

Dengue Virus and Blood Safety: A Mini-Review of Research Publications

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ABSTRACT

The growing demand for donated whole blood and blood products to save lives has both health benefits and health risks for blood recipients at the same time. Dengue virus, a re-emerging viral disease poses a threat to blood safety, and it has spread to over 128 countries in the world. Several studies have documented transfusion-transmitted (TT) dengue, with the first cases being reported in China in 2002 and Singapore in 2008. To understand the magnitude and broader picture of the dengue virus and blood safety, we conducted a mini-review of published literature from the Scopus database. The review focused on the number of publications related to the dengue virus among blood donors. Using keywords 'Dengue virus' AND 'Blood safety', 'Dengue virus' AND 'Blood donors' and 'Emerging infectious diseases' AND "Blood safety" were used to extract data from the Scopus database which was downloaded as a CSV Excel file covering a period 2004 to 2021. This was followed by a data-cleaning exercise and a descriptive analysis to generate the frequency of the number of publications. Most studies, as can be seen in the review, were concentrated in tropical regions of the world. Globally, South America and the Asian regions had the largest number of publications; while at the country level, Brazil and India had the highest number. More research output was witnessed during the years 2014 and 2018. The regions that experienced more frequent outbreaks of the disease, with the exception Africa, published most of the research work. Therefore, much more research work is needed to protect the safety of blood donors in Africa.

BACKGROUND INFORMATION

Emerging infectious diseases such as the dengue virus (DENV), chikungunya virus, and many others are believed to threaten blood safety and availability throughout the world.¹ Most of these threats arise from the rapid spreading and mutating of viral infections.² To address this challenge, the WHO regularly publishes epidemiological reports on emerging infectious diseases in blood safety through fact sheets to its member countries. Member countries can access these reports on an online Global Database on Blood Safety program created by the WHO and its partners.³ These reports assess data from different countries, highlight achievements, and address the challenges facing blood safety. It is worth noting that not all blood transfusion services have access to this database or follow the guidelines developed by the WHO.⁴ Screening blood donors for known and unknown transfusion-transmitted infectious diseases to ensure blood safety around the world is the sole responsibility of all blood transfusion services.⁵ It is therefore logical that these services do so much to protect blood recipients from emerging infectious diseases. Acquisition of infection by blood transfusion can be life-threatening and costly for various families struggling financially.

Dengue, a recurrent infection caused by DENV, poses

a threat to blood safety, and has spread to more than 128 countries around the world.⁶ It is estimated that half of the world's population is at a high risk of being infected with dengue virus.⁷ Dengue is a vector-borne disease spread by an *Aedes* mosquito species that are widely distributed in the tropical and subtropical regions of the world.⁸ An estimate of approximately 25,000 dengue-related deaths is reported annually from endemic regions of the world.⁹ However, there is evidence that DENV can also be spread through blood and tissue transplantation.¹⁰

Several studies have documented transfusion-transmitted (TT) dengue whereby the first case was reported in China in 2002 and a second case in Singapore in 2008. This mini-review was part of a large study that sought to understand the seroprevalence of the DENV among blood donors and its implications for blood safety.¹¹ To understand the magnitude and broader picture of the DENV and blood safety, we conducted a mini-review of existing literature from the Scopus database. The database was chosen purposefully because it contains STM journal articles and the references found in them are accessible enabling both forward- and backward-looking searches. The review focused on the number of publications related to the DENV among blood donors and their sources around

the world. This was to help us synthesize the current discussion on whether blood donors coming from dengue-endemic regions need to undergo testing. Using keywords 'Dengue virus' AND 'Blood safety', 'Dengue virus' AND 'Blood donors' and 'Emerging infectious diseases' AND 'Blood safety', data were extracted from the Scopus database, which was downloaded as a Ms. Excel CSV file. This was followed by a data-cleaning exercise and a descriptive analysis to generate the frequency of the number of publications. Ms. Excel was also used to present the global distribution of studies that focus on the DENV among potential blood donors from a global perspective.

Blood Transfusion as A Route For Dengue Virus

The burden and implication of the DENV on blood safety in some tropical and subtropical regions where the virus is endemic are currently unknown. Therefore, there is quite limited information on DENV transfusion-transmitted cases to help countries improve their disease surveillance systems within blood transfusion services.^{12,13} The current review provides a snapshot of what is happening globally and helps fill this gap. Blood transfusion services around the world, as recommended by the WHO, are required to analyse transfusion risks and determine whether emerging infectious diseases are threats to blood safety in their country.¹⁴ However, most of these countries lack the capacity to implement these recommendations.¹⁵ The dependence on the WHO and other international organizations for epidemiological data before acting is a limitation that requires immediate intervention from countries in low-middle income countries (LMIC). Most African countries fall into this category and have limited human and financial resources. A robust surveillance system for the DENV not only provides the information required to maintain a blood supply but also helps and supports a safe blood supply.¹⁶

There is evidence that all patients who received donated blood from asymptomatic blood donors develop dengue-related symptoms after a few days.¹⁷ Studies in Brazil, India, and Singapore have shown a 0.5% rate of dengue viremia among asymptomatic blood donors during DENV outbreaks.^{18,19} Another study among healthy blood donors in Saudi Arabia has shown a seroprevalence between 1-7% for the DENV-NS1 antigen, the anti-DENV IgM antibody, and the anti-DENV IgG antibody.⁹ Similarly, a study conducted in the northeast part of Mexico among blood donors using the enzyme-linked immunosorbent assay (ELISA) technique found 59% and 2% for IgG and IgM, respectively.²⁰ In India, a country that is the most affected by the DENV, a study conducted in the Pune region of western India showed seropositivity of 0.64% and 6.4% for NS1 and IgM respectively in 2017.²¹ Despite all this evidence, very little is being done to implement mandatory screening for the DENV among blood donors to ensure blood safety.²²

In the Sub-Sahara region, very little is known about the prevalence of DENV among blood donors, and the likelihood that transfusion-transmitted Dengue fever has never been reported.²³ Limited studies conducted in a few countries (Figure 1) have shown evidence of dengue seromarkers in asymptomatic blood donors. For example, a study conducted among Cameroonian blood donors

showed a seropositivity rate of 5% for all serological markers using a simple immunochromatographic (IM) diagnostic kit.²⁴ In Tanzania, a similar study finding showed a seroprevalence of 50.6% DENV IgG among blood donors in Zanzibar.²⁵ Thousands of efforts and investments are required to conduct research studies on emerging infectious diseases and blood safety in Africa.²⁶

Blood transfusion services (BTS) in most developing countries are faced with numerous challenges that hinder their ability to provide safe blood to their blood recipients. One of the challenges is the lack of financial support from their national government to enable them to perform their functions.²⁷ Consequently, there is an inadequate supply of blood products, and much worse infection-contaminated blood supplies. This situation, hinders the performance and delivery of BTS services as a state organ with the mandate to supply safer blood to its citizens. Providing quality blood products to patients who urgently need blood transfusion is a fundamentally essential element of a functional blood transfusion service for any country.²⁸ Therefore, this mini-review aimed to analyse the available literature and draw a conclusion on whether it was necessary to include DENV as a mandatory test in all countries with the presence of the disease.

Current Evidence of Post-Transfusion Dengue Fever

It is an accepted principle that population growth and the increasing incidence of diseases raise the probability that blood products from viraemic individuals could be provided to vulnerable blood recipients.^{29,30} Previous studies in Hong Kong and Singapore have documented dengue transmitted by transfusions through blood derived from asymptomatic individuals.^{31,32} In regions with frequent outbreaks of the DENV, blood services would be required to assess whether urgent steps are needed to ensure blood availability.

In a population where dengue is widespread, the possibility of receiving blood from asymptomatic viral donors is also not resolved by symptom-based exclusion.³³ To date, studies show that there is at least a duration of infectivity of 1-2 days before symptoms develop and therefore a donor donating his/her blood during this period could pose a threat to people who would receive the blood.³⁴ During the dengue outbreak, the occurrence of viremia among asymptomatic people, including blood donors, is unknown.³⁵ For example, in a study in Hong Kong and Singapore, four recipients who acquired the virus by blood transfusion endured a relatively mild course of the disease and eventually recovered with very minimal sequelae.³⁶ More details are still needed to establish a concrete conclusion on whether blood transfusion could be an alternative route of viral transmission. However, fear always comes from the loss of a potential blood donor pool due to deferral.

Global Distributions of Research Work Around the Dengue Virus among Blood Donors

Part of this review was to understand the distribution of research articles related to DENV among blood donors. As shown in Figure 1, most of the studies were concentrated in the tropical regions of the world. This shows a pattern similar to that seen in the distribution of the DENV in epidemiological studies.³⁷⁻⁴¹ South America and the Asian regions had the largest number of

publications; and at the country level, Brazil and India had the most publications. One of the explanations for this phenomenon is the increased number of dengue outbreaks in these regions in the recent past.⁴² Few countries in these regions have implemented additional tests for the DENV in their test algorithms.^{36,43-51} Thus, this raises the question as to why other regions do not implement dengue screening among blood donors, even with the predominant evidence. There are a number of reasons; first, several studies have documented the presence of viral markers (IgG, IgM, NS1, and RNA) among healthy donors in dengue-endemic regions.^{36,48,52} It is therefore a major challenge among transfusion experts in deciding whether to screen or not, given that viral markers can also be detected among healthy subjects in the endemic regions.⁵³⁻⁵⁵ Secondly, financial constraints and the cost of blood transfusion are some of the reasons in the literature to explain why there is a lack of predonation screening for the DENV.^{56,57}

As shown in this review, very minimal research activities were observed in the African region regardless of the presence of dengue on the continent. A similar observation has also been made in a limited number of epidemiological research activities on the continent.⁵⁸ For example, single studies have been conducted in Tanzania, Cameroon, Ghana, Nigeria, Egypt, Burkina Faso, and Sudan.^{24,59-62} Therefore, very little is known about the implications of the DENV among blood donors in tropical regions of Africa.⁶³ A simple intervention for Africa would be to implement a voluntary call system after a blood donation is made to the blood transfusion service about the appearance of clinical symptoms consistent with the infectious disease. This intervention is called a post-donation illness report (PDIR), which would be cheaper and more affordable in most poor countries. The passive approach of voluntary reporting does not require BTS to screen donors but requires the donors to report

post-donation illness. Studies to assess the effectiveness of PDIR as a mitigation for viral agents, such as DENV, would help improve blood safety.⁶⁴ In addition, there is an opportunity for African researchers to conduct studies with the aim to protect the safety of blood recipients.⁶⁵

Most of the investigations in the reviewed articles showed a high seroprevalence of dengue viral markers (IgM/IgG) among potential blood donors who were asymptomatic.⁶⁶⁻⁷⁴ Therefore, it is essential to practice meticulous preventive techniques to ensure the safety of blood transfusions and to prevent the spread of the DENV in an endemic area.⁷⁵

Distribution of Published Work on the Dengue Virus among Blood Donors Around the World

In recent years, the number (84) of publications related to the DENV among blood donors has increased drastically. As part of this mini-review and to understand research output, we purposed to establish the number of publications since the year 2004 to 2021. Between 5 and 12 research outputs were observed between 2014 and 2018 as shown in Figure 2. The main reason for this increase in production is probably related to the increased number of reported dengue outbreaks in endemic regions.⁷⁶ The impact of the COVID-19 pandemic on research output can also be seen in the decrease in the number of publications between 2019 and 2020. The reduction in the number of publications can be attributed to a change of focus to address the pandemic. However, a resumption of research output is also observed in 2021. This could have been due to understanding the current pandemic, which had an initial reaction full of uncertainties. This is a true reflection of what happens when there is a disease outbreak or a pandemic. The emergence of new viral infections can affect all aspects of our lives, including blood safety and availability.

FIGURE 1: Global Distributions of Research Work on Dengue Virus and Blood Safety

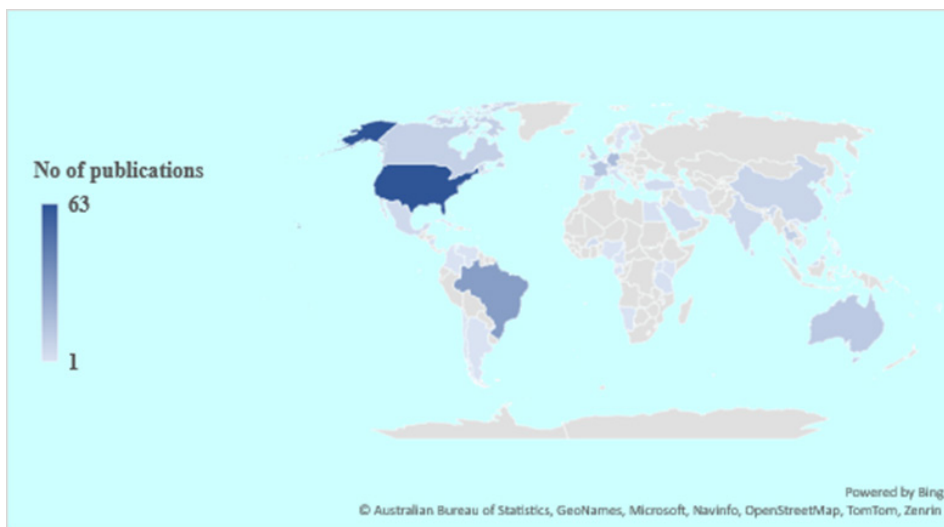
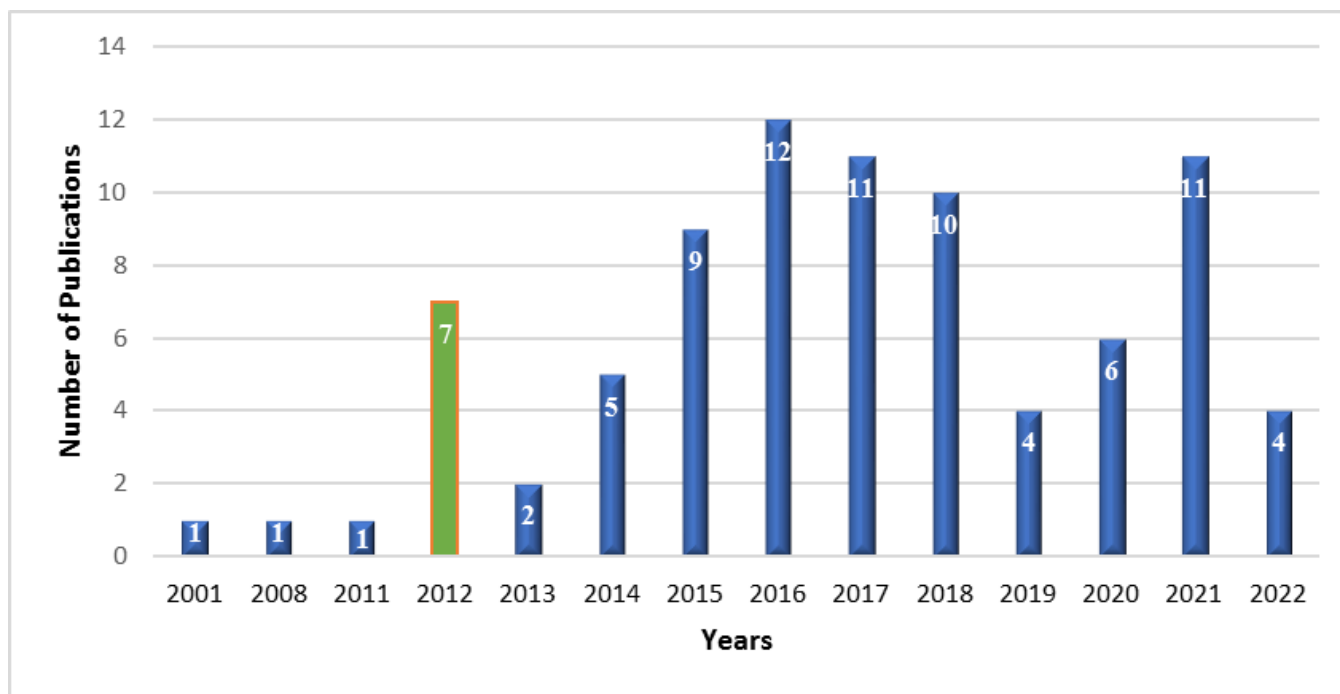


FIGURE 2: Distribution of Published Work From 2001 to 2022



CONCLUSION

This mini-review has shown that there is evidence that asymptomatic blood donors can transmit the DENV to blood recipients. Most of the research work was conducted in regions that experience frequent outbreaks of diseases, except in regions on the African continent. Therefore, much work is needed to protect the safety of blood donors in Africa.

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