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DENGUE FEVER OUTBREAK IN NORTH INDIA: A EPIDEMIOLOGICAL STUDY

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ABSTRACT **BACKGROUND & OBJECTIVES:-**Dengue virus infection produces a broad spectrum of symptoms, many of which are non-specific. After the onset of illness, the virus can be detected in serum, plasma, circulating blood cells and other tissues for 4–5 days. During the early stages of the disease, virus isolation, nucleic acid or antigen detection can be used to diagnose the infection. At the end of the acute phase of infection, serology is the method of choice for diagnosis. Thus, a diagnosis based only on clinical symptoms is unreliable. The objectives of the study were to know the incidence of laboratory confirmed dengue cases among the clinically suspected patients and to co-relate the above with the environmental conditions. **METHODS:** The present study was conducted retrospectively for a period of whole one year during the recent outbreak of dengue fever in Sitapur in the year 2018.Time of collection of the blood after the onset of fever is 1-6 days and after five days for NS1 antigen and IgM antibodies, respectively. Specimen transport is not a problem as immunoglobulins are stable at tropical room temperatures.**RESULTS -** Total 209 blood samples were collected and analyzed.Out of 209, 130 (62.2%) were male and 79 (37.8%) were female. In the present study, maximum number of positivity were observed in 21-30 yrs of (42.6%) age group. The maximum cases diagnosed of dengue fever ,were in October (53.6%), followed by september (26.8%).The number of samples positive for dengue virus specific IgM antibodies was 55.0%, suspected secondary infection was 23.7% & secondary infection was 21.3%.
INTERPRETATION & CONCLUSION-Effective and accurate diagnosis of dengue is of primary importance for clinical care,early detection of severe cases, case confirmation and differential diagnosis.

KEYWORDS : *Aedes aegypti* mosquito ,Dengue virus, dengue-specific NS1 antigen, ELISA , Immunoglobulins. Primary Dengue infection,Secondary Dengue infection,

INTRODUCTION :

Dengue fever (DF) has emerged as one of the world's major infectious diseases. Epidemics of dengue fever were first reported from the coastal area of Africa and later from Malaysia in the 19th century[1]. The infection is by now seen as a global epidemic with recorded prevalence in more than 120 countries[2]. In India, the first virologically confirmed epidemic occurred in Calcutta (now Kolkata) and the eastern coast of India in 1963-1964.[3]

A major widespread epidemic of dengue haemorrhagic fever (DHF) occurred in 1996 involving areas around Delhi and Lucknow[4],[5], since then, there has been a remarkable resurgence of the infection in north Indian plains that include the State of Uttar Pradesh. Once considered an urban problem, it has now penetrated into rural areas as well, due to high population density and other factors.[6]

The epidemiology of dengue circulation is changing in UP, with increased frequency of outbreaks, besides the establishment of dengue as an endemic disease in this region. [7],[8] .

The illness occurs throughout the year with a peak during monsoon and post-monsoon season due to high vector density. Major outbreaks have occurred in north India.[9]

The word "dengue" is derived from the Swahili phrase Ka-dinga pepo, meaning "cramp-like seizure".[9] Dengue viruses, single-stranded positive polarity ribonucleic acid (RNA) viruses of the family *Flaviviridae*, are the most common cause of arboviral disease in the world. Dengue viruses have four serotypes, designated dengue types 1-4; and are transmitted mainly by bite of *Aedes aegypti* mosquito and also by *Aedes albopictus*. More than two-fifths of the world's population (2.5 billion) live in areas potentially at risk for dengue. [10],[11] *Ae. aegypti* is one of the most efficient vectors for arboviruses because it is highly anthropophilic, frequently bites several times before completing oogenesis, and thrives in close proximity to humans.

Since *Aedes* are daytime biters and those people who spend time outdoors or in unprotected dwellings are at high risk of exposure, making the poor a preferential target. Low- income is a risk factor of dengue in multiple regions. In semi- urban areas, populations of *Aedes* spp. mosquitoes tend to fluctuate during the monsoon season.

The role of *Ae. Aegypti* as a principal vector had already been well documented in India.[12],[13]

The NS1 glycoprotein is produced by all flaviviruses and is secreted from mammalian cells. NS1 produces a very strong humoral response.Many studies have been directed at using the detection of NS1 to make an early diagnosis of dengue virus infection. Commercial kits for the detection of NS1 antigen are now available, though they do not differentiate between dengue serotypes. Their performance and utility are currently being evaluated by laboratories worldwide, including the WHO/TDR/PDVI laboratory network.

According to WHO [14] NS1 antigen can be detected up to 9 days after the onset of illness. IgM antibodies are detectable in 50% of patients by days 3-5 after the onset of illness, increasing to 80% by day 5 and 99% by day 10. IgM levels peak about 2 weeks after the onset of symptoms and then decline generally to undetectable level after 2-3 months.

Anti-dengue serum IgG is generally detectable at low titres at the end of the week of illness, increasing slowly thereafter with serum IgG still detectable after several months and probably even for the life.

MATERIALS AND METHODS

Study design :- Observational Study on Patients
Period : 1st Jan 2008- 31st Dec 2008
Place of study : Hind Institute of Medical Sciences { HIMS} Mau, Ataria, , a tertiary care hospital in Sitapur.

The study population comprised individuals of all age groups, attending the outpatient and inpatient departments of Hind Institute of Medical Sciences { HIMS} Mau, Ataria, , a tertiary care hospital in Sitapur. Blood samples were collected from 14,102 patients experiencing a febrile illness clinically consistent with dengue infection, selected according to the following inclusion and exclusion criteria.

Case-inclusion criteria
A case was included if there was high fever with clinical symptoms suggestive of dengue infection as per WHO criteria [15]

Case-exclusion criteria A case was excluded, if routine laboratory testing suggested bacterial or any viral infection other than dengue infection or any other disease. [15]

Laboratory diagnosis methods for confirming dengue virus infection may involve detection of the virus, viral nucleic acid, antigens or antibodies, or a combination of these techniques.

To test dengue-specific NS1 antigen, ELISA method was employed using BIORAD kits[16] MAC ELISA was performed using Vircell kits [17] to detect IgM antibodies. For detection of IgG antibodies BIORAD kits were used.[18] The instructions of the manufacturers were meticulously followed while performing the tests. When asked for testing IgM alone (Panel II) or both IgM and IgG antibodies (Panel IV) the blood was taken 5 days after the onset of fever. To test other panels no such discrimination was done.

RESULT

In 2018,Out of 14,102 cases (9010 from OPD , 5092 from IPD), 432 were suspected. 209(48.4%) were confirmed as serologically positive. Out of 209 confirmed cases, 130 (62.2%) were male and 79 (37.8%) were female,which was shown in Table I & Figure 1.

Table I : Demographic Distribution

Suspected cases	Confirmed cases			
432	209 (48.4%)			
	M	percentage	F	Percentage
	130	62.2 %	79	37.8%

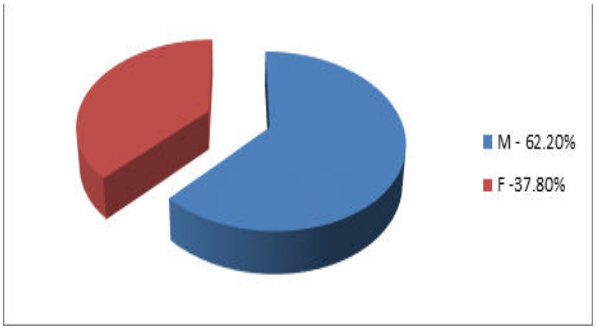

Figure 1 : Demographic Distribution

Table II : Age-wise Distribution Of Patients

Age –group	No. of patients	Percentage
0 -- 10 yrs	5	2.4 %
11 – 20 yrs	46	22.0%
21—30 yrs	89	42.6%
31- 40 yrs	41	19.6%
41---50 yrs	5	2.4%
51—60 yrs	18	8.6%
61- 70 yrs	5	2.4%
Total	**209**	**100.0%**

In the present study, Table -II shows the maximum number of positive cases in 21-30 yrs of (42.6%) age group.

The maximum cases diagnosed were in October (53.6%), followed by september (26.8%), which was shown in Table III & Figure 2.

The number of samples positive for dengue virus specific IgM antibodies was 55.0%, suspected secondary infection was 23.7% & secondary infection was 21.3%, which was shown in Table IV.

Table III : Month Wise Distribution Of Serologically Positive Cases During The Df Outbreak, 2016

Month	Serologically positive cases	
	Number	Percentage
Jan	---	---
Feb	---	---
March	---	---
April	---	---
May	---	---
June	---	---
July	---	---
Aug	3	1.4%
Sep	56	26.8%
Oct	112	53.6%
Nov	7	17.7%
Dec	1	0.5%
Total	**209**	**100.0%**

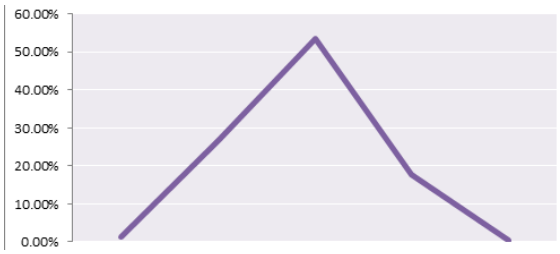

Figure 2: Month –wise distribution of serologically positive patients

Table IV : Month Wise Distribution Of Clinically Diagnosed And Serologically Positive Cases Amongst Primary And Secondary Cases During The Df Outbreak, 2016

Month	Total suspected cases		Serologically positive cases		Primary infection [IgM+]		Secondary infection [IgG+, IgM+]		Suspected secondary infection [IgG+]	
	Number	Percent	Number	percent	Number	percent	Number	Percent	Number	Percent
AUG.	21	5.0 %	3	1.4%	2	1.7%	---	---	1	2.0%
SEP.	173	41.0%	56	26.8%	19	16.1%	2	4.4%	3	6.0%
OCT.	153	36.1%	112	53.6%	75	63.6%	32	71.1%	35	70.0%
NOV.	70	16.5%	37	17.7%	22	18.6%	11	24.5%	11	22.0%
DEC.	6	1.41%	1	0.5%	---	---	---	---	---	---
TOTAL	**423**		**209**	**49.4%**	**118**	**55.0%**	**45**	**21.3%**	**50**	**23.7%**

Dengue were categorised into seven panels according to the investigations asked for such as

- Panel I - only NS1 antigen {early primary cases }
- Panel II - only IgM antibody {late primary cases }
- Panel III - NS1 antigen + IgM and IgG antibodies {late secondary cases }
- Panel IV -only IgM and IgG antibodies {late secondary cases }
- Panel V - NS1 antigen and IgM antibodies {late primary cases }
- Panel V I -NS1 antigen and IgG antibodies {early secondary cases}
- Panel VII -only IgG antibodies. {old cases who suffered from dengue previously }

Through panels I, II, III, IV, V, VI and VII, it was possible to diagnose dengue in panel (I) 37.5% , panel(II) 29.0% , panel (III) 6.4% , panel (IV) 4.7% , panel (V) 9.6%, panel (VI) 0.5% and panel (VII) 12.3% cases respectively.

Thus , in our study, highest percentage (37.5%) of early primary cases were found, followed by late primary cases (29.0%) , old cases who suffered rom dengue previously (12.3%) & rest defined categories were found less than 10.0% which is shown in table IV.

Table V : Panel Categorization Of Dengue Patients

Panel categorization	Serologically positive	Total no. of patients	Pecentage
PANEL I	Only NS 1 +	152	37.5%
PANEL II	Only IgM +	117	29.0%
PANEL III	All NS1 , IgG , IgM +	26	6.4%
PANEL IV	IgG & IgM +	19	4.7%
PANEL V	NS1 & IgM +	39	9.6%
PANEL VI	NS 1 & IgG +	2	0.5%
PANELVII	Only IgG +	50	12.3%
	TOTAL	**405**	**100.0%**

DISCUSSION

Here we report the annual trend of dengue virus infection as seen in

Sitapur, Uttar Pradesh, India, during the year 2018.

Our study reported 48.4% cases serologically positive, which is similar to All India Institute of Medical Sciences, New Delhi, during 2003–2005 reported 44.56% positivity in 1820 samples. longitudinal study for a period of 6 years (2005–2010) in Pune city involving 24 private and government clinics/hospitals.[19] who observed a positivity of 48.45%.

Reatively higher serologically positivity were found in Study [7], [20],[21], ,52.3% 54.5%,57.36% respectively. While relatively lower 38.3% were reported in study[22] .

Male to female ratio in our study were found as1 .6 :1, which is exactly similar to study[23], incidentally.M: F ratio 1.9:1 were also reported in study.[24]

Study [21]reported higher incidence in female i,e 1 :1.1.

Studies in South America generally report that both sexes are equally affected although a male to female ratio of 0.65:1 has been described as "typical" for dengue.[25]

However, contrasting results have also been reported in some cases. Three independent studies[5],[26],[27] from epidemics in India, found nearly twice the number of male patients infected with dengue compared to females, M:F being 1.9:1, 1:0.57, and 2.5:1, respectively. [5],[25],[26],[27] These studies were hospital-based and may represent those who sought care rather than the actual infected population.[25],[27]

It is widely recognised that in many Asian communities, lower disease incidence in women may be a statistical artefact related to lower reporting for women from traditional practitioners not reporting to public surveillance systems.[25]

Dengue affects humans of all age-groups. In 1996, maximum number of cases was in the 5-20 year age-group, while in 2003, maximum number of positive cases was in 21-30 year age-group.[22],[24],[28] In our study, maximum dengue cases (42.6%) were from the age group 21-30 years, almost similar result (30.8%)were found in same age group in study[23]. The 21–30 years age group was most affected by dengue throughout the 6 years in study [19]& aims study.

The age distribution of dengue has changed from a predominantly paediatric disease to one that affects all age groups.

The shift from pediatric/adolescent population to young adults getting affected reflects the presence of non-immune adult population falling prey to the circulating serotype of dengue virus.

In our study,the maximum cases diagnosed were in October(53.6%), followed by september (26.8%). The cumulative number of cases observed per month during the 6-year period showed that the largest numbers were observed in the month of October with a positivity of 57.9%

The role of environmental factors in infectious diseases is well-known. In most countries, dengue epidemics are reported to occur, during the warm, humid, and rainy seasons, which favor abundant mosquito growth and shorten the extrinsic incubation period as well. [29],[30]

In our study, the largest proportion of serologically positive cases was recorded in the post-monsoon period, which is in agreement with previousstudies.[30]

Dengue specific IgM antibodies were positive in 55.0 % of the acute phase sera in our study, which, incidentally, is similar to the 52.3% IgM seropositivity found in study[20]in 2003 sep nov outbreak & 52.0% in the 1996 outbreak.[24]

Study[7]also reported almost similar results 54.5% in January - December 2008, 51.9 % during January - December 2009, and during January - December 2010 ,64.9%were positive for anti DV IgM antibody. Relatively lower 38.9%, 22.28 %, 21.0% IgM positivity were reported in study[23],[21]during 2001 in Gwalior, Madhya Pradesh,[24] respectively.

In study [21] also found only IgG positivity & both IgG + IgM Abs positivity as 35.05%, 42.67% respectively, which is higher percentage that is reported by us, 23.7%, 21.3%.

On comparison of data tabulated in Table no. IV, Study[22] showed, similar percentage of early primay cases (35.98%) & relatively higher percentage of late primary cases (37.5%) **.** In contrast ,Other categories of this study showed quite higher percentage than found in our study. Last but not the least,.our study reported, 12.3 % old cases who suffered from dengue previously .which were not found in study[22].

Rain, temperature and relative humidity are reported as the major and important climatic factors, which could alone or collectively be responsible for an epidemic. In north India, the largest proportion of serologically positive cases have been recorded in the post-monsoon period[21]. Our findings were similar to those reported by other groups from this geographical region.[22][28]

In a study done in Bangladesh, the seasonal occurrence of positive cases has shown that post-monsoon period is the most affected period[29]. Studies have proposed that ecological and climatic factors influence the seasonal prevalence of the vector *Ae. aegypti* and dengue virus.[30]

In 2008 and 2009 the highest number of cases that were positive for anti DV IgM were from paediatrics population. In 2010, a shift was seen toward higher age group. In Asian countries where dengue has been epidemic for several years, this age shift is clearly observed, indicating an epidemiological change in dengue infection .

CONCLUSION:

Early laboratory confirmation of clinical diagnosis may be valuable because some patients progress over a short period from mild to severe disease and sometimes to death. In clinical practice to diagnose dengue serological tests, such as dengue-specific NS1 antigen and IgM and IgG antibodies are now often performed. Early intervention may be life-saving.

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Conflict of Interest: None

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