



# Vector Control Interventions to Prevent Dengue: Current Situation and Strategies for Future Improvements to Management of *Aedes* in India

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## Abstract

Dengue is the most widespread vector-borne infectious disease of humans, existing in around 125 tropical and subtropical countries worldwide. The causative agent, a *Flavivirus*, is transmitted from one person to another by female mosquitoes of the genus *Aedes*, primarily *Ae. aegypti* and *Ae. albopictus*, which breed in small, still bodies of freshwater such as storage tanks, buckets, plant pots and discarded household waste. Encouraging progress has been made in recent years towards the diagnosis and timely management of this debilitating and sometimes fatal disease. However, in the absence of an antiviral therapy or vaccine that is available and affordable in a low income setting, the means to combat dengue currently rely upon vector control measures that are directed against the immature aquatic stages, larvae and pupae, or adult mosquitoes. Although a number of different methods are in use, vector control has failed to prevent outbreaks from occurring and to avert an expansion of the geographical distribution of dengue. This is due to several limitations of present technologies that relate to dwindling financial resources, development of insecticide resistance, failure of long term sustainability and insufficient community involvement. In this context, there is a pressing need for an evidence-based selection process to determine how best to detect and exterminate the breeding of *Aedes* mosquitoes. This review considers existing vector control strategies as well as discussing some of the novel approaches that are in preparation, placing particular emphasis on relevance to the worsening public health issue of dengue endemicity in India.

**Keywords:** Dengue; *Aedes*; Mosquito; Vector; Control; Prevention; Intervention; India

## Introduction

Dengue is one of the major human pathogens belonging to the family Flaviviridae, which also includes other arthropod-borne (arbo) viruses that cause yellow fever, Japanese encephalitis, West Nile encephalitis and Zika fever. From an epidemiological perspective, dengue is the most rapidly spreading vector-transmitted disease globally [1,2]. Over the last fifty years the incidence of dengue has increased approximately 30-fold [3]. Today, more than 2.5 billion people in the tropics and subtropics are at risk of infection [4], and there are an estimated 390 million dengue infections annually in approaching 130 nations and territories worldwide [5]. Estimates of the global incidence range between 200-400 million clinical cases per annum [3]. In India, since the first outbreak occurred in 1963 in Calcutta, now Kolkata, dengue has been also reported from most other regions of the country [6-8]. For 2016, 27 of 35 states and union territories reported the clinical incidence of dengue [9].

## Clinical manifestations

Dengue infections can be asymptomatic or may develop into one of three traditionally recognized clinical manifestations; dengue fever, dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS) [10,11]. The World Health Organization (WHO) and the Special Programme for Research and Training in Tropical Diseases (TDR) recently revised the guidelines for dengue case classification. Clinical infection may be categorized as: mild self-limiting illness; dengue with a wide range of warning signs (abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, increasing haematocrit with decreasing platelets); or severe dengue (dengue with severe plasma leakage, severe bleeding, or organ failure) [1].

## Dengue virus serotypes, immunity and immunopathology

There are four closely related, antigenically distinct serotypes

(DENV-1 to DENV-4) of enveloped, positive sense, single-stranded RNA virus of the genus *Flavivirus*, the aetiological agent that causes dengue infections [10-12]. The existence of a fifth distinct serotype was mooted recently, although its recognition remains to be ratified [13]. Infection with one serotype confers life-long immunity to the exposed serotype but will provide only transient protection against others [14-16]. Secondary infection with a heterotypic serotype generates cross-reactive antibodies, which, when present in the peripheral circulation, increase the potential risk of antibody-dependent enhancement of disease, a form of immunopathology. Hence, recurrent infection is the major risk factor for the serious, often fatal, complications of DHF and DSS. Infants who are immunized passively via receipt of maternal antibodies from a dengue pre-immune mother are at high risk of severe dengue infection [17,18]. Different dengue serotypes vary in their capacity to cause severe illness, but there is no expert consensus as to the extent of a causal association [19]. Multiple serotypes are in circulation in India [20].

## Vector identification, behaviour and distribution

The dengue virus is transmitted between humans primarily by *Aedes*

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*aegypti* and *Ae. albopictus* [21]. These mosquito species typically bite at dawn and dusk but may do so at any time of day throughout the year [22]. By preference, female mosquitoes lay their eggs in artificial containers like flower vases, old automobile tyres, upturned buckets, and also in poorly disposed waste such as used metal cans [23]. *Ae. aegypti* displays a peridomestic habit and is the dominant vector mosquito species in urban areas, whereas *Ae. albopictus* is found more in semi-urban and rural environments [24]. The distribution of *Ae. albopictus* has expanded rapidly [25], and this species is a potential vector in areas where *Ae. aegypti* is not established. The principal factors which contribute to the spread of dengue in India include rapid and unplanned urbanization, human population growth, inadequate municipal services, and increased use of non-biodegradable household products [3]. All these determinants promote the establishment of *Aedes* mosquitoes in habitats in which they come into intimate proximity to many millions of Indian citizens.

### Dengue control strategies

Currently, there exists no specific therapy that is marketed for dengue, such as antiviral drugs or vaccination [26], placing a reliance on supportive treatments for symptoms, including oral rehydration, administration of intravenous fluids and/or blood transfusion. Significant progress in vaccine development during the last decade has led to the regulatory authority approval of the first product in 2016 [27]. However, its cost may prevent widespread use in developing countries, [28,29] where control of the mosquito vector will remain the most effective measure to combat dengue [30]. As such, the Partnership for Dengue Control, a unique global alliance of international health agencies created in 2013 to spearhead an integrated approach to sustainably control and prevent dengue, recommends health communities to continue to rely on vector control even when an effective dengue vaccine does become commercially available, since the two approaches should complement and enhance the effectiveness of one another [31]. Existing vector control strategies include environmental management and chemical or biological interventions.

Here, the current scenario of vector control in India is considered and a range of measures for possible future improvements is discussed.

### Vector Control Strategies

The aim of vector control strategies is to prevent transmission of virus by controlling mosquito vectors and interrupting human-vector contact [32]. A number of strategies has been developed, several of which have proved effective in various situations in different countries. Although each of these methods has been found to control dengue to a certain extent, in order to eradicate completely disease transmission it is envisaged that to be successful a control programme must integrate a combination of appropriate measures [11].

#### Environmental management

This is the most effective measure of vector control and includes prevention and reduction of vector propagation and human-vector contact by destruction, alteration, disposal or recycling of containers and natural larval habitats which produce the greatest number of adult mosquitoes [33,34]. Peridomestic sites in which mosquitoes are commonly observed to breed are indicated in Figure 1.

**Reducing vector habitats/breeding sites**—use of water storage containers, such as drums, overhead tanks and jars should be avoided or, if unavoidable, they should be covered with tightly fitting lids or screens [34]. Using polystyrene beads in water tanks also aids control



**Figure 1:** Representative common breeding sites of mosquitoes surrounding human dwellings: 1. Water in swimming pool; 2. Water collecting in flower pots; 3. Water trapped in fallen leaf litter; 4. Water collecting in discarded tyres; 5. Bucket filled with water; 6. Water leaking from drums or barrels; 7. Rubbish bin and discarded refuse; 8. Water trapped in air-conditioning unit; 9. Water collecting from gutter.

of mosquito breeding by preventing mosquitoes from laying eggs on the surface [35].

**Solid waste management**—solid waste refers to non-biodegradable items of household, community and industrial waste [34]. Accumulation of water in such solid wastes promotes breeding of dengue vectors; hence, the proper storage, collection and disposal of waste are essential for safeguarding public health [36]. Solid waste such as discarded tyres, bottles, and cans should be recycled on a regular basis [34].

**Modification of man-made breeding sites**—improvement to house designs in order to reduce entry of mosquitoes, drainage and cleaning of roof gutters, outdoor sinks and condensate collection units under refrigerators and air-conditioners, and chlorination of ornamental pool or fountains are some of the habitat management measures which minimize the risk of the breeding of mosquitoes near human dwellings [34]. Figure 2 shows the various approaches which can be undertaken as a means of vector control.

#### Biological control

Biological control measures exploit the innate behaviour of a living creature in order to limit the population size of a targeted vector species. Such natural enemies of mosquitoes include predators, parasitoids and pathogens [37].

**Predators**—feed on mosquitoes, e.g. dragonflies and damselflies (known colloquially in India as ‘mosquito hawks’), frogs, toads and their tadpoles (such as the spadefoot toad, green tree frog and giant tree frog), birds (notably swallows, martins and swifts, ducks and other waterfowl), fish (including goldfish, guppies, bass, bluegill and catfish). The most effective fish predator of mosquito larvae is *Gambusia affinis* (commonly called the ‘mosquito fish’) [37].

**Parasitoids**—are organisms the larval-like juvenile stage of which lives as a parasite inside a host mosquito before destroying it. A prime example is the protozoan *Ascogregarina culicis*, a parasite of *Ae. aegypti* larvae, that adversely affects the mosquito population [37]. Another bacterial parasite, *Wolbachia pipiensis*, has been demonstrated to reduce the life span of *Ae. aegypti* under laboratory conditions [38].

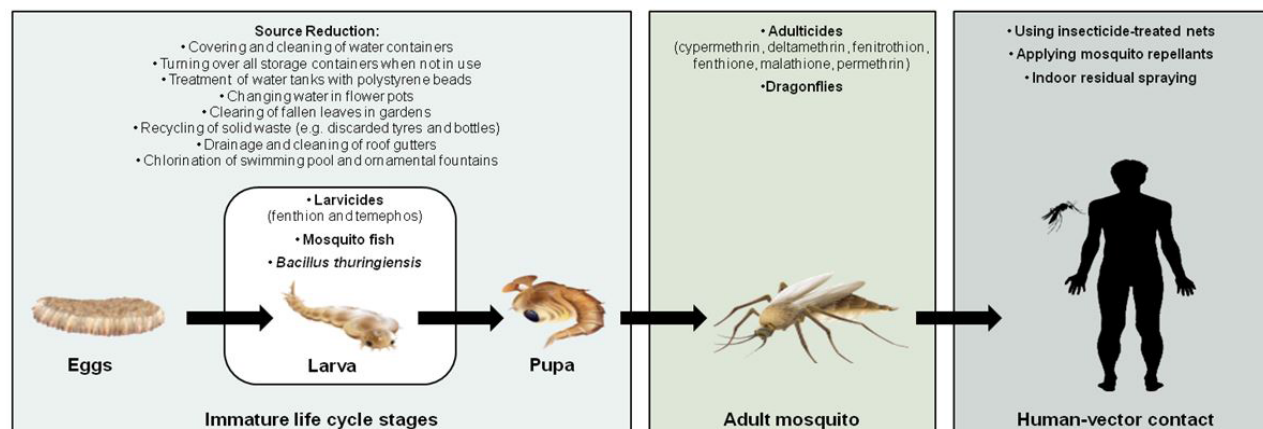


Figure 2: Different approaches to *Aedes* vector control for the prevention of dengue.

**Pathogens**—of mosquitoes include viruses, bacteria, fungi and protozoa. Infection of mosquitoes with these pathogens decreases their rates of growth and feeding on humans, checks their reproduction, and even kill or seriously disable them [37]. Examples of such pathogens include: spores of entomopathogenic fungi (such as *Beauveria bassiana* and *Metarhizium anisopliae*), which affect larval and adult stages of mosquitoes [39]; Csp\_P, a bacterium of the genus *Chromobacterium* that resides in the mosquito midgut and which reduces the survival of both larvae and adults [40]; and *Bacillus thuringiensis* H-14 (Bti), a mosquito larvicide that is commercially available under a number of trade names [34].

### Chemical control

Chemical control is the application of natural or synthetic compounds that possess insecticidal properties in order to reduce the mosquito population within the local environment. These are available as larvicides (applied directly to water to control larvae), adulticides (used in wide-area fogging and spraying to combat adult mosquitoes) and synergists (not toxic in themselves but able to increase the efficiency of other administered chemicals) [41]. Examples of insecticides that have been deployed worldwide include organophosphates (e.g. fenitrothion, fenthione malathione) and pyrethroids (e.g. cypermethrin, deltamethrin, permethrin) [42].

### Integrated vector management

Integrated vector management (IVM) is a rational decision-making process for the optimal use of resources for vector control [43]. This approach was first promoted in 2004 by the WHO with the aim of making vector control more efficient, cost-effective, ecologically sound and sustainable. According to the WHO, planning and implementation of vector control involves analyzing the local determinants of disease, assessing requirements and resources, and designing locally appropriate implementation strategies at a national level [43]. The five key elements of an IVM strategy are: i) advocacy, social mobilization and legislation; ii) collaboration within the health sector and with other sectors; iii) an integrated approach; iv) evidence-based decision making; and v) capacity building [44]. Effective dengue control activities require collaboration between agencies involved in strategic planning, project development and operational management, and their productive partnership with other stakeholders in promoting a community-based control programme [45].

## Dengue in India

### Ongoing challenges

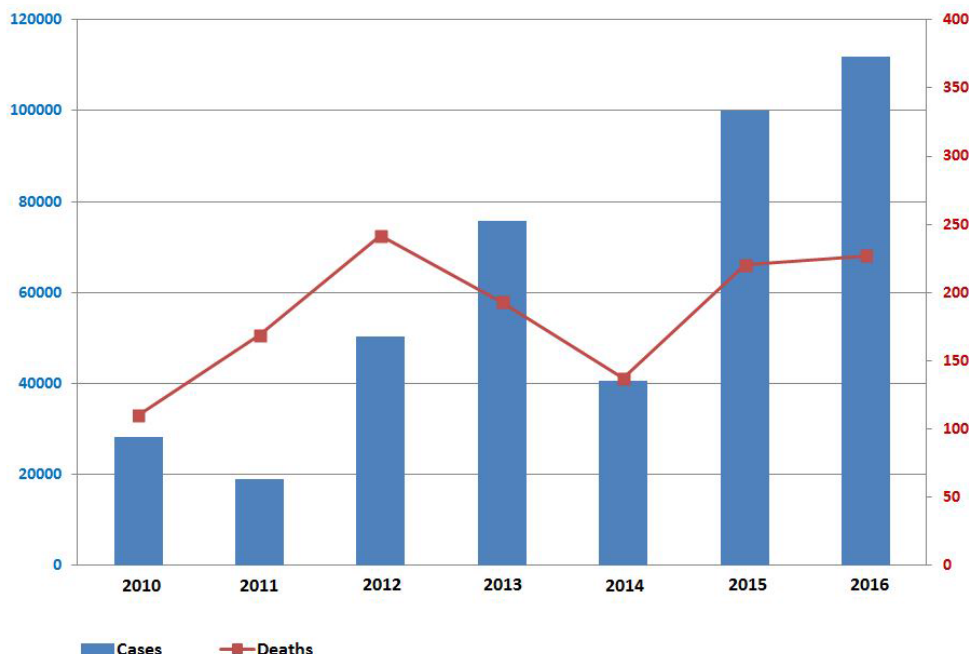
Under the Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India, the National Vector Borne Disease Control Programme (NVBDCP) is the central nodal agency for implementation of activities for prevention and control of vector-borne diseases across the country. These include the protozoan diseases malaria and kala-azar (visceral leishmaniasis), the nematode infection lymphatic filariasis (elephantiasis), as well as several arboviruses, notably dengue, yellow fever, Japanese encephalitis, chikungunya and Zika [46].

The NVBDCP is making extensive efforts to develop a suite of effective dengue control measures. Despite this programme the number of dengue cases, their severity and geographical distribution are escalating, as evidenced by the frequent outbreaks and re-emergence of dengue in several parts of the country. Disease is prevalent throughout India in most of the metropolitan cities and towns. Outbreaks have also been reported from rural areas of Haryana, Karnataka and Maharashtra [46]. Based on national statistics released by the NVBDCP, the last decade has witnessed a pronounced upward trend in the overall incidence of dengue, as represented since 2010 in Figure 3. The provisional total number of dengue cases reported in 2016 was 111,880, which resulted in 227 deaths [9].

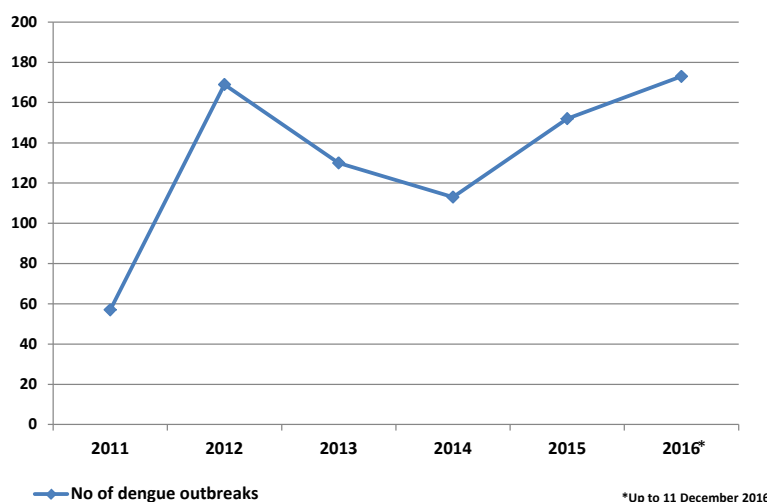
The sustainable control of dengue vectors is recognized as an arduous task [47]. The significant challenges for vector control programmes include dwindling financial resources, development of insecticide resistance, failure of long term sustainability, lack of community involvement, and limited public knowledge regarding dengue transmission and prevention [48].

### Historical control measures

In the early part of the twentieth century eliminating mosquito breeding grounds by drainage or poisoning with either the copper arsenite compound Paris green or pyrethrum, a naturally occurring *Chrysanthemum*-derived pyrethrin, was sometimes successful. While previous frequent use was also made of larvicides to combat mosquitoes in India, following the widespread introduction of the organochlorine insecticide dichlorodiphenyltrichloroethane (DDT) in the 1950s vector control became heavily dependent upon DDT spraying [49]. Once



**Figure 3:** Number of dengue cases and deaths in India reported by the National Vector Borne Disease Control Programme from 2010 to 2016.



**Figure 4:** Number of dengue outbreaks in India reported by the Integrated Disease Surveillance Programme from 2011 to 2016.

it was recognized as a persistent environmental pollutant and likely human carcinogen, by the 1990s DDT was banned in most developed countries but it remains available as an agricultural pesticide on the Indian subcontinent. However, as a consequence of extensive mosquito resistance, its application as a means of vector control is discouraged and has diminished considerably. Where DDT is still used it is applied not to crops but to the inside walls of houses to kill or repel mosquitoes, a practice now approved by the WHO in regions where malaria and dengue are of profound concern to public health. This intervention, called indoor residual spraying (IRS), greatly reduces environmental damage and the incidence of resistance to DDT and other pesticides used [50,51].

#### Current detection measures

Since 2007, the NVBDCP has facilitated the diagnosis and clinical

data collection for cases of dengue. Under the programme, 347 sentinel surveillance hospitals and 14 apex referral laboratories have been set up throughout the India. These are supplied with anti-dengue IgM capture ELISA test kits as a means of rapid detection by the National Institute of Virology located in Pune [52].

In order to strengthen disease detection across the country, an integrated disease surveillance programme (IDSP) was launched in 2004 to both detect and respond to disease outbreaks rapidly [53]. All disease outbreaks reported at a state level are compiled in the form of a Weekly Outbreak Report that is available on the IDSP website [54]. Figure 4 shows the national number of dengue outbreaks reported recently under the IDSP [55].



## Current control measures

The present day approach to vector control implemented by the NVBDCP is interdisciplinary and includes a blend of components under a policy of IVM. These include: larvicides (such as the organophosphate temephos); source reduction engaging minor engineering methods (clearing the margins around large bodies of water, de-weeding to ensure proper flow of water, closing off or filling in small repositories in which water temporarily collects); IRS, insecticide-treated nets (ITNs), adulticides, and measures for reducing human-vector contact [49].

The effect on the control of *Ae. aegypti* of implementing community-based eco-health measures has been examined in Chennai (formerly Madras) in eastern India [56]. This study revealed that environmentally friendly vector control methods like covering water containers, solid waste management and urban 'clean-up' campaigns involving women's groups and school children led to a substantial reduction in the density of dengue vectors. These findings suggest a way to optimize dengue vector control through an inclusive and translational approach that engages the local community as a partner in the control programme.

The combined factors of rainfall and power supply have a major influence on the spread of dengue [57]. Specifically, both poor rainfall and limited power supply prompt people to collect water in storage containers at times when electricity is available, thereby providing a man-made peridomestic habitat for *Aedes* to breed. Improved community education is called for in the furtherance of reducing this contemporary cause of dengue vector spread. To date, very few studies have been conducted to evaluate the cause and effect of variables on the frequent dengue outbreaks in different regions of India [20].

## Future Perspectives

Dengue is among the most important public health problems that faces India today. With a view to minimizing the impact of any dengue outbreak that may occur, state and federal governments should strengthen their vector control programmes. Moreover, strategies to increase the degree of active participation of the general public are desirable [45,58,59].

## Integrated vector management

Using multiple vector control methods simultaneously can help to reduce disease transmission to a very low level as compared to a single intervention [48]. This is evident from the evaluation of IVM as the most effective dengue vector control intervention, among several determined, in reducing entomological parameters (breteau index, container index and house index) [21]. Furthermore, instead of using multiple vector control measures for a single infectious disease, government ministries and health agencies should target multiple mosquito-borne diseases utilizing the same interventions and infrastructure. This will increase the cost effectiveness of the vector control programme.

## Novel vector control methods

The technological advancement of emerging vector control tools for large-scale deployment and to long-lasting effect progresses continuously. The RNAi-based release of insects carrying a dominant lethality (RIDL) system for mass rearing of male mosquitoes has been developed, a technique which involves injection of a lethal gene into mosquito eggs [60]. Integration of the lethal gene into the mosquito genome leads to formation of many toxic metabolites in the larva, causing either its death or sterility. Another pioneering study reported the  $\omega$ MelPop-CLA strain of *Wolbachia* as an effective agent for preventing dengue transmission by causing cytoplasmic incompatibility, reducing

the life span of *Ae. aegypti* and, in so doing, interfering with viral transmission [61]. Only older mosquitoes transmit the dengue virus, so this is predicted to reduce transmission. Over just a few generations, the bacterium is able to spread, infected mosquitoes replace the wild population, and reduce their reproductive capability. Both RIDL and *Wolbachia* are potentially powerful weapons in the fight against dengue, but their further development and field trial testing will require the overcoming of policy and regulatory barriers as well as cross-border collaboration among scientists, politicians and communities.

## Conclusions

In a bid to arrest the upsurge of dengue in India in recent times rather than to focus primarily on patient-centred, curative and medicine-intensive disease management, approaches to improve environmental health and to manage vector habitats should be prioritized. Dengue vector control is an effective tool in reducing *Aedes* mosquito populations, particularly when control strategies utilize a community-based and integrated approach, combined with educational programmes to increase knowledge, awareness, attitudes and practices of people in the local community.

While it is apparent that in India IVM has been implemented by NVBDCP as an ongoing vector control measure over the last decade as yet there has not been a follow-up survey to assess the relative success of its implementation. It would be worthwhile to conduct such studies in order to determine the current status of IVM and to identify challenges to implementation in both urban and rural areas of India. Monitoring and evaluation are integral to every aspect of the programme and critical to its success.

Taking a holistic perspective, for effective management of dengue, the coordinated and multidisciplinary efforts of different government departments with regard to sanitation, urban development and education are essential. Moreover, local communities must be engaged to take active responsibility for their own protection by supporting elimination of *Aedes* breeding sites and taking personal measures towards prevention of infection, such as use of mosquito repellents.

## Conflict of Interest

The authors declare that they have no competing issues of interest.

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