



# DENGUE FEVER IN TURKEY: CASES AND PUBLIC HEALTH IMPLICATIONS

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**SUMMARY** – Dengue virus is endemic in almost all tropical and sub-tropical countries which also are popular tourist destinations, and it is a major international public health problem. Presented herein are six travel-associated dengue fever cases diagnosed between 2016 and 2017 in Turkey. The current situation in Turkey and in the world, as well as epidemiological data regarding the vector and relationship between the disease and traveling are also discussed. This retrospective study evaluated dengue fever cases identified using serological and molecular methods between January 2016 and February 2017 in the National Virology Reference Laboratory. Two patients had a travel history to Maldives, two patients to Thailand, one patient to Sri Lanka, and one patient to Guiana. Fever was present in all cases. The most common other symptoms were fatigue, myalgia, and arthralgia. Increased liver enzymes (50%) and thrombocytopenia (66%) were the most commonly encountered laboratory changes. In conclusion, imported dengue fever cases are increasingly reported due to facilitation of international travels and increasing commercial activities. Before traveling to a region where dengue fever is endemic, consulting a travel medicine counseling desk or a doctor is suggested. Dengue fever should be kept in mind in a patient with travel history presenting with fever, elevated liver enzyme and thrombocytopenia.

**Keywords:** *Dengue fever; Dengue virus; Travelers*

## Introduction

Dengue virus, a member of the *Flavivirus* genus of the *Flaviviridae* family, exists as four types (DENV

1, DENV 2, DENV 3 and DENV 4)<sup>1-3</sup>. Human transmission occurs by the mosquito species *Aedes aegypti* and *Aedes albopictus*. The virus leads to a flu-like disease with fever, arthralgia and rash. The infection is rarely fatal. For the last decade, the incidence of dengue fever has shown a dramatic increase throughout America, South-East Asia, Western Pacific, Africa and Eastern Mediterranean. It is estimated that, annually, a total of 396 million people throughout the world are being infected with this virus, 96 million develop

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Received November 9, 2017, accepted September 13, 2018

symptoms, and nearly half of the human population are under risk<sup>4</sup>. Dengue fever is the most commonly encountered arboviral infection and it is prevalent among travelers<sup>5</sup>.

Presented herein are six travel-associated dengue fever cases diagnosed in 2016 and 2017 in Turkey. The current situation in Turkey and in the world, as well as epidemiological data regarding the vector and the relationship between the disease and traveling are also discussed.

## Materials and Methods

This retrospective study evaluated dengue fever cases identified using serological and molecular methods between January 2016 and February 2017 in the National Virology Reference Laboratory.

### Laboratory methods

All tests were performed in the Arboviral and Viral Zoonotic Diseases Unit, National Virology Reference Laboratory. Antibodies against DENV types 1, 2, 3 and 4 were assessed using enzyme-linked immunosorbent assay (ELISA) (Euroimmun, Lübeck, Germany) and immunofluorescence assay (IFA) (Euroimmun,

Lübeck, Germany); dengue virus real-time polymerase chain reaction (RT-PCR) was performed for molecular analyses. All samples were transported at +4 °C and stored at -25 °C until the day of analysis. Any possible cross reactions against flavivirus mosaic 1 virus, tick-borne encephalitis virus, yellow fever virus, West Nile virus and Japanese encephalitis virus were excluded by the respective IFA.

### Interpretation of data

A clinical and epidemiologic surveillance program was initiated upon the occurrence of 6 cases in 2016 and 2017. Clinical and laboratory characteristics of the cases were assessed, and environmental risk factors, as well as epidemiologic features of the countries that these patients had travelled to, were evaluated. Data regarding age, gender, place and duration of travel, clinical and laboratory findings and clinical course were analyzed.

## Results

Three cases were identified in June 2016, August 2016 and October 2016, and the remaining three were detected in January 2017. All patients were male

Table 1. Demographic, clinical and epidemiological characteristics of dengue fever cases in 2016 and 2017

Gender	Age (yrs)	City of residence	Travel history	Clinical characteristics	Laboratory results	Date of diagnosis	Outcome	Mosquito contact
Male	30	Istanbul	2 days before Guiana	Fever, thrombocytopenia, increased liver enzymes	IgM (+) IgG (+)	October 2016	Cure	Present
Male	26	Adana	6 days before Maldives	Fever, thrombocytopenia, increased liver enzymes	IgM (-) IgG (-) PCR (+)	August 2016	Cure	Present
Male	33	Istanbul	3 days before Thailand	Fever, myalgia	IgM (+) IgG (+) PCR (-)	June 2016	Cure	Present
Male	49	Istanbul	4 days before Maldives	Fever, fatigue, arthralgia	IgM (+) IgG (+)	January 2017	Cure	Present
Male	27	Bursa	10 days before Sri Lanka	Fever, thrombocytopenia, increased liver enzymes	IgM (+) IgG (+)	January 2017	Cure	Present
Male	50	Istanbul	9 days before Thailand	Fever, thrombocytopenia	IgM (+) IgG (+)	January 2017	Cure	Present

and aged 26-50 years. Four patients were reported from Istanbul, one from Adana, and one from Bursa as imported cases of dengue fever. Two patients had a travel history to Maldives, two patients to Thailand, one patient to Sri Lanka, and one patient to Guiana. All patients confirmed mosquito exposure. No risk factor such as being very young or very old, having immunosuppression or presence of a comorbid disease or re-infection was present in any of these patients.

Fever was present in all cases. The most common other symptoms were fatigue, myalgia and arthralgia. Increased liver enzymes (50%) and thrombocytopenia (66%) were the most commonly encountered laboratory changes. All patients were positive for dengue virus IgM and IgG antibodies, while one patient was also positive for dengue virus PCR. None of the cases showed abdominal pain, intense vomiting or bleeding, the warning signs of dengue hemorrhagic fever.

All cases recovered completely. Demographic, clinical and epidemiological characteristics of the patients are shown in Table 1. Most of our cases were travelers to a South-East Asian country. The reported numbers of cases from the countries that our patients had travelled to are listed in Figure 1<sup>6</sup>.

## Discussion

Diagnostic criteria for suspected dengue fever include the presence of fever and at least two of the following criteria in a patient who had been/traveled to an endemic region: nausea/vomiting, rash, myalgia/arthralgia, positive tourniquet test, and leukopenia<sup>7</sup>. Presence of fever, traveling to an endemic region, and myalgia/arthralgia were found in our cases.

According to the World Health Organization (WHO) classification, dengue fever ranges from asymptomatic disease, mild non-specific fever and classic dengue to dengue hemorrhagic fever. Infections with DENV-2 and DENV-3 types may have a more severe and mortal course<sup>8</sup>.

Following the bite of an infective *Aedes* mosquito, the virus starts to replicate in the lymph nodes and spreads hematogenously in 2-3 days. The incubation period is 4-10 days. In our patients, the incubation period ranged from 2 to 10 days. Patients usually have fever lasting for 2-7 days, severe headache, facial flushing, retro-orbital pain, severe myalgia/arthralgia, abdominal tenderness, nausea/vomiting, and hyperesthesia on the skin. As fever resolves in 3-4 days, macular and scarlatiniform rashes develop in 50% of the cases<sup>1,9,10</sup>. Neurological symptoms may be due to

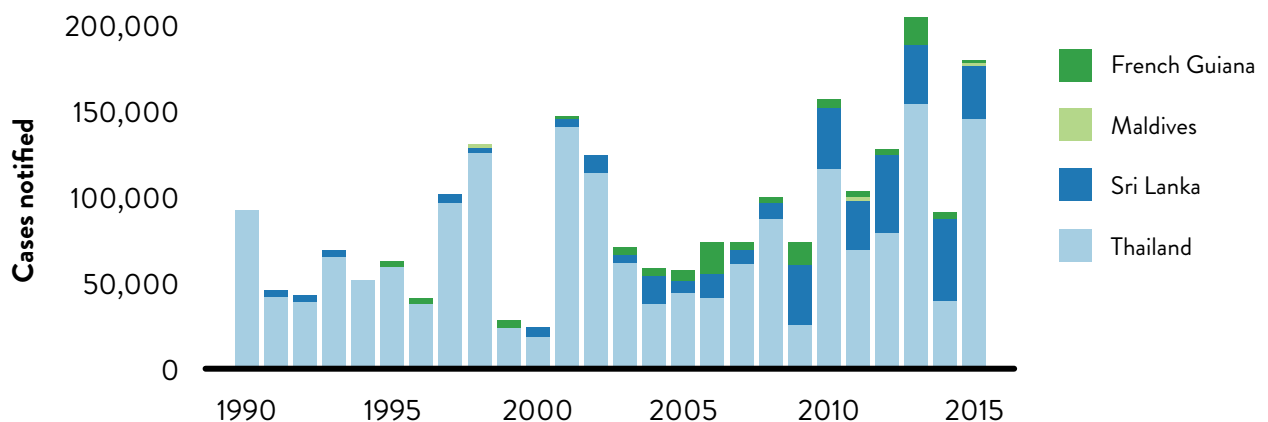


Fig. 1. Number and yearly distribution of dengue fever cases in countries where our patients had travelled to.

intracerebral hemorrhage or secondary to encephalitis by the virus<sup>1,9,10</sup>. All cases in our study had fever, and other common symptoms were arthralgia, myalgia and fatigue. Of all cases, 11% show hepatic enzyme elevations up to 10-fold<sup>9,10</sup>. Liver enzymes were found to be elevated in half of our cases.

A definitive diagnosis can be achieved through virus isolation, PCR detection of viral RNA, demonstration of seroconversion of IgM or IgG, or documentation of an at least 4-fold titer increase (confirmation is needed by re-testing a second sample after >7 days). In our study, definitive diagnosis of dengue fever was established by a positive PCR result in one patient, and by demonstrating increase in IgG titers in the remaining five cases. Dengue IgM can be detected in 50% of the patients within the first 3-5 days, in 80% of the patients after 5 days, and in 99% of the patients after 10 days after the onset of fever. Cross reactions may occur between malaria and leptospirosis. Therefore, laboratory results must be interpreted with clinical findings and epidemiological background. A novel rapid NS1 antigen test offers a sensitivity rate of 80%-87.5% on the first day of fever, without needing a re-test<sup>10-12</sup>.

The prevalence of dengue fever among travelers has been reported to be 7%-45%. It is the most commonly occurring febrile condition among those returning from Asia, Caribbeans and Latin America<sup>5</sup>. The results of four prospective studies reveal an incidence of 10.2-30/1000 person months, depending on the region and duration of stay. In our study, most of the patients had South East Asia travel history.

In vulnerable populations, these import cases may initiate dengue fever epidemics with attack rates of 50%-70%<sup>13-16</sup>. Except for a few fatal cases reported, dengue fever generally tends to show a milder course in travelers than in the cases residing in endemic areas<sup>17-19</sup>. In our study, all patients recovered completely.

In the GeoSentinel study, which was conducted in 24 countries, a total of 42,173 tourists between 2007 and 2011 were evaluated, and dengue fever was reported to be the third most commonly occurring travel-associated disease<sup>20</sup>. In Saudi Arabia, several epidemics of dengue fever were reported in 2006 (n=80), 2008 (n=160) and 2010 (n=147), which have been believed to be pilgrimage-related<sup>21</sup>. In a Canadian study in 4,365 tourists between 2009 and 2011, dengue fever prevalence was found to be 7.1% and it was reported

to be most prevalent among travelers to Latin America<sup>22</sup>. Another study in Germany evaluated a total of 119 dengue fever cases among travelers between 2007 and 2011, in which the authors report that the disease was most frequent among travelers from South East Asia (54.6%), the most common symptoms were fever (97.5%), headache (47.9%) and myalgia/arthralgia (42%), and the most common laboratory findings were leukopenia (26.1%), thrombocytopenia (32.8%) and liver enzyme elevations (32.8%), which are in full accordance with our findings<sup>9</sup>. A previous Czech study evaluating a total of 132 travel-associated dengue fever cases between 2004 and 2013 reports similar results. In that study, the infection was most frequently encountered in patients who had returned from South-East Asia (52.3%); fever (100%), headache (65.9%) and myalgia/arthralgia (68.2%) being the most common complaints<sup>23</sup>.

The first case of import dengue fever in Turkey was detected in 2013. On the other hand, the seroepidemiological surveillance studies in 1980 and 2013 documented seropositivities<sup>24-26</sup>. The *Aedes* species, which is also the vector of Zika, yellow fever and chikungunya viruses in addition to dengue virus, has been spreading increasingly from South-East Asia to Europe and America for the last three decades, thus playing important roles in the transmission of these arboviral infections<sup>27</sup>. Studies have estimated that a total of 60 different mosquito species, 11 of which belong to the genus *Anopheles*, 25 *Aedes*, 5 *Culiseta*, 2 *Coquillettidia*, 15 *Culex*, 1 *Orthopodomyia* and 1 *Uranotaenia* inhabit Turkey<sup>28</sup>. *Aedes* mosquitoes have recently been detected in the Thrace and the Black Sea regions<sup>29</sup>. This vector feeds during the night and day, receives the virus and gets infected upon sucking blood from a viremic person. Infected mosquitoes eventually bite other individuals and transmit the infection.

No specific treatment is available for dengue fever. Vector control strategies currently comprise the most effective disease-preventing measure. Additionally, a vaccine has recently been licensed.

As mosquitoes lay their eggs in stagnant water, caution should be taken that long standing water ponds do not occur and the containers filled with water are covered, emptied or destroyed<sup>30</sup>. *Aedes* larvae are most frequently detected inside old car tires filled with water, therefore these old car tires should be covered or

stacked so that rainwater does not accumulate inside them<sup>30</sup>.

Before traveling to a region where dengue fever is endemic, consulting a travel medicine counseling desk or a doctor is suggested. During the trip, repellents should be used, clothes should be worn covering arms and legs, air-conditioned indoor environments with fly nets on the windows and doors should be preferred, and mosquito bed-nets should be used when sleeping outside<sup>30,31</sup>.

Clinical awareness levels are high in countries such as Thailand, Nicaragua and Puerto Rico, where dengue fever constitutes 1/3 of all febrile diseases. Despite this, in the Thailand National Surveillance System, the factor for unreported cases is estimated to be 8-28. For instance, of the >5800 dengue fever cases with positive laboratory findings between 2008 and 2011, 80% were left unreported. In Thailand, half of the symptomatic dengue fever cases do not satisfy the reporting criteria and are left unreported, which impeded the vector control measures being held<sup>32</sup>.

## Conclusions

In summary, imported dengue fever cases are now seen in our country due to facilitation of international travels and increasing commercial activities. However, under the light of the previous seroepidemiological studies and the studies reporting the inhabitation of the *Aedes* mosquitoes in Turkey, it must be taken into consideration that there may also be local cases of dengue fever in our country. Dengue fever should be included in the differential diagnosis for the cases with fever, headache, retro-orbital pain, myalgia, arthralgia and rash, and a careful and detailed clinical history must be taken. It should not be forgotten that Zika, yellow fever or chikungunya disease may also occur in Turkey, as *Aedes* is also the vector for these infections.

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## Sažetak

## GROZNICA DENGA U TURSKOJ: SLUČAJEVI I JAVNOZDRAVSTVENE IMPLIKACIJE

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Virus denga endemski je u gotovo svim tropskim i subtropskim zemljama koje su ujedno i popularna turistička odredišta, pa je stoga velik međunarodni javnozdravstveni problem. Prikazujemo šest slučajeva groznice denga povezane s putovanjem dijagnosticirana 2016. i 2017. godine u Turskoj. Raspravlja se o sadašnjoj situaciji u Turskoj i u svijetu, kao i o epidemiološkim podacima o vektoru te o odnosu između ove bolesti i putovanja. U ovom retrospektivnom istraživanju ispitali smo slučajeve groznice denga koji su identificirani serološkim i molekularnim metodama između siječnja 2016. i veljače 2017. godine u Nacionalnom referentnom virološkom laboratoriju. Dvoje bolesnika imalo je povijest putovanja u Maldive, dvoje u Tajland, jedan bolesnik u Sri Lanku i jedan u Gvajanu. U svim slučajevima bila je prisutna groznica. Ostali najčešći simptomi bili su slabost, bolovi u mišićima i artralgija. Najčešće laboratorijske promjene bili su povišeni jetreni enzimi (50%) i trombocitopenija (66%). Zaključujemo da se uvezeni slučajevi groznice denga sve više prijavljuju zbog olakšanih međunarodnih putovanja i sve većih poslovnih aktivnosti. Zato se preporuča posjetiti savjetovalište za medicinu putovanja ili liječnika prije putovanja u područje u kojem je groznica denga endemska. Na groznicu denga treba pomisliti u bolesnika s poviješću putovanja koji ima groznicu, povišene jetrene enzime i trombocitopeniju.

*Ključne riječi: Groznica denga; Virus denga; Putnici*