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Beyond Mosquito Vectors: A Typical Transmission Routes of Dengue Virus

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Abstract

Dengue fever remains an annual worldwide threat to human health, even though *Aedes* eradication programs based on the typical route of mosquito- borne transmission have successfully controlled dengue epidemics to a considerable extent. Interestingly, most cases of dengue infection in humans reported in the tropical regions of Asia, Oceania, Africa, and the Americas are due to horizontal transmission. This suggests contribution of atypical transmission routes to continuous infections.

Keywords: Dengue virus; Transmission routes; Atypical transmission routes; Aerosol; Sexual route

Introduction

The first recorded outbreaks of dengue virus (DENV) in humans occurred in tropical regions worldwide, including the Caribbean Islands, Asia, Africa, and the Americas [1]. Epidemiological pattern tracking has shown their global occurrence every 20 to 40 years [2]. Pathological epidemiology research has elucidated the pathogenic underpinnings of DENV infections to understand their patterns better and develop more effective interventions. DENV belongs to the family *Flaviviridae* with four well-characterized serotypes, namely DENV-1–4. DENV-5 has also been identified but not thoroughly characterized [3]. DENV-1–4 infections can manifest as a range of symptoms, from the mild and self-limited form of dengue fever (DF) to the more severe and life-threatening forms of dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). In the past 50 years, the morbidity of these infections has increased substantially, and at least 120 countries have been classified as their epidemic areas [4].

Currently, 2.5 billion people are estimated to be at risk of DENV infections worldwide, with approximately 50 million newly diagnosed cases annually approximately 20,000 of which result in death [5]. In Asia, DHF/DSS has emerged as one of the most important causes of pediatric hospitalization and death. Despite appropriate supportive treatments following confirmed infection, the mortality rate remains high at approximately 5% [6].

Neither DENV-specific vaccines nor therapies are available due to the absence of an appropriate animal model to fully elucidate the vector-to- host pathogenesis of DENV infections. Current rudimentary knowledge on DENV transmission suggests a pattern of outward geographic spread of the virus between tropical (vector) environments into rural (human) communities via a primitive enzootic mosquito-human-mosquito cycle [7]. Thus, its epidemic spread to tropical urban communities is considered toprimarily occur via infected humans or mosquitoes [8].

Aedes aegypti and *A. albopictus* are the primary and secondary vectors of DENV horizontal transmission, respectively. The DENV in the blood of an infected human inhibits the innate immune response in the salivary glands of the uninfected feeding mosquito, leading to a higher salivary infection rate [9]. Within 8–12 days, the virus replicates repeatedly, reaching a titer sufficient to transform the mosquito into a viremic "vector" capable of DENV transmission to humans [10].

In contrast, an uninfected human bitten by an infected mosquito will develop viremia within 4 days, remaining viremic for 5–12 days (Figure 1) [11]. Although primary human DENV-1–4 infections are often asymptomatic, few cases may progress to DF and even fewer to DHF/DSS. However, the majority of secondary infections, with a different serotype from the first, result in DHF/DSS, characterized by increased vascular permeability and eventual hemorrhage [12], with rare cases of neurological abnormalities such as encephalitis [13].

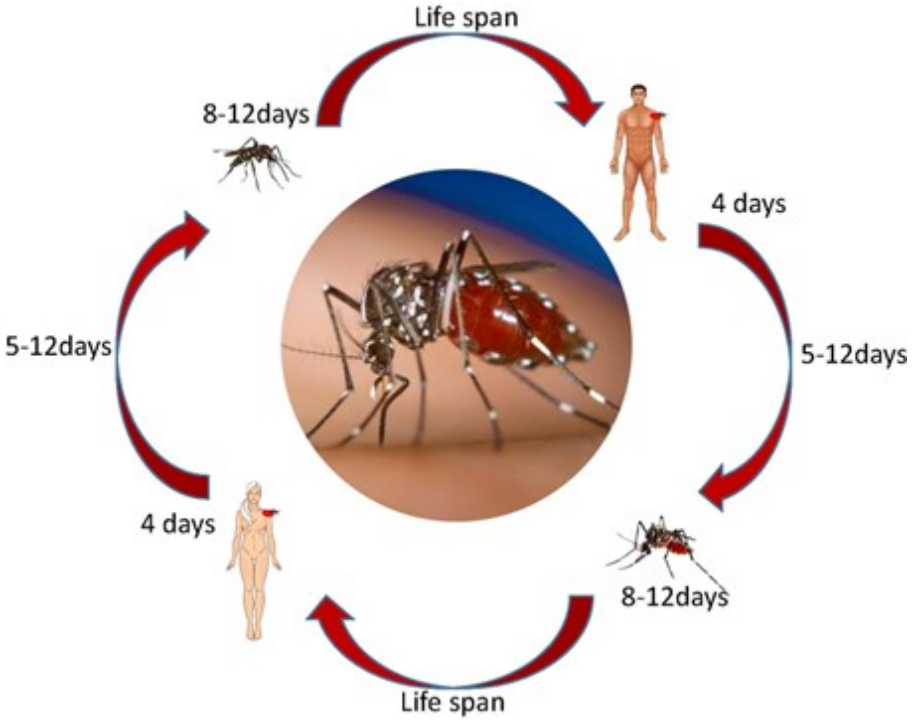

Figure 1: Mosquito-human-mosquito transmission cycle of the dengue virus (DENV). After the DENV enters a healthy host (such as when an uninfected human is bitten by an infected mosquito, or when an uninfected mosquito feeds on the blood of an infected human), it requires time to replicate in the host to reach a titer sufficient for transmission. This requires 4 days in humans, and 8–12 days in mosquitos. The transmission-viable time periods are indicated by red arrows (5–12 days for humans and life span for mosquitos).

In addition to mosquito vectors, human host- and vector-related pathogenic pathways have been investigated. Human antibodies responsive to mosquito salivary proteins have been identified and suggested as potential biomarkers of a mosquito-borne transmission route [14]. The mosquito- human-mosquito infection cycle has been extensively investigated [7]. Several mosquito larval factors and basic biological characteristics attributed to DENV transmission have been identified [15, 16], including Human lifestyle, population density, and immunity [17, 18]. Environmental factors, including climate and temperature, also affect its transmission in both mosquitoes and humans [19, 20, 21]. Finally, the interactive effect of other pathogens on DENV transmission has been identified, such as a potential protective effect of the arthropod-infecting bacterial genus *Wolbachia*, which led to the proposal of a *Wolbachia*-mediated blockade strategy of DENV transmission in some mosquitoes [21, 22, 23].

Both vertical and horizontal transmission modes of DENV are important, including atypical modes that bypass the mosquito vector route. This review focuses on some of the atypical transmission routes, especially aerosol and sexual transmission, which can serve as a guide for more effective monitoring and eradication strategies. This review highlights the importance of routine monitoring of populations at high risk for these atypical infection routes for the implementation of future dengue eradication programs.

Mosquito-Borne Transmission of DENV

The earliest recorded mosquito-borne DENV infection was reported in the Chinese Encyclopedia of Disease Symptoms and Remedies, published during the Chin Dynasty (265–420 AD) [24]. However, it was not until the mid-20th century that the role of *Aedes* mosquitoes in the transmission of DENV was established, following epidemiological studies conducted during several widespread outbreaks of DENV infections globally [10]. World War II and international business expansion have been implicated as important factors facilitating the transmission of mosquito-borne diseases worldwide [25].

A subsequent eradication program targeting the *Aedes* vector was implemented in the 1950s that helped to effectively control the

DENV epidemic over the next two decades [2]. However, after the program was discontinued in the 1970s, *Aedes* mosquitoes reinvaded the regions, followed by the reoccurrence of DENV epidemics [26]. From a pathological epidemiology standpoint, this phenomenon confirmed the theory that *Aedes* mosquitoes are the major transmission vectors of DENV. Laboratory researchers began to explore the molecular pathological basis of mosquito-borne DENV transmission in humans [27; 28]. Antigens for the different serotypes of DENV were detected in mosquitoes following their oral infection, and the resultant morbidities in newborn mice exposed to the mosquitoes intrathoracically inoculated with DENV were determined [29]. In addition, the presence and kinetics of actively replicating viruses were observed in immunocompromised mice (*Irf3/7*$^{-/-}$) [30]. Interestingly, different strains of *Aedes* mosquitoes were also found to exhibit varying sensitivities to different DENV serotypes [28; 31].

The natural vertical transmission of DENV among mosquitoes was determined to be an alternative transmission route [32], bypassing the human vector, supporting eventual human infection and the persistent increase in human epidemics [33]. To date, at least 42 studies have reported the natural vertical transmission of DENV in mosquitoes sourced from several countries (Cuba, Peru, Mexico, Argentina, Florida, Indonesia, Thailand, and India, among others) [34, 35, 36, 37, 38, 39].

Considering mosquitoes as the major transmission vectors of DENV, researchers have largely focused on insects to develop methods for the blockade of DENV transmission. These approaches have included manipulation of the mosquito genome for disrupting DENV replication in the salivary glands,[40] increasing the expression of mosquito anti- pathogen effectors, and replacing major vectors with laboratory- engineered incompetent vectors [41]. Both entomologists and epidemiologists have contributed to development in this research field by designing efficient methods to control DENV transmission in mosquitoes.

Aerosol Transmission of DENV

Cases of aerosol transmission are particularly intriguing amongst those of atypical DENV transmission reported since 1990 as intranasal or aerosol transmission routes have been confirmed among most arboviruses and influenza A viruses [42; 43] but not for DENV. However, 35–38% patients with DENV infections exhibit respiratory symptoms, including sore throat, cough, and nasal congestion [44], though the virus has been rarely isolated from their upper respiratory tract [45].

In 2008, a team from the Beth Israel Deaconess Medical Center (Boston, MA, USA) reported 21 confirmed cases of nosocomial dengue among healthcare workers during a serological screening performed in a hospital in India [46], leading them to consider aerosol transmission as the mode of infection [42].

Speculated that the results of experimental intranasal introduction of a DENV suspension in animals or human volunteers can further support the hypothesis of aerosol transmission. However, this has not been widely accepted in the research community. These arguments were based on findings from rare case reports of contact infections in laboratories or hospitals from infected *Aedes* mosquito bites or accidental inoculation of the virus into the skin. Any report of atypical transmission in DENV-endemic countries is not available in the publicly accessible literature. Therefore, it was proposed that contact between mosquitoes and patients with dengue and healthcare workers, owing to the lack of quarantine measures, can have ultimately caused infection in these 21 cases rather than aerosol transmission. We consider this to be unlikely for several reasons.

First, statistical analysis of data from DENV infections can yield anamorphic results because of the high rate of asymptomatic infections occurring after primary contact [47; 48]. Thus, it is possible that some healthcare workers in the hospital developed asymptomatic DENV infections over time, preventing detection. Even if the patients had developed DF, those not identified by the researchers/clinicians can have caused a misdiagnosis during the preliminary assessment as DF is a self- limited acute febrile illness, with non-specific symptoms [8].

Second, DENV transmission and infection are endemic to the region where this study was conducted. The primary exposure to the virus could have stimulated the immune response, such as when a healthcare worker came in direct contact with a DENV-con-

taminated sample. If this event remained unnoticed, the patient could have developed natural immunization to the virus [10]. The possibility of its aerosol transmission cannot be ruled out without thorough long-term serological screening, while tracking each member of the study population (i.e., healthcare workers) from the date of employment in each hospital and laboratory where they may have encountered the virus.

The latest epidemiological study on DENV was conducted in Bangkok, Thailand [49], which aimed to determine its transmission chain by analyzing sequencing data and serology. The results showed a remarkable absence of transmission chains, despite Bangkok being a considerably high-density area. This suggests the likely involvement of other routes of transmission in addition to the usual vector-borne transmission route. Human nasal inoculation studies were conducted in volunteers during World War II. With dosage of one million or ten thousand minimal infective dose per milliliter, two of six study participants presented with typical DF, with the remaining showing very mild or negligible illness and rash [10].

Our latest study [50] showed dose-dependent survival rates in suckling and immunodeficient adult mice after intranasal DENV-2 inoculations, and 100% mortality of the suckling and immunodeficient adult mice inoculated with either 60 or 6×10^3 plaque-forming DENV-2 units. Collectively, these data support the hypothesis of an aerosol transmission route for DENV of appropriate viral titer.

Sexual Transmission of DENV

A notable atypical DENV transmission route is sexual transmission (Figure 2), which was recently not only suspected [51] but also confirmed in a human case from a non-pandemic are [52]. This is biologically plausible given the well-documented sexual routes of infection for multiple vector- borne arboviruses [53; 54]. Moreover, DENV has been found in multiple body fluids [55; 56] and mucocutaneous contact infections have been quantitatively detected [57]. Notably, sexual transmission has been confirmed in *A. albopictus* [58]. However, until recently, only isolated sexual transmission cases of DENV were reported in humans, indicating that the natural mucous membrane-dependent transmission route, though feasible, is rarely occurs in pandemic areas.

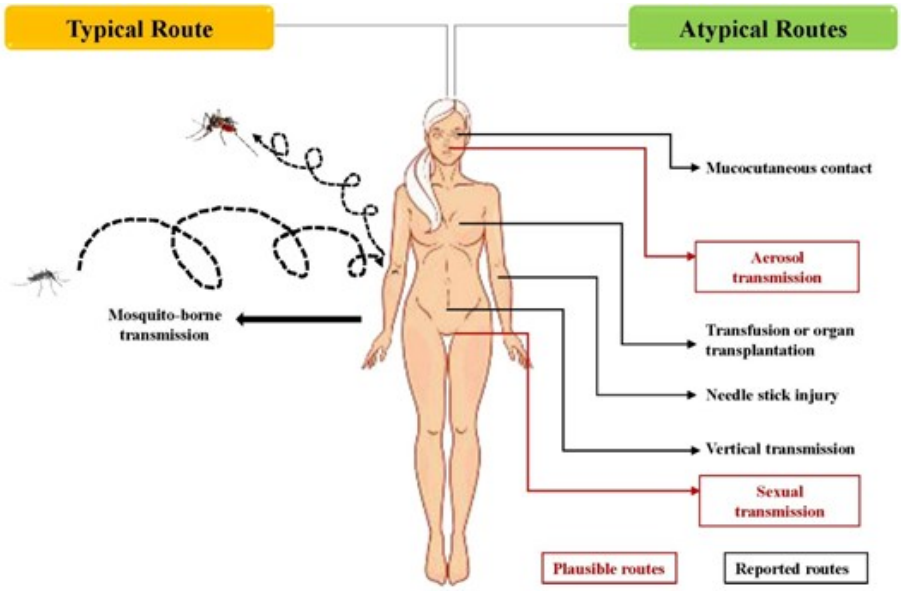

Figure 2: Transmission routes of the dengue virus presented in this review. The typical route is shown on the left, and the atypical routes on the right, with plausible routes in red and reported routes in black.

Other Atypical Transmission Routes of DENV

Other atypical transmission routes of DENV reported in literature include mucocutaneous contact, accidental exposure (needlestick injury, or contaminated blood or organs), and mother-to-fetus vertical transmission. In 2002, Chen and Wilson [57] reported a case wherein a healthcare worker was exposed to the virus due to accidental blood splash from an infected individual into their eyes, nose, and mouth. Typical symptoms of infection appeared 10 days later, suggesting the possibility of mucocutaneous transmission of DENV via exposure at appropriate viral titer. Since 1990, minimum five cases of human DENV infection caused by needlestick injury have been reported [59, 60, 61, 62]. All infected patients, who were the source of the contaminated fluid, were viremic at the time of observation (i.e., each milliliter of serum contained 10^9 copies of viral RNA) [63]. Therefore, despite the exceedingly low mean volume of contaminated blood delivered and rarity of such events, needlestick injuries are a seemingly viable route for DENV transmission [64].

Another atypical source of DENV exposure is receipt of blood or organs with undetected viral infection[65; 66; 67] which are supplied before the donor presents with any symptoms of infection. Therefore, infection is diagnosed only upon the development of typical DF symptoms in the donor, recipient, or both. The addition of DENV screening to routine diagnostic tests for donors can prevent such situations and reduce or eliminate the risks of such transmission [68]. Donor-recipient DENV transmission has persisted for nearly two decades because this atypical route has not been sufficiently explored.

Several cases of mother-to-fetus vertical transmission have been reported from 1994 to 2017[55, 69, 70, 71, 72, 73, 74]. In such cases, distinct trends of association between DENV infection during pregnancy and high rates of preterm birth, low birth weight, and miscarriages, but very few congenital abnormalities, have been observed. In few cases, severe infection led to maternal and fetal mortality [75]. DENV in breast milk was detected and quantified in a subsequent study [55], indicating the possibility of it being present in and transmitted via other body fluids as well, and further supporting the possibility of the sexual transmission route.

Conclusion

Infected mosquito bite (vector) is the best recognized and possibly the most common transmission route for DENV infection. Very few case reports suggest the possibility of other (atypical) transmission routes [46, 75, 76], causing atypical transmission routes and their existence or degree of contribution to the global burden of DENV infection to be largely unidentified.

This review elucidates the occurrence of DENV transmission via atypical routes and highlights its potential risk among researchers and healthcare workers. Based on this review of literature and our laboratory's investigative outcomes, we hypothesize the plausibility of aerosol and sexual transmission routes as alternative modes of transmission. Further research on these atypical routes is warranted.

Various established and readily available methods, including serological tests and mosquito salivary protein biomarker detection, can be used to investigate DENV transmission routes. Extensive research on this topic can provide insights for improving preventive measures in high-risk populations and instances of human contact with DENV infection.

Asymptomatic individuals potentially infecting mosquito vectors [47] indicates the danger of disregarding atypical routes of transmission and widespread serological testing, thus enabling the unmonitored spread of DENV infection. The evidences that DHF develops from previously undiagnosed infections when the DENV viral load exceeds the disease- causing threshold should be acted upon.

Healthcare and laboratory workers face an inherent and urgent risk of exposure to DENV. Although it is generally designated for low-risk containment in such settings, measures should be taken to increase awareness of potential atypical routes of infection, and methods of their prevention and control, especially among individuals working on culturing DENV, performing animal exper-

iments, and analyzing clinical samples.

We believe that relevant agencies and institutions, both public and private, should pay greater attention toward the testing and monitoring of asymptomatic DENV infections and their atypical transmission. Such efforts will provide an in-depth understanding of DENV and its pathogenesis and epidemiology, and help develop a comprehensive DENV prevention program with maximal effectiveness.

Author Contributions

LJT and QMY conceived and designed the study. QMY, ZLX, DXY, and ZXY acquired and analyzed the references. QMY and LJT drafted the manuscript. All authors revised it critically for important intellectual content. All authors gave approval for the final version to be published, and agree to be accountable for all aspects of the work.

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Declaration of Interests

None.

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