

## Will Dengue Virus Infection Endanger Blood Safety?

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### Brief Introduction to Dengue and its Virus

Dengue is an arthropod-borne viral disease caused by dengue virus, which is predominantly transmitted via the bites of infected mosquitoes of the genus *Aedes* (*Ae.*) *aegypti* and *Ae. albopictus*. The distribution of the disease is usually in tropical and subtropical areas. Dengue virus infections occur in more than 100 countries and regions in the world. Dengue constitutes a major public health concern and its outbreaks pose a substantial social economic burden. Dengue virus (DENV), a single-stranded positive-sense ribonucleic acid (RNA) virus with approximately 11,000 nucleotides in length, belongs to the Flaviviridae family and includes four serotypes (DENV-1, DENV-2, DENV-3, DENV-4) [1]. Infection with DENV is usually asymptomatic but each serotype is capable of causing dengue fever (DF) and the clinically more severe disease including dengue hemorrhagic fever (DHF) and dengue shock syndromes (DSS) [2]. Although dengue has lasted for several decades and widely distributed in various countries, whether dengue virus infection endangers blood safety remains unclear. Most recently, the risk of dengue transmission through blood products from infected donors was recognized.

### Why DENV May be Transmitted by Blood Products?

Except for mosquito biting, DENV may be accidentally acquired after transfusion of blood products. So there exists potential risk of dengue transmission by blood transfusion. This is because DENV can be present for about one week in the blood of infected patients, while approximately 75% of the DENV carriers don't appear any symptoms of dengue during this period. Since asymptomatic carriers may offer to donate blood, studies have shown that there are viremic donors during outbreaks in all investigated areas [3]. Although mandatory screening of donated blood products has tremendously reduced the risk of hepatitis B, hepatitis C and human immunodeficiency virus transmission, DENV has not been included in blood routine screening procedures. Therefore DENV remains significant risks and endangers transfusion safety especially during its outbreaks.

### Evidence for the Transmission of DENV by Blood Products

Despite the fact that the major route of DENV transmission occurs through the mosquito vector in the world, there are five case reports of DENV transmission through blood products in the literature to demonstrate that DENV infection endangers blood safety. The first report involved a 76 year-old woman who developed low-grade fever 2 days after a blood transfusion in a Hong-Kong hospital in 2002. The fever resolved spontaneously 3 days later and the patient recovered uneventfully. The blood product she received was donated by a patient who was asymptomatic at the time of donation but developed symptoms of Dengue Fever one week after blood donation. Molecular testing performed on an archived sample from the donation was positive for DENV-1. Two months after transfusion, the woman recipient was recalled for blood testing and found to be IgM antibody positive. This case was the first documented cases of transfusion-transmitted dengue in the literature and it was the first time that dengue viruses has been

recognized as a transfusion-transmitted pathogen in 2008 [4]. The second observation from Tambyah et al. [5] consisted of a cluster of three cases contaminated in Singapore by an asymptomatic blood donor who developed a fever after blood donation. An investigation of the donor's blood product confirmed that it was positive for dengue virus type 2 performed by a PCR assay in his stored serum sample. Two days after transfusion, two of three recipients had a symptomatic infection and were positive for dengue virus type 2, whereas the platelet recipient was asymptomatic but demonstrated serological evidence of dengue infection. Eventually they all recovered. The third study from Stramer et al. [6] traced back to the outbreak of dengue that occurred in Puerto-Rico in 2007. A total of 15,350 donation samples tested individually for DENV RNA by transcription-mediated amplification (TMA) assay, 29 were found positive for DENV genome. Three of the 29 recipients who received these contaminated samples were tested. One of them who were transfused with red blood cells containing 10<sup>8</sup> copies/ml DENV-2 developed dengue-related symptoms consistent with DENV infection. He was confirmed positive for DENV and developed DHF three days post transfusion. Sequencing results confirmed that the virus in both the donor and the patient samples showed 100% sequence identity, confirming its transfusion-transmitted in nature. The fourth observation published in 2015 also reported a rare case of DENV transmitted by transfusion [7]. A 37-year-old female who was found to have a decrease in hemoglobin (Hb) concentration, ten days after admission to hospital, was treated with transfusion of red blood cells (RBC). Four days after the blood transfusion, the patient became febrile and the fever persisted. Two days later, the patient was found to show thrombocytopenia. Serology test demonstrated that she was infected with DENV. She was suspected to be infected by transfusion. Further investigation indicated both the donor and the recipient blood samples are positive for DENV-2 and Sanger sequencing was done to confirm that both of them had a 100% nucleotide sequence homology, indicating the patient did acquire dengue infection by transfusion. The last case report also published in 2015 [8]. It involved a recipient who was hospitalized and displayed dengue symptoms three days after transfusion during a dengue outbreak in São Paulo city. It was found that the donor was diagnosed to be DENV positive a few days after donation, but her blood had already been transfused into two patients. One of them developed dengue symptom, with high viral load. Laboratory evidence demonstrated that the patient acquired DENV infection through transfusion.

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## Conclusion

As discussed above, all these patients acquired DENV infection through blood transfusion. The main reason for this transfusion-transmitted DENV infection is that the blood donors might be in virus incubation period with no dengue-related symptoms at the time of blood donation and recovered spontaneously several days later. This is also the reason why dengue virus infection through blood transfusion has not been noticed before the first case of transfusion-transmitted DENV was reported. The increasing prevalence of DENV infection has been widely reported globally. These cases serve as evidences that DENV is indeed transmissible by blood transfusion and endangers blood safety. Moreover, transfusion-transmitted DENV also impacts on public health. No approved vaccine is currently available for the prevention of dengue. At present, stopping dengue virus transmission depends entirely on the control of mosquito vectors [9]. In addition to prevent the virus spreading through mosquito bites, it is necessary to develop efficient measures to prevent DENV transmission by blood products in order to secure blood safety. Although spreading through blood transfusion is relatively rare, it does occur. Dengue virus screening of donor blood is an important and effective method to avoid dengue transmission through blood products [10], especially for donors in endemic areas during outbreaks.

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