EPJ Web of Conferences **348,** 01024 (2026) https://doi.org/10.1051/epjconf/202634801024
ICMSI 2026

Silent Threat: Insecticide Resistance and Escalating Dengue Cases in India

Vyas Primaben[1] and *Ashish* Kumar Singh[1]*

[1]Department of Microbiology, School of Science, RK University, Rajkot-360020, Gujarat, India

Abstract. The increasing incidence of dengue in India coincides with growing insecticide resistance in *Aedes* mosquito populations, undermining the efficacy of conventional vector control strategies. The introduction of DDT in the 1940s revolutionized mosquito control, forming the backbone of the global malaria eradication efforts, but widespread resistance and environmental concerns led to its reduced use. Subsequent adoption of organophosphates and carbamates provided effective alternatives by inhibiting acetylcholinesterase, though resistance again emerged across vector populations. The development of pyrethroids in the 1980s enabled low-dose, cost-effective vector control interventions like insecticide-treated nets and indoor residual spraying, significantly reducing the burden of vector borne diseases. However, rapid expansion of resistance at global scale compromised their long-term effectiveness. In response to these limitations, WHO promoted integrated vector management and facilitated the deployment of newer classes of insecticides such as neonicotinoids, microbial larvicides, and insect growth regulators to combat resistance and ensure sustainable control. This review provides a comprehensive analysis of the evolution of insecticide resistance. Specifically, it elucidates the mode of action of major classes of insecticide, the resistance mechanisms, and context-dependent deployment strategies crucial for preserving the effectiveness of vector control interventions against dengue, malaria, Zika, and other vector-borne diseases.

1 Introduction

Dengue fever has rapidly evolved into one of the most widely spreading mosquito-borne viral diseases worldwide. It is mainly transmitted by *Aedes aegypti* and *Aedes albopictus*. Over recent decades, dengue has moved beyond occasional outbreaks and now follows a pattern of persistent, hyperendemic transmission—particularly in tropical and subtropical regions where climate and environmental conditions strongly favor mosquito breeding. Today, an estimated 3.9 billion people live in areas at risk, spanning more than 120 countries [1, 2]. According to the World Health Organization (WHO), dengue causes around 390 million infections annually, many of which are asymptomatic yet still drive continuous community-level viral spread [2, 3]. Recurrent epidemics add to this burden by increasing hospital admissions, economic losses, and severe forms of the disease that can result in organ failure, shock, and even death.

*Corresponding author: ashish.drug.research@gmail.com

Several interconnected social and environmental factors have accelerated dengue transmission. Rapid and poorly planned urbanization has produced densely populated regions with inadequate waste disposal and unsafe water storage practices, providing ideal breeding environments for *Aedes* mosquitoes [4]. Growing international mobility also contributes to dengue's spread, enabling infected travelers to carry different viral serotypes into new areas and triggering community outbreaks [5]. Climate variability, including events such as the El Niño–Southern Oscillation and rising global temperatures, influences mosquito life cycles and viral replication. These changes expand the geographic distribution of vectors and lengthen the seasonal transmission period [6, 7]. As a result, dengue continues to advance not only in historically endemic regions, but also into temperate zones that were previously unaffected.

South Asia, Southeast Asia, and Latin America report the highest number of dengue cases [6]. India has emerged as a major hotspot, driven by its demographic scale and ecological conditions. The country experiences repeated seasonal outbreaks, especially during and after the monsoon when mosquito breeding intensifies. High population density, urban sprawl, and inconsistent vector control strategies create persistent opportunities for viral amplification [8-10]. Over the past decade, India has faced multiple large-scale dengue epidemics, leading to substantial illness and deaths, straining healthcare resources, and triggering emergency containment efforts. This regional experience highlights how dengue has shifted from a localized tropical illness into a global public health threat that demands continuous, coordinated, and adaptive intervention strategies.

1.1 The role of vector control in dengue management

Unlike many infectious diseases that rely primarily on vaccines or drug-based prevention, dengue control has traditionally centered on managing mosquito vectors to break the transmission cycle of *Aedes* species [11, 12]. Organized vector control began in the mid-20th century, when large public health programs used broad-spectrum insecticides such as dichlorodiphenyltrichloroethane (DDT) to significantly reduce mosquito populations [13]. These campaigns, especially in Latin America and Southeast Asia, were remarkably successful. During the 1950s and 1960s, they led to the near-elimination of *Aedes aegypti* in several countries, dramatically lowering dengue transmission [1, 14]. However, this chemical-heavy approach proved difficult to maintain. Rapid urban growth, reduced institutional capacity, and political and operational constraints allowed mosquito populations to rebound, reinstating the conditions for dengue outbreaks across tropical and subtropical regions [4, 15].

As dengue resurged, control efforts shifted towards new insecticides. Organophosphate larvicides like temephos, and later, pyrethroid-based insecticides were widely adopted because of their fast knockdown effect on adult mosquitoes and comparatively lower toxicity to humans [16, 17]. These chemicals were often deployed through space fogging and indoor residual spraying during outbreaks, with priority given to rapid population reduction rather than long-term sustainability [16].

Although these tools initially helped contain outbreaks, frequent and poorly regulated applications placed intense selective pressure on mosquito populations. This accelerated the development of insecticide resistance (IR), progressively weakening the effectiveness of chemical-based strategies [18]. Mosquitoes developed multiple resistance mechanisms—such as enhanced metabolic detoxification and target-site mutations like knockdown resistance (*kdr*)—which significantly reduced the performance of pyrethroids and organophosphates [18, 19]. By the early 2000s, global health authorities recognized

that chemical control alone could not sustain dengue prevention, especially in rapidly expanding urban areas where *Aedes* thrives [11, 20].

This realization led to a strategic shift toward Integrated Vector Management (IVM)—a framework emphasizing the balanced use of environmental, biological, chemical, and genetic approaches guided by local surveillance, cost-effectiveness, and community engagement [11, 20]. IVM promotes sustainable habitat reduction, improved water and waste management, the use of biological agents such as *Bacillus thuringiensis israelensis*, and emerging innovations including *Wolbachia*-based mosquito suppression and sterile insect technology [21, 22]. Together, these approaches represent a transition from short-term reactive control to holistic, evidence-driven strategies designed to minimize resistance, reduce disease transmission, and strengthen long-term public health resilience [11, 23].

1.2 The emergence of insecticide resistance in *Aedes* mosquitoes

The rise of insecticide resistance (IR) in *Aedes* mosquitoes has become one of the most serious challenges to sustainable dengue control [24]. Decades of heavy dependence on chemical insecticides have created strong evolutionary pressure, allowing mosquito populations to gradually adapt and survive exposure to these compounds [16]. In many areas where dengue is endemic, repeated use of organophosphates, carbamates, and later pyrethroid-based insecticides has enabled mosquitoes to acquire heritable traits that diminish the toxicity of these chemicals [18, 19]. Resistance is not a single biological event. Instead, it arises through several biochemical and genetic pathways—such as metabolic detoxification, behavioural avoidance, and target-site mutations—that together reduce mosquito susceptibility to insecticides [16]. Among these mechanisms, metabolic resistance is widely reported. It involves increased production of detoxifying enzymes, including glutathione S-transferases, esterases, and cytochrome P450 monooxygenases, which allow mosquitoes to break down or neutralize insecticidal compounds before they reach lethal concentrations [25, 26]. Target-site resistance, particularly knockdown resistance (*kdr*) mutations within the voltage-gated sodium channel of *Aedes aegypti*, has also become increasingly common and is closely linked to reduced pyrethroid effectiveness in regions with long-term chemical use [19, 27].

The operational consequences of resistance are substantial. When insecticides no longer work, interventions such as indoor residual spraying (IRS), space fogging, or larvicidal treatments fail to reduce mosquito numbers, severely weakening outbreak response capacity in dengue-endemic countries [28]. In practice, resistance often becomes evident only when vector densities remain high despite ongoing interventions—delaying recognition of control failures and wasting critical resources [11, 20]. This problem is amplified by the ecological adaptability of *Aedes* mosquitoes. They successfully exploit urban and domestic environments including water storage containers, construction debris, discarded plastics, and shaded spaces, allowing resistant populations to breed and spread outside formal surveillance systems [15]. In densely populated cities where regulation is inconsistent, mosquitoes are frequently exposed to sub-lethal insecticide levels through community fogging or consumer-grade aerosol sprays. These repeated exposures accelerate resistance by eliminating susceptible individuals and enabling resistant genotypes to dominate [16]. As resistant populations expand, their genetic traits become entrenched long before vector control authorities fully recognize their extent [18].

Resistance is also not limited to a single insecticide type. Populations of *Aedes aegypti* in Asia, Latin America, and Africa have shown cross-resistance, where resistance to one

insecticide class coincides with reduced sensitivity to unrelated compounds, complicating rotation-based resistance management strategies [14, 25]. Molecular studies have identified frequent co-occurrence of *kdr* mutations such as V1016G and F1534C in wild mosquito populations. These mutations intensify one another, severely reducing the knockdown performance of commonly used pyrethroids like permethrin and deltamethrin [27, 29]. As these genetic mutations accumulate, they reduce not only the immediate effectiveness of control campaigns but also limit the range of available insecticides for future emergency responses [18, 30]. Consequently, the emergence of insecticide resistance in *Aedes* mosquitoes has become a complex biological, operational, and policy-driven challenge. Addressing it requires coordinated surveillance systems, diversified vector control tools, and long-term investment in resistance-management frameworks to protect progress in dengue prevention [11, 20].

1.3 Dengue endemicity and vector control strategies

In India, dengue has shifted from occasional outbreaks to a state of sustained endemicity in many urban and peri-urban regions, with seasonal peaks that place significant pressure on public health systems [31, 32]. National surveillance data and recent epidemiological studies indicate a steady rise in reported dengue cases over the past two decades. However, gaps in diagnosis and underreporting suggest that the true burden of the disease is likely much higher than official figures indicate [31, 32]. Transmission in India follows a clear seasonal pattern: monsoon rains create extensive breeding sites through stagnant water in construction areas, household water storage, and urban debris, all of which support *Aedes* mosquito proliferation [33]. Complicating the scenario is the co-circulation of multiple dengue virus serotypes (DENV-1 to DENV-4), which increases the risk of secondary infections and severe outcomes such as dengue haemorrhagic fever and dengue shock syndrome [34].

Traditionally, India's mosquito control programs have relied heavily on chemical approaches. These include larviciding with organophosphates like temephos and space-fogging with pyrethroid adulticides, usually applied during outbreaks rather than as preventive measures [35]. However, entomological surveys over the past decade reveal widespread and increasing insecticide resistance in *Aedes aegypti* and *Aedes albopictus*, particularly to pyrethroids and, in some regions, to organophosphates. This resistance poses major challenges to routine vector control efforts [36-38]. Molecular studies indicate that resistance in Indian Aedes mosquitoes involves both enhanced metabolic detoxification and *kdr* mutations in voltage-gated sodium channels, which together reduce the effectiveness of commonly used insecticides [36-40].

The operational impact is evident, mosquito densities often remain high despite repeated fogging, leading to resource wastage and reduced public confidence in control campaigns. These challenges highlight the need for a strategic shift toward Integrated Vector Management (IVM), which combines environmental sanitation, community participation, biological larvicides, and evidence-based insecticide use [11, 20, 35]. Recent research emphasizes strengthening routine entomological surveillance, creating spatial resistance maps, and incorporating insecticide susceptibility data into municipal decision-making. These measures are critical to maintaining chemical intervention efficacy while promoting sustainable, long-term non-chemical strategies for dengue control [39, 41].

1.4 Scope and objectives of the review

This review aims to consolidate current knowledge on dengue epidemiology, vector biology, and insecticide resistance, with a special focus on India, where the disease is endemic and vector control faces both operational and ecological challenges [32, 39]. Dengue continues to impose a significant public health burden due to the co-circulation of multiple virus serotypes, high population susceptibility, and the rapid spread of *Aedes* mosquitoes in urban and peri-urban areas. Understanding the dynamics of transmission is therefore critical for designing effective control strategies [33].

A key objective of this review is to evaluate both historical and current approaches to vector control—including chemical, biological, and environmental methods—and to explore the emergence, mechanisms, and operational consequences of insecticide resistance in *Aedes aegypti* and *Aedes albopictus* populations [18, 42].

Additionally, the review aims to identify knowledge gaps in surveillance, monitoring, and resistance management. It emphasizes the importance of Integrated Vector Management (IVM) strategies that combine evidence-based insecticide use with environmental modifications, community engagement, and innovative biocontrol interventions [11, 20, 39]. By compiling epidemiological data, entomological evidence, and resistance profiles from published literature and national surveillance reports, this review provides a practical resource for policymakers, researchers, and public health practitioners to guide targeted interventions and optimize resource allocation [35].

The review also highlights the broader implications of insecticide resistance, showing how it undermines traditional outbreak response strategies and underscores the need for adaptive, evidence-informed planning to maintain the effectiveness of vector control programs [16, 25]. Ultimately, the goal is to bridge the gap between entomological research, epidemiological surveillance, and practical vector management, offering insights to support the design of long-term, sustainable, and context-specific strategies for reducing dengue transmission and public health risks in India and other endemic regions [11, 20].

2 Dengue epidemiology in India

2.1 Major dengue outbreaks and shifting endemicity

Over the past twenty years, dengue in India has shifted from occasional urban outbreaks to a complex and persistent public health challenge. In the early 2000s, outbreaks were generally short-lived and mostly confined to large metropolitan cities such as Delhi, Kolkata, Mumbai and Chennai (Table 1). Cases surged after the monsoon season, when *Aedes aegypti* mosquitoes thrived in water storage containers and discarded household items [43]. The Delhi outbreak in 2003, followed by the major epidemic of 2006—with more than 10,000 confirmed cases and many patients hospitalized for dengue hemorrhagic fever—exposed the weaknesses in urban infrastructure and surveillance systems [43]. During this period, molecular evidence indicated that DENV-2 was the dominant serotype, while DENV-1 and DENV-3 were detected sporadically, suggesting that dengue was still geographically concentrated and serotypically limited [39].

After 2010, dengue transmission became more widespread, affecting broader regions and more diverse populations. Rapid and unplanned urban growth, the expansion of peri-urban settlements, increasing mobility, and environmental changes promoted its spread. Multi-state outbreaks between 2010 and 2012—especially in Maharashtra, Karnataka, Gujarat, Punjab and Delhi—demonstrated that areas once considered low risk

were now vulnerable, marking India's movement toward sustained hyper-endemicity [44]. By the mid-2010s, this shift was undeniable. In 2015 alone, India reported more than 100,000 laboratory-confirmed cases, with Delhi, Tamil Nadu and Kerala bearing a large share of the burden [45]. The alternating dominance of DENV-2 and DENV-3, along with periodic surges of DENV-1, reflected an increasingly dynamic viral ecosystem. Immunological factors such as antibody-dependent enhancement likely played a role, increasing secondary infections and disease severity [46, 47].

From 2016 onward, dengue was no longer confined to large cities. It spread into peri-urban regions, smaller towns and even some rural areas. Persistent viral circulation was noted in states such as Telangana, Odisha, Rajasthan and parts of Northeast India. This expansion was linked to improved road networks, informal housing, changes in household water storage and shifts in rainfall and temperature patterns [48]. Studies from 2017–2019 highlighted the re-emergence of DENV-3, especially in Delhi, Pune, Chandigarh and Bengaluru, accompanied by a rise in hospital admissions [49, 50]. The simultaneous detection of all four dengue serotypes in several states during this period confirmed the establishment of a mature hyper-endemic environment, heightening the risk of sequential infections and severe clinical outcomes [47].

Table 1. Major Epidemiological Observations and Trends for Dengue in India (2000–2023)

Year	Reported Epidemiological Pattern / Key Observations	Representative Source
2000–2004	Sporadic outbreaks moving beyond traditional major cities; early signals of increasing endemicity.	[32]
2005–2007	Growing urban outbreaks; increasing proportion of severe cases; geographical expansion.	[32] [43]
2008–2009	Sustained circulation; increasing detection in new districts; rising hospitalization reports.	[32], [44]
2010–2013	Large, multi-state outbreaks; high laboratory-confirmed prevalence (~38% of suspected cases); widespread urban hotspots.	[8]
2014–2015	Continued surge; reported dengue cases climb sharply; notable spread to peri-urban/rural areas.	[54]
2016–2018	Shift from focal outbreaks → sustained endemicity; serotype co-circulation intensifies; rising diagnostics (NS1, IgM).	[50], [54]
2019	One of the highest nationwide dengue burdens with exceptional state-level spikes; emergence in previously low-risk regions.	[39], [51], [52]
2020	Case reports dipped due to COVID-19 mobility restrictions, masking true transmission.	[51]
2021	Rebound of cases as restrictions lifted; DENV-2 dominance confirmed in many molecular investigations.	[52]

2022	Strong resurgence with regional variability; co-circulation of DENV-1/2/3; high hospitalization burden.	[46], [50]
2023	Very large burden spike reported nationally; dengue expands in states previously considered non-endemic; increased deaths in some regions.	[39],[51], [65]

The COVID-19 pandemic further altered this landscape. Reduced access to hospitals, disruptions in vector control and delays in public health responses led to under-reporting in 2020, masking real levels of community transmission. Once restrictions eased, outbreaks resurged sharply between 2021 and 2023, particularly in Uttar Pradesh, Rajasthan, Gujarat and West Bengal, often concentrated in dense urban settings and expanding peri-urban belts [51]. During these years, serotype patterns became less predictable: DENV-2 and DENV-3 alternated in dominance, and DENV-4 began to appear more frequently. Compounding this problem were widespread reports of pyrethroid resistance in *Aedes aegypti*, including resistance to deltamethrin, cyfluthrin and lambda-cyhalothrin—a development that undermined traditional vector control strategies and contributed to persistent transmission [44, 52]. Together, these trends demonstrate how dengue in India has evolved from sporadic outbreaks in a few cities to a nationwide, complex system of hyper-endemic transmission shaped by biological, ecological and infrastructural forces.

2.2 Geographic distribution and hotspots of dengue cases across Indian states

The geographic spread of dengue in India has steadily expanded, with transmission now reported across nearly all states and union territories, though the intensity varies significantly. Historically, Maharashtra, Karnataka, Tamil Nadu, Kerala, and the National Capital Region have consistently been high-burden states. More recently, Uttar Pradesh, Gujarat, West Bengal, Rajasthan, and Punjab have reported recurrent large-scale outbreaks, reflecting the spread of dengue from metropolitan epicenters to secondary cities and peri-urban districts [35]. Major metropolitan areas—including Delhi, Mumbai, Bengaluru, and Kolkata—continue to record the highest absolute case counts, owing to high population density, peri-domestic breeding sites, and human mobility. Secondary urban centers and peri-urban belts now function as independent endemic foci, sustaining year-to-year transmission and seeding seasonal outbreaks in surrounding districts.

Environmental and socio-demographic determinants significantly influence geographic heterogeneity. Coastal and southern states, with warm, humid climates and prolonged monsoon seasons (e.g., Kerala, Tamil Nadu, Karnataka, Goa), show extended transmission periods and frequent outbreaks, whereas northern states in the Gangetic plains (e.g., Uttar Pradesh, Bihar) experience large post-monsoon epidemics linked to heavy rainfall and inadequate drainage systems [53]. Urban micro-environments with high population density, informal settlements, irregular water supply, and construction activity provide abundant larval habitats, creating persistent hotspots within specific neighborhoods. Serotype mapping reveals spatial clustering, with DENV-2 and DENV-1 dominating northern and central states, while DENV-3 and emerging DENV-4 produce focal outbreaks in southern regions [44, 54]. Climatic variability, urban heat islands, and population mobility further

modulate hotspot dynamics, often shifting high-incidence districts within metropolitan areas from year to year.

State-wise dengue data for 2023 illustrate this heterogeneity: West Bengal, Uttar Pradesh, Kerala, Maharashtra, Karnataka, and Delhi contributed the highest case burdens nationally, while smaller northeastern states and union territories experienced localized surges. Kerala's elevated death count relative to cases highlights potential regional differences in clinical severity or reporting [35]. These spatial patterns confirm the expansion of hyper-endemic transmission beyond traditional urban centers and underscore the need for geographically tailored vector control and surveillance strategies.

2.3 Viral serotypes and changing dengue transmission dynamics

Dengue virus circulation in India is characterized by the co-existence of all four serotypes—DENV-1, DENV-2, DENV-3, and DENV-4—with dynamic shifts in dominance that have reshaped transmission intensity and clinical severity patterns over the last two decades. Historically, DENV-2 and DENV-3 predominated in northern and western India in the early 2000s, as evidenced by outbreaks in Delhi, Haryana, and Gujarat, which were associated with increased rates of severe dengue and hospitalization [55]. This period marked the transition from sporadic outbreaks to multi-year cyclic epidemics, driven by immunological susceptibility in naive populations and the expansion of *Aedes aegypti* urban habitat.

During 2010–2014, India experienced a broader geographic diversification of serotypes, with DENV-1 resurgence and widespread DENV-2 circulation. The 2010–2011 outbreaks in north and western India were primarily linked to DENV-1 genotype V, which replaced previous DENV-3 dominance [56-60]. This shift coincided with large outbreaks in Delhi and Rajasthan, suggesting that inter-serotype replacement events may be early indicators of epidemic waves. Simultaneously, southern states such as Tamil Nadu and Kerala documented frequent DENV-2 and DENV-3 circulation, reinforcing the regional heterogeneity in serotype ecology [59, 61].

After 2015, India entered a phase described as "hyperendemicity," characterized by simultaneous co-circulation of all serotypes across multiple regions, which significantly increased the risk of sequential infections—a well-recognized driver of severe disease manifestations due to antibody-dependent enhancement (ADE) [6]. The 2015–2017 epidemic period, particularly in Delhi and Bengaluru, demonstrated strong dominance of DENV-2 lineage IV, which was associated with higher hospitalization rates and severe dengue presentations relative to earlier outbreaks [58, 62]. The lineage replacement phenomenon likely resulted from the ecological advantage of DENV-2, which tends to generate robust epidemic waves under high population immunity to other serotypes.

In recent years, shifts toward DENV-3 and episodic emergence of DENV-4 have raised new concerns regarding disease severity and outbreak potential. For example, the large-scale 2019 outbreaks were driven by DENV-2 in many states but accompanied by the re-emergence of DENV-3 in Maharashtra, Telangana, and parts of Kerala, suggesting cyclical serotype replacement [47, 54, 63]. The detection of DENV-4 genotype I in southern India and the Andaman archipelago underscores the expanding diversity of dengue genotypes circulating within the country, though DENV-4 remains relatively less prevalent overall [64, 65].

The circulation of multiple serotypes affects not only transmission dynamics but also clinical risk, as infection with one serotype provides lifelong immunity to that serotype but only temporary and partial cross-protection to others. Subsequent infections with

heterologous serotypes increase the likelihood of severe dengue due to immune-mediated enhancement mechanisms, contributing to the rising burden of complicated cases reported across Indian hospitals [66, 67]. The expansion of serotype diversity, coupled with rapid urbanization and intensified mosquito breeding environments, has accelerated dengue endemicity, turning India into one of the largest global ecosystems of sustained serotype co-circulation.

2.4 Limitations in current dengue surveillance and reporting

Despite improvements in dengue monitoring, India's surveillance system faces significant operational and methodological limitations. NVBDCP relies on passive case reporting from public health facilities, but underreporting from private and informal clinics remains substantial [53, 68]. Misdiagnosis with other febrile illnesses, inconsistent diagnostic availability across states, and delays in reporting further compromise data quality [62, 69]. Sentinel surveillance exists in selected regions for serotype monitoring and outbreak prediction, but coverage is limited, and integration with entomological data is often lacking [52, 56, 58]. Climatic variability, seasonal population movements, and urbanization exacerbate these challenges, making early detection and timely response difficult. Strengthening integrated disease surveillance, expanding laboratory coverage, standardizing diagnostic protocols, and incorporating geospatial and entomological data are critical to improving dengue control and outbreak preparedness in India.

3 Insecticide resistance in dengue vectors

Insecticide resistance in dengue vectors has emerged as a central barrier to effective vector control in India, with *Aedes aegypti* and *Aedes albopictus* increasingly showing reduced susceptibility to compounds used in larval and adult mosquito management. Resistance is not a single phenomenon but a multi-dimensional adaptive response, shaped by years of intensive insecticide use, operational practices, and environmental pressures. Historically, India relied on organochlorines such as DDT for malaria control and later adopted pyrethroids and organophosphates for urban dengue programs [46]. The repeated, often unmonitored application of these insecticides has resulted in selection pressure, allowing resistant genotypes and phenotypes to proliferate.

Aedes aegypti, the dominant urban vector, is highly anthropophilic, container-breeding, and capable of completing its life cycle in small water collections. These behavioral traits ensure frequent exposure to chemical interventions, especially space spraying and larvicides [70]. Across India, Ae. aegypti populations have shown phenotypic resistance to deltamethrin, permethrin, malathion, temephos, and DDT. Mechanistically, resistance in this species is often linked to knockdown resistance (*kdr*) mutations in the voltage-gated sodium channel and metabolic detoxification via cytochrome P450 monooxygenases, esterases, and glutathione-S-transferases [39]. Such adaptations reduce mortality, prolong adult lifespan, and increase transmission potential, particularly in hyperendemic urban centers.

Aedes albopictus, historically confined to peri-urban and rural ecosystems, has expanded into urban environments due to climate shifts, human mobility, and ecological plasticity. Its resistance profiles in India mirror those of Ae. aegypti, though typically at lower intensities. Bioassay studies reveal low-to-moderate resistance to pyrethroids and emerging temephos tolerance, with pockets of high DDT resistance in regions with past anti-malaria spraying. Importantly, Ae. albopictus often inhabits vegetative or semi-natural

habitats, where sub-lethal pesticide exposure from agriculture contributes to cross-resistance, a phenomenon increasingly reported in north-eastern and southern India [39].

3.1 Overview of key insecticide classes used in Indian public health programs

Controlling *Aedes aegypti* and *Aedes albopictus* mosquitoes remains the cornerstone of dengue prevention in India. Over the years, public health programmers have relied on four major classes of insecticides—pyrethroids, organophosphates, carbamates, and DDT—each with distinct chemical properties, mechanisms of action, and operational uses [71, 72].

Pyrethroids are synthetic derivatives of natural pyrethrins and form the backbone of adult mosquito control in India. Their rapid knockdown effect, low toxicity to humans, and suitability for indoor residual spraying (IRS) and space-spraying/thermal fogging make them ideal for outbreak response and routine vector management in urban and peri-urban settings [39, 42]. Commonly used pyrethroids include permethrin, deltamethrin, and alpha-cypermethrin. They target mosquito neurons by disrupting voltage-gated sodium channels, causing paralysis and death. Although pyrethroids are sometimes applied to bed nets or window screens, their overall effectiveness against *Aedes* is limited because these mosquitoes are primarily day-biting and indoor-resting, unlike malaria vectors [72].

Organophosphates, such as temephos and malathion, have been widely employed for both larval and adult mosquito control. Temephos is applied to water storage containers, drains, and other breeding habitats, where it inhibits acetylcholinesterase in larvae, disrupting nerve function. Malathion, mostly used for adulticiding during outbreaks, works through a similar enzymatic mechanism. Organophosphates are particularly useful in areas where pyrethroid resistance has emerged or where larval habitats are extensive [39, 42].

Carbamates, including propoxur, also inhibit acetylcholinesterase but are less commonly used in India due to higher costs, environmental persistence, and moderate toxicity to mammals. Their use is generally restricted to targeted IRS during outbreaks or experimental trials aimed at managing resistant mosquito populations [42].

DDT (dichloro-diphenyl-trichloroethane), an organochlorine insecticide, has played a historical role in India's vector control, especially for malaria. Although it is largely phased out in urban dengue programs due to widespread resistance, environmental concerns, and human health risks, DDT may still be applied in peripheral regions where *Aedes* populations remain susceptible [39, 42].

In practice, selecting an insecticide in India depends on entomological surveillance, resistance monitoring, operational feasibility, and environmental safety. The extensive and frequent use of pyrethroids and organophosphates, combined with domestic mosquito-control measures such as coils and sprays, has exerted strong selective pressure on *Aedes* populations. This has accelerated the emergence and spread of insecticide resistance, posing a significant challenge to the effectiveness of national dengue control programs [42, 73].

3.2 Status of phenotypic resistance in *Aedes* species across India

Phenotypic resistance in *Aedes aegypti* and *Aedes albopictus* has become a major hurdle for dengue control in India, with considerable variation across regions due to differences in insecticide exposure, vector ecology, and operational practices. Standardized WHO larval and adult bioassays are commonly used to measure this resistance, assessing mosquito

mortality after exposure to diagnostic doses of widely used insecticides including pyrethroids, organophosphates, carbamates, and DDT [71].

Larval resistance, particularly to temephos, has been widely reported in urban and peri-urban populations of *Aedes aegypti*. Studies from cities like Delhi, Mumbai, Bengaluru, and Chennai reveal a gradual decline in larval susceptibility over the past decade, with some populations showing mortality below the WHO-recommended threshold (<80%) at standard diagnostic doses [39]. Aedes albopictus populations in southern and northeastern states show similar trends, though resistance levels are generally lower. This difference likely reflects Ae. albopictus's preference for sylvatic or peri-domestic habitats, which reduce its exposure to domestic and public health insecticides [42]. Since larval control remains central to outbreak response, particularly in water-storage-intensive urban areas, temephos resistance has clear operational consequences.

Adult mosquito resistance is equally concerning. WHO tube tests and CDC bottle assays consistently show widespread resistance to pyrethroids—the primary class used in adulticiding via space-spraying and indoor residual spraying. Deltamethrin, permethrin, and alpha-cypermethrin display variable efficacy across the country. High-level resistance (mortality <80%) is frequently observed in Delhi, Kerala, Maharashtra, Tamil Nadu, and Gujarat, while some northeastern and central states maintain moderate susceptibility [42, 73]. Resistance to organophosphates, such as malathion, is emerging in localized areas but remains lower than pyrethroid resistance overall. DDT resistance, reflecting decades of historical use, is widespread and persistent in *Aedes aegypti* across multiple regions [39, 42].

These resistance patterns underscore the heterogeneous nature of insecticide susceptibility in India. Urban Ae. aegypti populations, repeatedly exposed to pyrethroids through outbreak-driven fogging, domestic insecticide use, and commercial pest control, exhibit the highest resistance levels. In contrast, rural and peri-urban Ae. albopictus populations, with less frequent insecticide contact, often retain partial susceptibility. Nevertheless, continuous monitoring is essential to detect emerging resistance before it undermines control efforts.

The operational implications are significant. Declining mortality in larval and adult bioassays correlates directly with reduced effectiveness of vector control measures. To address this, programs must implement rotational insecticide strategies, integrate multiple vector management approaches (IVM), and explore innovative tools such as larvivorous fish, *Wolbachia*-based biocontrol, and spatial repellents [23, 73].

In conclusion, phenotypic resistance in *Aedes* mosquitoes is widespread in India, particularly for pyrethroids and DDT, with sporadic organophosphate resistance. Resistance intensity is closely linked to urbanization, historical insecticide exposure, and control practices, emphasizing the need for continuous bioassay monitoring and context-specific, evidence-based vector management to sustain the effectiveness of dengue control programs.

3.2.1 Resistance to Pyrethroids

Pyrethroids, including deltamethrin, permethrin, and alpha-cypermethrin, are the cornerstone of adult *Aedes* control in India due to their rapid knockdown effect and low mammalian toxicity. However, widespread and intensive use in urban outbreak response, household sprays, and IRS has exerted strong selective pressure, leading to extensive phenotypic resistance in *Aedes aegypti* populations. WHO adult bioassays conducted in metropolitan centers such as Delhi, Bengaluru, Chennai, and Mumbai consistently report mortality rates below the 80% WHO threshold, indicating confirmed resistance [39, 42, 73].

Resistance is typically higher in urban and peri-urban areas, where repeated outbreak-driven fogging and domestic insecticide use accelerate selection. *Aedes albopictus* also exhibits pyrethroid resistance, although generally at lower levels, likely due to its more rural and peri-domestic breeding habits [42]. Operationally, this resistance reduces the efficacy of space-spraying and indoor residual applications, necessitating alternative strategies such as rotational use of insecticides, integrated vector management, and novel control tools.

3.2.2 Resistance to Organophosphates

Organophosphates, including larvicidal temephos and adulticidal malathion, have historically been widely used in Indian dengue control programs. Larval bioassays across multiple states—Delhi, Maharashtra, Tamil Nadu, and Kerala—show variable temephos resistance in *Aedes aegypti*, with mortality rates ranging from moderate to low depending on local exposure history [39]. Adult resistance to malathion remains less prevalent than pyrethroid resistance but has been detected in localized hotspots in southern and western India [42]. The emergence of organophosphate resistance is attributed to both operational overuse and domestic exposure through larvicides in water storage containers. Such resistance compromises the effectiveness of larval control programs, particularly in urban environments where water storage is common, underscoring the need for continuous monitoring and judicious insecticide rotation.

3.2.3 Resistance to Organochlorines (DDT) and Carbamates

DDT, an organochlorine historically used for malaria vector control, continues to exhibit widespread resistance in *Aedes aegypti* populations across India, with adult bioassay mortality rates frequently below 50–60% in both urban and rural settings [39, 42]. Although its use in contemporary dengue control is limited, persistent resistance indicates historical selection pressure and environmental persistence. Carbamates, such as propoxur, have been evaluated in a few experimental and outbreak-prone areas. Resistance to carbamates remains relatively low but has been reported in localized populations of *Aedes aegypti* exposed to repeated IRS or targeted control programs [42]. Overall, the combined resistance to multiple classes of insecticides highlights the urgent need for integrated vector management approaches, including non-chemical interventions, larval habitat reduction, biological control, and systematic resistance monitoring to sustain the effectiveness of dengue control strategies.

3.3 Molecular mechanisms of resistance

Insecticide resistance in *Aedes aegypti* and *Aedes albopictus* is driven by a combination of target-site alterations and metabolic adaptations, which reduce susceptibility to commonly used chemical classes. Understanding these molecular mechanisms is crucial for designing effective control strategies and interpreting phenotypic resistance patterns observed across India.

3.3.1 Target-site mutations

Target-site resistance primarily involves mutations in the voltage-gated sodium channel (VGSC) gene, commonly referred to as knockdown resistance (*kdr*) mutations, which confer reduced sensitivity to pyrethroids and DDT. Key *kdr* mutations identified in Indian *Aedes aegypti* populations include V1016G, F1534C, S989P, and their combinations, which alter the sodium channel conformation, preventing insecticide binding and resulting in knockdown failure [25, 74, 75]. Studies from Delhi, Bengaluru, Mumbai, and Chennai report high frequencies of F1534C and V1016G alleles, correlating strongly with phenotypic resistance observed in adult bioassays [39, 76].

kdr mutations are not uniformly distributed; urban populations with repeated pyrethroid exposure typically show higher allelic frequencies, whereas rural or sylvatic populations, such as *Aedes albopictus* in northeastern India, exhibit lower mutation prevalence. Combined mutations (e.g., V1016G + F1534C) have been associated with higher resistance intensity, explaining some of the failures in pyrethroid-based space spraying campaigns during major outbreaks [73]. These findings underscore the importance of genotyping alongside phenotypic bioassays to guide insecticide selection and resistance management.

3.3.2 Metabolic resistance

Metabolic resistance arises when mosquito populations upregulate detoxifying enzymes, which metabolize or sequester insecticides before they reach their target sites. The principal enzyme families implicated in *Aedes* resistance in India include cytochrome P450 monooxygenases (CYP450s), carboxylesterases, and glutathione-S-transferases (GSTs) [42, 76]. Elevated CYP450 activity is strongly associated with pyrethroid resistance, whereas increased esterases primarily mediate organophosphate detoxification, including temephos and malathion. GSTs are often linked to DDT resistance, consistent with historical exposure patterns.

Biochemical assays and molecular expression studies in Indian *Aedes aegypti* populations have revealed region-specific patterns. For example, urban populations in Delhi, Mumbai, and Chennai show marked overexpression of CYP6 and CYP9 family genes, correlating with phenotypic pyrethroid resistance [39, 76]. Similarly, increased carboxylesterase activity has been documented in Maharashtra and Tamil Nadu, contributing to temephos tolerance. Metabolic resistance often acts synergistically with *kdr* mutations, resulting in high-intensity resistance that diminishes the operational effectiveness of standard insecticide applications [73].

These molecular mechanisms highlight the complex interplay between genetic mutations and biochemical adaptations, emphasizing that effective resistance management requires an integrated approach: rotation of insecticide classes, combination with non-chemical vector control tools, and continuous molecular and biochemical surveillance.

3.4 Spatial and temporal mapping of resistance profiles in India

Understanding where and when insecticide resistance occurs is crucial for designing effective, evidence-based dengue control programs in India. Both phenotypic and molecular resistance in *Aedes aegypti* and *Aedes albopictus* show substantial geographic variation, influenced by urbanization, vector ecology, insecticide use, and historical control measures [42].

Urban metropolitan centers—including Delhi, Mumbai, Bengaluru, Chennai, and Kolkata—consistently report the highest levels of pyrethroid resistance. Adult bioassays often show mortality rates below the WHO threshold, and molecular studies frequently detect *kdr* mutations such as V1016G, F1534C, and S989P [73, 76]. Larval resistance to temephos is also most pronounced in these cities, reflecting repeated larvicide applications and high vector proliferation driven by dense human populations.

By contrast, peri-urban and rural areas generally show lower, but gradually emerging, resistance patterns. *Aedes albopictus* populations in northeastern states—such as Assam, Meghalaya, and Nagaland—as well as hilly regions of Himachal Pradesh and Uttarakhand, often retain moderate susceptibility to pyrethroids and organophosphates. However, isolated pockets show elevated metabolic resistance, likely due to localized exposure to domestic insecticides or agricultural pesticide drift [39, 42]. Coastal states like Kerala and Tamil Nadu illustrate microgeographic variability: while urban centers exhibit high pyrethroid resistance in Ae. aegypti, rural villages along the coast often maintain partial susceptibility [39, 76].

Temporal analyses reveal a worrying increase in resistance over the last two decades. In Delhi and Mumbai, pyrethroid resistance in adult Ae. aegypti populations has escalated from moderate susceptibility in the early 2000s to widespread confirmed resistance by 2015–2020 [73]. Similarly, temephos resistance in larval populations across southern and western India has gradually intensified, correlating with continuous vector control interventions and domestic insecticide use. DDT resistance remains widespread and stable nationwide, reflecting historical selection pressures and its long environmental persistence [39].

Mapping these spatial and temporal patterns is essential for guiding targeted resistance management. High-resolution GIS analyses combined with entomological surveillance help identify resistance hotspots, inform rotational insecticide strategies, and guide alternative interventions such as *Wolbachia*-based biocontrol or larvivorous fish deployment in high-risk areas [23, 42, 73]. Such spatially and temporally integrated approaches also enable predictive modeling of outbreak risk, supporting proactive vector control and more efficient resource allocation.

In summary, India's insecticide resistance landscape is highly heterogeneous. Urban Ae. aegypti populations show the highest levels of pyrethroid resistance, organophosphate resistance is emerging in several states, and DDT resistance remains widespread. Continuous monitoring, mapping, and integration of phenotypic and molecular data into national vector management programs are critical to sustaining effective dengue control in the face of evolving resistance.

4 Correlating resistance with dengue incidence

4.1 The hypothesis "reduced insecticide efficacy leads to higher vector density and transmission risk"

The increasing prevalence of insecticide resistance in *Aedes aegypti* and *Aedes albopictus* has raised concerns regarding its impact on dengue transmission dynamics in India. The central hypothesis posits that reduced insecticide efficacy, driven by both phenotypic and molecular resistance mechanisms, leads to higher vector densities, thereby enhancing the probability of virus transmission and escalating the risk of outbreaks [42, 73]. Pyrethroids, temephos, and other chemical interventions constitute the backbone of dengue vector

control programs; however, resistance diminishes the mortality of both larvae and adult mosquitoes, allowing populations to persist despite intensive control measures.

In urban and peri-urban settings, where human population density is high and water-storage practices are common, ineffective insecticide applications can lead to rapid recovery of mosquito populations following control interventions. Surviving mosquitoes not only reproduce but may also have longer lifespans, increasing the probability of acquiring and transmitting dengue virus [39]. Studies suggest that in regions with confirmed pyrethroid resistance, standard space-spraying campaigns fail to achieve expected reductions in adult *Aedes aegypti* densities, thereby sustaining or even exacerbating transmission cycles [76].

Additionally, sublethal exposure to insecticides can have behavioral and physiological consequences, such as delayed mortality, reduced knockdown effect, or avoidance behavior, which further contributes to ongoing transmission despite continued chemical interventions. The hypothesis is reinforced by ecological and epidemiological observations indicating that outbreaks often coincide with areas reporting high insecticide resistance, suggesting a functional link between reduced chemical efficacy, elevated vector abundance, and increased dengue incidence [42, 73].

4.2 Review of field studies linking insecticide failure to escalating dengue cases

Empirical evidence from field studies across India suggests a correlation between insecticide resistance in *Aedes* mosquitoes and sustained or escalating dengue incidence, although establishing direct causality remains complex. In urban centers such as Delhi, Mumbai, and Chennai, entomological surveys conducted during major outbreak years have documented high levels of pyrethroid resistance in adult *Aedes aegypti* populations alongside elevated dengue case numbers. For instance, bioassays performed in Delhi during the 2015–2017 outbreaks revealed widespread resistance to deltamethrin and permethrin, coinciding with persistent adult mosquito populations despite intensive fogging campaigns [39, 76].

Similarly, larval resistance to temephos has been observed in southern India, particularly in Chennai and Bengaluru, in areas reporting recurrent dengue transmission. Populations exhibiting reduced susceptibility to temephos correlated with higher larval indices and increased dengue incidence, highlighting operational failures in standard larvicidal interventions [39, 42]. In Mumbai, integrated surveillance combining entomological, molecular, and epidemiological data demonstrated that wards with high *kdr* mutation frequencies and elevated detoxifying enzyme activity experienced prolonged dengue outbreaks, reinforcing the link between molecular resistance markers and epidemiological outcomes [73].

International studies further support this association. Observations from Southeast Asia and South America indicate that insecticide-resistant *Aedes* populations often coincide with higher vector densities and larger outbreaks, suggesting that resistance undermines routine chemical control efficacy [73]. Although these studies provide robust correlative evidence, disentangling the effects of resistance from confounding factors such as urbanization, climate variability, and serotype dynamics remains challenging. Nonetheless, field data consistently indicate that insecticide failure contributes to the persistence of high vector populations, which, in turn, sustains or amplifies dengue transmission.

Collectively, these studies underscore the operational significance of resistance monitoring and the need to integrate molecular, biochemical, and phenotypic data into

vector control decision-making. Targeted interventions informed by resistance profiles can enhance the efficiency of chemical control measures, reduce vector densities, and potentially mitigate the risk of dengue outbreaks in high-burden regions [39, 76].

4.3 Challenges in establishing a direct causal link

Although field studies suggest a correlation between insecticide resistance and increased dengue incidence, establishing a direct causal link is inherently challenging due to multiple confounding factors. Urbanization is a primary driver of dengue transmission, particularly in Indian metropolitan and peri-urban regions. Rapid population growth, unplanned construction, poor waste management, and widespread water storage create abundant breeding habitats for *Aedes* mosquitoes, independent of chemical control efficacy. Consequently, even in areas with effective insecticide application, high vector densities can persist, complicating the attribution of outbreak intensity solely to insecticide failure [6, 53].

Climate variability further confounds the relationship between resistance and dengue incidence. Temperature, humidity, and rainfall patterns strongly influence mosquito survival, breeding frequency, and viral replication rates. Unusually heavy monsoon rainfall or prolonged warm periods can amplify *Aedes* populations and accelerate dengue transmission, regardless of insecticide susceptibility, creating a scenario in which outbreaks may occur even when chemical control is moderately effective [6, 53, 77].

Shifts in viral serotypes and co-circulation of multiple serotypes also impact disease dynamics. Changes in predominant serotypes, such as the transition from DENV-1 to DENV-2 or DENV-3 in specific regions, can lead to increased case numbers and severe disease through mechanisms like antibody-dependent enhancement, independent of vector abundance or control interventions [47]. These virological factors make it difficult to isolate the contribution of insecticide resistance to outbreak magnitude.

Moreover, operational variability in vector control practices, including the frequency, coverage, and quality of insecticide applications, further complicates causal inference. Inconsistent intervention strategies, combined with human behavioral factors (e.g., water storage habits, domestic insecticide use), produce heterogeneous vector populations and disease outcomes across space and time [73].

In summary, while resistance clearly undermines chemical control efficacy and can contribute to higher vector densities, urbanization, climatic fluctuations, and viral dynamics collectively influence dengue incidence, making it challenging to attribute outbreaks solely to insecticide failure. This underscores the importance of integrated, multifactorial approaches combining entomological, environmental, and virological data to understand and predict dengue transmission patterns effectively.

4.4 Modeling the economic and public health impact of resistance-driven control failures

Mathematical and epidemiological modeling provides a quantitative framework to understand the public health and economic consequences of insecticide resistance in dengue vectors. Resistance-driven failures in chemical control can lead to sustained high *Aedes* densities, prolonging transmission seasons and amplifying dengue incidence, which in turn places a significant burden on healthcare systems [73, 77]. Simulation studies suggest that reductions in insecticide efficacy, even by 20–40%, can result in proportional

increases in adult mosquito populations and disease incidence, particularly in densely populated urban areas where transmission intensity is high [77].

Economic models incorporate the direct and indirect costs of resistance-driven outbreaks, including hospitalization expenses, outpatient care, vector control interventions, and productivity losses. In India, where dengue is hyperendemic in multiple states, model projections indicate that ineffective chemical interventions due to resistance can lead to substantial financial losses, both for public health programs and for affected households [39]. For instance, wards with high pyrethroid resistance may require repeated space-spraying or alternative interventions, increase operational costs while delivering diminishing returns on vector suppression.

Furthermore, models that integrate entomological, epidemiological, and resistance data enable identification of high-risk zones and prediction of outbreak magnitude under different control scenarios. Such models demonstrate that targeted resistance management strategies, including insecticide rotation, integrated vector management (IVM), and deployment of non-chemical tools such as *Wolbachia*-infected mosquitoes or larvivorous fish, are both more effective in reducing vector density and more cost-efficient compared to unplanned blanket spraying campaigns [39, 73].

Overall, modeling studies highlight that resistance-driven control failures have multifaceted consequences, increasing both dengue incidence and associated economic burden. These insights emphasize the critical need for routine resistance monitoring, predictive modeling, and evidence-based intervention planning to mitigate the public health and financial impact of dengue in India.

5 Challenges and future directions in vector management

5.1 The need for integrated vector management (IVM) strategies

The increasing prevalence of insecticide resistance in *Aedes* mosquitoes, coupled with rising dengue cases across India, underscores the urgent need to move beyond chemical interventions alone. Integrated Vector Management (IVM) offers a comprehensive, sustainable, and evidence-based approach to vector control. By combining chemical, biological, environmental, and community-based strategies, IVM can be adapted to local ecological and epidemiological contexts, making interventions more effective and long-lasting [11, 20, 42]. A key feature of IVM is the rational use of insecticides, including rotating between different classes with distinct modes of action, which helps delay resistance development while minimizing environmental and human health risks.

Beyond chemical control, IVM emphasizes source reduction and environmental management. Measures such as eliminating stagnant water, improving waste disposal, and covering water storage containers directly reduce mosquito breeding opportunities. Biological interventions—including the use of larvivorous fish, Bacillus thuringiensis israelensis (Bti), and Wolbachia-infected mosquitoes—offer additional tools that target immature or adult vectors without creating selective pressure for insecticide resistance [23, 73, 78]. Community engagement is central to IVM, ensuring sustainability by involving local populations in habitat management and personal protective measures.

Evidence from India and other countries shows that IVM strategies are far more effective than single-method approaches, especially in urban areas facing high levels of insecticide resistance. By integrating entomological surveillance, resistance monitoring, and

ecological management, IVM can reduce vector densities, lower dengue transmission risk, and optimize resource allocation [39, 42]. Importantly, IVM also allows adaptive management, enabling programs to respond to emerging resistance, climate variability, and shifting disease patterns.

In conclusion, adopting IVM in dengue-endemic regions of India is essential not only to combat insecticide resistance but also to ensure sustainable and cost-effective vector control. It represents a paradigm shift from reactive chemical spraying to proactive, integrated, and locally tailored strategies—critical for long-term reduction of dengue burden.

5.2 Recommendations for resistance management

Effective management of insecticide resistance in *Aedes* mosquitoes is critical for sustaining the efficacy of vector control programs and reducing dengue transmission in India. Resistance management strategies must be proactive, evidence-based, and integrated within broader vector control frameworks, combining chemical and non-chemical approaches while adapting to local ecological and epidemiological contexts [39, 73].

5.2.1 Rotational use of insecticides and synergy agents

One of the cornerstone strategies for managing insecticide resistance is the rotational or mosaic use of insecticides with different modes of action. Rotating chemical classes—such as pyrethroids, organophosphates, carbamates, and bio-larvicides—can reduce selective pressure on mosquito populations, delaying the development of target-site and metabolic resistance [42, 71]. Additionally, synergy agents, such as piperonyl butoxide (PBO), can be used in combination with pyrethroids to inhibit detoxifying enzymes like CYP450s, thereby restoring susceptibility in resistant populations [73]. Field trials in Indian urban centers have shown that PBO-treated nets or sprays can temporarily enhance knockdown and mortality rates in pyrethroid-resistant *Aedes aegypti*, although repeated monitoring and careful rotation remain essential to prevent resistance evolution to synergy agents themselves.

5.2.2 Strengthening insecticide resistance monitoring (IRM) systems

Continuous surveillance through robust Insecticide Resistance Monitoring (IRM) systems is indispensable for guiding evidence-based vector control strategies. IRM involves periodic bioassays, molecular genotyping for *kdr* mutations, and biochemical assays for metabolic resistance, providing real-time information on resistance patterns at local and regional scales [39, 76]. In India, current IRM efforts are often fragmented, underfunded, or limited to selected urban centers, which constrains timely intervention planning. Strengthening IRM systems would involve the expanding geographic coverage to include peri-urban and rural regions, standardizing methodologies for phenotypic and molecular resistance assessment, Integrating IRM data with dengue surveillance and entomological indices to inform predictive models. Further ensuring rapid dissemination of resistance data to local vector control teams for adaptive management.

By implementing these measures, resistance management can shift from reactive to proactive strategies, enabling public health authorities to anticipate resistance-driven failures and tailor interventions accordingly. Effective IRM, combined with rotational

insecticide use and integration with IVM principles, forms the backbone of sustainable dengue vector control in the context of escalating insecticide resistance.

5.3 Novel and alternative vector control tools

Given the widespread insecticide resistance in *Aedes* mosquitoes and the limitations of conventional chemical interventions, novel and alternative vector control tools are increasingly recognized as essential components of sustainable dengue management in India. These approaches complement Integrated Vector Management (IVM) strategies and aim to reduce reliance on insecticides while targeting multiple stages of mosquito life cycles.

5.3.1 Biological control

Biological control methods have emerged as promising alternatives to traditional chemical-based vector management. The introduction of Wolbachia-infected *Aedes aegypti* mosquitoes, for instance, reduces vector competence by limiting the ability of mosquitoes to transmit dengue virus. Field trials in Brazil and Indonesia have demonstrated significant reductions in dengue incidence following *Wolbachia* releases, and pilot stu dies are underway in several Indian cities to assess feasibility and scalability [78, 79]. Additionally, the use of larvivorous fish, such as Gambusia affinis, in water storage tanks and natural water bodies offers a simple, cost-effective, and environmentally friendly approach to suppress larval populations in both urban and peri-urban settings [80]. These biological methods exert minimal selective pressure for chemical resistance and can be integrated with other interventions for enhanced impact.

5.3.2 Environmental management and source reduction

Environmental management, including source reduction, remains a cornerstone of sustainable dengue control. Eliminating potential breeding sites—such as uncovered water containers, discarded tires, and blocked drains—significantly reduces *Aedes* larval habitats. Success depends heavily on community engagement and behavioral change, as local participation ensures sustained habitat management and monitoring. Educational campaigns, participatory clean-up drives, and stakeholder involvement at the household and neighborhood level have been shown to effectively reduce mosquito densities and interrupt transmission cycles [20, 43, 53]. Integrating environmental management with larvicidal and adulticidal interventions strengthens the resilience of vector control programs, particularly in areas facing high levels of insecticide resistance.

5.3.3 New chemical classes and larvicides

While insecticide resistance limits the efficacy of traditional classes, research into new chemical compounds and larvicides offers potential alternatives. Novel larvicides, such as insect growth regulators (IGRs) like pyriproxyfen and diflubenzuron, target mosquito development stages and have been effective in reducing larval survival without selecting strongly for resistance [73]. Additionally, exploration of new chemical classes with unique modes of action can provide temporary relief from resistance-related control failures when deployed judiciously in combination with rotational strategies. The integration of these

novel chemicals into broader IVM frameworks ensures sustainability, while careful monitoring prevents the rapid emergence of resistance.

In conclusion, the incorporation of biological control, environmental management, and novel chemical tools provides a multi-pronged strategy to combat dengue transmission in India. When combined with traditional interventions, resistance management, and community participation, these innovative approaches offer the potential for sustainable, cost-effective, and adaptive vector control, essential for addressing the ongoing public health challenge of dengue.

5.4 Policy implications for India's national vector borne disease control programme (NVBDCP)

The escalating challenge of insecticide resistance in *Aedes* mosquitoes and the concurrent rise in dengue incidence necessitate strategic policy interventions under India's National Vector Borne Disease Control Programme (NVBDCP). Traditional reliance on blanket chemical control is increasingly inadequate due to widespread resistance, highlighting the need for policy reforms that prioritize integrated, evidence-based, and adaptive vector management strategies. Policy directives should focus on strengthening resistance monitoring, entomological surveillance, and data-driven decision-making to ensure timely identification of emerging resistance hotspots and optimize intervention deployment [39, 73].

Integration of Integrated Vector Management (IVM) principles into NVBDCP guidelines is critical, promoting a combination of chemical, biological, environmental, and community-based interventions. Policies should encourage rotational use of insecticides, deployment of synergy agents, and incorporation of novel larvicides to delay resistance development and maintain control efficacy [11, 39]. In addition, NVBDCP strategies must incorporate community engagement and capacity-building, empowering local stakeholders to participate in source reduction, breeding site surveillance, and outbreak preparedness, thereby enhancing sustainability and operational efficiency.

Investment in research and innovation is also essential. Policies should support trials and scale-up of biological control tools such as Wolbachia-infected mosquitoes, sterile insect techniques, and larvivorous fish, as well as environmental interventions tailored to urban and peri-urban contexts. Furthermore, establishing national guidelines for mapping and modeling resistance and outbreak risk will allow predictive planning and optimized allocation of resources, reducing both public health and economic burdens [23, 73, 77].

Finally, cross-sectoral coordination between public health authorities, municipal bodies, urban planners, and community organizations is crucial to address the multifactorial drivers of dengue transmission. Policy frameworks should incentivize interdepartmental collaboration, standardized reporting, and integration of vector control into urban development and climate adaptation plans, thereby strengthening India's resilience against dengue and other vector-borne diseases in the era of rising insecticide resistance.

6 Conclusion

Dengue has evolved from intermittent outbreaks to a persistent endemic threat in India, with its spread fueled by rapid urbanization, human mobility, climatic variability, and inadequate urban infrastructure [43, 53]. This epidemiological shift has been exacerbated by rising insecticide resistance in *Aedes aegypti* and *Aedes albopictus*, particularly to pyrethroids, organophosphates, carbamates, and DDT, thereby undermining the

performance of essential vector control tools such as space spraying and larval interventions [39, 42]. Although disentangling causality is challenging due to serotype dynamics, population immunity, and environmental drivers, mounting evidence indicates that reduced insecticide susceptibility contributes to higher vector densities and sustained dengue transmission [73, 81]. To counter this "silent threat," India must transition from a chemical-centric approach toward integrated vector management, incorporating biological and genetic tools such as Wolbachia, environmental management, and systematic resistance monitoring [79]. Without proactive investment, operational research, and evidence-based policy alignment, insecticide resistance threatens to erode past gains in dengue control and impose compounding health and socioeconomic burdens.

6.1 Summary of key findings and the critical nature of the "silent threat"

Over the past two decades, dengue has emerged as a major public health challenge in India, with shifting epidemiology marked by increased endemicity, geographic expansion, and co-circulation of multiple viral serotypes. Concurrently, *Aedes aegypti* and *Aedes albopictus*, the primary vectors of dengue, have developed widespread resistance to multiple insecticide classes, including pyrethroids, organophosphates, carbamates, and DDT. Field studies and surveillance data indicate that resistance contributes to reduced efficacy of vector control interventions, allowing mosquito populations to persist and potentially amplifying dengue transmission [39, 73].

Unlike virological outbreaks that manifest rapidly, insecticide resistance is a slow-burning crisis. It increases vector density without immediate visibility, increases adult survival, and enables persistent dengue transmission even during aggressive control campaigns. Consequently, resistance is a hidden amplifier of risk, influencing outbreak severity, intervention efficacy, and long-term disease ecology.

This phenomenon has been aptly described as a "silent threat", as the impacts of resistance are often not immediately visible but can gradually undermine control efforts, leading to sustained or escalating dengue incidence. The interplay of insecticide resistance with urbanization, climate variability, and shifting serotype dynamics complicates outbreak prediction and control. Moreover, limitations in resistance monitoring, inadequate policy frameworks, and fragmented surveillance systems exacerbate the risk of control failures, emphasizing the need for adaptive, evidence-based strategies to safeguard public health [42, 43].

6.2 Future research priorities

Addressing the challenges posed by insecticide resistance and escalating dengue incidence in India requires a comprehensive and forward-looking research agenda. First, there is an urgent need for enhanced surveillance and resistance mapping, including expansion of geographic coverage, standardization of bioassay and molecular techniques, and integration of resistance data with entomological and epidemiological indicators to inform targeted interventions. Concurrently, the development and evaluation of innovative vector control tools such as *Wolbachia*-infected mosquitoes, sterile insect techniques, environmentally friendly larvicides, and new chemical classes with unique modes of action should be prioritized to complement existing control strategies. Predictive modeling of transmission dynamics represents another critical area, integrating data on vector resistance, climatic variability, urbanization patterns, and circulating viral serotypes to anticipate outbreaks and optimize resource allocation. Operational research is also essential to assess the

effectiveness, cost-efficiency, and community acceptability of integrated vector management approaches under real-world conditions. Finally, mechanistic studies on the molecular, biochemical, and behavioral basis of resistance are needed to guide rational use of insecticides, rotational strategies, and deployment of synergists. Collectively, these research priorities aim to build a robust, adaptive, and sustainable framework for dengue control in India, addressing the "silent threat" posed by insecticide resistance while minimizing public health and socio-economic impacts.

The author wishes to thank the faculty members of RK University, Rajkot 360020, India, for their valuable support and insights. This research did not receive any specific grant. The work was supported entirely by the authors' personal resources (self-financed). We have no conflict of interest to declare. PV performed the literature survey and prepared the original draft of the manuscript. AKS performed critical evaluation, provided supervision, and conducted a time-bound review and revision of the manuscript.

References

1. S. Bhatt, P.W. Gething, O.J. Brady, J.P. Messina, A.W. Farlow, C.L. Moyes, J.M. Drake, J.S. Brownstein, A.G. Hoen, O. Sankoh, M.F. Myers, D.B. George, T. Jaenisch, G.R. Wint, C.P. Simmons, T.W. Scott, J.J. Farrar, S.I. Hay, The global distribution and burden of dengue. Nature. **496**, 504-507 (2013). https://doi.org/10.1038/nature12060
2. W.H. Organization, Dengue-global situation. Disease Outbreak News. **21**, (2023).
3. O. World Health, Dengue and severe dengue, 2023.
4. D.J. Gubler, Dengue, Urbanization and Globalization: The Unholy Trinity of the 21(st) Century. Trop Med Health. **39**, 3-11 (2011). https://doi.org/10.2149/tmh.2011-S05
5. A. Wilder-Smith, D.J. Gubler, Geographic expansion of dengue: the impact of international travel. Med Clin North Am. **92**, 1377-1390, x (2008). https://doi.org/10.1016/j.mcna.2008.07.002
6. J.P. Messina, O.J. Brady, N. Golding, M.U.G. Kraemer, G.R.W. Wint, S.E. Ray, D.M. Pigott, F.M. Shearer, K. Johnson, L. Earl, L.B. Marczak, S. Shirude, N. Davis Weaver, M. Gilbert, R. Velayudhan, P. Jones, T. Jaenisch, T.W. Scott, R.C. Reiner, Jr., S.I. Hay, The current and future global distribution and population at risk of dengue. Nat Microbiol. **4**, 1508-1515 (2019). https://doi.org/10.1038/s41564-019-0476-8
7. C. Huang, C.M. Yeh, C. Ufongene, T. Fashina, R.V.P. Chan, J.G. Shantha, S. Yeh, J.C. Mwanza, Impact of El Nino Southern Oscillation and Climate Change on Infectious Diseases with Ophthalmic Manifestations. Trop Med Infect Dis. **10**, (2025). https://doi.org/10.3390/tropicalmed10100297
8. P. Ganeshkumar, M.V. Murhekar, V. Poornima, V. Saravanakumar, K. Sukumaran, A. Anandaselvasankar, D. John, S.M. Mehendale, Dengue infection in India: A systematic review and meta-analysis. PLoS Negl Trop Dis. **12**, e0006618 (2018). https://doi.org/10.1371/journal.pntd.0006618
9. P.P. Nayak, B.J. Pai, S. Govindan, N.N. Babu, Influence of climatic and land use factors on post-monsoon distribution of *Aedes* mosquito vectors in Udupi taluk. Sci Rep. **15**, 36649 (2025). https://doi.org/10.1038/s41598-025-20413-y
10. P.P. Nayak, B.J. Pai, S. Govindan, V. Sanagapalli, Spatial epidemiology of dengue and chikungunya in Karnataka using GIS-based analysis. Glob Health Action. **18**, 2543198 (2025). https://doi.org/10.1080/16549716.2025.2543198
11. O. World Health, Handbook for integrated vector management, WHO Press2012.

12. T. Fox, Y. Sguassero, M. Chaplin, W. Rose, D. Doum, I. Arevalo-Rodriguez, G. Villanueva, *Wolbachia*-carrying *Aedes* mosquitoes for preventing dengue infection. Cochrane Database Syst Rev. **4**, CD015636 (2024). https://doi.org/10.1002/14651858.CD015636.pub2
13. S. Sadasivaiah, Y. Tozan, J.G. Breman, Dichlorodiphenyltrichloroethane (DDT) for indoor residual spraying in Africa: how can it be used for malaria control? Am J Trop Med Hyg. **77**, 249-263 (2007).
14. K.E. Jones, N.G. Patel, M.A. Levy, A. Storeygard, D. Balk, J.L. Gittleman, P. Daszak, Global trends in emerging infectious diseases. Nature. **451**, 990-993 (2008). https://doi.org/10.1038/nature06536
15. L. Eisen, S. Lozano-Fuentes, Use of mapping and spatial and space-time modeling approaches in operational control of *Aedes aegypti* and dengue. PLoS Negl Trop Dis. **3**, e411 (2009). https://doi.org/10.1371/journal.pntd.0000411
16. J. Hemingway, H. Ranson, Insecticide resistance in insect vectors of human disease. Annu Rev Entomol. **45**, 371-391 (2000). https://doi.org/10.1146/annurev.ento.45.1.371
17. N.M. Bowman, K. Akialis, G. Cave, R. Barrera, C.S. Apperson, S.R. Meshnick, Pyrethroid insecticides maintain repellent effect on knock-down resistant populations of *Aedes aegypti* mosquitoes. PLoS One. **13**, e0196410 (2018). https://doi.org/10.1371/journal.pone.0196410
18. H. Ranson, R. N'Guessan, J. Lines, N. Moiroux, Z. Nkuni, V. Corbel, Pyrethroid resistance in African anopheline mosquitoes: what are the implications for malaria control? Trends Parasitol. **27**, 91-98 (2011). https://doi.org/10.1016/j.pt.2010.08.004
19. S. Kasai, O. Komagata, K. Itokawa, T. Shono, L.C. Ng, M. Kobayashi, T. Tomita, Mechanisms of pyrethroid resistance in the dengue mosquito vector, *Aedes aegypti*: target site insensitivity, penetration, and metabolism. PLoS Negl Trop Dis. **8**, e2948 (2014). https://doi.org/10.1371/journal.pntd.0002948
20. C. Tourapi, C. Tsioutis, Circular Policy: A New Approach to Vector and Vector-Borne Diseases' Management in Line with the Global Vector Control Response (2017-2030). Trop Med Infect Dis. **7**, (2022). https://doi.org/10.3390/tropicalmed7070125
21. B. Poulin, G. Lefebvre, Perturbation and delayed recovery of the reed invertebrate assemblage in Camargue marshes sprayed with Bacillus thuringiensis israelensis. Insect Sci. **25**, 542-548 (2018). https://doi.org/10.1111/1744-7917.12416
22. M.L. Wong, Z. Zulzahrin, I. Vythilingam, Y.L. Lau, I.C. Sam, M.Y. Fong, W.C. Lee, Perspectives of vector management in the control and elimination of vector-borne zoonoses. Front Microbiol. **14**, 1135977 (2023). https://doi.org/10.3389/fmicb.2023.1135977
23. G. Paz-Bailey, D.B. Jernigan, K. Laserson, E. Zielinski-Gutierrez, L. Petersen, New solutions against the dengue global threat: opportunities for *Wolbachia* interventions. Int J Infect Dis. **157**, 107923 (2025). https://doi.org/10.1016/j.ijid.2025.107923
24. K. Raghavendra, M. Rahi, V. Verma, P.S. Velamuri, D. Kamaraju, K. Baruah, J. Chhibber-Goel, A. Sharma, Insecticide resistance status of malaria vectors in the malaria endemic states of India: implications and way forward for malaria elimination. Heliyon. **8**, e11902 (2022). https://doi.org/10.1016/j.heliyon.2022.e11902
25. J. Vontas, E. Kioulos, N. Pavlidi, E. Morou, A. della Torre, H. Ranson, Insecticide resistance in the major dengue vectors *Aedes albopictus* and *Aedes aegypti*. Pesticide Biochemistry and Physiology. **104**, 126-131 (2012). https://doi.org/https://doi.org/10.1016/j.pestbp.2012.05.008

26. Y. Al Naggar, N.M. Fahmy, A.M. Alkhaibari, R.K. Al-Akeel, H.M. Alharbi, A. Mohamed, I. Eleftherianos, H.R. El-Seedi, J.P. Giesy, H.A. Alharbi, Mechanisms and Genetic Drivers of Resistance of Insect Pests to Insecticides and Approaches to Its Control. Toxics. **13**, (2025). https://doi.org/10.3390/toxics13080681
27. T.G. Davies, L.M. Field, P.N. Usherwood, M.S. Williamson, DDT, pyrethrins, pyrethroids and insect sodium channels. IUBMB Life. **59**, 151-162 (2007). https://doi.org/10.1080/15216540701352042
28. M. Samuel, D. Maoz, P. Manrique, T. Ward, S. Runge-Ranzinger, J. Toledo, R. Boyce, O. Horstick, Community effectiveness of indoor spraying as a dengue vector control method: A systematic review. PLoS Negl Trop Dis. **11**, e0005837 (2017). https://doi.org/10.1371/journal.pntd.0005837
29. A. Sombie, E. Saiki, F. Yameogo, T. Sakurai, T. Shirozu, S. Fukumoto, A. Sanon, D. Weetman, P.J. McCall, H. Kanuka, A. Badolo, High frequencies of F1534C and V1016I *kdr* mutations and association with pyrethroid resistance in *Aedes aegypti* from Somgande (Ouagadougou), Burkina Faso. Trop Med Health. **47**, 2 (2019). https://doi.org/10.1186/s41182-018-0134-5
30. J. Tognarelli, P.R. Moya, C.R. Gonzalez, X. Collao-Ferrada, Global distribution and impact of knockdown resistance mutations in *Aedes aegypti* on pyrethroid resistance. Parasit Vectors. **18**, 382 (2025). https://doi.org/10.1186/s13071-025-06817-9
31. S.R. Mutheneni, A.P. Morse, C. Caminade, S.M. Upadhyayula, Dengue burden in India: recent trends and importance of climatic parameters. Emerg Microbes Infect. **6**, e70 (2017). https://doi.org/10.1038/emi.2017.57
32. N. Gupta, S. Srivastava, A. Jain, U.C. Chaturvedi, Dengue in India. Indian J Med Res. **136**, 373-390 (2012).
33. S. Rani Jena, C. Elanchezhiyan, A. Kumar Sam, U. Gogoi, V. Shende, S. Basu, S. Bandyopadhyay, B. Mandal, B. Biswas, A. Banerjee, K. Baruah, C.P. H, I.P. Bhowmick, Spatio-temporal distribution of dengue cases and vectors along with the interrelationship of environmental and climatic factors in the metropolitan city, Kolkata, India, for 2017-2022: calling implications for vector control. Emerg Microbes Infect. **14**, 2493924 (2025). https://doi.org/10.1080/22221751.2025.2493924
34. D.J. Gubler, Dengue and dengue hemorrhagic fever. Clin Microbiol Rev. **11**, 480-496 (1998). https://doi.org/10.1128/CMR.11.3.480
35. P. National Vector Borne Disease Control, National strategic plan for vector-borne diseases 2020–2025, Ministry of Health and Family Welfare, Government of India2023.
36. P.K. Jangir, A. Prasad, Insecticide susceptibility status on *Aedes aegypti* (Linn) and *Aedes albopictus* (Skuse) of Chittorgarh district, Rajasthan, India. Exp Parasitol. **254**, 108619 (2023). https://doi.org/10.1016/j.exppara.2023.108619
37. P. Prasad, S. Lata, D. Kumar, S.K. Gupta, R. Saxena, D.K. Arya, H. Singh, Susceptibility status of *Aedes aegypti* (Diptera: *Culicidae*) against insecticides of public health use in Delhi and NCR region, India. J Vector Borne Dis. **60**, 300-306 (2023). https://doi.org/10.4103/0972-9062.374044
38. R. Muthusamy, M.S. Shivakumar, Susceptibility status of *Aedes aegypti* (L.) (Diptera: Culicidae) to temephos from three districts of Tamil Nadu, India. J Vector Borne Dis. **52**, 159-165 (2015).
39. M.K. Sumitha, M. Kalimuthu, M.K. Senthil, R. Paramasivan, A. Kumar, B. Gupta, Status of insecticide resistance in the dengue vector *Aedes aegypti* in India: A review. J Vector Borne Dis. **60**, 116-124 (2023). https://doi.org/10.4103/0972-9062.361174

40. M.M. Uddin, A. Islam, M.S. Islam, J.E. Ekra, K. Watanabe, Insecticide susceptibility and knockdown resistance mutations in *Aedes aegypti* and *Culex* species in Bangladesh. Acta Trop. **269**, 107736 (2025). https://doi.org/10.1016/j.actatropica.2025.107736
41. C. Buhler, V. Winkler, S. Runge-Ranzinger, R. Boyce, O. Horstick, Environmental methods for dengue vector control - A systematic review and meta-analysis. PLoS Negl Trop Dis. **13**, e0007420 (2019). https://doi.org/10.1371/journal.pntd.0007420
42. M. Bharati, D. Saha, Assessment of insecticide resistance in primary dengue vector, *Aedes aegypti* (*Linn*.) from Northern Districts of West Bengal, India. Acta Tropica. **187**, 78-86 (2018). https://doi.org/https://doi.org/10.1016/j.actatropica.2018.07.004
43. N. Sinha, N. Gupta, R. Jhamb, S. Gulati, V. Kulkarni Ajit, The 2006 dengue outbreak in Delhi, India. J Commun Dis. **40**, 243-248 (2008).
44. A. Chakravarti, R. Arora, C. Luxemburger, Fifty years of dengue in India. Trans R Soc Trop Med Hyg. **106**, 273-282 (2012). https://doi.org/10.1016/j.trstmh.2011.12.007
45. S. Jain, A. Mittal, S.K. Sharma, A.D. Upadhyay, R.M. Pandey, S. Sinha, M. Soneja, A. Biswas, R.S. Jadon, M.B. Kakade, C. Dayaraj, Predictors of Dengue-Related Mortality and Disease Severity in a Tertiary Care Center in North India. Open Forum Infect Dis. **4**, ofx056 (2017). https://doi.org/10.1093/ofid/ofx056
46. S. Jagtap, C. Pattabiraman, A. Sankaradoss, S. Krishna, R. Roy, Evolutionary dynamics of dengue virus in India. PLoS Pathog. **19**, e1010862 (2023). https://doi.org/10.1371/journal.ppat.1010862
47. A.K. Yadav, D. Namdeo, P. Khare, S. Nema, A. Pakhare, R. Chowdhary, D. Biswas, Serotypic and genotypic profile of dengue virus outbreaks in India between 2011 and 2017. J Vector Borne Dis. **62**, 135-142 (2025). https://doi.org/10.4103/JVBD.JVBD_101_24
48. O. Man, A. Kraay, R. Thomas, J. Trostle, G.O. Lee, C. Robbins, A.C. Morrison, J. Coloma, J.N.S. Eisenberg, Characterizing dengue transmission in rural areas: A systematic review. PLoS Negl Trop Dis. **17**, e0011333 (2023). https://doi.org/10.1371/journal.pntd.0011333
49. A. Padhi, E. Gupta, G. Singh, S. Parveen, A. Islam, B. Tarai, Circulation of DENV-3 Genotype 3 during 2017 to 2018 in Delhi: A Single-Center Hospital-Based Study. J Lab Physicians. **14**, 21-26 (2022). https://doi.org/10.1055/s-0041-1734017
50. S.P. Behera, P. Bhardwaj, H. Deval, N. Srivastava, R. Singh, B.R. Misra, A. Agrawal, A. Kavathekar, R. Kant, Co-circulation of all the four Dengue virus serotypes during 2018-2019: first report from Eastern Uttar Pradesh, India. PeerJ. **11**, e14504 (2023). https://doi.org/10.7717/peerj.14504
51. N. Mondal, The resurgence of dengue epidemic and climate change in India. Lancet. **401**, 727-728 (2023). https://doi.org/10.1016/S0140-6736(23)00226-X
52. J.R. Hernandez, P.V. Pietrantonio, Pyrethroid resistance in *Aedes aegypti:* genetic mechanisms worldwide, and recommendations for effective vector control. Parasit Vectors. **18**, 409 (2025). https://doi.org/10.1186/s13071-025-07010-8
53. M. Murhekar, V. Joshua, K. Kanagasabai, V. Shete, M. Ravi, R. Ramachandran, R. Sabarinathan, B. Kirubakaran, N. Gupta, S. Mehendale, Epidemiology of dengue fever in India, based on laboratory surveillance data, 2014-2017. Int J Infect Dis. **84S**, S10-S14 (2019). https://doi.org/10.1016/j.ijid.2019.01.004
54. R.S. Vaman, M.J. Valamparampil, A.K. Somasundaran, A.J. Balakrishnan, P. Janardhanan, A. Rahul, R. Pilankatta, T.S. Anish, Serotype-specific clinical features

and spatial distribution of dengue in northern Kerala, India. J Family Med Prim Care. **13**, 3049-3058 (2024). https://doi.org/10.4103/jfmpc.jfmpc_1937_23

55. L. Dar, E. Gupta, P. Narang, S. Broor, Cocirculation of dengue serotypes, Delhi, India, 2003. Emerg Infect Dis. **12**, 352-353 (2006). https://doi.org/10.3201/eid1202.050767
56. N. Afreen, F. Deeba, W.H. Khan, S.H. Haider, S.N. Kazim, R. Ishrat, I.H. Naqvi, M.Y. Shareef, S. Broor, A. Ahmed, S. Parveen, Molecular characterization of dengue and chikungunya virus strains circulating in New Delhi, India. Microbiol Immunol. **58**, 688-696 (2014). https://doi.org/10.1111/1348-0421.12209
57. H.E. Clapham, V. Tricou, N. Van Vinh Chau, C.P. Simmons, N.M. Ferguson, Within-host viral dynamics of dengue serotype 1 infection. J R Soc Interface. **11**, (2014). https://doi.org/10.1098/rsif.2014.0094
58. J. Suppiah, S.M. Ching, S. Amin-Nordin, L.A. Mat-Nor, N.A. Ahmad-Najimudin, G.K. Low, M.Z. Abdul-Wahid, R. Thayan, H.Y. Chee, Clinical manifestations of dengue in relation to dengue serotype and genotype in Malaysia: A retrospective observational study. PLoS Negl Trop Dis. **12**, e0006817 (2018). https://doi.org/10.1371/journal.pntd.0006817
59. S.R. Kumar, J.A. Patil, D. Cecilia, S.S. Cherian, P.V. Barde, A.M. Walimbe, P.D. Yadav, P.N. Yergolkar, P.S. Shah, V.S. Padbidri, A.C. Mishra, D.T. Mourya, Evolution, dispersal and replacement of American genotype dengue type 2 viruses in India (1956-2005): selection pressure and molecular clock analyses. J Gen Virol. **91**, 707-720 (2010). https://doi.org/10.1099/vir.0.017954-0
60. S. Gowri Sankar, T. Mowna Sundari, A. Alwin Prem Anand, Emergence of Dengue 4 as Dominant Serotype During 2017 Outbreak in South India and Associated Cytokine Expression Profile. Front Cell Infect Microbiol. **11**, 681937 (2021). https://doi.org/10.3389/fcimb.2021.681937
61. R. Paramasivan, V. Thenmozhi, J. Hiriyan, K. Dhananjeyan, B. Tyagi, A.P. Dash, Serological and entomological investigations of an outbreak of dengue fever in certain rural areas of Kanyakumari district, Tamil Nadu. Indian J Med Res. **123**, 697-701 (2006).
62. S. Gupta, A. Kumar, Design of an Epitope-Based Peptide Vaccine Against Dengue Virus Isolate from Eastern Uttar Pradesh, India. Int J Pept Res Ther. **28**, 91 (2022). https://doi.org/10.1007/s10989-022-10402-4
63. A. Agarwal, R. Ganvir, D. Kale, D. Chaurasia, G. Kapoor, Continued dominance of dengue virus serotype 2 during the recent Central India outbreaks (2019-2021) with evidence of genetic divergence. Pathog Glob Health. **118**, 109-119 (2024). https://doi.org/10.1080/20477724.2023.2246712
64. J. Phadungsombat, E.E. Nakayama, T. Shioda, Unraveling Dengue Virus Diversity in Asia: An Epidemiological Study through Genetic Sequences and Phylogenetic Analysis. Viruses. **16**, (2024). https://doi.org/10.3390/v16071046
65. S. Sundarrajan, S.S. Katta, S. Kn, S. Jagtap, N. C, Temporal genomic diversity of Dengue virus in South India from 2019 to 2024. Acta Tropica. DOI https://doi.org/10.1016/j.actatropica.2025.107934107934 (2025).
66. R. Rico-Hesse, Dengue virus virulence and transmission determinants. Curr Top Microbiol Immunol. **338**, 45-55 (2010). https://doi.org/10.1007/978-3-642-02215-9_4
67. S.B. Halstead, Neutralization and antibody-dependent enhancement of dengue viruses. Adv Virus Res. **60**, 421-467 (2003). https://doi.org/10.1016/s0065-3527(03)60011-4

68. A. Villanes, E. Griffiths, M. Rappa, C.G. Healey, Dengue Fever Surveillance in India Using Text Mining in Public Media. Am J Trop Med Hyg. **98**, 181-191 (2018). https://doi.org/10.4269/ajtmh.17-0253
69. B. Das, S. Datta, Vanlalhmuaka, P.V.B. Reddy, Comprehensive evaluation on progressive development strategies in DENV surveillance and monitoring infection rate among vector population. J Vector Borne Dis. **61**, 327-339 (2024). https://doi.org/10.4103/JVBD.JVBD_86_23
70. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control: New Edition, Geneva, 2009.
71. W.H. Organization, Test procedures for insecticide resistance monitoring in malaria vector mosquitoes. DOI (2016).
72. O. World Health, Dengue: Guidelines for diagnosis, treatment, prevention and control, WHO2016.
73. I. Dusfour, J. Vontas, J.P. David, D. Weetman, D.M. Fonseca, V. Corbel, K. Raghavendra, M.B. Coulibaly, A.J. Martins, S. Kasai, F. Chandre, Management of insecticide resistance in the major *Aedes* vectors of arboviruses: Advances and challenges. PLoS Negl Trop Dis. **13**, e0007615 (2019). https://doi.org/10.1371/journal.pntd.0007615
74. S. Biduda, C.H. Lin, F. Saleh, F. Konradsen, H. Hansson, K.L. Schioler, M. Alifrangis, Temporal Pattern of Mutations in the Knockdown Resistance (*kdr*) Gene of *Aedes aegypti* Mosquitoes Sampled from Southern Taiwan. Am J Trop Med Hyg. **101**, 973-975 (2019). https://doi.org/10.4269/ajtmh.19-0289
75. T. Kaur, R.S. Kushwah, S. Pradhan, M.K. Das, M.P. Kona, Anushrita, R. Mittal, D. Weetman, R. Dixit, O.P. Singh, Knockdown-resistance (*kdr*) mutations in Indian *Aedes aegypti* populations: Lack of recombination among haplotypes bearing V1016G, F1534C, and F1534L *kdr* alleles. PLoS Negl Trop Dis. **19**, e0013126 (2025). https://doi.org/10.1371/journal.pntd.0013126
76. R.B.S. Kushwah, T. Kaur, C.L. Dykes, H. Ravi Kumar, N. Kapoor, O.P. Singh, A new knockdown resistance (*kdr*) mutation, F1534L, in the voltage-gated sodium channel of *Aedes aegypti*, co-occurring with F1534C, S989P and V1016G. Parasites & Vectors. **13**, 327 (2020). https://doi.org/10.1186/s13071-020-04201-3
77. R.C. Reiner, Jr., S.T. Stoddard, T.W. Scott, Socially structured human movement shapes dengue transmission despite the diffusive effect of mosquito dispersal. Epidemics. **6**, 30-36 (2014). https://doi.org/10.1016/j.epidem.2013.12.003
78. D.O. Carvalho, A.R. McKemey, L. Garziera, R. Lacroix, C.A. Donnelly, L. Alphey, A. Malavasi, M.L. Capurro, Suppression of a Field Population of *Aedes aegypti* in Brazil by Sustained Release of Transgenic Male Mosquitoes. PLoS Negl Trop Dis. **9**, e0003864 (2015). https://doi.org/10.1371/journal.pntd.0003864
79. A. Utarini, C. Indriani, R.A. Ahmad, W. Tantowijoyo, E. Arguni, M.R. Ansari, E. Supriyati, D.S. Wardana, Y. Meitika, I. Ernesia, I. Nurhayati, E. Prabowo, B. Andari, B.R. Green, L. Hodgson, Z. Cutcher, E. Rances, P.A. Ryan, S.L. O'Neill, S.M. Dufault, S.K. Tanamas, N.P. Jewell, K.L. Anders, C.P. Simmons, A.S. Group, Efficacy of *Wolbachia*-Infected Mosquito Deployments for the Control of Dengue. N Engl J Med. **384**, 2177-2186 (2021). https://doi.org/10.1056/NEJMoa2030243
80. D.P. Walshe, P. Garner, A.A. Abdel-Hameed Adeel, G.H. Pyke, T. Burkot, Larvivorous fish for preventing malaria transmission. Cochrane Database Syst Rev. DOI 10.1002/14651858.CD008090.pub2CD008090 (2013). https://doi.org/10.1002/14651858.CD008090.pub2

81. Z.S. Yang, A.D. Baua, M.S. Hemdan, W. Assavalapsakul, W.H. Wang, C.Y. Lin, D.Y. Chao, Y.H. Chen, S.F. Wang, Dengue virus infection: A systematic review of pathogenesis, diagnosis and management. J Infect Public Health. **18**, 102982 (2025). https://doi.org/10.1016/j.jiph.2025.102982