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Geographical distribution of primary & secondary dengue cases in India – 2017: A cross-sectional multicentric study

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***Background & objectives*: Dengue virus infection is endemic in India with all the four serotypes of dengue virus in circulation. This study was aimed to determine the geographic distribution of the primary and secondary dengue cases in India.**

***Methods*: A multicentre cross-sectional study was conducted at Department of Health Research / Indian Council of Medical Research (DHR)/(ICMR) viral research and diagnostic laboratories (VRDLs) and selected ICMR institutes located in India. Only laboratory-confirmed dengue cases with date of onset**

[#] Equal contribution

of illness less than or equal to seven days were included between September and October 2017. Dengue NS1 antigen ELISA and anti-dengue IgM capture ELISA were used to diagnose dengue cases while anti-dengue IgG capture ELISA was used for identifying the secondary dengue cases.

***Results*: Of the 1372 dengue cases, 897 (65%) were classified as primary dengue and 475 (35%) as secondary dengue cases. However, the proportion varied widely geographically, with Theni, Tamil Nadu; Tirupati, Andhra Pradesh and Udupi-Manipal, Karnataka reporting more than 65 per cent secondary dengue cases while Srinagar, Jammu and Kashmir reporting as low as 10 per cent of the same. The median age of primary dengue cases was 25 yr [interquartile range (IQR 17-35] while that of secondary dengue cases was 23 yr (IQR 13.5-34). Secondary dengue was around 50 per cent among the children belonging to the age group 6-10 yr while it ranged between 20-43 per cent among other age groups.**

***Interpretation & conclusions*: Our findings showed a wide geographical variation in the distribution of primary and secondary dengue cases in India. It would prove beneficial to include primary and secondary dengue differentiation protocol in the national dengue surveillance programme.**

Key words Dengue - geographic variation - India - primary - secondary - viral research and diagnostic laboratories

In recent decades, the global incidence of dengue has reached 390 million dengue infections per year, resulting in about 500,000 hospital admissions annually[1,2]. There is a 30-fold increase in dengue burden over past two decades[3,4]. Severe dengue infection has resulted in 372 disability-adjusted life years (DALYs) per million population[4,5]. Southeast Asia including India accounts for 75 per cent of the current global burden of dengue[5-7]. Dengue is endemic in India with cases being reported from all over the country with increased seasonal activity during the post-monsoon period. According to National Vector Borne Disease Control Programme (NVBDCP), Government of India, there was 188,401 confirmed dengue cases including 325 deaths in 2017[8]. The NVBDCP data only represent the sentinel surveillance laboratories in the government sector. All four serotypes of dengue virus have been reported from India[9-11].

Dengue virus infection does not confer immunity against heterologous dengue virus serotype infection, and as a result, re-infections are common[12,13]. Majority of dengue virus infections are asymptomatic[7]. It has been proposed that antibody-dependent enhancement due to the pre-existing sub- or non-neutralizing anti-dengue antibody is the main pathogenesis in severe dengue[7,14,15]. Secondary dengue has been believed to be associated with the dengue haemorrhagic fever and dengue shock syndrome or severe dengue with organ involvement[7,16-18].

The NVBDCP surveillance uses only dengue NS1 antigen ELISA assay and IgM capture ELISA assay as confirmed diagnosis of dengue virus infection. There is no mechanism to differentiate between primary and secondary dengue cases. As severe dengue is often associated with secondary dengue[19] and the currently available dengue vaccine can only be used in a population with high level of secondary dengue exposure[20], it is important to differentiate primary and secondary dengue cases to understand the transmission dynamics and epidemiology of dengue in India. In this context, this study was conducted as a multicentre cross-sectional study to understand the geographical distribution of primary and secondary dengue cases in India.

Material & Methods

The study was conducted at Department of Health Research / Indian Council of Medical Research (DHR)/(ICMR) viral research and diagnostic laboratories (VRDLs) and selected ICMR Institutes. ICMR VRDL at Manipal Centre for Virus Research, Kasturba Medical College, Manipal, coordinated the study. A total of 16 VRDLs were involved in the study (Box).

A cross-sectional study design was used. All laboratory-confirmed dengue cases with date of onset of illness less than or equal to seven days were included from all participating centres as part of the dengue surveillance from September to October 2017. Consecutive sampling was done due to the short period of study.

Laboratory assays: Dengue NS1 antigen ELISA (Panbio Dengue early ELISA, Lot No. 01P40B010, Standard Diagnostics, Inc., Gyeonggi-do, Republic of Korea) and anti-dengue IgM capture ELISA (ICMR-National Institute of Virology, Pune) were used

Box. Viral research and diagnostic laboratories (VRDLs) involved in the study

1. Government Medical College (GMC), Amritsar
2. Bangalore Medical College and Research Institute (BMCRI), Bangaluru
3. All India Institute of Medical Sciences (AIIMS), Bhopal
4. ICMR-Regional Medical Research Centre (RMRC), Bhubaneswar
5. Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh
6. ICMR-Regional Medical Research Centre (RMRC), Dibrugarh
7. National Institute for Research in Tribal Health (NIRTH), Jabalpur
8. Sawai Man Singh (SMS) Medical College, Jaipur
9. ICMR-National Institute of Cholera and Enteric Diseases (NICED), Kolkata
10. King George's Medical University (KGMU), Lucknow
11. ICMR-National Institute of Malaria Research (NIMR), New Delhi
12. ICMR-Regional Medical Research Centre (RMRC), Port Blair
13. Sher-e-Kashmir Institute of Medical Sciences (SKIMS), Srinagar
14. Government Medical College (GMC), Theni
15. Sri Venkateshwara Institute of Medical Sciences (SVIMS), Tirupati
16. Manipal Centre for Virus Research, Kasturba Medical College, Manipal Academy of Higher Education, Manipal

to diagnose dengue as per the NVBDCP guidelines[8]. Further, the confirmed dengue cases were tested with anti-dengue IgG capture ELISA (Panbio Dengue IgG capture ELISA, Lot No. 01P10C001, Standard Diagnostics, Inc, Gyeonggi-do, Republic of Korea) for identifying the secondary dengue case.

A primary dengue case was defined as a laboratory-confirmed dengue infection with Dengue NS1 antigen ELISA and/or IgM capture ELISA positive and IgG capture ELISA negative. A secondary dengue case was defined as a laboratory-confirmed dengue infection with Dengue NS1 antigen ELISA and or IgM capture ELISA positive along with positive IgG capture ELISA.

This study was of surveillance in nature and was done with anonymized samples received by participating DHR/ICMR VRDLs and ICMR Institutes as part of routine virological surveillance and/or diagnosis. The ethical approval was taken from the respective institutions for the same.

Results & Discussion

A total of 1372 serologically confirmed dengue cases were enrolled from all the centres during the study period. The median age of confirmed dengue cases was 24 yr [interquartile range (IQR) 16-34], and male to female ratio was 1.6:1 (Table).

Of the 1372 dengue cases, 897 (65%) were classified as primary dengue and 475 (35%) as secondary dengue. However, the proportion varied widely geographically, with Theni, Tamil Nadu; Tirupati, Andhra Pradesh and Udupi-Manipal, Karnataka reporting more than 65 per cent secondary dengue cases while Srinagar, Jammu and Kashmir reporting as low as 10 per cent secondary dengue cases (Table). The median age of primary dengue cases was 25 yr (IQR 17-35), and male to female ratio was 1.6:1. The median age of secondary dengue cases was 23 yr (IQR 13.5-34), and male to female ratio was 1.7:1 (Table). Secondary dengue was around 50 per cent among the children belonging to the age group 6-10 yr while it ranged between 20 and 43 per cent among other age groups (Table). There was no significant difference in the distribution of primary and secondary dengue concerning gender (Table). Only Theni site had a higher proportion of children among the confirmed dengue cases with respect to other centres.

A wide geographical variation was observed in the distribution of primary and secondary dengue cases in India. The study sites in the States of Andhra Pradesh, Karnataka and Tamil Nadu showed that two-thirds of the dengue cases were secondary while in other States, it was predominantly primary dengue. Analysis of age group did not reveal any significant pattern except that secondary dengue accounted for nearly half of dengue cases among 6-10 yr of age. However, most of the cases were from Theni, Tamil Nadu where secondary cases predominated. While confirmed dengue infection showed a male preponderance, there was no significant gender difference between the proportion of primary and secondary dengue cases.

Laboratory confirmation of secondary dengue infection case is challenging. While several methods are available, we used a well-established anti-dengue IgG capture ELISA[21,22] for identifying the secondary dengue cases among the confirmed dengue cases.

Since the first report of virologically confirmed dengue outbreak in India in 1963-1964 in Calcutta (now Kolkata)[23], dengue infections have become endemic and periodic outbreaks or epidemics have

Table. Demographic characteristics of primary and secondary dengue cases (n=1372)

Characteristics	Confirmed dengue (n=1372)	Primary dengue (n=897), n (%)	Secondary dengue (n=475), n (%)
Age (yr)			
Median (IQR)	24 (16-34)	25 (17-35)	23 (13.5-34)
Age groups			
≤5	70	43 (61)	27 (39)
06-10	123	60 (49)	63 (51)
11-15	137	90 (66)	47 (34)
16-20	185	121 (65)	64 (35)
21-25	240	162 (68)	78 (33)
26-30	183	131 (72)	52 (28)
31-35	117	83 (71)	34 (29)
36-40	101	69 (68)	32 (32)
41-45	62	36 (58)	26 (42)
46-50	51	31 (61)	20 (39)
51-55	32	23 (72)	9 (28)
56-60	34	24 (71)	10 (29)
61-65	21	12 (57)	9 (43)
66-70	10	8 (80)	2 (20)
71-75	6	4 (67)	2 (33)
Sex			
Male	855 (62)	554 (62)	301 (63)
Female	517 (38)	343 (38)	174 (37)
Place			
Amritsar	85	52 (61)	33 (39)
Bangaluru	124	64 (52)	60 (48)
Bhopal	91	72 (79)	19 (21)
Bhubaneswar	9	9 (100)	0 (0)
Chandigarh	80	68 (85)	12 (15)
Dibrugarh	47	39 (83)	8 (17)
Jabalpur	100	68 (68)	32 (32)
Jaipur	98	61 (62)	37 (38)
Kolkata	81	71 (88)	10 (12)
Lucknow	91	73 (80)	18 (20)
New Delhi	134	113 (84)	21 (16)
Port Blair	49	40 (82)	9 (18)
Srinagar	77	69 (90)	8 (10)
Theni	100	27 (27)	73 (73)
Tirupati	99	33 (33)	66 (67)
Udupi, Manipal	107	38 (36)	69 (64)

IQR, interquartile range

been reported from almost all parts of India[6,24] with co-circulation of multiple serotypes of dengue virus[9]. This has led to an increase in population pool with successive exposure to different serotypes of dengue leading to secondary dengue infection. This was evidenced by the current findings that several States from South India

where dengue disease burden is high, had a significant proportion of clinical dengue infections presenting as secondary dengue cases.

Dengue was initially an urban disease which earlier affected the metropolitan cities of India, namely Calcutta (presently Kolkata), Delhi, Bangalore (presently Bengaluru) and Madras (presently Chennai)[25]. Currently, the disease has spread to much-wider geographic locations as peri-urban, rural areas are being urbanized as part of the country's evolution. This is essentially due to the rapid urbanization of peri-urban and rural areas as part of the developmental activities which enables the expansion of vector breeding sites as well as wider exposure to the disease. Hence, the difference in the distribution of primary and secondary dengue in the country was seen.

Most reports on dengue infection published from India have not distinguished primary and secondary dengue. However, there are a few reports from the north as well as south India, reporting the varying proportions of primary and secondary dengue cases among laboratory-confirmed dengue[26-28] as has been observed by us.

Understanding the distribution of primary and secondary dengue is important on several counts. First, to identify geographical regions for strengthening clinical management of dengue cases to reduce mortality. Second, to identify the geographical areas with predominant secondary dengue cases for vaccine introduction as currently available dengue vaccine is recommended only in a population with predominant secondary dengue distribution[29]. Third, to identify areas with limited spread or recent introduction to implement disease prevention and control strategies.

Our study had certain limitations also. First, the study period was brief and entirely from tertiary care centres leading to a bias in the inclusion of larger proportion of severe cases which might have influenced the proportion of secondary dengue cases. Second, only a single acute serum sample was used, and lack of convalescent serum would have affected case classification.

In conclusion, the distribution of primary and secondary dengue infection was widely varied geographically. Incorporating the primary and secondary dengue differentiation protocols as part of the existing national dengue surveillance programme could provide more representative dengue epidemiology in India.

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