Asia Pacific Blood Network
Connecting Blood Communities

APBN WHITE PAPER

DENGUE AND THE BLOOD SUPPLY

UPDATED JANUARY 2019

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Why is Dengue a threat to the Safety and Sufficiency of the Blood Supply in the Asia Pacific Region

Dengue is the most common arthropod-borne infection worldwide, affecting as much as two-fifths of the world's population. The first known epidemic of severe dengue occurred in the Philippines in 1953. Since then, it has been spreading to involve much of Asia and Latin America and is a leading cause of hospitalisation and death among children and adults in these regions. Dengue is now endemic in a large proportion of countries in Asia and the Western Pacific region.

Surveillance in several countries indicates that an increasing proportion of dengue infection occurs in adults with a higher incidence in young adults. There is growing spread into suburban and rural areas. Increasing efficiency is also observed in the breeding cycle of the mosquito vector. Higher epidemic activity is likely to result in the emergence of strains or genotypes with greater epidemic potential.

The burden of disease varies between countries and is capable of significant outbreaks. Dengue would be expected to continue to expand its territory due to a confluence of factors - population growth, urbanisation, inadequate water management, potential new vectors, lack of effective mosquito control, global travel, and changes in weather patterns. This poses a significant economic and disease burden in countries with high dengue incidence. {Shepard 2013}

Blood supplies in the region may also be affected. During severe dengue outbreaks, the proportion of the population available to donate blood will be reduced. and at the same time the requirements for blood and blood components may increase. The potential for dengue to be transmitted through blood transfusion and to result in adverse consequences in the recipients will also need to be addressed. {Teo, 2009}

Background Information

The dengue virus is a single stranded RNA virus, from the *Flaviviridae* family. There are four serotypes based on immunological properties of the virus – DEN-1, DEN-2, DEN-3 and DEN-4. Infection confers immunity against the serotype of the infecting virus, but only transient protection against other serotypes. {Teo 2009; Stramer, 2009}

The primary vector for the dengue virus is the *Aedes aegypti* mosquito, but it may also be transmitted by *Aedes albopictus* and *Aedes polyniensis*. The *Aedes aegypti* mosquito is highly domesticated, preferring to rest in-doors, and exhibits peak biting activity at dawn and dusk.

Its tendency to bite multiple persons in a single blood meal and preference for human hosts has led to explosive spread even in the presence of a low vector population. {Teo, 2009}

The primary mode of transmission for the dengue virus is through the mosquito, but infected humans are the main carriers and amplification host. Female mosquitoes acquire the virus when they bite infected humans in the viraemic phase. Following an extrinsic incubation phase (replication of virus in vector) of 7 to 14 days, the mosquito transmits the virus at every subsequent feeding. The length of the extrinsic phase depends on ambient temperature and the virus. {Teo, 2009}

After the bite of an infected mosquito, there is an intrinsic incubation period (replication of virus in the infected human) of 3 to 14 days, with an average of 4 to 7 days. {Stramer, 2009} Infectivity during the incubation period is not well defined, although early studies have indicated that infected persons can transmit virus as early as or even earlier than 2 days before symptoms develop. {Teo, 2009} Viraemia is usually detectable between 2 to 7 days, peaking at the time of or shortly after the onset of illness. The period of viraemia generally corresponds to the period of fever and may last up to 14 days. {Vaughn, 2009; Teo, 2009; Stramer, 2009}. During a large Brazilian epidemic, dengue RNA was estimated to be detectable in asymptomatic or presymptomatic donors for a period of approximately 9 days (95% CI, 4.4-13.9). {Busch, 2016}

Dengue produces a wide spectrum of clinical manifestations ranging from asymptomatic seroconversion to severe clinical illness. The current World Health Organisation (WHO) dengue case classification {WHO, 2009} classifies dengue into three categories for clinical management according to levels of severity and based on the following criteria:

- Probable dengue - live/travel to dengue endemic area, fever and two of the following: nausea/vomiting, rash, aches and pains, tourniquet test positive, leucopaenia, any warning sign);
- Dengue with warning signs - abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver enlargement, increasing haematocrit with decreasing platelets; and
- Severe dengue - one or more of the following: dengue with severe plasma leakage leading to shock (dengue shock syndrome), severe bleeding or severe organ impairment.

Dengue is a self-limiting disease in most patients with a mortality of less than 1%. However, in patients with severe dengue, mortality rates can exceed 20% without appropriate care. {WHO, 2019}

Vector control programs and personal protection from the bites of infected mosquitoes remain the cornerstone of dengue prevention. An experimental World Mosquito (*Wolbachia*) programme has been implemented in many countries in the Asia Pacific region. *Wolbachia* is a naturally occurring insect-specific bacteria that is not normally present in *Aedes aegypti.* Once released into and established in the mosquito population, it is able to interfere with the replication of dengue viruses within the *Aedes* mosquito {Hilgenfeld, 2018}.

In Australia, despite continued dengue importations from travellers, almost no dengue transmission has occurred after establishment of *Wolbachia* in the local *Aedes aeqypti* populations. {Ritchie 2018}.

A new dengue vaccine – Dengvaxia - is now available and may help to reduce dengue transmission. Although clinical trials demonstrated safety and efficacy in people with previous history of dengue infection, it is now recognised that there is increased risk of severe dengue in seronegative vaccine recipients who experience their first dengue infection after vaccination. Caveats therefore remain in the use of vaccination as part of dengue control programmes, including either the need for pre-vaccination screening or its use only in areas with high rates of sero-positivity. In children below 9 years of age the vaccine is not recommended. {WHO, 2018}

What are the challenges facing blood services

1. Mitigate the potential for transmission through blood transfusion

Since the first documented case of dengue acquired through blood transfusion in Hong Kong in 2002, several more cases have been reported from Singapore, Brazil and Puerto Rico. {Chuang, 2008; Tambyah, 2008; Stramer 2010; Levi 2015; Busch 2016; Sabino 2016}. Reports of transmission through other non-arthropod means include vertical transmission with intra-partum transmission, nosocomial transmission by mucocutaneous exposure and needlestick injury, renal transplant, and bone marrow transplant. {Tan, 2005; Teo, 2009; Chen, 2005; de Wazieres, 1998}

Transfusion-transmitted dengue is likely to be under-reported. It is difficult to differentiate between non-mosquito and mosquito transmissions in endemic areas, and diagnostic laboratories are often not available to conduct the necessary investigations. Mild or asymptomatic illness may also be undetected. {Bianco, 2008; Teo, 2009}

Studies have indicated the presence of viraemia in blood donations collected from countries experiencing high dengue infection rates in the population. This included the detection of viral RNA and the isolation of live virus. {Linen, 2008; Mohammed, 2008; Busch, 2016; Sabino 2016}

There is also evidence of viraemia in persons infected with dengue and who are asymptomatic, including the presence of viral RNA and viral isolation. Studies have shown the presence of asymptomatic or subclinical infection varying from 52.5 to 87% depending on the population and conditions studied. {Rodriguez-Figueroa, 1995; Cobelens, 2002}

Increased dengue prevalence in the population increases the risk that blood will be collected from a viraemic donor during the asymptomatic or subclinical phase of infection. {Seed, 2009} The efficiency of transmission through blood transfusion will depend on the amount and stability of the virus, and the volume of blood transfused. {Teo, 2009} The risk of infection will depend on the size of the population exposed and the presence of immunity from prior infection, bearing in mind the different serotypes present. Not all dengue RNA-positive donations seem to be infectious; the role of heterotypic and homotypic antibodies to prevent transfusion-transmitted dengue is still in progress. In dengue endemic countries, it is estimated that more than one third of components from RNA-positive donations may transmit infection during epidemics. {Sabino, 2016}

Reports to date suggest that infection acquired through blood transfusion does not result in more serious disease than vector-acquired dengue. However, superimposed dengue may subject the recipient to additional risk as a result of coagulation and/or platelet abnormalities or increased complications following dengue. {Oh, 2015} No information exists regarding the risk to patients associated with secondary infection involving a different serotype, and whether this is different from secondary infection through primary routes. {Teo, 2009}

2. Mitigate the impact on the availability of blood donors

During a dengue outbreak, healthy uninfected donors are less available to donate blood if the outbreak affects many in the community, family and workplace. As the modal age of infection increases, a higher proportion of eligible blood donors especially youths and young adults will be affected.

An increase in donor deferral will result from the introduction of exclusion criteria for donors who are or have been infected by dengue, who have a history of fever, or who have travelled to dengue-affected areas. The impact of such donor exclusion criteria will have a greater effect on regular blood donors, particularly apheresis donors. {Teo, 2009; Seed, 2009}

3. Manage the demand for blood and blood components

An increased demand for blood and blood components is generally observed during outbreaks of dengue, which may be exacerbated by inappropriate ordering and use of platelet transfusions. Inappropriate ordering of blood components also exposes patients unnecessarily to the risks of blood transfusion.

There is a need to develop clear and evidence-based guidelines for the use of platelet and fresh frozen plasma transfusions in treatment of dengue. Although the presence of thrombocytopenia is associated with clinically significant bleeding, there is no direct correlation between platelet count and clinical bleeding. {Wong 2016} Studies have shown that in adult patients with dengue and thrombocytopenia, prophylactic platelet transfusion is not superior to supportive care in preventing bleeding, and might be associated with adverse events. {Lee, 2016; Lye, 2017}. The prevention of haemorrhage in severe dengue is better achieved through early detection and management of circulatory imbalance and shock than through blood transfusions.

What measures are available to reduce the risk to the blood supply

1. Exclusion of at-risk donors

Donors who are at higher risk of being infected or who may be exhibiting early symptoms of infection are excluded from donating blood. They would include the following:

a) Donors who have been potentially exposed to infected mosquitoes, for example, those with a recent history of travel to a dengue endemic country or outbreak area, and those who have had recent close contact with a dengue-infected individual where competent vectors exist;
b) Donors with a clinical history consistent with dengue, for example, fever, rash or malaise;
c) Donors with a recent history of dengue infection.
d) Donors with house-hold contact with a dengue-infected individual (where competent vectors exist).

Where donor deferral measures are implemented, it is recommended that donors who have a history of possible exposure to dengue infection should be deferred from donating blood for a period not less than 28 days from the time of the last exposure.

Donors with a clinical history consistent with dengue or a recent history of dengue infection should be deferred for a period not less than 28 days following the full resolution of symptoms.

The minimum deferral periods have been recommended based on durations of twice the estimated maximum incubation period {Stramer, 2009; Teo, 2009} and maximum viraemic period in sub clinical infection, both 14 days. {Seed, 2009} The use of a deferral period of at least 28 days provides for a substantial safety margin enabling minimum infectious risk without compromising blood supply through unnecessary loss of donors.

Systems should be in place for donors to report a post-donation illness. For example, this might include a proactive online warning message to raise awareness during active transmission.

Systems should also be in place to manage recall of potentially infected blood and blood components, and to notify the attending clinician. Where donor notification of suspected or confirmed dengue infection is made within 28 days of the donation consideration should be given to initiate recall and quarantine of blood components present in inventory and notification of the hospital or clinician if the blood components have been transfused. The clinician should consider whether further investigation or notification of the patient is appropriate based on the risk of transfusion-transmission and the individual patient's circumstances including the medical history, transfusion date and symptoms.

2. Testing of the blood supply

Any test considered for blood supply screening should have the appropriate sensitivity and specificity for the country and context. The test should also be scalable to meet the needs of the blood service, which includes timeliness in release of blood products for clinical use. Antibody tests inherently lack the required sensitivity for acute infection and thus donor screening.

Because RNA is the first detectable marker in acute infection, RNA tests are the most appropriate for donor screening. {Linnen, 2008; Mohammed, 2008} Licensed RNA tests are now commercially available for the purpose of donor screening. {Stramer, 2012; Stramer, 2013}. In-house developed RNA tests may be suitable but would need to be properly validated for donor screening.

Although NS1 antigen is detectable shortly after RNA NS1 antigen-based tests are not as sensitive as RNA-based tests and transmission of dengue has been reported with NS1 antigen-negative RNA-positive red cells. {Matos, 2016}

3. Pathogen reduction of blood components

Pathogen reduction technology (PRT) is currently licensed and available for plasma and platelets, but not for red cells. Pathogen reduction of plasma and platelets coupled with selective red cell inventory hold would be a possible interim measure until licensed PRT is available for all blood components. However, PRT is expensive and therefore may not be cost effective or cost effective only when it is able to replace the need for other interventions, such as donor screening tests or component modification by irradiation and filtration. {Stramer, 2009; Bianco, 2008; Teo, 2009; Custer, 2009}

What is the approach to selecting an appropriate risk reduction strategy

1. Factors for consideration

Any risk reduction strategy must take into consideration the epidemiology of the virus in the country or geographical area. These may be classified into endemic, non-endemic, and seasonal or periodic outbreaks. Reference to the WHO Classifications is recommended to determine the endemic status for dengue, as well as to existing regional networks or infectious disease surveillance and scanning tools for updated information on disease outbreaks. The appendices provide useful links and sources of information.

Where available, the prevalence of dengue infection in blood donors, is important in determining the risk of viraemic donations in the blood supply. The prevalence should be estimated to consider seasonal variation effects and, when possible, taking into account epidemic variation in dengue-endemic countries. Where this information is not available, the prevalence of dengue infection in the population eligible to donate blood may help to provide an indirect assessment of risk. {Seed, 2009}

The process of donor deferral is associated with low sensitivity and specificity, and has limited effectiveness except in situations where outbreaks are contained or travel to outbreak areas minimal. Donor deferral has also been shown to have a negative effect on the donor, resulting in low donor attendance and exacerbating donor loss. Loss of selected blood components occurs if the donor is restricted to donation of source plasma intended for fractionation.

Testing is likely to incur significant cost and may be associated with false positive results, which may result in loss of selected blood components due to system constraints such as discards and outdates resulting from resolution processes. It may also result in loss of donors. Introduction of test systems based on RNA tests will require appropriate laboratory facilities and infrastructure to be in place.

Pathogen reduction has an advantage in being effective against most other pathogens. However, it will involve additional steps in processing leading to delays in release of components and potentially higher platelet outdate. There is also a reduction in component yield, and insufficient data regarding long term toxicity for some systems. The cost benefit of each strategy being considered should be properly assessed using an appropriate tool or model. {Custer, 2009}

2. Suggested risk reduction strategies

The decision to implement any strategy needs to take into consideration blood supply sufficiency, operational impacts and its cost effectiveness in reducing disease morbidity in relation to the overall health situation in the country, especially in countries with limited resources.

In countries with high dengue prevalence, the risk of transmission through blood transfusion will be high. However, transfusion-transmitted dengue will represent a very small fraction of the total infections during an epidemic. {Sabino, 2016} The introduction of a screening test or pathogen reduction will prevent transmission of dengue through transfusion, but the proportion will be low compared to the number of infections acquired through primary means.

In countries with low overall prevalence but regular seasonal outbreaks of dengue, targeted testing of donors visiting or residing in outbreak affected areas may be a cost effective strategy to mitigate the loss of donors and donations. The operational complexities associated with “switching” testing on and off, as well as the potential to miss asymptomatic, viraemic cases early in outbreaks, may justify year round testing in outbreak-prone areas. {Bianco, 2008; Seed, 2009}

In countries with low dengue prevalence, the risk of transmission through blood transfusion will be low. Introduction of a screening test or pathogen reduction is not likely to be cost effective. {Faddy 2013} Donor deferral may be appropriate in these circumstances. In some situations, restricting donors returning from outbreak areas to source plasma may help to mitigate donor loss. {Coglan, 2018}

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Useful sources of information

AABB – accessed through www.aabb.org
Emerging Infectious Diseases – accessed through www.cdc.gov/ncidod/eid
European Upfront Risk Assessment Tool (EUFRAT) http://eufrattool.ecdc.europa.eu/
Pro-MED mail – accessed through www.promedmail.org
US Communicable Diseases Center – accessed through www.cdc.gov
World Health Organisation – accessed through www.who.int
WHO Regional Office for the South-East Asian Region – accessed through www.searo.who.int
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Contact Us

For more information about this white paper or the Asia Pacific Blood Network, contact us at apbn@redcrossblood.org.au