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# Seasonal Distribution of Dengue Fever in the Central Highlands Region, Vietnam (2010- 2015)

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**Abstract** **Background**: Dengue virus infection has emerged as a notable public health problem in recent decades in terms of the mortality and morbidity associated with it. Dengue has been known to be endemic in the Central Highlands region, Vietnam for over 30 years. Here we have reported the trend of Dengue fever cases in the Central Highlands region, Vietnam for a period of 2010- 2015. **Methods**: Serum samples from clinically suspected cases of dengue virus infection were collected. All samples were tested for Dengue IgM by indirect ELISA and by RT-PCR for presence of Dengue virus RNA. **Results**: A total of 3272 serum samples were tested, of which 1229 (37.5%) were positive for dengue. The Dengue positive patients were 565 males and 664 females. All four serotypes of Dengue virus have found in the Central Highlands region. DENV-2 was predominant in 2010, 2012 and 2013. DENV-3 and DENV-4 was predominant in 2014 and 2015; respectively. The Dengue affected cases were more in 20-40 years age group. Dengue cases were more during May to September in rainy season when weather conditions were prefer for mosquito bleeding and vector activity. **Conclusions:** The findings of this study indicate that all four serotypes of dengue virus are circulating in the Central Highlands region, Vietnam. The data enable to notice seasonal distribution of Dengue fever in the Central Highlands region, Vietnam over five years (2010-2015) with regards to outbreaks and peak incidences in the disease.

***Keywords:*** *dengue virus, serotype, the central highlands, vietnam*

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## 1. Introduction

Dengue fever (DF) is the most important arboviral disease in many tropical and subtropical regions of the world. Dengue virus (DENV) belongs to the genus *Flavivirus* and family *Flaviviridae*. It is an enveloped positive sense single stranded 11000 nucleotides long RNA virus including four different serotypes of Dengue virus; DENV-1, DENV-2, DENV-3 and DENV-4 [1]. The World Health Organization (WHO) indicated that the incidence of dengue has dramatically increased 30-fold since 1955 to 2010, and estimated 50-100 million new infections occurred annually over 100 endemic countries, especially hundreds of thousands of severe cases increased, in Southeast Asian countries [2].

Dengue fever (DF)/Dengue hemorrhagic fever (DHF) is endemic in the Central Highlands region of Vietnam with all four DENV serotypes co-circulating. The Central Highlands had major outbreaks of dengue caused by various dengue virus serottypes in 1981, 1983, 1985, 1991, 1992, 1998, 2004 [3,4,5,6]. Major epidemics of DF/DHF in the Central Highlands region were reported in 2010 and 2012 with more than 13,000 cases and 18,000 cases; respectively [6,7]. Dengue outbreaks have, since then, been continuously reported and a burden of disease in this region. Therefore, this study was conducted to determine the distribution of DENV serotypes and trend of dengue infection in outbreaks between 2010 and 2015 to shed light on the overall situation which is essential to control and prevent dengue infection in the Central Highlands region, Vietnam.

## 2. Materials and Methods

### 2.1. Study Site and Samples Collection

The Central Highlands area consists of five provinces, which are Kon Tum, Gia Lai, Dak Lak, Dak Nong and Lam Dong (arranged from the north to the south). It has a population of 5.28 million, ethnic minorities account for 38.7% of the population as a whole. The Central Highlands area is 54,474 square kilometers accounting for 16.8% the total area of the whole country and located at altitude ranged from 500–1,500 meters above sea level. The climate of the Central Highlands is divided into two seasons, rainy season from May to October and dry season from November to April. The Central Highlands is mainly an agriculture area for growing industrial crops. Coffee is the most important industrial crop in the region.

The study was performed in the Central Highlands during 2010-2015. A total number of 3272 acute phase

blood samples were collected from clinically suspected cases of dengue virus infection, coming to various outpatient departments and admitted patients in provincial and district hospitals, and primary health care centers in the Central Highlands, over a period of 6 years from 2010 to 2015.

### 2.2. Enzyme Immunoassay

All the samples were tested for the presence of anti-dengue IgM using ELISA using commercial kit (IBL International GmbH, America). Absorbances were read using an ELISA reader (Biotex, USA) at a wavelength of 450 nm. The colour intensity is directly related to the dengue antibody concentration in each test sample.

### 2.3. Viral RNA Extraction and Semi-nested RT-PCR

Serum samples obtained in early phase of disease (within 5 days of illness) (n=1753) were tested for Dengue viral RNA using RT-PCR. RNA was extracted from serum samples using QIAGEN QIAamp viral RNA mini kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. The extracted RNA was used for the identification of the DENV serotypes using RT-PCR. The identification was carried out by RT-PCR followed by nested PCR by demonstrating the presence of virus specific RNA employing dengue group-specific as well as serotype-specific primers targeting C-prM gene junction following the protocol of Lanciotti et al. as described previously [8].

### 2.4. Statistical Analysis

Statistical Package for GraphPad Prism version 5.0 (Graph Pad Software, USA) was used for data entry, processing and statistical analysis.

## 3. Results

A total of 3272 serum samples were tested for anti-dengue IgM antibodies and dengue RNA during the period (2010-2015). Year wise distribution of the number of dengue tested samples was 927 in 2010, of which 471 (50.8%) were positive; 194 in 2011, of which 35 (18.0%) were positive; 462 in 2012, of which 94 (20.3 %) were positive; 459 in 2013, of which 174 (37.9 %) were positive; 430 in 2014, of which 67 (15.6%) were positive and 800 in 2015, of which 388 (48.5%) were positive (Table 1).

**Table 1. Age-wise distribution of Dengue fever cases**

| Year/age group | | 0-10 | 11-20 | 21-30 | 31-40 | 41-50 | >50 | Total |
|---|---|---|---|---|---|---|---|---|
| 2010 | Tested | 80 | 231 | 269 | 175 | 94 | 78 | 927 |
| | Positive (%) | 40 (50.0) | 135 (58.4) | 136 (50.5) | 84 (48.0) | 43 (45.7) | 33 (42.3) | 471 (50.8) |
| 2011 | Tested | 16 | 36 | 45 | 34 | 37 | 26 | 194 |
| | Positive (%) | 1 (6.25) | 9 (25.0) | 4 (8.8) | 10 (29.4) | 6 (16.2) | 5 (19.2) | 35 (18.0) |
| 2012 | Tested | 39 | 80 | 147 | 89 | 47 | 60 | 462 |
| | Positive (%) | 4 (10.2) | 24 (30.0) | 34 (23.1) | 15 (16.8) | 11 (23.4) | 6 (10.0) | 94 (20.3) |
| 2013 | Tested | 35 | 92 | 128 | 71 | 68 | 65 | 459 |
| | Positive (%) | 6 (17.1) | 37 (40.2) | 53 (41.4) | 23 (32.4) | 30 (41.1) | 25 (38.4) | 174 (37.9) |
| 2014 | Tested | 62 | 78 | 94 | 76 | 63 | 57 | 430 |
| | Positive (%) | 9 (14.5) | 15 (18.2) | 10 (10.6) | 15 (19.7) | 5 (7.9) | 13 (22.8) | 67 (15.6) |
| 2015 | Tested | 59 | 154 | 196 | 157 | 112 | 122 | 800 |
| | Positive (%) | 21 (35.6) | 71 (46.1) | 114 (58.1) | 86 (54.7) | 48 (42.8) | 48 (39.3) | 388 (48.5) |
| Total | Tested | 291 | 671 | 879 | 602 | 421 | 408 | 3272 |
| | Positive (%) | 81 (27.8) | 291 (43.4) | 351 (39.9) | 233 (38.7) | 143 (33.9) | 130 (31.8) | 1229 (37.5) |

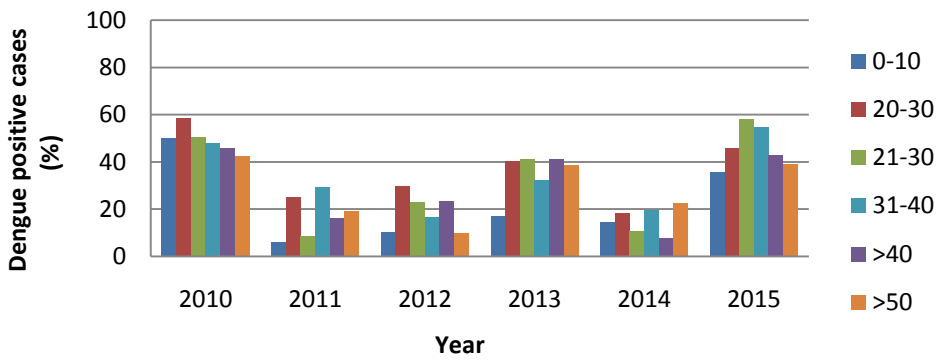


**Figure 1.** Distribution of Dengue fever cases by age in the Central Highlands region, Vietnam (2010–2015). Dengue disease occurs in children and adults. The most cases of Dengue fever between 2010 and 2015 are age group between 11-40 years

### 3.1. Age Distribution of Dengue Fever

The Central Highlands region, Dengue infection was observed in children and adults, with most cases occurring in individuals aged between 11 years and 40 years. However, there has been a shift in age group predominance of dengue disease from younger towards older individuals over 20 years of age (Figure 1).

### 3.2. Gender Wise Distribution

In Dengue patients, 565 out of 1229 Dengue positive cases (46.0%) were males compared to 664 positive cases (54.0%) of females.

Overall, male to female ratio of dengue positive cases were 0.85:1 [0.96:1 (in year 2010); 0.75:1 (in year 2011); 0.84:1 (in year 2012); 1.04:1 (in year 2013); 0.72:1 (in year 2014) and 0.69:1 (in year 2015) (Table 2).

### 3.3. Monthly Distribution of Dengue Fever

The Dengue cases were distributed throughout all months. However, cases of Dengue fever started increasing between May and August annually and reached at peak in July which due to seasonal changes in climate and the association between the active season of the vectors and the wettest months. Rainy season in the Central Higlands region begins around April and lasts till October. Average annual temperatures range from 15°C to 32°C in the rainy season (Figure 2).

**Table 2. Gender wise distribution of Dengue positive cases**

| Gender | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | Total |
|---|---|---|---|---|---|---|---|
| Male (%) | 231 (49.0) | 15 (42.8) | 43 (45.7) | 89 (51.1) | 28 (41.8) | 159 (41.0) | 565 (46.0) |
| Female (%) | 240 (51.0) | 20 (57.2) | 51 (54.3) | 85 (48.9) | 39 (58.2) | 229 (59.0) | 664 (54.0) |
| Total | 471 (100) | 35 (100) | 94 (100) | 174 (100) | 67 (100) | 388 (100) | 1229 (100) |
| Ratio (M/F) | 0.96:1 | 0.75:1 | 0.84:1 | 1.04:1 | 0.72:1 | 0.69:1 | 0.85:1 |

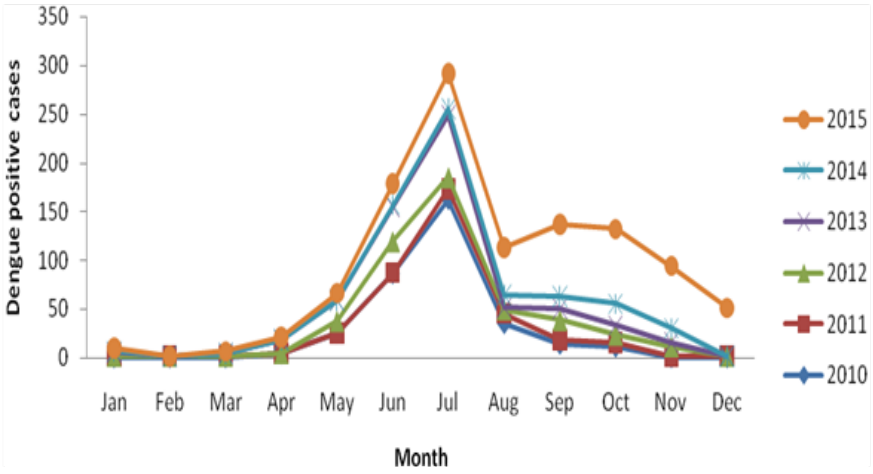


**Figure 2.** Distribution of positive cases of dengue by month in the Central Highlands region, Vietnam (2010–2015). The most incidence of Dengue fever is between May and September due to changes in temperature and humidity in months of rainy season and vector activity

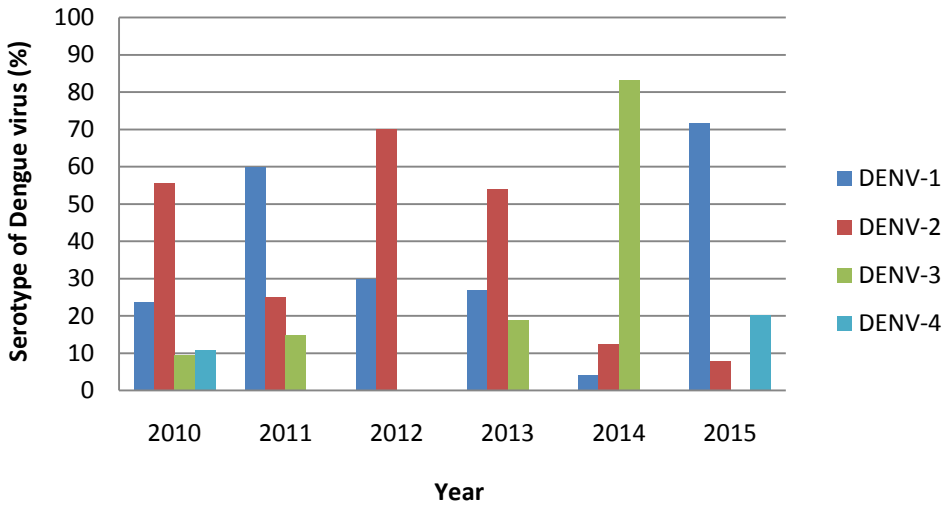


**Figure 3.** Distribution of circulating Dengue virus serotypes by year in the Central Highlands region, Vietnam (2010–2015). There was a reduction in the proportion of DENV-2 and a change in the proportion of DENV-1, DENV-3, and DENV-4 by time in region

### 3.4. DENV Serotype Distribution

All four serotypes of dengue (DENV-1, DENV-2, DENV-3 and DENV-4) were co-circulating and DENV-2 was the dominant serotype in 2010 and 20112 outbreak. DENV-1 was predominant in 2011. In 2013, DENV-2 was predominant serotype again. However, during the years 2014, DENV-3 was more commonly. In 2015, the most commonly identified serotype was DENV-1, representing over half of all those isolated (71.74%) (Figure 3).

## 4. Discussion

Dengue fever is one of the world's fastest-growing vector-borne diseases in different geographical regions of the world [9]. The Central Highlands region continues to face challenges with Dengue fever outbreak due to problems with mosquito and the close proximity to regions with high incidences of DENV infection.

In our study, 45.89% (564/1229) of Dengue positive cases were reported in the age group of 21- 40 years with gradual increase in mean age of Dengue affected patients from 2010 to 2015. Some of studies done in the Central Highlands region before 2010 showed higher Dengue positive cases in younger age group (<15 years) [3,4,5]. Results of this study indicated that the active and young adults (20–40 years) were the most affected and the epidemiological shift as around 69.7% of Dengue positive cases were reported in age ≥ 20 years, which is contrary to the popular belief that Dengue is a pediatric disease [10-15]. The trend for the increased incidence of Dengue infection among older age groups in both Latin America and southeast Asia was observed in previous studies [16-21], there is also a trend toward infections in younger age groups in countries such as Venezuela, Brazil, and Nicaragua [22,23,24]. More exposure and more activity during the day time provide more chances for the vector bites and hence higher infection rate. These differences may be related to the following factors: 1) the level of economic, political and social development [25], 2) host and epidemiologic factors [26], 3) the predominance of different virus genotypes or *Aedes* mosquito [27], and 4) a progressive shift in age-distribution [28]. In addition, the adult predominance and recent shift in age pattern toward adults might be caused by the fact that most of the clinically evident cases are actually secondary infections. The understanding of change in epidemiologic pattern of Dengue cases has important implications for control and prevention to reduce the number of Dengue cases. In Asian countries where Dengue has been epidemic for several years, this age shift is clearly observed, indicating an epidemiological change in dengue infection.

A better understanding of gender differences in infection rates of disease is important for any dengue control and prevention program. The gender wise distribution of DENV infection indicates no significant difference between the male and female populations (46.0% & 54.0% respectively) infected in the Central Highlands region (Table 2). Our finding is similar to a study in Thailand [29], but constrast to studies in Malaysia and in China [15,30]. The possible reason for this may be different in social and cultural characteristics and due to differences between the sexes in health-seeking behavior [29]. Women are mostly restricted to remain inside homes in Asian community. In the Central Highlands, Vietnam, there is a huge number of working women which increases the chances exposed to infection. This suggests that chances of positive Dengue are higher in clinically suspected cases among females. Most of Dengue cases were found to occur in rainy months which are analogous to the findings of other studies which showed rise in incidence of Dengue infection in rainy season, when conditions are perfect for mosquito breeding and cause the spread of Dengue in the area [15]. This seasonal outbreak of disease transmission emphasizes the importance for appropriate vector control. All four serotypes of Dengue virus (DENV-2, DENV-2, DENV-3 and DENV-4) have all been isolated during previous dengue outbreaks in the Central Highlands region, but only serotype has always predominated. A Dengue outbreak in 2010, circulation of four serotypes was observed and DENV-2 was prodominant. DENV-2 has been previously reported to be the predominant serotype in post-epidemic periods like in the year 1983, 1987, 1991 outbreak [4,5]. Our finding of two or more serotypes co-circulating every year during the study period highlights the extent of hyperendemincity of dengue serotypes in this region. However, the following years 2011 and 2015, the emergence of an other Dengue serotype leads to a outbreak. During the year 2011, we observed that DENV-1 was the most common circulating serotype. Thus, DENV-1 replaced DENV-2 and DENV-3 to establish itself as the predominant strain in the Central Highlands region. In the year 2012 and 2013, DENV-2 was re-ermerging to become predominant. These findings indicate replacement of the circulating serotype leads to the Dengue outbreak in this region. Introduce of serotype DENV-4 after an absent interval of 4 years was probably leading to an increased sharply number of Dengue cases in 2015 outbreak in this region. The emergence of a newer dengue serotype after a long period has always caused to major outbreaks, which is a matter of concern due to causing the outbreaks in future. The data on serotypes is very important as this will help to develop improved, proactive, laboratory-based surveillance systems that can predict impending Dengue outbreak. The trend for the increased incidence of Dengue infection among young adults has been observed in this study and has important implications for control and prevention.

## 5. Conclusion

The incidence, mortality, and case fatality of dengue are affected by the Dengue virus serotypes circulating for a particular time period. The co-circulation of all four dengue serotypes has been found in the Central Highlands region, Vietnam. It is imfortant to be noted that the co-circulation of more than one serotype warning the occurrence of more cases of Dengue infection.

## Abbreviations

**DENV:** Dengue virus **DHF:** Dengue hemorrhagic fever **ELISA:** Enzyme-linked immunosorbent assay **RT-PCR:** Reverse transcriptase polymerase chain reaction

## Ethics Approval and Consent to Participate

The study was approved by the institutional review boards of Tay Nguyen Institute of Hygiene and Epidemiology, Vietnam.

## Competing Interests

The authors declare that they have no competing interest.

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## Authors' Contributions

LVT, NTTV and PTD conceived the idea and designed the study; LVT, NTTV, PTTN, LDMQ collected the data; LVT analyzed the data and drafted the manuscript. All authors commented the paper and approved the final manuscript.

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