Dengue virus type 2 infection in a traveler returning from Saudi Arabia to Japan

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Received: January 4, 2019. Accepted: April 11, 2019
Published online: April 26, 2019
DOI: 10.7883/yoken.JJID.2018.537
Title page

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Running head: Dengue in a traveler returning from Saudi Arabia

Keywords: Dengue fever, traveler, Saudi Arabia, Middle East

Summary:

In July 2018, a Japanese traveler returning from Saudi Arabia was diagnosed with dengue. Dengue virus type 2 gene was detected from the whole blood sample. Phylogenetic analysis revealed that the strain clustered with isolates from Singapore and India. Travelers to Saudi Arabia should be cautious about mosquito bites.
Dengue virus (DENV) infection is endemic in many parts of the world, particularly Southeast Asia. Although dengue is not common in the Middle East, it has become endemic in some countries (1). Some experts suggested that the incidence of dengue in the Middle East are expected to increase as a result of social and ecologic factors; for example, from increasing immigrant workers and travelers to and from dengue-endemic areas (1, 2). In Saudi Arabia, several dengue outbreaks have been reported, and dengue is now considered endemic in certain cities, such as Jeddah and Makkah (3, 4). However, a limited number of case reports have been published about travelers who returned from the Middle East and were diagnosed with dengue (5, 6). We report a dengue case imported from Saudi Arabia to Japan in 2018.

In July 2018, a 30-year-old Japanese man presented to the National Center for Global Health and Medicine (NCGM) with a 2-day history of fever. He had traveled to Jeddah, Saudi Arabia for four days on business. Four days after his return to Japan, he experienced high-grade fever, retro-orbital pain, and myalgia. He presented to NCGM on the next day and was admitted on the same day. Although he had a short layover in Dubai during his trip to Jeddah, he had never been another country during the past two weeks before onset.
On physical examination, his body temperature was 39.2°C; he had bilateral conjunctival injection and showed no hemorrhagic manifestation. Laboratory test results showed normal white blood cell count (4.4×10³ cells/mm³), platelet count (21×10⁴ cells/mm³), and normal liver aminotransferase level. Dengue rapid diagnostic test (Dengue Duo NS1 Ag + Ab Combo; Alere) was positive for non-structural protein 1 antigen and negative for IgM and IgG. RNA was extracted from the patient’s whole blood obtained on the day of admission. Real-time reverse transcription PCR (RT-PCR) with DENV 1-4 primers and probes revealed that the sample was positive for DENV-2 (cycle threshold value 21.1). The patient recovered spontaneously without exhibiting any warning signs within a week and was discharged on the 8th hospital day.

Phylogenetic analysis of the envelope (E) protein-coding region by direct sequencing revealed that the DENV-2 detected from the patient belonged to the Cosmopolitan genotype, sharing 99% identity with a strain isolated in Singapore in 2010 (GenBank accession no: JN030333) (Figure). The sequence of DENV-2 from the patient was also 98% identical to the strains isolated in Singapore (accession nos: JN030340 and JN030334), and India (accession nos: KY427085 and KT781518). Phylogenetic analysis also revealed that the strain detected from the patient clustered not with the strains previously isolated from Saudi Arabia, but with the strains isolated from India.
and Singapore (Figure). DENV-2 was successfully isolated from the patients’ sample using Vero cells. Informed consent was obtained from the patient for the publication of this report.

In western Saudi Arabia, three serotypes of DENV (DENV-1, DENV-2, and DENV-3) have been commonly isolated from 1994 to 2015 (7, 8). Zaki et al. (7) performed a phylogenetic analysis of DENV-2 E gene with the strains isolated from Saudi Arabia between 1994 and 2004 and showed that all isolates belonged to the Cosmopolitan genotype. Also, in 2014, El-Kafrawy et al. (9) isolated DENV-2 from a patient in Jeddah, Saudi Arabia, and showed that the isolate also belonged to the Cosmopolitan genotype according to the phylogenetic analysis of E gene (accession nos. KJ830750). They suggested that DENV-2 was introduced to Saudi Arabia at least four times between 1994 and 2014 because the strains isolated in Saudi Arabia formed four distinct sublineages (9). In the present analysis, the strain detected from our patient formed a distinct cluster from the strains previously isolated in Saudi Arabia. Our result suggested that the DENV-2 that was currently circulating in Saudi Arabia might have been introduced from dengue-endemic countries, including India and Singapore, after 2014.
Although data regarding the surveillance of vectors is limited, several reports demonstrated the occurrence of *Aedes aegypti* and *Aedes albopictus* in the Middle East, including Saudi Arabia (1, 10). It is common in the Middle East to use open water storage containers that act as breeding grounds for mosquitoes. This is described as one of the reasons for DENV being autochthonous in the Middle East (1, 2).

Some people travel to Jeddah each year, for reasons including business, sightseeing and the annual Hajj pilgrimage to the nearby Makkah (3). However, few travelers and health care workers know that dengue is endemic in Saudi Arabia. The findings of this report indicate that the endemicity of dengue in Saudi Arabia should be brought to the attention of travelers and health care workers before travel so that they can be cautious of mosquito bites. It also suggests considering DENV infection when health care workers examine febrile travelers from Saudi Arabia.

**Acknowledgments**

This work was partly supported by research grants from the Emerging/Re-emerging Infectious Diseases Project of Japan of the Japan Agency for Medical Research and Development, AMED (JP18fk0108009 and JP18fk0108035), and grants from Japan’s National Center for Global Health and Medicine (grant no. 27-6001 and 29-1018). The
funding sources had no role in the study design, data collection, data analysis, decision
to publish, or preparation of the manuscript.

Conflicts of interest: We have no conflict of interest to disclose.

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**Figure legends:**

Figure: Phylogenetic analysis of the DENV-2 obtained from a patient returning from Jeddah, Saudi Arabia, to Japan in 2018 (arrow) with reference dengue virus strains.
Viral genotypes are shown on the right. Phylogenetic trees were constructed by using the neighbor-joining method. Analyses were performed using MEGA7 software (http://megasoftware.net). Scale bar represents substitutions per nucleotide position. Bootstrap values for each node are shown to indicate the robustness of the tree.