

Regional Review

Dengue fever in the Indian subcontinent: an overview

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Abstract

The Indian Subcontinent has emerged as a scene of many mosquito-borne infectious diseases, including malaria and dengue fever. After the 1990s, the rate of malaria declined owing largely to preventive measures, but at the same time dengue fever (DF) and dengue hemorrhagic fever (DHF) were increasing in the region. Outbreaks were recorded in all countries of the Indian Subcontinent with India, Pakistan, Bangladesh and Sri Lanka on the forefront and suffering from the largest number of cases and deaths. We discuss annual cases of DF/DHF in these four countries and possible factors involved in DF outbreaks. We also discuss prevalent serotypes in this region where data suggest the emergence of DEN2 and DEN3 as the most dominant and lethal serotypes. Climate is an important factor influencing DF outbreaks, and rainfall, temperature and humidity play a pivotal role in DF outbreaks. Finally the economic impact of DF/DHF cases is discussed showing that direct and indirect economic loss due to DF/DHF reaches millions of USD each year.

Key words: Dengue Fever, Outbreaks, Indian subcontinent

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Introduction

Dengue fever (DF) has become a prominent infectious disease with outbreaks in many parts of the world. DF epidemics have reached almost 120 countries and in many of these countries it has a high incidence [1]. According to historical accounts dengue fever emerged from Africa almost 500 to 600 years ago, and the first outbreaks reached different parts of world such as Asia, South America and Africa concurrently in the 1780s [2]. During recent decades DF has become the second most prevalent mosquito-borne infection after malaria. Cases of DF have reached 40 million, while cases of Dengue hemorrhagic fever (DHF) are touching a staggering several hundred thousand per year. The most endemic regions include Southeast Asia, Latin America, Asia, and the Caribbean. Many dengue infections in travellers remain asymptomatic; a more serious issue is the travel-related spread of a more virulent dengue virus strain in an area with a less virulent strain, and also the spread of the virus in non-endemic regions with a high vector (*Aedes aegypti* and *Ae. albopictus*) population [3-5].

Historical background

Isolation and detection of dengue virus date back to World War II. Further characterization led to postulation of dengue virus as an agent involved in various past outbreaks exhibiting dengue-like symptoms. Dengue-like disease is illustrated in ancient Chinese manuscripts dating back to 992 and also to the 1600s in the West Indies [6]. The first detailed account of dengue shock syndrome (DSS) was recorded by Benjamin Rush in 1780 when an outbreak was reported in Philadelphia among people living near the Delaware River [7]. North America saw similar disease patterns in the 18th and 19th centuries along the Atlantic coast, on the Caribbean Islands, and also in the Mississippi basin [8]. *Ae. aegypti* mosquito as a vector of dengue virus was first discovered by Bancroft [9]. However, it was only in 1943-44 that the modern chapter of dengue research started. This was when for the first time dengue virus was cultured and later isolated from suckling mice brain [10,11].

Dengue virus belongs to the Arbovirus group of viruses that are transmitted through insect vectors. Virions are 40-50 nm in diameter and spherical in shape with 11kb single-stranded RNA containing a

single open reading frame. Dengue virus consists of ten proteins, three of which are structural and seven non structural, and it has four serotypes, namely DENV1, DENV2, DENV3 and DENV4.

The Indian subcontinent is mainly affected by DENV2 and DENV3 serotypes. DENV1 and DENV4 were identified by studying neutralizing antibodies in the blood of volunteers in 1973 [12] while DENV1 and DENV2 were isolated as a consequence of the failure of viral strains to cross-protect human volunteers [13]. All four virus serotypes cause similar illness, but severe and fatal hemorrhagic disease is more often associated with DENV2 and DENV3 infections [6]. DEN2 type (genotype IV) and DEN3 (genotype III) are the most commonly isolated genotypes [14,15].

DF/DHF in the Indian subcontinent

DF was first observed in Africa, but later with the increase in trade DF reached all parts of the world including Asia, South America and the Indian subcontinent which includes India, Pakistan, Bangladesh and Sri Lanka. These countries experience outbreaks each year with cases reaching thousands in numbers. Here we discuss cases, outbreaks, prevalent serotypes, climatic, and economical issues related to dengue virus infections in the Indian subcontinent based on data available from various governmental and nongovernmental data resources.

India

The first outbreak of dengue fever in India was recorded in 1812 [16]. In spite of preventive measures taken by the respective governments since then, recurrent outbreaks have occurred, and over the last 10 to 15 years DF has been the major cause of hospitalization and mortality after acute respiratory and diarrhoeal infections among children [17]. New Delhi, the capital of India located in the northern region of the country, experienced seven major outbreaks between 1967 and 2003 [18,19]. Then in 2006 another major outbreak occurred with more

than 11,000 reported cases and 165 reported fatal cases. Figure 1 shows data obtained from the World Health Organization (WHO) exhibiting the number of DF cases reported in India from 1991 to 2008 as well as the annual reported fatality rate during this period [20].

Prevalent serotypes

Samples isolated from Gujrat state showed that the epidemics of 1988-89 were dominated by DENV2 [21]. With the passage of time, dengue virus outbreaks reached different states of India. In 1992 Jammu also saw an outbreak of DENV2 [22]. The serotype isolated in the Haryana outbreak was DENV2 as well [23]. DENV2 was prevalent in Northern India where outbreaks were seen in Delhi, Lucknow and Gwalior [24-25]. However, DENV1 was the predominant serotype in the outbreak of 1997 in New Delhi [26]. The Gwalior outbreaks of 2003-04 were dominated by DENV3 [27,28], and DENV3 was also prominent in 2004-05 [29]. This co-circulation of serotypes in the same area might be the reason behind the large number of DHF cases reported this year [30].

Recent trends

Rapid growth of the population and sudden climatic changes have contributed to the increase in cases of DF/DHF in India [31]. During 1997 until 2004, DENV1 was seen as the causative agent of most DF/DHF cases but later in 2005, DENV3 became the leading source of dengue outbreaks [32]. According to the WHO in 2006, the total number of reported cases reached 12,317, while in 2007 fewer cases occurred (5,534) owing greatly to preventive measures taken by both the public and private sectors. In 2009, however, DF cases again reached 11,476 by November. The first cases were reported in July 2009 with the greatest number of cases seen in October. These trends demonstrate that DENV has penetrated deep into India, with DENV2 and DENV3 predominating among different DENV serotypes.

Figure 1: DF reported cases and deaths in India from 1991 till 2008.

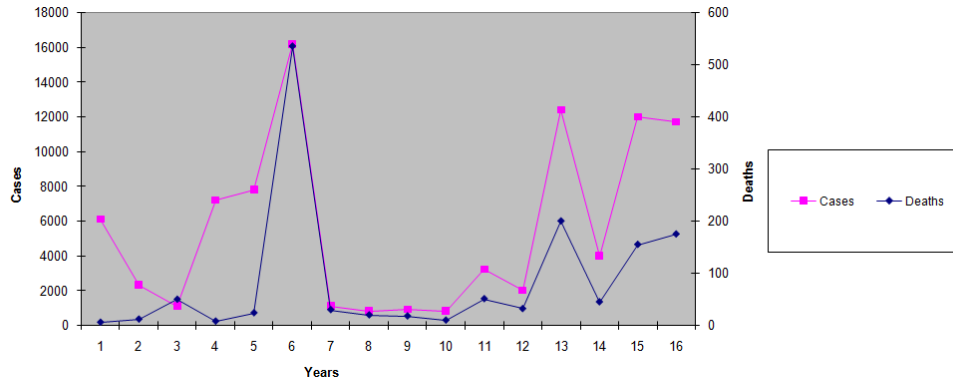
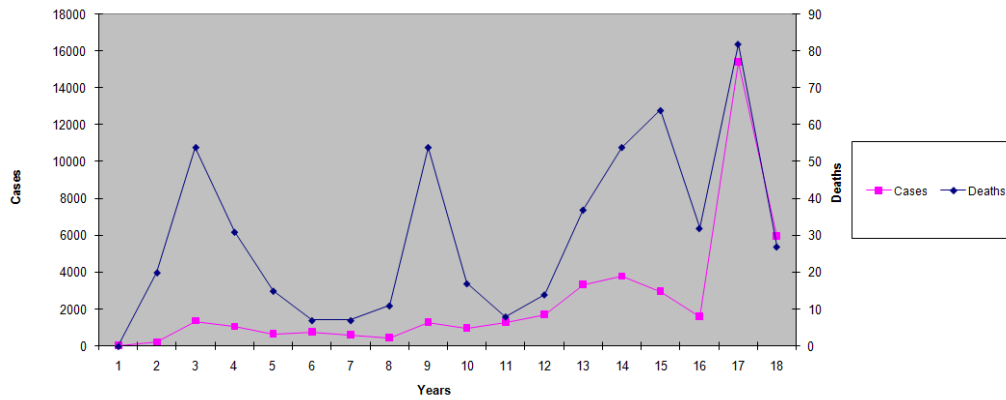


Figure 2: Annual reported DF cases and deaths in Srilanka from 1988 till 2009.



Sri Lanka

Dengue outbreaks in Sri Lanka date back to the early 1900s. Before 1989, the country had all four dengue virus serotypes and many cases were observed but there were very few cases of dengue hemorrhagic fever. In 1989 there was rapid expansion of DHF and the numbers have been rising steadily reaching into the thousands every year since [33,34]. Many major outbreaks occurred in Sri Lanka after 2003, the worst of which took place in 2004. DF cases from 1990 until 1999 were uniform in the range of 2,000 per year but the years 2000 to 2003 saw a surge of DF cases to about 3,000 per year with a sudden climb to 15,000 in 2004 (Figure 2) [35]. Since 2000 Sri Lanka has been struck by periodic

outbreaks of DF with the highest number of cases occurring in 2005. The case fatality rate has also steadily increased since 2000 (Figure 2).

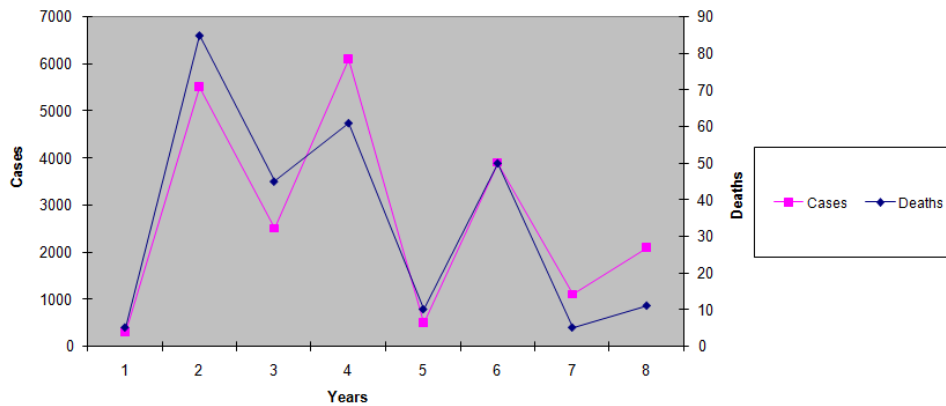
Prevalent serotypes

Dengue outbreaks in Sri Lanka have been historically and regularly documented. In the period of 1980-1985, the majority of cases were of DENV2 (Table 1) [35] while DENV3 was the second most serotype. This trend continued through the 1990s but 1999-2001 saw a surge in DENV2 while astoundingly there were also cases of DENV1 and DENV4, and DENV3 cases reached 71.4% in 2004. A similar trend can be seen until 2006, with DENV2 and DENV3 causing most cases of DF/DHF.

Table 1: Percentage of different serotypes, cases and deaths in Sri Lanka up to 2008

Year	Percentage of serotypes				Cases	Deaths
	DEN1%	DEN2%	DEN3%	DEN4%		
1989	18%	42%	38%	2%	203	20
1999	1%	90%	8%	1%	1688	14
2004	2%	37%	60%	1%	15408	82
2005		60%	40%		5965	27
2006	10%	40%	43%	7%	11964	44
2007	No Data Available				7135	24
2008	No Data Available				5644	19

Figure 3: A: DF cases and deaths reported in Bangladesh from 1999 till 2006

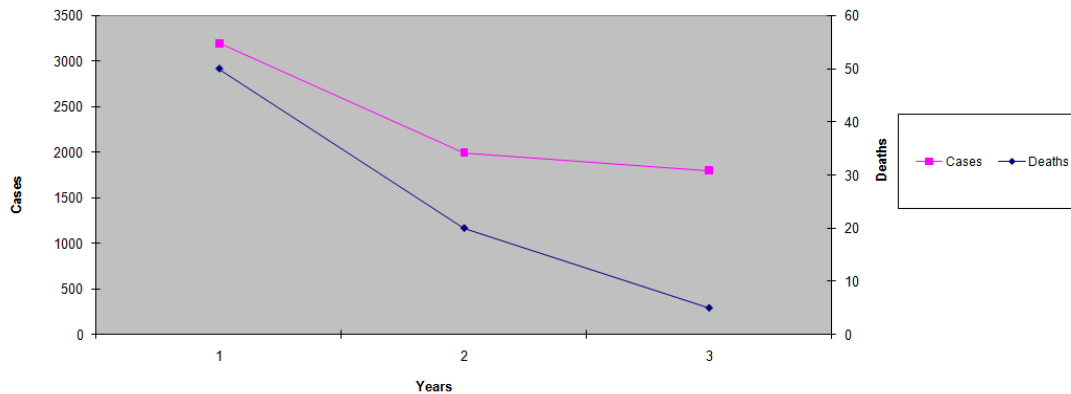


Recent trends

From 2006 to 2008 the total number of reported cases reached more than 24,000 with a peak in 2006, nearing 12,000. The year 2008 saw half the number of cases as seen in 2006 [35]. The morbidity rate was also significantly less in 2008 with 5.644 cases; however, morbidity was consistent in 2006 to 2007. During the last year reported cases reached a staggering 35,000 with more than 340 dengue associated deaths [36]. Owing largely to different mosquito (*Ae. albopictus*) control strategies initiated at the government level, it is hoped that the rate of DF/DHF will decline in the near future. Sri Lanka is an island nation with a prolonged monsoon period and thus it is always a hot spot for DF/DHF. Climatic and socioeconomic factors might be two main reasons for such high numbers of DF/DHF cases in recent years.

Bangladesh

According to historical accounts, Bangladesh saw its first recorded outbreak of DF in 1964 known as “Dhaka/Decca fever” [35]. A limited number of cases of DF were observed during 1977-78 by the Institute of Epidemiological Disease Research (IEDR). Cases were also detected by the WHO until the late 1980s. There were no official data until 1986 and mostly it was assumed that the large cities of Bangladesh were safe from DHF [37]. However, 2000 to 2002 saw a sudden surge in DF cases with more than 5,000 cases and 93 deaths in the year 2000. Similarly in 2001 it was reported that there were 2,430 DF cases with 44 deaths and 6,104 cases with 58 deaths in 2002 (Figure 3) [38,39].

Figure 4: Reported DF cases and deaths in Pakistan from 2006 till 2008.

Prevalent serotypes

Until 2000 three serotypes of dengue were prevalent in Bangladesh (DENV1, DENV2, and DENV3) with the highest number of reported cases attributed to DENV3 [40]. A similar situation can be seen in other countries such as India and Sri Lanka where DENV3 has been reported most of the time in DF/DHF related cases [32,41,42].

Recent trends

Urban localities of Bangladesh have numerous cases of DF/DHF as Bangladesh experiences floods almost every year. In 2007 there were 466 cases. The case fatality rate was the highest in 2006, but there were no reported deaths in 2007-8. The heavy rainfalls each year contribute to the country's many inland water bodies such as rivers, lakes and ponds, resulting in massive flooding which provides an optimal environment for the vector population.

Pakistan

There is a lack of valid data on reported cases of DF/DHF for Pakistan until 1994. Research conducted in 1985 showed that 50-60% of Pakistanis from Karachi between the ages of 6 and 65 years were haemagglutination inhibition (HI) antibody positive for three common flaviviruses including West Nile, Japanese encephalitis and DENV2. The authors

further showed that the intensity of HI seroantibody positive cases rapidly ascended from July until October for DENV2 involving individuals aged 6 to 20 years [3]. The year 1994 saw a major outbreak in which the initial diagnosis of 16 hospitalized patients revealed that 15 had dengue IgM, diagnosed through IgM capture enzyme-linked immunosorbent assay using DENV2 antigen and monoclonal antibodies [44]. Figure 4 illustrates data from three years in Pakistan.

Prevalent serotypes

It is still not known which serotype is most prevalent among the Pakistani population [45]. In 1998, a monoclonal-antibody based ELISA study of few patients revealed presence of DENV1 and DENV2 [46], and in 2005 DENV3 was reported among the few tested patients [47]. An outbreak in 2006 was dominated by DENV2 and DENV3 again [48]. In a recent study it was observed that children living in slums of Karachi had high levels of anti-dengue IgM antibody [49]. Since these serotypes were reported in all major outbreaks in Bangladesh, India, and Sri Lanka, a similar pattern can be observed in Pakistan. The DENV3 involved in the 2006 outbreak was closely related to the DENV3 (subtype III) which caused the outbreak in New Delhi in 2004 [50].

Figure 5: A: Predicted percentages of rainfall, humidity, temperature and number of monthly cases in Indian-subcontinent.

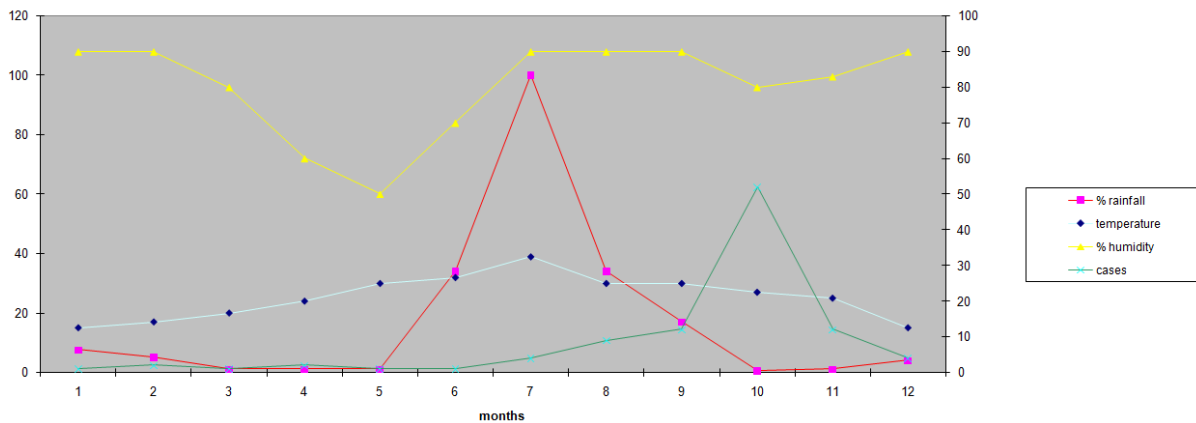
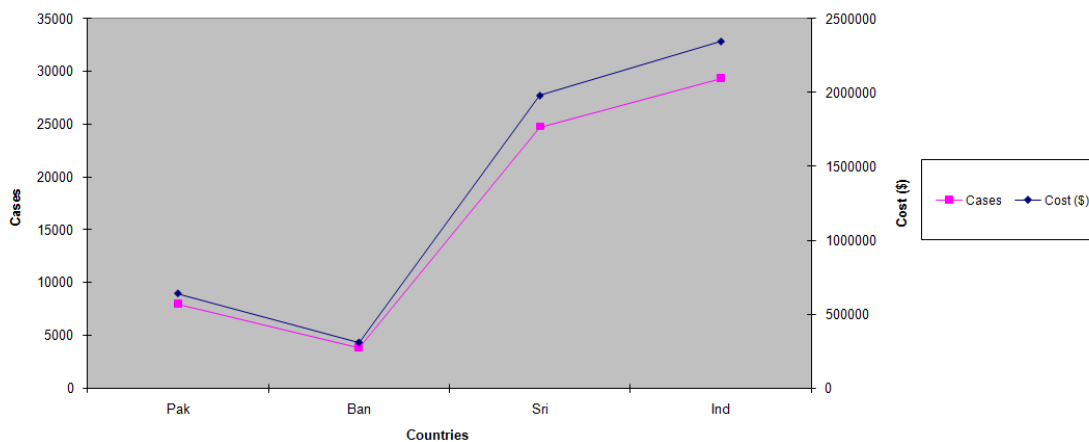


Figure 6: A: Estimated cost of DF cases in Pakistan, Bangladesh, Srilanka and India (1 case/US\$80).



Seasonal trends of dengue fever

Climate and environmental aspects play a critical role in the distribution and prevalence of both the dengue virus and its vectors (*A. aegypti* and *Ae. albopictus*) [51,52]. Dengue fever is regulated by seasonal variations in the southeast Asian region, where ideal conditions for the vectors exist, especially during the monsoon period, when there is abundant rainfall and high relative humidity, with daily temperatures reaching mid 30°C. These climatic conditions allow maximum breeding and growth opportunities for *Aedes* mosquitoes resulting in increased chances of outbreaks [53,54]. The weather can be divided into three seasons according to rainfall: the pre-monsoon from February to May; the monsoon season from June to September; and the post-monsoon season from October to January.

According to hospital data, most dengue cases are recorded between September and November with the highest numbers seen in October. Figure 5 shows

the expected annual percentage of rainfall, temperature, humidity levels, and reported DF cases in the Indian Subcontinent as reported by the Meteorology Department, Government of Pakistan.

Economic impact of DF/DHF

It is difficult to assess the economic impact of dengue virus infections on the Indian subcontinent due to systemic problems in record keeping and centralized databanks sharing. Direct and indirect economic losses resulting from dengue outbreaks are rarely recorded. Outbreaks in Thailand in 1976-77 and 1994 cost USD seven million and USD 51 million, respectively [55,56]. The 1998 epidemic patient cost was USD two million, while one million was spent on countrywide anti-dengue campaigns. USD three million was also assigned to coping with any possible future DF/DHF threats [57]. In 2005-06 a study was conducted in some Asian (Cambodia, Malaysia, and Thailand) and American (Brazil, El

Salvador, Guatemala, Panama, and Venezuela) countries simultaneously to determine the cost; the total annual financial cost of cases and deaths in these countries came out to be USD 587 million [58]. If unreported cases had been included, the amount would have reached USD 1.8 billion. Economic losses in Cuban DHF outbreaks were estimated at USD 103 million in 1981. Expenses for control measures and medical care were nearly USD 43 million and 41 million, respectively; furthermore, loss of productivity reached USD 14 million and loss of salaries of adult patients was nearly USD 5 million for 344,203 patients [59]. In Pakistan, the total diagnostic cost per case is nearly USD 70, while hospital charges are nearly USD 100. According to our estimates, the number of cases from the Indian subcontinent during 2006-8 reached 70,000 and their cost mounts well over USD 20 million. Figure 6 illustrates the estimated costs per dengue cases in relation to dengue cases reported in the Indian subcontinent from 2006-08.

Preventive measures

Dengue fever has developed into a global threat and more people are at risk than ever before. In 2009 a large-scale epidemic struck Bolivia where the patient toll was above 10,000 cases, causing the government to impose a state of emergency. The northern provinces of Argentina, including Salta, Jujuy and Chaco, had more than 26,000 reported cases in 2009 [60,61]. These figures show that larger outbreaks are still emerging worldwide. Accordingly, large-scale efforts are required to curb this global problem and minimize the number of future cases. Some of the preventive measures to reduce or stop future outbreaks include using larvicides to spray stagnant water which might serve as mosquito breeding sites; using mosquito nets in areas with high vector density; and covering water storage containers [62]. Travelers visiting dengue prevalent regions should use mosquito repellents. Children and elderly people should take special precautions. Campaigns on public and private levels should be launched to create awareness among the masses. Schoolchildren can also be educated through classroom visits by doctors and scientists giving short lectures regarding safety and preventive measures against dengue fever and dengue hemorrhagic fever.

Conclusion

According to the historical records, outbreaks of dengue in the Indian subcontinent were rare before

the year 2000, when only a few outbreaks occurred, and they were not so random. However, after 2000 many outbreaks occurred with thousands of reported and unreported DF/DHF cases and hundreds of deaths each year. During the last few decades DENV2 and DENV3 were predominant in most of the outbreaks, with either one or both serotypes isolated in each major outbreak. Before the 1990s, all four serotypes were seen with no single dominating serotype. Later with the increase in travel and certain climatic changes, the rate of dengue surged and it emerged as one of the most widespread mosquito-borne illnesses. Countries which were most adversely affected included Bangladesh, India, Pakistan and Sri Lanka. Climate has a vital role in the spread of DF/DHF as the Indian subcontinent is located in a region where there is a very long annual monsoon period from July to September. During these months pools of stagnant rainy water provide *Ae. aegypti* maximum breeding places while the humid environment and steady mid 30°C temperature also contribute to the increasing vector population. DF/DHF have also economic consequences: diagnostic and ambulatory costs can exceed USD 300 per case while hospital charges can also mount up to USD 200. Therefore, on a large scale, the economic loss can reach millions of dollars annually. To curb this menace, effective anti-vector campaigns in high vector density areas should be initiated before and during the monsoon season targeting. More and improved surveillance is needed for travellers from epidemic regions as well. A number of public awareness campaigns should be launched involving print and electronic media and finally more funds should be allocated toward vaccine and antiviral research for dengue virus.

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