

Seroepidemiology of dengue viral infection at a tertiary care hospital, Bommakal, Karimnagar, India

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Abstract

Introduction: Dengue viral fever has become a disease of major concern. India in last decade has faced many outbreaks with varied epidemiological characteristics. The present study is designed.

Aim: Know the prevalence of dengue viral infection in the north east region of Telangana state Bommakal, Karimnagar, the prevalence of acute primary and recent secondary dengue viral infection and the influence of various demographic factors.

Materials and Methods: A retrospective observational study was designed during the period Jan. 2015 –Dec. 2016 from 6706 suspects of dengue fever. Dengue NS1 antigen, IgM and IgG antibodies were detected using rapid immunochromatographic test from J. Mitra co.

Results: About 2686 (40.05%) gave a positive serological test for dengue viral infection. Acute primary dengue infection was diagnosed in 2375 (88.42%) of the suspected dengue fever cases and recent secondary in 37 (1.37%) presumptively. Male predominance of 68.92% was noticed in suspected cases and as well as seropositives as 64.18%. The most affected age group was 16-30 years followed by 31-45 years as 58.32% and 25.39%. Further it is noticed that infection was prevalent throughout the year with seasonal spurts in monsoon and post monsoon. Highest percentage of suspects and cases were observed during the months Sep – Nov 72.93% and 81.57%.

Conclusion: Dengue primary infection is very high in this particular region of Telangana state and seasonal upsurge is seen during monsoon and post period of the year. High male preponderance is seen with maximum affected in the productive age group. Dengue ICT test are most suitable for point of care testing for early case detection and management but couldn't provide specific clue on disease epidemiology; which is essential for monitoring, surveillance and implementing effective vector control measures.

Keywords: [Dengue, NS1 antigen, IgM and IgG antibodies, Acute primary and recent secondary infection, Rapid Immunochromatography test].

Introduction

The history of dengue fever dates back to 17th century where in the physician Benjamin Rush described the condition as “break bone fever”. Since then it has been affecting humans in epidemics. The clinical spectrum of dengue viral infection ranges from asymptomatic infection, symptomatic mild self-limiting acute febrile illness, Dengue fever [DF] and to the severest forms of disease like dengue haemorrhagic fever [DHF] and dengue shock syndrome [DSS]. In majority of the cases virus is transmitted by the bite of the insect vector; female mosquito *Aedes aegypti* [the urban bug] and to a lesser extent by some other species of *Aedes*. The virus belongs to the family Flaviviridae and has got 4 different serotypes; DENV-1,2,3 & 4. Immunity is lifelong and homotypic to the infecting serotype. Among the four serotypes Denv-1 is more prevalent and has been responsible for several outbreaks in Asia and Africa.¹ Over the decades there has been several variations in the disease epidemiology; with respect to age, gender, disease severity and geographic distribution. Earlier it used to strike mostly the urban population, and in sporadic or epidemic forms as mild self-limiting illness. Today, it has emerged as a serious live threatening public health problem with growing case incidence and varied epidemiological features.² According to Bradey et al³ report as quoted by Srinivas

RM et al⁴ in last 50 years the case incidence of dengue fever has gone up by 30 times with about 30-54% of the world's population i.e. 2.05 -3.47 billion at a risk of infection living in more than 100 different countries. The British medical bulletin 2010⁵ quoted in article by Thirupati RJ et al⁶ reports that 50 -528 million people are infected and approximately 10,000 to 20,000 die annually all over the world. The 2013 report by Bhat et al estimates around 3 million infections annually of which 96 million manifests clinically.⁷ As per WHO/TDR report 2009 more than 2.5 billion people get affected annually, of these 975 million live in tropical and subtropical countries in south east Asia, the Pacific and the Americas with Africa bearing the major brunt of the disease amounting to 900 million cases annually.^{7,8} And almost 70% of the global population exposed to dengue live in Asia Pacific regions.⁷ Risk of mortality in treated cases of DHF/DSS is 1%, and in untreated cases of DHF/DSS it escalates to 20% -30%.^{2,9,10} There has also been an increase in the incidence of adult dengue in comparison to childhood as reported by Ajay G et al, Srinivas R et al, Smita T et al & Ukey PM et al.¹²⁻¹⁵ Higher prevalence among females was reported by Ajay G et al, Srinivas M et al & Chakravarti A et al 2016.¹²⁻¹⁶ **Indian Scenario:** Dengue infection has been known to be endemic in India for over two centuries as a benign and self-limiting illness.⁴ Since mid1990's epidemics of

dengue have become more frequent in many parts of India. Kolkata in India was the first to witness the epidemic in 1963 after which many more regions of the country reported the same in different time frames, Vishakapatnam in 1964, Vellore in 1968, Ajmer in 1969, Kanpur in 1969, Jalore in 1985, Chandigarh in 2002, Mumbai in 2004, Ludhiana in 2007; New Delhi in India has faced several outbreaks during the last two decades beginning from 1996, 2003, 2006, 2010 till 2015, Chennai in 2006-2008, and Kerala in 2008.^{9,17,18} Further, in 2015 New Delhi in India recorded the worst outbreak since 2006, with over 15000 cases reported.² Like the global changes noted in disease epidemiology; India too in the last two decades has seen tremendous variations. The mild self-limiting type of clinical presentation observed earlier has changed to the severest form of disease as DHF & DSS in at least 20% of the diagnosed¹⁶⁻¹⁹ Further an increase in frequency of outbreaks is also noticed.^{4,20} In 2015 nearly 64 058 cases were reported of which 135 cases died till October 25th 2015.² India alone has contributed to 34% [33 million] infections of the total global dengue cases during the year 2010.⁴ Highest number of cases were reported from Punjab followed by Tamil nadu, Gujarat, Kerala and Andhra Pradesh.²²⁻²³ At present dengue is endemic in 31 states and union territories of India.² All four serotypes are prevalent & isolated from India.²⁰ A total of 82327 dengue cases have been reported during 1998- 2009 and 213607 cases observed from 2010-2014.⁴ Hence, overall dengue cases incidence had increased tremendously during last five years. Earlier it was known to be an urban disease, but now has spread to rural areas of India as well.²⁴ Andhra Pradesh, in India has observed several outbreaks in recent years and the frequency of these outbreaks has gradually increased year by year in various districts of Andhra Pradesh.⁴ This rise in dengue cases is most probably driven by complex interactions between hosts, vector, and the virus which are influenced by environmental, climatic, demographic and socio-economic factors.^{4,25-26}

Therefore, we are in a stage where the epidemiology of dengue is still evolving with time and appears as complex and poorly understood. Many field observations have raised questions on widely accepted epidemiological characteristics of dengue.^{4,27,28} Therefore, it becomes essential to conduct epidemiological studies from time to time and understand the evolving pattern and trends of dengue and determine how far the existing laboratory test are suitable for the disease monitoring and surveillance.^{4,27}

Aim

The present study is designed to obtain information on:

The prevalence of dengue viral infection in north eastern region and rural population of Bommakal and nearby villages of Karimnagar district, Telangana state.

The prevalence of primary and recent secondary dengue viral infection among the seropositive suspects. The impact of various demographic factors on prevalence of dengue viral infection.

Materials and Methods

Materials: This is a retrospective observational study conducted for a period of two years from January 2015 to December 2016 in a tertiary care hospital, CAIMS, Bommakal village, Karimnagar. Data on the serological status of 6706 patients with acute febrile illness, suspected of dengue fever was retrieved from medical & laboratory records, referred from various inpatient and outpatient departments of CAIMS hospital to virology section of microbiology laboratory.

Inclusion Criteria: Any patient with acute febrile illness and with two or more of the following manifestations: Headache, myalgia, retro orbital pain, rashes, haemorrhagic manifestations, leucopenia and supportive serology or occurrence at the same location and time as other confirmed cases of DF [WHO case definition]

Exclusion Criteria: febrile cases with laboratory confirmed typhoid, malaria and urinary tract infection were excluded from study and serologically negative for dengue markers.

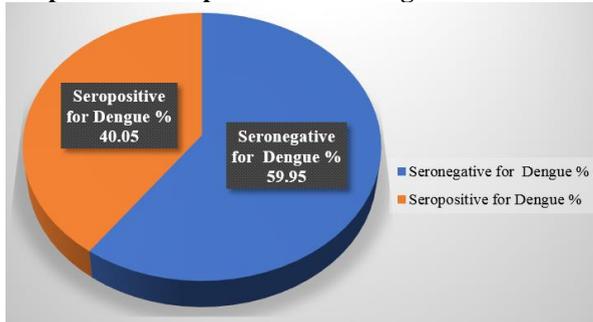
Methods: Serological test for dengue viral infection was performed using the screening test for dengue fever, based on the principle of rapid solid phase immunochromatography. Presence of dengue NS1 [nonstructural antigen 1 of dengue virus], IgM and IgG antibodies to the virus in the serum of infected individuals was checked by taking informed consent from all suspected cases and collecting 2ml of venous blood by venipuncture under strict aseptic precautions. Presence of colored band in control area for NS1Ag and IgM, IgG antibodies in the test cassette is must; as it validates the test results indicating that the test cassette and reagents are working properly. Presence of a colored band in the test zone for NS1 antigen or IgM, IgG indicates that the patient specimen is positive for that particular marker. The test has got varying sensitivity and specificity for different markers as follows: Dengue NS1 Ag the sensitivity is 100% and specificity as 99.94%, Dengue IgM/IgG antibodies the sensitivity is 100% and specificity as 99.88%.

Results

Of the total 6706 suspected dengue fever cases during the period January 2015- December 2016, around 2686 [40.05%] gave a positive serological test for dengue viral infection as shown in [Graph 1]. Seropositivity in suspected cases was observed, either for the presence of NS1 antigen, IgM and IgG antibodies alone, or as a combination of different markers of dengue virus infection. However, a significant drop in seroprevalence was noticed in these two years from 1846/4063 [45.39%] positive cases in 2015 to 840/2643

[31.78%] in 2016 with a p value of < 0.05 using chi square analysis.

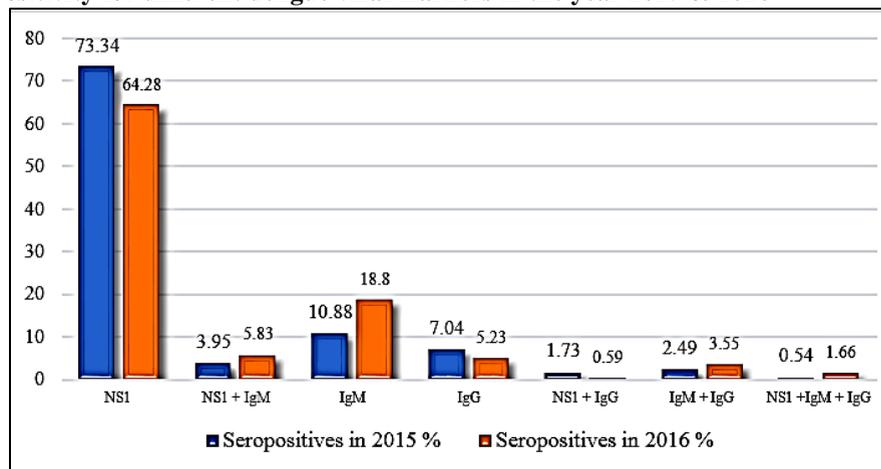
Graph 1: Overall prevalence of dengue viral infection



Further it is noticed that of the total 2686 seropositives for dengue viral infection around 1894 [70.51%] were positive for NS1 antigen alone, 1354 /1846 [73.34%] in the year 2015 and 540 /840 [64.28%] in the year 2016. Dengue IgM antibody alone was detected in 359 /2686 [13.36%] of the seropositives, 201/1846 [10.88%] in 2015 and 158 /840 [18.80%] in

2016. Dengue IgM antibodies along with NS1 Ag was positive in 122/2686 [4.54%] seropositives, 73/1846 [3.95%] in 2015 and 49/840 [5.83%] in 2016. Similarly, dengue IgG antibody was found in 174/2686 [6.47%] of the seropositives, 130/1846 [7.04%] in 2015 and 44/840 [5.23%] in 2016. Dengue IgG antibody along with NS1 Ag was detected in 37/2686 [1.37%] 32/1846 [1.73%] in 2015 and 5 /840 [0.59%] in 2016. Dengue IgM and IgG together was positive in 76/2686, [2.82%] of the seropositives, 46/1846 [2.49%] in 2015 and 30/840 [3.55%] in 2016. A combination of all the three markers i.e. NS1 Ag, IgM and IgG antibodies was seen in 24/2686 [0.89%] of the seropositives, 10/1846 [0.54%] in 2015 and 14/840, [1.66%] in 2016 [Graph 2]. As per this information acute primary dengue infection was diagnosed presumptively in 2375/2686 [88.42%] of the suspected dengue fever cases who were seropositive for NS1 antigen alone, IgM alone and IgM with NS1Ag [1894 +359+122=2375]. Recent secondary infection where NS1 Ag along with IgG antibodies were present in the serum of 37/2686 [1.37%] of seropositives presumptively.

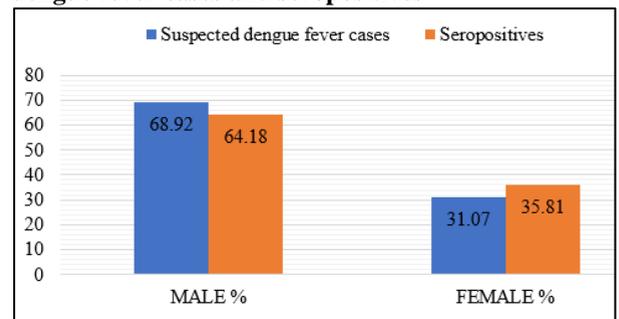
Graph 2: Seropositivity for different dengue viral markers in the year 2015 & 2016



Demographic Profile

A male predominance was noted in both suspected dengue fever cases and seropositives for dengue viral infection. Of the total 6706 suspected cases of dengue fever, 4622/6706 [68.92%] were males and 2084/6706, [31.07%] females; with male to female ratio as 2.2:1. Similarly in 2686 dengue seropositives, around 1724/2686 [64.18%] were males and 962 /2686 [35.81%] females. The male to female ratio in seropositives being 1.8 :1 [Graph 3]. However, gender variation was found to be insignificant using chi square analysis with p value 0.197.

Graph 3: Gender wise distribution of suspected dengue fever cases and seropositives



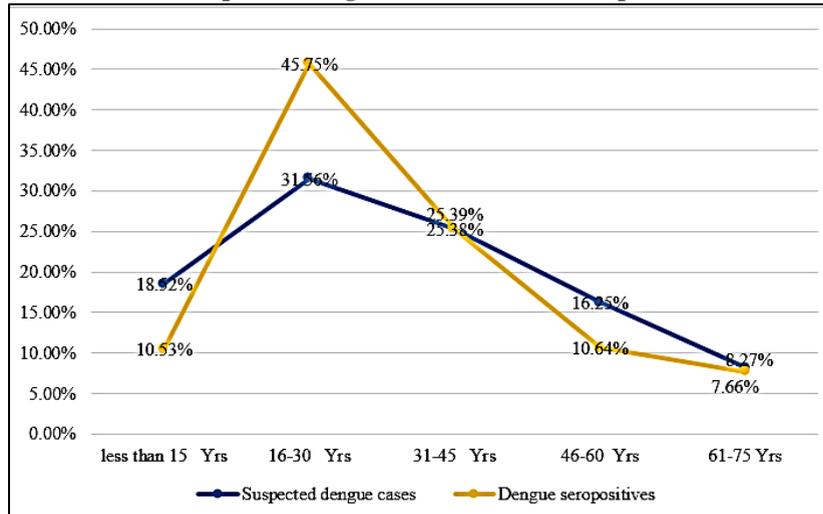
The age group of the studied subjects was in the range of 1 month to 75 years. And it is observed that majority of the suspected cases 2117/6706 [31.56%] were in the age group 16 -30 years, followed by 1702

/6706 [25.38%] in 31-45 years ;1242 /6706 [18.52%] in pediatric age group i.e. 1 month – 15 years, then 1090/6706 [16.25%] in 46- 60 years and finally 555/6706 [8.27%] in 61-75 years' age group.

Among the seropositives for dengue fever, an almost similar pattern of age distribution was noted except for the pediatric age group which is in 4th position

in seropositives and 3rd position in the suspects. Majority of seropositives 1229/2686 [45.75%] were seen in the age group 16-30 years, followed by 682/2686 [25.39%] in 31-45 years, 286/2686 [10.64%] in 46-60 years 283/2686 [10.53%] in 1- 15 years and 206/2786 [7.66%] in 61-75 years. The present finding is significant with a p value less than 0.5 as shown in [Graph 4].

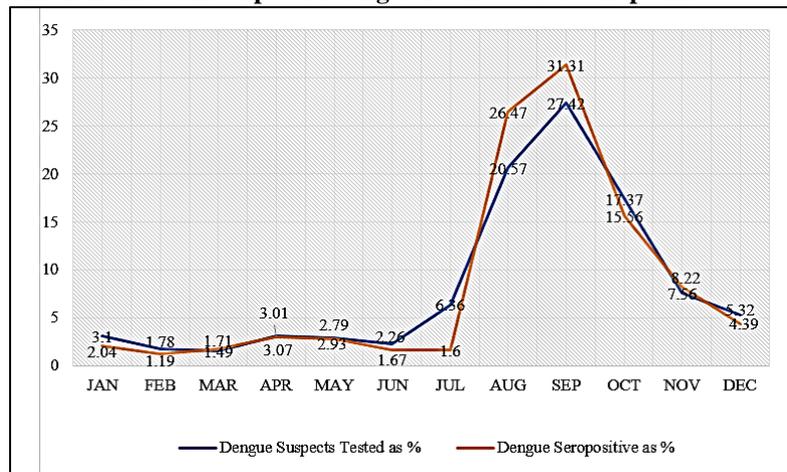
Graph 4: Age wise distribution of suspected dengue fever cases and seropositives



With respect to climate, dengue viral infection was prevalent throughout the year in Karimnagar district of Telangana state with significant seasonal variations. Majority of the suspected and seropositives were noted in the following months of the year - August, September, October and November with a peak in the month of September. During the year 2015, a total of 1846/4063 [40.10%] were seropositive of which 1496/1846 [81.04%] were positive during Aug- Sep. period only.

Similarly, in 2016 840/2643 [31.78%] were seropositive and 695/840 [82.73%] were found to be positive during the above said period only. Further it is observed that during both the years around 4891 of the 6706 suspected cases [72.93%] were tested for dengue and 2191/2686 [81.57%] of seropositives were found positive in the above said period only as shown in [Graph 5] with a significant p value of 0.003 using F test for two sample variances.

Graph 5: Seasonal variations noted in suspected dengue fever cases & seropositives



Discussion

In the present study dengue serology was positive for 40.05% of the suspected dengue fever cases which is

in correlation with the findings of R Sujatha et al as 37.5%, Arvind N et al as 32.86% and Soumya K et al. as 32.73%.²⁹⁻³¹ A high prevalence rate was reported by

Srinivas R MS et al. 53.2%, Ajay G et al 56% which is not seen in our study.¹²⁻¹³ This could be probably due to geographical variations noticed in host, vector and environment relationship.⁴ NS1 antigenemia alone was seen in 70.05% of the seropositives which is similar to the report by R.Thomas et al, as 70.98% and less when compared to the findings of Sunil PS as 86.9% and Anand et al as 83.3% & Samiullah as 92%.^{17,32-34} High NS1 antigenemia indicates acute viraemia and signifies early case detection & impending outbreak. Dengue IgM antibody alone and in combination with NS1 antigen was detected in 17.90% of the seropositives which indicates acute primary dengue viral infection. Therefore, acute primary dengue fever or primary infection, based on the serological pattern of the results obtained was diagnosed in [70.98% +17.90% = 88.88%] of the seropositives, which is an alarming figure and of great epidemiological concern. Further it insists on inclusion of NS1 antigen assay, by rapid immunochromatography or elisa method as a mandatory parameter in serological testing for dengue infection in tropics to alleviate the risk of high mortality in absence of resources to manage, detect and isolate virus by RT-PCR and culture. Because high viral antigen levels correlates with the disease severity and outcome.¹ Dengue IgG alone and in combination with NS1 antigen and IgM was seen in 6.47% and 5.1% of the positives, with an overall figure of 11.57%. All three seromarkers for dengue viral infection were found positive in 0.89% of the seropositives. Presence of all 3 markers in the screening test doesn't provide any clarity on specific disease status unless we test by Mac Elisa for confirmation. Recent secondary dengue infection was observed in 1.37% of seropositives which is less when compared to studies by Ajay G et al as 53.57%, Srinivas R MS et al as 82.24%, 46.59% by R Thomas et al.^{1-13,32} The reason for low recent secondary infection rates could be due to the use of rapid immunochromatography test [ICT] for presumptive diagnoses of dengue viral infection which does not provide enough clarity between primary and secondary infections. In order to apply exact epidemiological definitions as primary and secondary dengue viral infection, as per WHO guidelines it is always recommended to tests by Mac Elisa for IgM & IgG antibodies and to demonstrate actual antibody titre; or rise or fall in its titres during the course of illness using paired sera. But our study failed in doing so; as it is a matter of patient affordability, ease of performance in remote settings and a very important factor which affects the test results is; patient time of approach to the health care services. Hence the laboratory opted for rapid ICT which no doubt helps in early diagnosis and case management, as it is the most appropriate test for point of care testing [POCT]. However, it lacks the specificity for proper epidemiological case definition and future research.¹

Further; a drop in overall prevalence of dengue fever during the two years of study is noted, in the year 2015

it was 45.43% and in 2016 it is 31.78%, a 13.65% drop in the annual prevalence no doubt is a good sign of excellent disease monitoring and surveillance program at district level but is too early to derive conclusions. Various studies done earlier had demonstrated karimnagar as an endemic zone and a hot spot for dengue, which is reconfirmed by us.⁴ Regular surveillance and monitoring, check on vector breeding and improvement in sanitation facilities need to be strengthened to bring down the disease burden further.

A male predominance of 64.18% is seen in present study when compared to females as 35.81% which is in accordance with most of the studies with male seropositivity of 65% by Manisha et al, Arvind N et al as 63.19%, Md. Yousuf et al as 62.66%, Ajay G et al as 62.22%, Thirupathi R J 62%, K Soumya et al as 61.5%, R Sujatha et al as 61.3%, Samiullah et al as 59%, SP Singh as 56.3%, Srinivas R MS et al, and R Thomas as 53.08%, except for Chakravarti et al who noted a female preponderance in her study of 54%.^{6,12-13,15,17,21,29-31,35} The male to female ratio was 1.79 in present study which is almost similar to that of Manisha P et al as 1.9: 1 and Soumya et al as 1.6: 1.^{31,35} However, the gender difference was statistically insignificant which could be due to the fact that males dominated the study group. Other reasons could be due to predominant outdoor lifestyle and lack of use of protective clothing, mosquito repellants and nets by male population which leads to increased exposure to vector bite and the disease incidence.

The most affected age group was 16-30 years in the present study with a significant p value of less than 0.05 and percentage as 45.75% of the seropositives. Followed by 31-45 years as 25.39% and least affected were elderly above 60 years as 7.66%. These findings are in correlation with the reports by Ajay G et al as 48.90%, 46.2% by Sunil PS et al, Thirupathi RJ 45%, Soumya K et al 54.94% in 16-30 years and 17.56% in 31-45 years, Md. Yousuf et al as 59.33%, Manish P et al as 51% in the age group 18-35 years, Modi KP et al as 48.19% in 16-30 years and 14.61% in 31-45 years, as 41.44% by Arvind N et al in the age group 21-30 years and 24.72% in the 31-40 years. R Thomas et al reported a high prevalence in a wider age group of 16- 50 years as 61.4%.^{6,12,17,21,30-32,32,35,36} There are some reports contrary to our finding where seropositivity was noted more in paediatric age group by Ajay G as 57.14% in 0-10 years and Srinivas R MS et al as 35.84% in less than 10 years' age group, Smita T and Ukey PM.¹²⁻¹⁵ However, in our study paediatric age group had a lower prevalence rate of 10.53%. This could be again because of host, environment and virus factors which needs to be studied further. Determinants in dengue fever emergence are human population growth accelerated urbanization, increased international transport lack of proper public health infrastructure as well as lack of effective vector control and disease surveillance programs.⁴

Further it is noted that here in karimnagar district of Telangana state which caters to the health needs of almost all the surrounding villages and its neighboring district borders; seropositivity for the dengue virus is seen throughout the year, as observed and labelled by other authors as an endemic zone and hotspot for dengue viral infection.⁴ Anyhow, within the year seasonal spurts during monsoon and post monsoon period are observed. There is a gradual increase in the prevalence from the month of august reaching a peak of 81.57% for positive cases in September, October and November; followed by a decline in the month of December. Similar seasonal variations in dengue seropositivity were also noted by other authors like Manisha P as 72.92% during similar months, 69.23% by Soumya K, R Sujatha as 49.3% in October and 22.6% in November, R Thomas as 45% in September – October and then 25.64% in November Ajay G et al 49.3% in October and 22.96% in November.^{12,29,31,32,35}

Conclusion

Dengue fever has been included by WHO in the list of the diseases which can become a public health emergency of international concern. In Karimnagar district of Telangana state dengue viral infection is endemic, with peak prevalence during monsoon and post monsoon periods affecting people more in the productive age group. Acute dengue viral infection is high in the region when compared to secondary recent infection.

Recommendations

Further the use of rapid test for dengue viral infection screening, lacks epidemiological clarity on case definition as acute primary and recent secondary dengue fever. Therefore, the use of this test needs to be limited only to setups lacking technical skills and resources and those which need immediate diagnosis and management i.e. point of care testing, ward based and hospital-based testing. And in order to derive proper epidemiological information and aid in proper disease monitoring and surveillance we recommend that all tertiary care centers and district level hospitals, to use Mac Elisa test for detection and actual demonstration of fourfold rise in dengue IgM & IgG antibodies in paired sera. Further, all resource poor centers to refer blood samples of the suspected dengue fever cases and provisionally diagnosed cases to the higher centers for confirmation and better disease monitoring and surveillance. Lastly in absence of specific antiviral agents to cure the disease, and with no vaccine in hand for prevention of dengue fever; we need to collect all seropositive samples and refer them to district and state referral laboratories for proper serotyping &

identification studies by neutralization assay for research and development of most appropriate vaccine.

Limitations

The study couldn't perform MAC ELISA for demonstrating actual rise in antibody titre using paired sera from patients. For proper case definition of dengue fever i.e. to obtain accurate information on primary or secondary dengue infections we need to go for MAC ELISA testing which differentiate between acute primary and secondary dengue infection. Moreover, complete patient history is also lacking to aid in diagnosis as primary and secondary infection. Because the day of fever helps in interpretation of test results.

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Conflict of Interests: Authors have declared that no competing interests exist.

Authors' Contributions

Dr. Sarwat Fatima contributed to the study by writing the abstract & manuscript, collecting references and preparing graphs.

Dr. Arc. Archana accumulated data and collected few references.

Mr. Ravi performed the test and did statistical calculations.

Consent: Patient consent was taken before sample collection for testing

Ethical Approval: Ethical clearance from college ethical committee was taken prior to the study.

Abbreviations

WHO: World Health Organization

AG: Antigen

ICT: Immunochromatography Test

POCT: Point of Care Testing

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