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Dengue infection in Agra region, Uttar Pradesh: An observational study of seroprevalence, clinicoepidemiological profile, and serotype of dengue virus from tertiary care center

Vikas Kumar[1], Mridul Chaturvedi[2], Arti Agrawal[3], Geetu Singh[4], Pavan Maurya[5], Ankur Goyal[6], Sanjeev Kumar[7]

[1,3]Assistant Professor, [6]Professor, [7]Junior Resident, Department of Microbiology, [2]Professor, [5]Postgraduate Student, Department of Medicine, [4]Assistant Professor, Department of Community Medicine, Sarojini Naidu Medical College, Agra, Uttar Pradesh, India

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ABSTRACT

Background: Dengue is the most widespread mosquito-borne viral infection, found in tropical and subtropical climates worldwide. The World Health Organization has included dengue as one of the 10 threats to global health in 2019 with rapidly evolving epidemiology. **Aims and Objectives:** Given the limitation of data in regard to dengue burden, we have planned the present study with the objectives to provide a comprehensive overview of the seroprevalence, clinicoepidemiological profile, and serotype of dengue virus in Agra region of Uttar Pradesh. **Materials and Methods:** We conducted an observational study at viral diagnostic and research laboratory, Sarojini Naidu Medical College, Agra, Uttar Pradesh, from August to December 2021. Our study included all blood specimens received at virology laboratory from clinically suspected cases of dengue infection. For the identification of serotype, NS1-positive samples were sent to King Georges Medical University, Lucknow. For clinical-epidemiological profile of dengue positive patients, data were obtained from records of 203 patients from our hospital. **Results:** We received total of 5457 serum samples from suspected patients for dengue serology during the study period. In total, positivity rate was 27.29% (1489/5457) and peak of cases was reported in month of October. Median age of dengue positive cases was 17 years. Dengue hemorrhagic fever (DHS) was diagnosed in almost 41% of patients of 203 patients admitted in our hospital. DEN-2 was reported to be most common serotype (97.1%). In our analsyis, we found that in most patients fall in platelets levels below 50,000 happened during the 5th and 6th day in Dengue fever. **Conclusion:** We conclude that our study showed higher seroprevalence of dengue in Agra region with the age group of 0–20 years being infected most. DEN-2 was most prevalent circulating strain, which leads to more severe dengue infection.

Key words: Dengue virus; Dengue fever; NS1 antigen; Seroprevalence; Serotype; India

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INTRODUCTION

Vector-borne diseases are among the most important public health problems across globe and are associated with significant economic burden in affected countries. Dengue is the most widespread mosquito-borne viral infection, found in tropical and subtropical climates worldwide. Dengue virus (DENV) belongs to the Flavivirus genus, has four serotypes (DEN-1, DEN-2, DEN- 3, and DEN-4), and transmitted through the bite of *Aedes* mosquitoes.[1]

Address for Correspondence:
Dr. Geetu Singh, Assistant Professor, Department of Community Medicine, Sarojini Naidu Medical College, Agra, Uttar Pradesh, India.
Mobile: +91-7376043771. **E-mail:** geetu.singh1701@gmail.com

The World Health Organization (WHO) has included dengue as one of the 10 threats to global health in 2019 with rapidly evolving epidemiology.[2] DENV disease may present with a range of acute clinical manifestations from undifferentiated symptoms, such as fever, myalgia, and headache, to the severe disease including plasma leakage, hemorrhage, and eventually death.[3]

Across the globe, there is substantial increase in cases of dengue from 2.2 million in 2010 to over 4.2 million in 2019 with 129 countries being endemic for this viral disease. More than 70% of the global population at risk (~1.8 billion) for dengue inhabits in the WHO South-East Asia Region (SEAR) and Western Pacific Region. These estimates are far less than actual burden of dengue disease because of gross underreporting and misclassification of dengue cases. India contributed to 6% of total dengue cases of SEAR during 2009, which has increased to 33.5% in 2018.[4] In a national survey (2017), age-specific seroprevalence of dengue infection in India was found to be 48.7% and a meta-analysis from India reported seroprevalence of dengue infection as 56.9%.[5,6]

Based on the transmission dynamics, India has been placed in Group "A" countries in SEAR by the WHO in 2011; where dengue is a major public health problem, a major cause of hospitalization among children, with hyperendemicity and multiple virus serotypes circulating among population.[7] Most Indian states have been classified as being endemic for dengue. This wide spread across country is attributable to expanding distribution of *Aedes* mosquito, geographic distribution of the virus, diverse climatic conditions, and landscape of India.[4] There is an 11-fold decadal increase (2011–2019) in cases of dengue than previous decade (2000–2009) in the country; however, it is not uniform.[5] However, there is dearth of data about burden of dengue because of poor surveillance systems and reporting.[6] Given the limitation of data in regard to dengue burden, we have planned the present study with the objectives to provide a comprehensive overview of the seroprevalence, clinicoepidemiological profile, and serotype of DENV in Agra region of Uttar Pradesh.

Aims and objectives

The objectives of our analysis were (1) to determine seroprevalence and month-wise trend of dengue cases in Agra region; (2) to determine age, sex, area-wise distribution of dengue positive cases; and (3) to determine sociodemographic profile, clinical features, laboratory findings severity of disease (DF/DHS/dengue shock syndrome (DSS) of admitted patients, and serotype of DENV to estimate number of cases with dominant strain.

MATERIALS AND METHODS

We conducted an observational study at Viral Diagnostic and Research Laboratory, Sarojini Naidu Medical College, Agra, Uttar Pradesh, from August 2021 to December 2021. The Institute Ethics Committee of college approved (SNMC/IEC/2021/55) the study protocol.

Study population

The present study included all blood specimens received at virology laboratory of our microbiology department, from clinically suspected cases of dengue infection, during this duration. Serum samples were received for serological testing from suspected cases of dengue as advised by consultants from various departments in hospital. Samples were also received from the district public health authorities for laboratory confirmation of suspected cases. Acute-phase blood samples collected from suspected dengue fever (DF) patients[7] (fever, fever with rash/arthralgia, or fever with hemorrhagic manifestations). Laboratory-confirmed dengue cases were defined as suspected dengue cases with positive dengue serology.

Serology (diagnosis of dengue infection) and serotype identification

For diagnosis of dengue infection, serum samples were tested to detect dengue NS1 antigen or dengue IgM antibodies in the microbiology laboratory of the hospital. Detection of at least one component (NS1 or IgM antibodies) will be considered to be positive for serodiagnosis. Serum samples from clinically suspected patients having a history of fever for ≤5 days were tested for NS1 antigen (J. Mitra and Co. Pvt. Ltd.) while those having fever for more than 5 days were tested for dengue-specific IgM antibodies by using IgM antibody capture enzyme-linked immunosorbent assay kit supplied by ICMR-National Institute of Virology, Pune. Manufacturer's instructions were strictly followed for performing the test and interpreting the results.

For the identification of serotype, a total of 145 NS1-positive samples from the month of September to October 2021 were sent to the Department of Microbiology, King Georges Medical University, Lucknow, Uttar Pradesh, by maintaining cold chain. These samples were analyzed by reverse transcription polymerase chain reaction. The data were recorded in Microsoft Excel and analyzed using statistical software, Microsoft Excel (Version 16.49). The results are presented accordingly in the form of descriptive statistics.

RESULTS

We received total of 5457 serum samples from suspected patients for dengue serology during the study period. Among the samples tested, 1489 samples were positive

for either dengue NS1 antigen or dengue IgM antibodies. In total, positivity rate was 27.29% (1489/5457). Month-wise trend of dengue-positive cases is shown in Figure 1 which shows that peak of cases was reported in month of October (745) followed by November (472) and September 2021 (240). Few cases were found in August (6) and December 2021 (26). The age, sex, and area-wise distribution of dengue cases (N=1489) in Agra region are shown in Figures 2-4. The highest number of dengue positive cases was observed in the age group of 11–20 years (29.35%), followed by 21–30 years (24.84%), 0–10 years (21.89%), 31–40 years (9.20%), 41–50 years (5.00%), 51–60 years (2.89%), and 60+years age group (2.82%). Median age of dengue positive cases was 17 years while range of cases fall between 2 months and 91 years.

We did analysis of 203 dengue-positive cases admitted in our hospital (Table 1). In context of age profile, most patients belonged to the age group of 11–20 years (42.45%), followed by 21–30 years (33.49), 31–40 years (10.84%), 41–50 years (8.37%), and 51 plus years (4.43%). Among the admitted patients, 51.23% were male and 48.77% were female while 40% of patients' were from rural area. Fever (100%), myalgia (84%), and headache (79%) were most common symptom reported by patients. Other common symptoms were nausea, vomiting, fatigue, and abdominal pain. Thrombocytopenia and leukopenia were most common laboratory finding in dengue patients. Mean total leukocyte for 203 patients was 4732 and mean hematocrit value was 33.21. We classified patients according to severity of dengue infection; dengue hemorrhagic fever (DHF) (DHS) was diagnosed in almost 41% of patients. DEN-2 was the predominant strain in Agra region (Table 1). Correlation between platelet count and duration between day of onset of fever and day of investigation is shown in Figure 5. In our analsyis, we found that in most patients fall in platelets levels below 50,000 happened during the 5th and 6th day in Dengue fever.

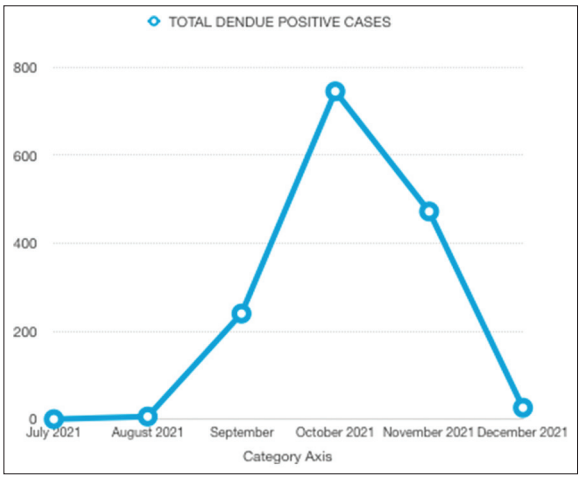

Figure 1: Month-wise distribution of dengue-positive cases in Agra region

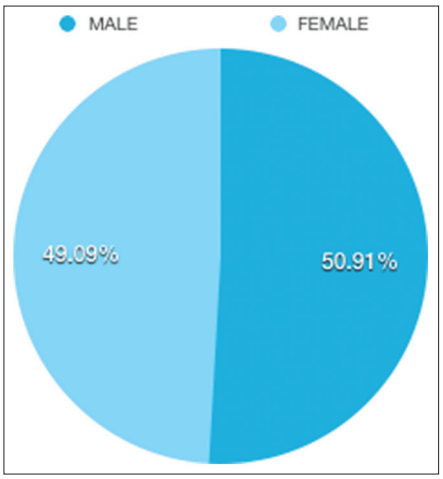

Figure 3: Sex-wise distribution of dengue-positive cases (N=1489)

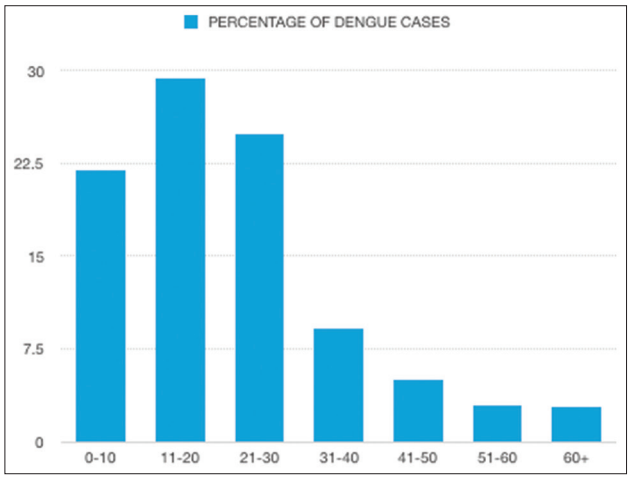

Figure 2: Age-wise distribution of dengue-positive cases (N=1489)

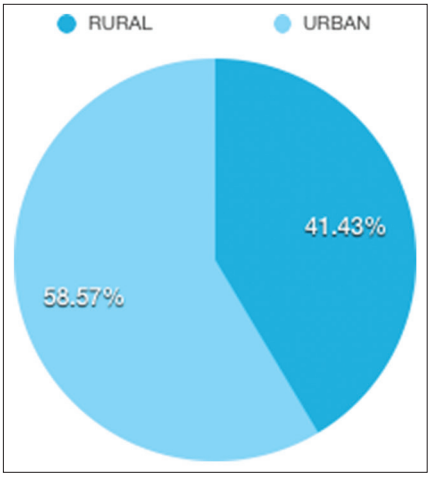

Figure 4: Area-wise distribution of dengue-positive cases (N=1489)

Table 1: Clinical and laboratory profile of patients admitted at our hospital (N=203); serotype of DENV

Parameters	N=203
Platelet count	
<50,000	105 (51.72)
50,000–1 lac	68 (33.50)
1 lac–1.5 lac	21 (10.34)
>1.5 lac	9 (4.43)
Total leukocyte count/mm^3	
<4000	59 (29.06)
4000–11,000	139 (68.47)
>11,000	5 (2.46)
Mean leukocyte count	4782
Mean hematocrit	33.21
Severity of dengue infection	
Dengue fever	108 (53.02)
Dengue hemorrhagic fever	82 (40.39)
Dengue shock syndrome	13 (6.40)
Serotypes of dengue virus (N=67)	
DEN-1	1 (1.49)
DEN-2	65 (97.01)
DEN-3	1 (1.49)
DEN-4	0 (0.00)
Multitypic	0 (0.00)

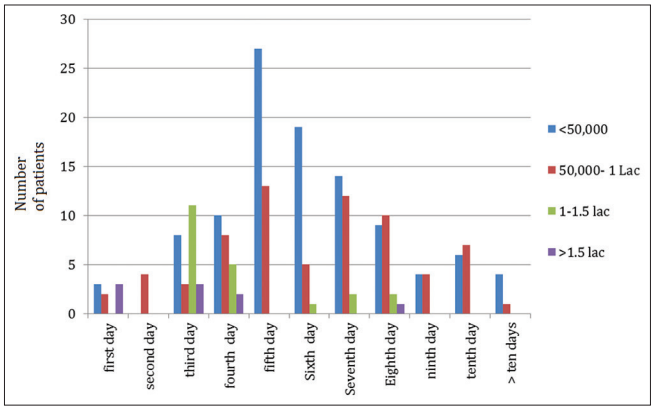

Figure 5: Relation between platelet count and days between onset of fever and day of blood investigation

DISCUSSION

The first large epidemic of DENV in India began in Calcutta in 1946. Extending northwards, dengue reached state of Uttar Pradesh in 1968. Since then, the epidemiology of dengue circulation has changed in state, with increased frequency of outbreaks, endemicity, and multiple serotypes found in this region. The resurgence of dengue has been notable in India and dengue epidemics have been frequently reported in the country both from urban and rural regions.[8] The present study analyzed the samples of 5457 suspected patients and positivity rate of 27.29% (1489/5457) was found. Similar estimates of the prevalence of laboratory-confirmed dengue infection (28.4%) were reported in the surveillance data (2014–2017) from 52 laboratories.[9] A meta-analysis[6] (until 2017, 180 studies) and community-based survey[5] (2017–2018, 17,930 individuals) reported higher seroprevalence of 56.9% and 48.7%, respectively. Hospital-based studies from Delhi between 2012 and 2015 and from Rajasthan (2014–2018) showed that the total dengue seropositive cases were 39%, 27.7%, and 14.85, respectively.[3,10] Seropositivity from Uttar Pradesh was found to be 22% (2011–2013) and 50% (2012–2017) over the years.[9,11]

The present study revealed trend of cases from August to December 2021; peak of cases was reported in month of October and November. Most researchers reported maximum cases during September–November.[3,9-11] Dengue positivity was higher between the months of August and November, corresponding to monsoon and post-monsoon season in most states in India.[6] Recent analysis of the past two decades highlighted that, in India, transmission pattern of dengue has changed and widened with shift in peak post-monsoon; shifting toward November from October in the recent decade from irregular peak of the previous decade. However, the present pattern in shift of transmission is clearly evident that dengue cannot be considered as a seasonal disease.[4]

Dengue was first reported from Kolkata in India in 1963, which means that the DENV has been in circulation for almost the past 50 years.[12] This circulation resulted in the buildup of immunity in older individuals, driving the average age of primary and secondary infection toward younger age groups.[3] Median age of dengue positive cases was 17 years while range of cases fall between 2 months and 91 years. 0–20 years of patients comprise more than 50% (51.24%). A study from North India showed similar observation of most cases of dengue from the age group of 0 to 15 years.[13] Dengue epidemic between 1990 and 2006 from Delhi, Tamil Nadu, Madhya Pradesh, Pondicherry, and Uttar Pradesh (2003–2006) found most cases in the 5–12-year age group.[14,15] The lack of immunity among children could be the possible role of the high fatality rate.[11] Authors found that about 25% of cases belonged to 21–30 years age group. A meta-analysis from India on dengue infection observed mean age for dengue infection as 22 years and population-based study reported median age for this epidemic as 25 years.[5,6] Two recent hospital-based studies (2020 and 2021) described that majority patients were of age group 20–31 years.[3,11] Studies supporting young adults as predominantly affected are during epidemics in various states of India.[14,16] In general, all age groups are affected by dengue infections in India.[11] Population-based study[5] highlighted that the dengue seroprevalence increased with age with maximum being found in the age group of 18–45 years with somewhat similar age group affected in few other studies.[17]

In the present analysis, dengue positivity was higher in males as compared with females. This finding of more males being reported with dengue is consistent with studies from several other countries,[18,19] India and Uttar Pradesh also; similar finding was also observed in most studies from tertiary care hospitals in India.[3,11,13,20] Possible explanations for this male dominance are (i) greater exposure of males to dengue-carrying mosquitoes or (ii) differences in the healthcare-seeking behavior of males and females rather than the true burden or (iii) social and cultural biasing as India is male predominant country. Although most research mentioned male preponderance in dengue infection, there are studies with results of no difference in male and female distribution of cases.[5] It is very inconclusive to say which gender is prone to dengue infection.[5,21] This male predominance is reported from most of the outbreaks in India.[11]

We found that the urban population was more affected than rural. Large community-based survey showed more seroprevalence in urban (70.9%) versus rural areas (42.3%),[5] also some other studies reported somewhat similar distribution of cases.[22] These findings resonate with the rapid urbanization in India.[5,23] The mosquitoes flourish vigorously in urban and semi-urban localities congested with human population usually during rains. Research shows where seropositivity is reported to be more; 50–70% of population from rural areas had evidence of dengue infection, signifying that dengue transmission is also frequent in rural areas as well.[5,6] Henceforth, once cogitated an urban problem, it has now penetrated into rural areas as reported from Uttar Pradesh[11] also due to due to high population density and from other states as well (Haryana, Tamil Nadu, and Maharashtra).[21,24]

Dengue infections vary in severity, ranging from influenza-like self-limiting illness to life-threatening DHF and DSS, which, if left untreated, is associated with significant mortality. As per the WHO 1997 classification, symptomatic DENV infection has been classified into DF, DHF, and DSS.[7] Fever, myalgia, and thrombocytopenia were the most common clinical features reported by patients with dengue infection in our study and most studies from country.[11,13,25,26] DF was reported in 53.02% of patients, DHS in 40.49%, and DSS in 6.40% of patients infected with DENV. Almost similar findings were reported from Ajmer region in 2019.[13] A comparison of year 2011–2013 NVBDCP (National Vector Borne Disease Control Program) data with that of previous years indicated a shift from mild illness towards a more severe manifestation of the disease, which could be interpreted as an epidemiologic transition pattern and is a sign of hyperendemicity of the DENV in UP. In addition, genotypic changes in dengue viruses may contribute further to emergence of severe dengue[8].

The DENV has four genetically distinct serotypes (DENV 1–4) that can cause either febrile flu-like symptom, that is, DF or severe form called DHF and DSS, which is characterized by vascular permeability and plasma leakage. Further, severe clinical manifestations are commonly seen with DENV-2, hemorrhagic manifestations with DENV-4, and liver involvement with DENV-3; while DENV-1 usually has mild clinical presentation.[10] In context of serotype of circulating DENV in this epidemic of 2021 in Agra region, because of resource limitations, molecular testing could be performed in 67 seropositive cases of which almost all cases were of DEN-2 serotype (65). DEN-2 is the most prevalent serotype circulating in India over the past 50 years.[27] A meta-analysis from India (51 studies) specified circulation of all the four-dengue serotypes, with DEN-2 and DEN-3 being the most common across country while DEN-2 and DEN-1 dominant in the northern region.[6] A population-based serosurvey on dengue showed that in northern regions, most dengue infections were multitypic in nature, a reason of high prevalence of dengue cases here.[5]

An analysis from 24 laboratories of Virus Research Diagnostic Laboratory Network in 2018 reported DEN-2 as dominant serotype in Uttar Pradesh.[27] A study done between 2011 and 2013 in Lucknow, UP, found that DV-2, DV-1, and DV-3 were the dominant circulating serotypes.[8] D4 serotype is also reported from Uttar Pradesh, India. In conclusion, the cocirculation of multiple DENV serotypes and genotypes is alarming in most populous state of India. Similarly, cocirculation of multiple serotypes was evident from the published studies in Delhi.[3,6,10] The most common serotype detected in 2016–2017 was DEN-3, followed by DEN-2 in tested samples from Rajasthan[3] and DEN-4 was reported from Tamil Nadu in 2017 outbreak.[27] It is recognized so far that infection with one dengue serotype provides lifelong homologous immunity, but only transient cross-protection against other serotypes. The change in prevalent serotype is the major factor responsible for the enormous number of dengue cases in subsequent epidemic with other serotype. Dengue patients infected with multiple serotypes of DENV are more prone to have severe manifestations than with monoinfection.

Limitations of the study

Serotype data of only limited number of patients was analyzed because of resource constraint. Clinical symptoms and outcome of only hospitalized patients was assessed.

CONCLUSION

Thus, we conclude that our first study showed higher seroprevalence of dengue in Agra region with the age group of 0–20 years being infected most. DEN-2 was most

prevalent circulating strain, which leads to more severe dengue infection. The disease has various presentations and features; henceforth, secondary prevention (early diagnosis and management) is essential to reduce mortality significantly. Furthermore, it is necessary to improve the epidemiological surveillance and reporting for forecasting epidemic early.

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Authors' Contributions:
VK- Inception of research question, design of the study, and data analysis prepared first draft of manuscript; **PM-** Reviewed the literature and manuscript preparation; **MC, AG-** Concept, coordination, and interpretation of results; **GS-** Methodology, statistical analysis, drafting, and revision of the manuscript; **PV, SK-** Data analysis and review of literature; and **AG-** Revision of manuscript and coordination.

Work attributed to:
Sarojini Naidu Medical College, Agra - 282 002, Uttar Pradesh, India.

Orcid ID:
Dr. Mridul chaturvedi - https://orcid.org/0000-0003-0500-2067
Dr. Arti Agarwal - https://orcid.org/0000-0002-0983-4189
Dr. Geetu Singh - https://orcid.org/0000-0001-8546-5322
Dr Pawan Maurya - https://orcid.org/0000-0003-2288-0099
Dr. Sanjeev Kumar - https://orcid.org/0000-0001-5558-809X

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