

Original Research Article

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Seroprevalence of Dengue Infection in Patients Suffering from Acute Febrile Illness in a Tertiary Care Centre–Time to Introduce Dengue Vaccine CYD-TDV to Susceptible Population

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ABSTRACT

Dengue, an important vector-borne viral disease and one of the most common causes of acute febrile illness (AFI), is considered as a notable public health problem because it spreads rapidly by the bite of infected mosquito and has high incidence of mortality, morbidity and economical challenges associated with it. Bihar, having a population of 104, 099, 452, average annual rainfall of 1,186 mm and having a breeding place for vector *Aedes*, is prone to dengue outbreaks. Recently, the first dengue vaccine, Dengvaxia (CYD-TDV) has been introduced. Objective of the study is to determine seroprevalence of dengue infection in patients suffering from AFI, seroprevalence of susceptible population and to ascertain whether it is appropriate time to introduce dengue vaccine CYD-TDV to susceptible population. A retrospective cross sectional observational study, of records of all patients of AFI, whose sera was subjected to simultaneous detection of dengue NS1 antigen, anti-dengue IgM and IgG antibody was done from July 2016 to July 2017 at a tertiary care center in eastern India. Out of 384 samples tested, a total of 38 (9. 9%) samples tested positive for dengue infection and the remaining, i.e. 346/384 (90. 20%) were negative and the patients were considered susceptible to dengue infection. The seroprevalence of dengue was high especially in post-monsoon period. Besides continuing preventive and control measures, authorities should consider introduction of the dengue vaccine CYD-TDV.

Keywords

Acute febrile illness (AFI), Dengue, Dengue vaccine CYD-TDV, Vector borne viral disease

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Introduction

Acute febrile illness (AFI) is a major cause of morbidity and mortality (Robinson *et al.*, 2018). Dengue, an important vector-borne viral disease, and one of the most common causes of AFI, is considered as a notable public health problem because it is spread rapidly by the bite of infected mosquito and there the high incidence of mortality, morbidity and economical challenges

associated with it (World Health Organization, 2009). The three main factors responsible for spread of dengue infection are: dengue virus, *Aedes* mosquito (vector) and environment favouring breeding of mosquitoes. Dengue virus has four different serotypes DENV-1, DENV-2, DENV-3, DENV-4. Human infection with one serotype provides life-long immunity to the individual against that specific serotype, but does not provide immunity against other serotypes. On the

contrary, due to cross-reactive antibodies it enhances the severity of disease caused by subsequent infection by other serotypes. Thus, in dengue endemic countries, people are likely to be infected more than once over their lifetime with more severe disease after a secondary infection with a heterologous serotype (WHO, 2018; Halstead, 2007; Martina *et al.*, 2009). In 2016, there were reports of co-circulation of all the four dengue virus serotypes in India (Shrivastava *et al.*, 2018). Although various steps have been taken at household, community and government levels to control dengue, but its global incidence has grown dramatically in recent decades and is estimated to cause 50 to 100 million cases of Acute febrile illness (AFI) every year (Halstead, 2007; Brady *et al.*, 2012; Chakravarti *et al.*, 2012; Brady *et al.*, 2012; Bhatt *et al.*). What is of more alarming significance, is that many dengue infection cases present with severe disease leading to death. In 2015, out of 2.35 million dengue cases reported from Americas alone, 10, 200 cases were diagnosed as cases of severe dengue infection resulting in 1181 deaths. In 2016, there were reports of large dengue outbreaks throughout the world resulting in many deaths (WHO, 2018). The main emphasis for preventing or controlling dengue at present is to combat vector mosquitoes. Recently, the first dengue vaccine, Dengvaxia (CYD-TDV), by Sanofi Pasteur, has been introduced. It is alive recombinant tetravalent 3 dose dengue vaccine which is administered as 0, 6, 12 months schedule. It was introduced in late 2015 and early 2016 and was registered for use in individuals 9-45 years of age living in endemic areas in several countries. WHO recommends that only those countries where epidemiological data indicate a high burden of dengue disease, should consider introduction of the dengue vaccine CYD-TDV.

Bihar, having a population of 104, 099, 452 and average annual rainfall of 1,186 mm and having a breeding place for vector *Aedes*, is

prone to dengue outbreaks. To the best of our knowledge every few studies have been done in this part of Bihar to evaluate the seroprevalence of dengue infection amongst AFI cases especially after the availability of dengue vaccine.

Keeping this in mind we decided to do this study with the aim to find out the seroprevalence of dengue infection in patients suffering from Acute febrile illness, seroprevalence of dengue infection negative but susceptible population in a tertiary care centre and to ascertain whether it is appropriate time to introduce dengue vaccine CYD-TDV to the susceptible population.

Materials and Methods

Ethical approval

Ethical approval from the Institutes Ethical committee was obtained for the study

Study area

The data was collected from the virology lab of a tertiary care centre in Eastern India which provides services to the local community as well as for other population coming from different regions of Bihar.

Study design

A retrospective cross sectional observational study of all the consecutive records of patients suffering from AFI, whose serum was subjected to simultaneous detection of dengue NS1 antigen, anti-dengue IgM and IgG antibody test from July 2016 to July 2017 was done.

Inclusion criteria

Records of patients, presenting with symptoms of fever for more than five days duration, with more than or equal to two of the following:

joint pain, rash, myalgia, retro-orbital pain, headache and haemorrhagic manifestation and subjected to simultaneous detection of dengue NS1 antigen, anti- dengue IgM and IgG antibody test by solid phase ICT (SDBIOLINE) from July 2016 to July 2017, were included in the study.

Intervention that was done:

The records were obtained and data was analyzed. The patient whose sera was found to be positive for either or all of the three parameters, i.e. IgG, IgM and NS1 was considered to be positive for dengue infection, either current or past infection. The patient whose sera was found to be negative for all three parameters, i.e. IgG, IgM and NS1 was considered to be negative for dengue infection but susceptible to dengue infection. Primary dengue was identified when either NS1 antigen or IgM was positive with a negative IgG test, while secondary dengue was diagnosed when either of the above was associated with IgG positivity.

Results and Discussion

Out of 384 samples tested, a total of 38 (9.9%) samples were tested positive for either one or more of the three markers i.e. NS1 Ag, IgM and IgG antibody tested. The remaining samples, i.e. 346/384 (90.20%) tested negative for all the three markers.

Out of the 38 serum positive samples, 20 (52.63%) patients were positive for NS1 Ag only, 6 (15.78%) positive for IgM only, while 1 (2.6%) were positive for IgG only. More than one marker was detected in the remaining 11 (28.94%) samples.

Maximum number of samples for testing of dengue infection was received in the post-monsoon period, i.e. in the month of September, October and November.

Maximum number of serologically positive cases were also found in the month of September (11/81= 13.5%), October (11/81= 13.5%) and November (6/74= 10.81%). Though dengue was present throughout the year there was significant dip in the receipt of sample and sample testing positive for dengue infection in the month from January to June.

Primary dengue was detected in 33 (86.84%) cases and secondary dengue infection was detected in 5 (13.16%) cases.

In this retrospective cross sectional observational study, in which records of patients suffering from AFI whose serum was subjected to simultaneous detection of dengue NS1 antigen, anti- dengue IgM and IgG antibody test by solid phase ICT (SDBIOLINE) from July 2016 to July 2017 was studied and analyzed. The patient whose sera was found to be positive for either or all of the three parameters, i.e. IgG, IgM and NS1 was considered to be positive for dengue infection, whether current or past infection. The patient whose sera was found to be negative for all three parameters, i.e. IgG, IgM and NS1 was considered to be negative for dengue infection and susceptible to dengue infection. Primary dengue was identified when either NS1 antigen or IgM was positive with a negative IgG test, while secondary dengue was diagnosed when either of the above was associated with IgG positivity.

In this study we found that, out of 384 samples, a total of 38 (9.9%) samples tested positive for either one or more of the three markers i.e. NS1Ag, IgM and IgG antibody. Out of the 38 positive serum samples, 20 (52.63%) were positive for NS1Ag only, 6 (15.78%) were positive for IgM only, while 1 (2.6%) sample were positive for IgG only. More than one marker was detected in the remaining 11 (28.94%) samples. Maximum number of samples for testing of dengue infection was

received in the post-monsoon period, i.e. in the month of September, October and November. Maximum number of serologically positive cases were also found in the month of September (11/ 81=13. 5%), October (11/81= 13. 5%) and November (6/ 74= 10. 81%).

Though dengue was present almost throughout the year, there was a significant dip in the receipt of sample and sample testing positive for dengue infection in the month from January to June. Primary dengue was detected in 33 (86. 84%) cases and secondary dengue

infection was detected in 5 (13. 16%) cases. The dengue infection has been reported earlier from various regions of India including Nagpur (Rodrigues *et al.*, 1972), Parbhani and Dhulein Maharashtra (Mehendale *et al.*, 1991; Padbidri *et al.*, 1996), Bangalore (George and Soman, 1975) Punjab (Kaur *et al.*, 1997) and Delhi (Gupta *et al.*, 2005). In the present study, maximum number of dengue cases occurred during the post-monsoon season, i.e., from September to November only, which is similar to most of the previous outbreaks in India (Kaur *et al.*, 1997; Gupta *et al.*, 2005).

Table.1 Seroprevalence of dengue infection positive and negative cases

Dengue infection	Total	Percentage (%)
Positive (either or all of IgG, IgM and NS1 positive)	38	38/384(9.9%)
Negative (IgG, IgM and NS1 negative)	346	346/384(90.20%)

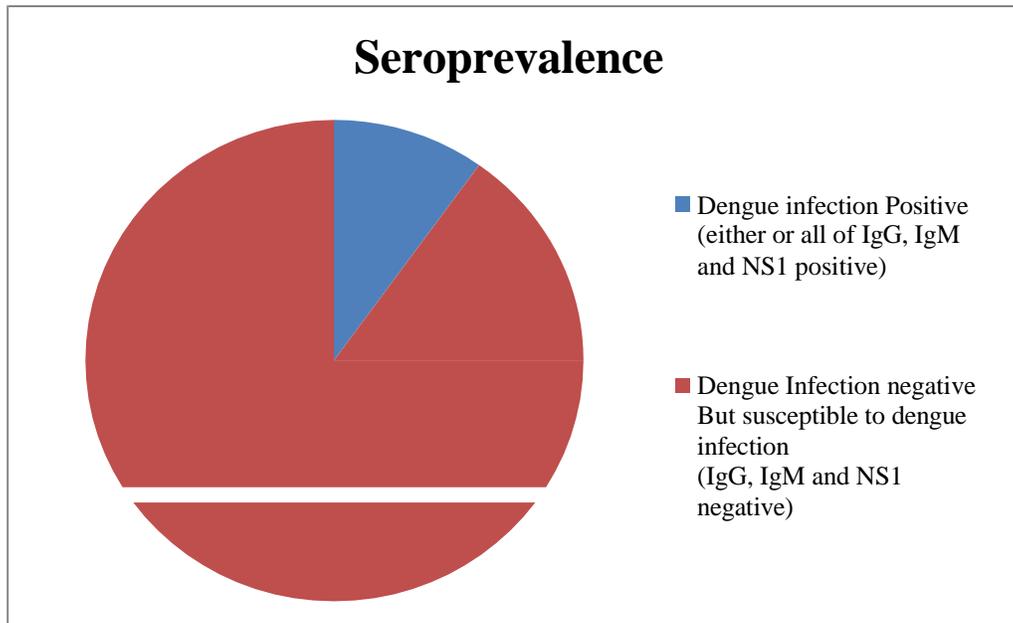


Table.2 Distribution of various dengue specific parameters

Parameter	Total	Percent (%)
Only IgM positive	6	15.78%
Both NS1 and IgM positive	7	18.42%
Only IgG positive	1	2.6%
IgG and NS1 positive	1	2.6%
IgG and IgM positive	1	2.6%
IgG, IgM and NS1 positive	2	5.2%
Only NS1 positive	20	52.63%
Seropositivity	38	9.57%

Chart.1 Showing month wise distribution of total sample received and number of seropositive case

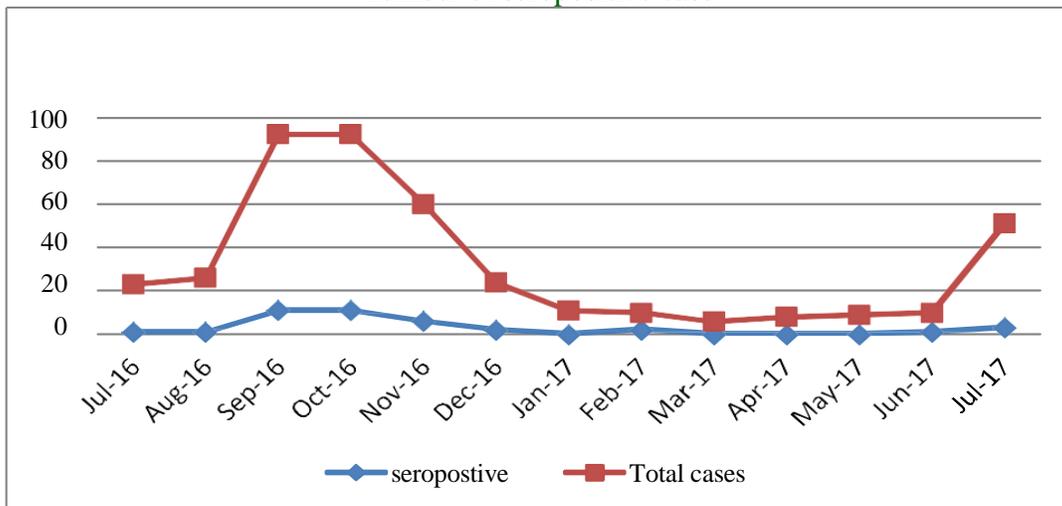


Table.3 Showing distribution of primary and secondary dengue infection

Parameter	Total	Percent (%)
Only NS1 positive	20	52.63%
Only IgM positive	6	15.78%
Both NS1 IgM positive	7	18.42%
Primary Infection	33	86.84%
Only IgG positive	1	2.6%
IgG and NS1 positive	1	2.6%
IgG and IgM positive	1	2.6%
IgG, IgM and NS1 positive	2	5.2%
Secondary Infection	5	13.16%

In the present study, out of 384 samples were tested, a total of 38 (9.9%) samples tested positive for dengue infection and the remaining sample, i.e. 346/384 (90.20%) though negative. The patients with sera negative for dengue infection were considered susceptible to dengue infection in future. The study also indicated that the seroprevalence of dengue is still high especially in post-monsoon period.

Since the epidemiological data indicate a high burden of dengue disease, authorities should consider introduction of the dengue vaccine CYD-TDV especially during pre-monsoon and post-monsoon period. Preventive measures at household, community and government levels should also continue side by side to control dengue infection and all patients suffering from AFI should be subjected to dengue virus screening to initiate necessary management.

Strength of the study

To the best of our knowledge very few studies have been done in this part of Bihar to evaluate the seroprevalence of dengue infection amongst AFI cases especially after the availability of dengue vaccine. In this context, the current study becomes highly relevant as it gives a platform for future investigation to ascertain whether it is appropriate time to introduce dengue vaccine CYD-TDV to susceptible population.

Limitations of the study

This was a small study done only at one center based only on the serology records of virology lab at a tertiary care center of eastern India. Since strong antibody cross reactivity exists among the flavi virus family, so confirmation should be done by RT-PCR in human sera/plasma during first 5 days of suspected dengue infection. In this study, we could not trace the actual confirmed cases to find the actual prevalence of the diseases, actual prevalence of susceptible population, actual prevalence of primary and secondary dengue cases nor could we ascertain the serotype

prevalent in this part of Eastern India. We could not correlate between concurrent infection of dengue with more than one serotype and severity of the disease symptoms.

Future research implicated

Recently, increasing number of DHF and DSS cases are being reported in India, which may be either due to secondary infection with a different serotype or may be due to concurrent dengue virus (DENV) infections with different serotypes. Therefore, accurate determination of the occurrence of DENV serotype infection and co-infections should be done in various DENV prone parts of India. Moreover since human infection with one serotype provides lifelong immunity to the individual against that specific serotype, but does not provide immunity against other serotypes.

On the contrary, since, cross-reactive antibodies enhances the severity of disease caused by subsequent infection by other serotype, thus, in dengue endemic countries, further research is needed to determine the patients immunological status prior to implementation of vaccination with tetra valent vaccine in endemic areas.

Author's contribution

Dr Nidhi Prasad was the principal investigator who gave significant input in the development of this article. Dr Vidyut and Dr Keshav were involved in analyzing the data and completion of this manuscript. All authors read and approved the final manuscript.

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