,[12] and a multicentric study by Morch et al. (17%).[8] On the contrary to the present study, Barua et al. done during 2016 in Mumbai reported a higher malaria positivity of 30%,[15] whereas, studies by Andrews MA et al. in Kerala[9] and Robinson ML et al.[16] in Maharashtra during 2018 reported lower rates of 2.87% and 6 % respectively.

Infections with chikungunya showed a positivity of 3.1% which was similar to findings of Robinson ML et al. (2%) in 2018[16] and Singh J et al. done in 2018.[10]

Co-infection rates were variable among recent studies conducted across India and 19.1% was observed in the present study [Table 4]. In a systematic review by Salam et al.[7] dengue and chikungunya rates were 19% in 2013 and 25% in 2016, dengue and malaria co-infections rates were 3% in 2016 and 3.7% in 2017[8]. 8% was observed by Barua et al. in 2016[15] and the present study found Dengue and malaria co-infections rate as 0.8%.

Table 4: Dengue, chikungunya, malaria and coinfections among various studies

Study	Total (%)	DEN (%)	†CHK (%)	Malaria (%)	DEN + †CHK (%)	DEN + malaria (%)
Andrews MA et al.[9] (Kerala, 2018)	70.1	43.5	-	2.87	-	-
Robinson ML et al.[17] (Maharashtra,2018)	44	15	2	6	1	
Morch et al.[8](multicentric, 2017)	-	16	6	17	1.6	3.7
Present study	38.3	61.8	3.1	16	18.3	0.8

V. Conclusion

Dengue, chikungunya and malaria infections often affect the same population due to shared endemicity and mosquito vectors. Continuous surveillance by simultaneous testing for these mosquito borne infections in AFI cases and informing the clinicians and public health officials in endemic regions will guide in clinical management and taking up of preventive measures.

Conflicts of interest: None

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