

# Dengue Fever in Iran: A Minireview on Current Trends, Challenges, and Strategies for Control and Prevention

Amir Mohammad Naghshe Javaheri<sup>1</sup>, Mohammadreza Ghorani<sup>2\*</sup>, Mahdiye Shirafkan<sup>1</sup>, Alireza Naseri<sup>3</sup>, Ali Mosayebzadeh<sup>4</sup>, Hannaneh Besharat Damirchi<sup>1</sup>, Negar Naseri<sup>5</sup>

<sup>1</sup>Faculty of Veterinary Medicine, University of Tabriz, Tabriz, Iran

<sup>2</sup>Department of Pathobiology, Faculty of Veterinary Medicine, University of Tabriz, Tabriz, Iran

<sup>3</sup>School of Medicine, Arak University of Medical Sciences, Arak, Iran

<sup>4</sup>Department of Theriogenology, Faculty of Veterinary Medicine, Urmia University, Urmia, Iran

<sup>5</sup>Islamic Azad University of Medical Sciences, Sari Branch, Sari, Iran

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## \*Corresponding Author:

Mohammadreza Ghorani,  
Email: mo\_gh66@yahoo.com

## Abstract

Dengue fever (DF), caused by the dengue virus (DENV), is a major global health issue, exhibiting a significant rise in incidence and mortality over recent decades. *Aedes aegypti* and *Aedes albopictus* have been identified as the primary vectors responsible for the transmission of the virus. The disease is spreading notably in regions adjacent to endemic areas. Iran, sharing borders with dengue-endemic countries like Pakistan and Afghanistan, faces an elevated risk of outbreaks. Since the first dengue case in Iran in 2008, there have been multiple instances of imported cases, emphasizing the role of international travel in the dissemination of the virus. Recent seroprevalence studies and the identification of DENV in Iranian provinces without travel history suggest the establishment of indigenous transmission.

The presence of *Aedes aegypti* and *Aedes albopictus* in southern Iran has been confirmed by morphological and molecular analyses, with documented cases of these vectors isolated within the country. This co-occurrence of vectors and autochthonous dengue cases indicates a high risk of sustained transmission. The clinical spectrum of dengue fever ranges from mild febrile illness to severe dengue hemorrhagic fever, necessitating accurate diagnostic methods such as ELISA, virus isolation, and RT-PCR. These tests are crucial for proper identification due to the persistence of DENV antibodies post-infection.

To control dengue disease, Iran has proposed a strategic framework focusing on research, capacity building, inter-organizational collaboration, community mobilization, and enhanced disease management. The experience of the COVID-19 pandemic has highlighted the need for consistent resource allocation towards dengue surveillance. Additionally, the potential role of domestic dogs as reservoirs in the transmission cycle of dengue has been observed, necessitating further research to understand their impact.

In conclusion, Iran must adopt comprehensive and collaborative strategies to prevent dengue outbreaks, considering its proximity to endemic regions and the presence of competent mosquito vectors within its borders. Enhanced diagnostic capabilities, public health initiatives, and robust vector control measures are essential to effectively mitigate the dengue threat.

**Keywords:** Dengue fever (DF), *Aedes aegypti*, Iran, Seroprevalence, Vector control

## Introduction

Dengue fever (DF) is a vector-borne viral infection posing a substantial global health challenge.<sup>1</sup> Dengue virus (DENV) is the causative agent of dengue fever (DF), a globally significant arboviral infection. Severe manifestations, including dengue hemorrhagic fever (DHF), can occur.<sup>2</sup> The incidence of DF has exhibited a marked escalation over the past two decades, with a dramatic surge in reported cases to the WHO from 500-000 in 2000 to 5.2 million in 2019. Mortality associated with DF has experienced a dramatic quadrupling between 2015 and 2019, escalating from 960 to 4032 fatalities.<sup>3</sup>

Approximately 3.9 billion individuals reside in countries endemic for dengue, including Afghanistan and Pakistan, which share a land border with Iran.

## Epidemiology

The endemicity of DENV in neighboring countries, such as Afghanistan and Pakistan, which share a border with Iran, is considered a significant risk factor for the potential introduction and subsequent spread of the virus into Iran.<sup>4</sup> DENV emerged as a public health concern in Iran in 2008 following the index case of dengue fever, identified in a patient with a history of recent travel to

Malaysia.<sup>5</sup> The second instance of DENV importation into Iran was documented in 2015. A patient with a recent travel history to India exhibited clinical manifestations consistent with dengue fever and subsequently tested positive for DENV-2 genotype 4, identical to strains circulating in India.<sup>6</sup> These findings underscore the crucial role of international travel in the dissemination of the disease, facilitating the translocation of pathogens from endemic to non-endemic regions. The identification of DENV cases among individuals without a travel history, specifically residing in Iranian provinces bordering Pakistan (Sistan and Baluchestan) and Iraq (Kurdistan), strongly implies the establishment of indigenous dengue transmission within Iran due to geographic proximity to endemic regions. Seroprevalence studies conducted between 2016 and 2017 indicated a DENV positivity rate of 6.27% among patients presenting with rash and fever, indicating a significant presence of the virus in the studied population.<sup>7</sup> The seroprevalence data conclusively demonstrate the endemic circulation of DENV within Iran, particularly in regions adjacent to DENV-endemic nations. Evidence indicates the widespread presence of dengue virus in Iran, with confirmed human cases detected in multiple provinces. These provinces include Sistan and Baluchestan, Bushehr, Hormozgan, Kerman, Yazd, South Khorasan, Razavi Khorasan, Khuzestan, Ilam, Kurdistan, Tehran, Mazandaran, and Gilan. This geographic distribution highlights the significant challenge posed by dengue in Iran and underscores the need for comprehensive prevention and control measures.<sup>5,7-10</sup>

### **Aedes Aegypti and Aedes Albopictus**

*Aedes aegypti* and *Aedes albopictus* are indeed the primary vectors responsible for the transmission of dengue virus (DENV). Their prevalence in tropical and subtropical regions aligns with the geographic distribution of dengue. The dengue virus circulates in a simple transmission cycle involving only humans as hosts and *Aedes* mosquitoes as vectors. There is no intermediate host involved in this process. Consequently, the spatial heterogeneity in vector populations significantly impacts the epidemiological patterns of the disease.<sup>1,4,11</sup> Recent morphological and molecular analyses have verified the presence of *Aedes aegypti* in southern Iran.<sup>12</sup> Both *Aedes aegypti* and *Aedes albopictus* were independently isolated within Iranian borders in 2009 and 2013.<sup>13</sup> *Aedes albopictus*, a highly adaptable mosquito capable of inhabiting diverse climatic conditions, poses a significant threat. This species, along with *Aedes unilineatus*, has been documented in southeastern Iran between 2012 and 2014. Notably, *Aedes unilineatus* has been implicated as a dengue virus vector in Karachi, Pakistan, raising concerns about its potential role in the transmission of dengue within Iran.<sup>14</sup> The co-occurrence of competent vectors of dengue virus, *Aedes aegypti* and *Aedes albopictus*, within Iranian territory, coupled with documented autochthonous dengue cases,

underscores a heightened risk of sustained dengue transmission and potential outbreaks within the region.

### **Symptoms and Diagnostic Tests of Dengue Virus Infection**

Dengue virus infection exhibits an incubation period ranging from 4 to 10 days, followed by a heterogeneous clinical presentation characterized by a spectrum of symptoms and unpredictable disease progression.<sup>15</sup> The majority of dengue infections manifest as a self-limiting illness characterized by mild symptoms including fever, cephalalgia, rash, and myalgia/arthritis, leading to complete recovery.<sup>1</sup> A minority of patients experience severe dengue, characterized by acute abdominal pain, cardiovascular, pulmonary, and hepatic dysfunction, and plasma leakage, which may or may not culminate in hemorrhagic manifestations, collectively termed dengue fever or dengue hemorrhagic fever. The hemorrhagic manifestation of dengue can be misdiagnosed as other hemorrhagic diseases. Definitive diagnosis of DENV infection typically involves laboratory testing, including ELISA for antibody or antigen detection, virus isolation, and RT-PCR. Notably, DENV antibodies may persist in the bloodstream for up to 2-3 months post-infection.<sup>1,9,15</sup>

### **Dengue Vector Prevention and Control Policies**

Five strategic frameworks have been proposed for the prevention and control of dengue, a disease vectorially transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes, within the Iranian territory.<sup>16</sup> The following strategic interventions were proposed:

1. Investment in fundamental and applied research to optimize vector control strategies and foster the development of novel tools, technologies, and approaches;
2. Enhancement of human, infrastructural, and public health system capacities at all societal levels to facilitate the prevention, control, surveillance, and carrier assessment of dengue;
3. Augmentation and fortification of inter-organizational and external collaborative networks;
4. Mobilization and engagement of community members in the control of mosquito breeding sites;
5. Expansion and integration of disease management capabilities and tools.

A comprehensive and collaborative approach involving sustained support from local, national, and regional stakeholders is imperative to optimize the long-term efficacy of these policies.

### **Treatment**

Dengue is an acute febrile illness predominantly prevalent in tropical regions. While most cases are self-limiting, severe disease characterized by dengue hemorrhagic shock can result in fatal outcomes. While presumptive diagnosis is commonly employed by tropical medicine practitioners for dengue, a definitive diagnosis necessitates

the utilization of immunological or virological assays. The primary therapeutic intervention for dengue focuses on symptomatic relief and supportive care. While the development of antiviral drugs for dengue fever has been historically limited, recent research efforts have significantly intensified in pursuit of effective therapeutic interventions.<sup>17</sup>

### Dengue Fever in Domestic Dogs

A recent study conducted in Thailand revealed the presence of dengue virus strains circulating within domestic dog populations in dengue-endemic regions.<sup>18</sup> DENV serotypes 2 and 3 were identified as circulating in the domestic dog population of the dengue-endemic region. The canine subjects exhibited no overt signs of illness during the study period, aligning with observations made in non-human primate models.<sup>19,20</sup> In accordance with WHO guidelines, the diagnosis of dengue virus infection currently relies on a combination of serological, virological, and molecular detection methods.<sup>21</sup> A variety of mammalian cell lines, including those derived from monkey, baby hamster, and dog kidney tissues, have been assessed for their susceptibility to DENV infection.<sup>21-28</sup> The collective findings of these studies support the hypothesis that DENV possesses the capacity to infect canine cells, suggesting the potential for dogs to serve as hosts for the virus. RT-PCR exhibits exceptional sensitivity in detecting minimal viral RNA concentrations in a sample, enabling the identification of active viral replication.<sup>28,29</sup> Investigations into the hematophagic behavior of *Aedes* species have identified canines as potential host organisms. *Aedes albopictus* mosquitoes in rural areas of Singapore exhibit hematophagic behavior targeting both humans and canines.<sup>30</sup> A study by Ponlawat et al revealed that both *Aedes aegypti* and *Aedes albopictus* mosquitoes collected from various regions of Thailand between 2003 and 2004 had blood-fed on both humans and dogs.<sup>31</sup>

### Conclusion

Dengue fever is an arboviral infection transmitted to humans primarily through the bite of infected *Aedes* mosquitoes, posing a significant and escalating global health threat. Iran, traditionally considered a non-endemic region for dengue, faces a growing risk due to its geographic proximity to dengue-affected nations and the presence of suitable mosquito vectors within its borders. Multiple dengue virus genotypes have been detected in Iran, with epidemiological evidence indicating both imported and locally acquired cases. A comprehensive strategy to mitigate the risk of dengue fever necessitates a multi-faceted approach encompassing robust vector control measures, extensive public health education initiatives, and enhanced diagnostic and therapeutic capacities. Two distinct dengue virus serotypes have been identified within asymptomatic canine populations. Canine hosts may serve as potential reservoirs for the dengue virus, facilitating its transmission through

hematophagous arthropod vectors. Further research is imperative to elucidate the precise role of domestic canines in the transmission cycle of dengue virus, including their potential as viral reservoirs and amplifying hosts.

### Competing Interests

The authors declare that there is no conflict of interest.

### Data Availability Statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

### Ethical Approval

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

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