Incidence of dengue illness among children in an urban setting in South India: A population based study

Winsley Rose, Kulandaipalayam Natarajan Sindhu, Asha Mary Abraham, Gagandeep Kang, Jacob John

A R T I C L E   I N F O

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Objectives: Our main objective was to estimate population based dengue incidence estimates in children with fever >3 days.

Methods: The study used the ‘National Surveillance System for Enteric Fever in India’ (NSSEFI) cohort at the Vellore site. Children aged 6 months to 14 years from a peri-urban setting in Vellore were followed up for a year for the presence of fever. All children who had fever >3 days were eligible for blood culture to diagnose typhoid. All children that presented with fever >3 days on alternate days of the week were also tested for dengue. Dengue incidence estimates were then calculated.

Results: There were 6648 children followed up with a cumulative observation period of 5800 child years. There were 11753 fever episodes with 3171 (27%) episodes lasting >3 days. Totally, 784 children with 868 episodes of fever were tested for Dengue. NS1 antigen or Dengue IgM or both were positive in 82 (9.4%) of those tested for Dengue. Dengue PCR was positive in 33/64 (51.6%) of the samples positive samples. The annual incidence rate of dengue was 49.5 per 1000 child years among children with fever >3 days.

Conclusions: There is high burden of dengue in peri-urban Vellore.

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Introduction

Dengue is a fast emerging and rapidly spreading systemic viral infection with global estimates of 390 million infections per year, of which 96 million are apparent infections and 3.97 billion people in 128 countries are at risk of dengue infection (Bhatt et al., 2013; Brady et al., 2012). These estimates are based largely on databases that track infectious diseases and reports on dengue outbreaks. Diagnostic accuracy and locational information on dengue cases are often not robust. For control of dengue, the World Health Organization (WHO) advocates an active laboratory based surveillance programme and sentinel surveillance of fever (WHO, 2018a). Community based surveillance data on dengue is lacking and burden estimates of dengue are often based on modelling studies that use laboratory based surveillance data and sentinel surveillance data.

The first virologically confirmed epidemic of dengue in India was reported in 1963–64 along the East coast (Chaturvedi and Nagar, 2008). Since then, a number of outbreaks have been reported in India with an alarming increase since the 2000s. The early ones were sporadic with fewer numbers in peri-urban areas and a low number of severe cases. However, in recent outbreaks, the outbreaks are larger, more frequent with expansion to rural areas, with a greater proportion of severe cases and deaths; and progression to hyperendemicity (Chakravarti et al., 2012). With high burden of dengue in India, control is imperative. Large scale vector control strategy has been the mainstay of dengue control till recently. With the development of vaccines and possible immunotherapies against dengue, there is potential for a different dimension to dengue control. In 2016, a live attenuated chimeric dengue vaccine in a yellow fever 17D backbone (CYD-TDV) vaccine was approved by WHO for use in geographic settings with high burden of disease (WHO, 2016). However, prior dengue infection is an important pre-requisite for this vaccine to be effective (Aguiar and Stollenwerk, 2018). Many more different vaccine types such as live attenuated, inactivated and non-replicating vaccines, DNA and subunit vaccines are in various phases of development (Rather et al., 2017). With more vaccines being developed, it is important to have population based dengue incidence data for estimate of disease burden and for conducting vaccine studies, especially for high burden regions like in India.
In this paper, we report population based dengue incidence among children who present with fever over one year taking into account the seasonal variation that occurs with dengue.

Methods

This study was conducted to find population based dengue incidence among children with fever >3 days in a high burden region. It was nested within the ‘National Surveillance System for Enteric fever in India’ (NSSEFI) study in the Vellore site (John et al., 2018). The study was conducted prospectively for a period of 1 year from July 2017 to June 2018 in a peri-urban setting in Vellore, Tamil Nadu after Institutional Review Board approval from the Christian Medical College, Vellore.

Age eligible children between 6 months and 14 years from families that provided informed consent and age appropriate individual assent were included. All enrolled children were contacted once each week by a combination of direct home visits and telephone contact with the primary care giver. A network of healthcare facilities that were either accredited or established for the study used standardized diagnostic algorithms for children presenting with fever. Any febrile illness in the cohort was identified through a combination of the caregiver contacting the study team, surveillance of accredited healthcare facilities and the weekly home visits. All febrile episodes were monitored through daily visits to document diagnosis, course of illness and treatment received. All children who presented with fever on alternate week days (Mondays, Wednesdays and Fridays alternating every week with Tuesdays, Thursdays and Saturdays) with fever for 72 h or more between July 2017 and June 2018 were tested for dengue (NS1, Dengue IgM and Dengue IgG) using the Dengue Day 1 Test, a rapid card test from J. Mitra and Co. Pvt. Ltd. (Dengue Day 1 Test, 2018) along with blood culture for the NSSEFI study. Those who had positive NS1 or Dengue IgM were tested with Dengue polymerase chain reaction (PCR). The reverse transcriptase real time PCR assay used for the detection and typing of dengue virus was adopted from the CDC protocol described by Santiago et al. (Santiago et al., 2013).

All surveillance and clinical data were collected using an electronic data capture system. Descriptive analysis including monthly incidence risk and incidence rate of dengue illness was calculated using Stata 15 (StataCorp, 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC, 2017).

Results

Flow chart of children tested for dengue

A cohort of 6648 children was followed during the study period between 3rd July 2017 and 5th July 2018 with an observation period of 5800 child years. There were 11753 fever episodes during this period with a mean duration of 2.32 days. There were 2329 (35%) children with 3171 (27%) episodes of fever that lasted > 3 days. Using the sampling strategy of doing dengue tests on alternate weekdays, there were 784 children with 868 episodes of fever that were tested for Dengue. NS1 antigen or Dengue IgM or both were positive in 82 (9.4%) of those tested for Dengue. One child tested positive for Dengue IgM twice three months apart. The proportion of children tested that had Dengue was 10.3%. Forty-five (54.9%) were positive for NS1 antigen, 32 (39%) for Dengue IgM and 5 (6.1%) for both NS1 antigen and Dengue IgM. None were positive for Dengue IgG. Dengue PCR was performed in 64 of the 82 samples that were positive for NS1 or Dengue IgM. The rest could not be performed due to inadequate sample availability. The Dengue PCR results are shown in Table 1. Dengue PCR was positive in 33/64 (51.6%) of the total samples that were analyzed. Of the 33 positive by Dengue PCR, 28 (84.8%) were DENV 1, 4 (12.1%) were DENV 2 and 1 (3.1%) was DENV 4.

The mean duration of fever at which the Dengue test was done was 4.94 days (SD 0.173 days). Seven children (9%) required hospitalization. All children recovered completely.

The mean age of the NSSEFI cohort was 6.2 years (SD 3.8 years) and 6.6 years (SD 3.7 years) in the sample of children tested for dengue. There were 49.3% females in the NSSEFI cohort and 43.1% females in the sample of children tested for dengue. There were 592 (75.5%) and 66 (80.5%) children who were less than 9 years of age in those who were tested for dengue and those positive for dengue respectively.

The monthly frequency distribution of those with fever tested for dengue and the proportion of children testing positive for dengue is depicted in Figure 1. The highest risk of dengue illness was in the month of October (25%) and least in May (none). Dengue illness was diagnosed in most months of the year except May. Assuming that the proportion of children who were tested had dengue among all the children who had fever >3 days would be representative of the population (2238 children) and the person time of the population (1952 years) that was tested for dengue, the incidence rate calculated was 49.5 per 1000 child years in children presenting with fever >3 days.

Discussion

Our study is one of the first studies to report a population based incidence of dengue in children. We found an incidence rate of 49.5 cases per 1000 child years in children who had fever >3 days. This incidence is likely to be an under-estimate because children with fever <3 days were excluded and we would have missed cases of dengue with fever lasting <3 days. The dengue cases reported for the whole of India in 2017 as per Government of India figures is 153,635 with 22,197 cases reported from the state of Tamil Nadu, where our study was also conducted (National Vector Borne Disease Control Programme, 2018). Since these national figures rely on passive laboratory based surveillance, it is likely that these figures would grossly under-estimate the true burden of dengue. Our rate is also much higher than the 0.721 cases of classic dengue fever per 1000 person years reported from Latin America and the Caribbean derived primarily from passive surveillance data (Cafferata et al., 2013). The high burden of dengue in our study may be linked to the endemcity of dengue in Vellore and the active surveillance nature of our study. Dengue has been reported from Vellore since 1958 and all four serotypes of the Dengue virus were recognized to be prevalent since 1968 (Myers et al., 1970; Cherian et al., 1994).
In our study, distinct seasonality of dengue was observed with the highest incidence being in October and the least in July, though detected all year round. This seasonality is linked to climatic conditions such as mean temperatures and precipitation levels which affect the extrinsic incubation period of the Dengue virus (Lee et al., 2017; Mutheneni et al., 2017). The average rainfall and the average number of rain days in Vellore increase from July onwards to a maximum in October from the North-east monsoon and our monthly incidence risks of dengue reflect the post monsoon seasonality of dengue (Weather Atlas, 2018; Shastri et al., 2017). Increases in rainfall have been correlated with increase in dengue incidence 2 months later and likely explains the high incidence months being October to January in our study (Morales et al., 2016). The distinct seasonality with absence of cases in the other months has been observed earlier (Sharma et al., 2012). However, in recent years, as in our study, dengue is diagnosed all year round from the Indian sub-continent (Morales et al., 2016).

Dengue PCR was positive only in 51.6% of those positive by the rapid test. However, in those who were NS1 positive and Dengue IgM negative, the positivity was 87.9% and in those that were NS1 negative and Dengue IgM positive, the PCR positivity was only 3.8%. This observation is in keeping with the fact that Dengue PCR and NS1 are positive in the same phase of Dengue illness and Dengue IgM becomes positive later in the illness when PCR is often negative (Pak et al., 2010). In our study, DENV-1 (84.7%) was by far the most predominant strain circulating in the community and DENV-3 was absent. All four strains of the Dengue virus are known to circulate during epidemics in India. (Shrivastava et al., 2018; Gupta and Ballani, 2014). DENV-1 has been the most prevalent strain in epidemics in Delhi, but has not been reported to be the most prevalent from South India. The preponderance of DENV-1 in our study may indicate an epidemiological shift.

The majority of children (80.5%) who were positive for dengue in our study were less than 9 years of age. In hospital based studies, the majority of children with dengue are below 9 years of age. Anju Aggarwal et al. from Delhi, India reported that 45% of the children were below the age of 6 years and Oncog et al. from Philippines reported 48% of the children being 4–7 years of age (Aggarwal et al., 1998; Oncog and Pondoc, 2018). This information needs to be taken into account at a time when the only vaccine registered to be used for dengue can only be used in children over 9 years of age and preferably those with documented prior exposure (WHO, 2018b). Vaccine development needs to take into account that the bulk of dengue infections in children are in those less than 9 years of age.

Our study has several limitations. Firstly, we only tested a proportion of those who presented with fever for dengue, though they were sampled systematically. We could have missed some children with fever. However, these missed cases are unlikely to be differential in whether they had dengue or not. Secondly, the dengue test used for initial diagnosis was a rapid test. It would have been ideal to use an enzyme immunoassay based or a PCR based diagnostic test to diagnose dengue. Cost constraints, ease of performing the rapid test and rapid turn-around time were factors which influenced us to use the rapid test. Thirdly, we did not include children who had fever for less than 3 days. Hence, our estimate of dengue incidence is likely to be an under-estimate. We also do not have information on asymptomatic infections. Fourthly, the study was done only for one year and it is possible there would be yearly variation in the dengue transmission which would not be captured in our study. Lastly, none of the children in the study were

### Table 1
<table>
<thead>
<tr>
<th>PCR positive</th>
<th>NS1 Positive, IgM Positive</th>
<th>NS1 Positive, IgM Negative</th>
<th>NS1 Negative, IgM Positive</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR positive</td>
<td>3 (60%)</td>
<td>29 (47.9%)</td>
<td>1 (3.8%)</td>
<td>33 (51.6%)</td>
</tr>
<tr>
<td>PCR negative</td>
<td>2 (40%)</td>
<td>4 (12.1%)</td>
<td>25 (96.2%)</td>
<td>31 (48.4%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>5</td>
<td>33</td>
<td>26</td>
<td>64</td>
</tr>
</tbody>
</table>

**Figure 1.** Month-wise distribution of fevers and patients positive for dengue in the study population.
positive for Dengue IgG. It is likely that many were primary infections. However, since our study was based on a card test and not ELISA, it is possible that low levels of IgG may not have been picked up in the card test and we may have missed some secondary infections.

In conclusion, we report a high incidence of dengue in urban Vellore among children with dengue transmission happening all year round with a peak post monsoon incidence between October and January, and the majority of patients being less than 9 years of age.

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Ethical approval

The study was approved by Institutional Review Board and Ethics Committee of Christian Medical College Vellore.

Conflict of interest

All authors declare that they have no conflicts of interest.

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