

Current epidemiology and clinical practice in arboviral infections – implications on blood supply in South-East Asia

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Arthropod-borne viruses (arboviruses) are a growing threat to global health. Complex vector–virus–host interactions lead to unpredictable epidemiological patterns. Difficulties in accurate surveillance including imperfect diagnostic tools impair effective response to outbreaks. With arboviral infections causing a wide spectrum of disease severity, from asymptomatic infection to fatal neuroinvasive and haemorrhagic fevers, the potential impact on blood safety is significant. Asymptomatic or presymptomatic individuals may introduce virus into the blood supply by donation, while recipients can potentially suffer severe consequences. Dengue, West Nile and chikungunya outbreaks have led to responses by blood transfusion services which can inform future planning. Reports of transfusion-associated transmission demonstrate the potentially fatal consequences of lack of haemovigilance. South-East Asia remains vulnerable to arboviruses with permissive climate and high levels of endemic transmission as well as the potential for emerging and re-emerging arboviral diseases. Resource limitations constrain the use of expensive technologies for donor screening. Continued surveillance and research will be required to manage the arboviral threat to the blood supply.

Key words: blood donation testing, epidemiology, NAT testing, pathogen inactivation, transfusion-transmissible infections, viral safety of plasma derivatives

Arthropod-borne viruses (arboviruses) comprise over 500 viruses mainly in three families (Togaviridae (genus Alphavirus), Flaviviridae and Bunyaviridae) united by their vectors: haematophagous mosquitoes, ticks and sandflies [1]. Over 100 infect humans, who may be either the primary host species or a dead-end host peripheral to zoonotic transmission in maintenance or amplifying hosts such as livestock [2]. As such, the viral epidemiology varies significantly from sporadic cases, to low-level continuous endemic transmission, to massive outbreaks involving millions of cases. Vaccines are available for a

few (yellow fever, Japanese encephalitis and tick-borne encephalitis) and have been deployed successfully in national programs. However, even these retain the potential for spread to new areas with susceptible populations given vector competence.

The ecology of these infections is complex: viruses are maintained in a host population that may be human or non-human. Vectors feed on viremic hosts, after which there is an extrinsic incubation period where virus amplification occurs in the vector. Upon subsequent feeding on a second host (which may be of a different species), virus is then transmitted and undergoes an intrinsic incubation period where amplification occurs in the index case and may cause clinical illness, depending on immune status and other host and viral factors. Thus, permissive conditions for active transmission comprise viremic maintenance hosts, suitable climatic conditions for the vector and ecological interactions between hosts and vectors. This multistage life cycle constrains viral evolution and may limit viral fitness [3]. The danger to the blood supply occurs during the intrinsic incubation period, which is

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presymptomatic, and during any subsequent clinical illness before the immune system eliminates the virus from the bloodstream.

Despite not being taxonomically related, arboviral diseases generally present with three main acute febrile syndromes: acute benign fever (often with arthralgia), for example chikungunya; central nervous system infection as with West Nile neuroinvasive disease or Japanese encephalitis; and haemorrhagic fever such as dengue [4]. As arthropod vectors require high ambient temperatures for reproduction, they generally occur in tropical areas and during summer in subtropical and temperate areas. There is often a large overlap in clinical presentation with other common acute febrile illnesses, especially in the early phase. In less well-resourced areas, these are often managed without recourse to institutionalized medicine. Even when doctors are consulted, pathogen identification may not be of high priority compared with clinical triage of severe illness. Hence, there will be large numbers of symptomatic viremic cases unaware of their status in addition to asymptomatic and presymptomatic infections.

In assessing the threat of infectious disease agents to the blood supply, two aspects were identified by the American Association of Blood Banks (AABB) in determining prioritization: (i) the public health impact established epidemiologically and (ii) the public reaction, which may be driven by emotional and political concerns [5]. Quantifying the former requires four elements: (i) risk of human infection, (ii) risk of transmission via blood products, (iii) risk of introduction to blood supply and (iv) disease severity. Risk of human infection is well established for known disease-causing viruses such as dengue and West Nile, although precise correlations of viral titres and risk are not well established. There remains a danger from viruses known primarily from their sylvatic cycles, where ecological factors prevent their transmission to humans and whose potential remains for infecting humans is poorly understood. Risk of transmission via blood products is affected by such factors as the relative affinity of virus to blood cells or plasma [6] and sensitivity of virus to blood processing. This may be estimated from episodes of known transfusion-associated transmission. Determining risk of introduction to the blood supply involves knowledge of dynamic incidence, donor behaviour and efficacy of screening procedures. Finally, disease severity after transmission has taken place is dependent on such factors as viral load, host status and viral virulence. Such complex interplays are best estimated using modelling, discussed further below. The AABB review determined that three of eight high-priority (Red/Orange) infectious agents for blood safety in the United States are arboviruses, having excluded WNV as under control.

Testing of prevalence of arboviruses in the blood supply has resulted in estimates that vary both spatially and temporally. Dengue has potentially the largest susceptible population with half the world's population at risk [7] and an estimated 390 million infections a year [8]. Frequency of positive samples by nucleic acid testing (NAT) of dengue viruses in blood donation samples from endemic countries has been reported from Puerto Rico in 2005 (0.07%) [9] and 2007 (0.19%) [10], Honduras in 2004 (0.3%) [11], São Paulo, Brazil in 2003 (0.06%) [11] and 2010 (0.4%) [12]. Modelling estimates using various techniques have suggested a daily prevalence of 0.07% in Puerto Rico between 1995 and 2010 [13], 0.016–0.06% in Singapore in 2005 [14], and in Cairns, Australia, 0.014% in 2008 [15] and 0.017% in 2004 [16]. These appear to correlate reasonably well and demonstrate the real risk that is present.

It may be surprising that only three clusters of transfusion-associated transmission of dengue virus have been reported – in Hong Kong in 2002 [17], Singapore in 2007 [18] and Puerto Rico in 2007 [10], the latter two resulting in cases of dengue haemorrhagic fever. The Hong Kong cluster was identified by delayed incidental pickup of the donor during active case finding in the context of an unexpected outbreak. In Singapore, donor callback due to febrile symptoms facilitated prompt investigation. Retrospective repository testing established the link via sequencing of donor and recipient samples in Puerto Rico. Likely reasons for lack of additional reporting may be an overestimation of viral infectivity when based on NAT positivity; the presence of donor or pooled viral antibodies reducing risk of transmission; lack of recognition of disease outcomes in recipients; and efficacy of donor deferral systems in excluding symptomatic viremic cases. Initially, NS1-based testing and now NAT screening of donations for dengue are taking place in Puerto Rico under an FDA investigational new drug (IND) protocol, but with no FDA-approved test available yet [19]. During the 2012 outbreak in Madeira, Portuguese authorities also undertook RT-PCR testing for donors from affected areas [20].

In comparison, West Nile virus is the only arbovirus to have a stringent blood safety monitoring system in place. After an initial restricted outbreak in New York in 1999 [21], concern for the risk to the blood supply was modelled and a mean risk of 0.018% estimated [22]. With the expansion of WNV infection in the United States, regulatory concern coincided with documented transfusion-associated transmission, which led to the implementation of FDA-approved nucleic acid testing in 2003 on top of an initial withdrawal of frozen donor products from outbreak areas and subsequent donor deferral strategies [23]. Initial minipool-based testing was refined using various

strategies for switching to individual donor NAT as an estimated 5% of ID NAT positive cases negative for IgM would have been missed by MP NAT [24]. A total of 13 WNV positive donors leading to TAT events were missed between the initiation of NAT in 2003 to 2013, including a recent fatality [25]. Canada has implemented NAT screening on the US model [26]. The EU uses a donor deferral system of 28 days after exposure to an area with documented human transmission of WNV, with Italy implementing NAT during its 2008 outbreak and during subsequent seasons in affected provinces, and Greece similarly in 2010 [27]. In both, positive donors were identified, but no TAT event occurred (though one organ donation-related transmission was reported from Italy [28]).

Chikungunya is the final arbovirus with documented impact on blood collection practice. The 2006–2007 epidemic on Ile de La Réunion resulted in over 30% of the population being infected [29]. Local whole-blood donation was suspended to prevent TAT, and platelet component donation was subject to pathogen inactivation to prevent TAT in addition to NAT screening for CHIKV [30]. The mean risk at the epidemic peak from January to May 2006 was estimated at 0.7%, compared to an observed 0.4% rate of CHIKV positivity in platelet donations [31]. No cases of CHIKV TAT were identified though one needlestick transmission occurred [32]. Autochthonous transmission of CHIKV occurred in Italy in 2007. Within days of the first confirmed human CHIKV infection, blood donations were discontinued in the municipalities concerned (for up to 44 days) and enhanced donor questionnaires used for early detection of possible CHIKV infection [33]. Postdonation quarantine was used to exclude febrile illness after donation. No NAT testing took place due to the absence of approved testing methodologies, and pathogen reduction technologies were not implemented as sufficient products were imported from other regions. A mathematical model was used to estimate risk weekly, with a threshold of 1/380 000 used as the current estimate of the risk of post-transfusion hepatitis B virus transmission in the serological window period. A cost to the blood transfusion service in excess of 1 million euros was estimated from this 6-week-long interdiction [33].

Reviewing the information required for dynamic estimation of risk to the blood supply, we see the need for detailed information from one health-type surveillance [34]. ArboNet in the United States, co-ordinated through the CDC, combines information from livestock, mosquito and human surveillance [35]. Similar networks in Asia are being initiated [36]. Vector biology, including vector population dynamics, vector–virus interaction and vector–host ecology, is a first step towards understanding the

potential for arbovirus spread. The change in vector transmissibility demonstrated during the Reunion CHIKV epidemic is a good example of vector biology affecting our estimate of epidemic spread [37]. In addition, detailed knowledge of length of human viremia, both presymptomatic and postsymptomatic, is vital to estimate risk. Correlating viremia with risk of transmission requires longitudinal monitoring and adequate haemovigilance. Ideally, both seroprevalance studies and active surveillance for clinical cases would need to be done simultaneously to establish the ratio of asymptomatic to symptomatic infections. Asymptomatic viremia poses a key problem for introduction of virus into the blood supply, with asymptomatic/symptomatic ratios of 1:1–13:1 being reported in different settings for dengue [38]. An unanswered question is the extent of viremia in asymptomatic cases: one study which examined this reported worryingly no difference in the viral loads of asymptomatic and symptomatic dengue-infected individuals [39]. Studies of diagnostic accuracy are also critical to aid in accurate estimation of cases, given the difficulties in arboviral laboratory diagnosis, including short viremia and antigenemia, delay in acute antibody titre rise, long period of seropositivity after infection and cross-reactivity among large virus serogroups. Subsequently, key issues in blood banking that need further elucidation include donor deferral strategies (e.g. period of deferral after febrile illness [40], travel to endemic areas [41] or postdonation quarantine), testing strategies (use of NAT vs antibody testing, pooled vs individual testing [24], triggers for switching between testing methods based on case surveillance or season [42,43]) and finally pathogen reduction (photochemical systems such as INTERCEPT [44] and Mirasol [45], solvent/detergent [46] or heat treatment [47]).

In South-East Asia, there remain many challenges to adequate protection of the blood supply from arboviral threats. The region remains an epicentre with high transmission intensity of arboviruses, such as in the well-described Kamphaeng Phet paediatric cohort, with a consistent dengue infection rate of 6.9% (range 5.2–9.9%) per season over 4 years [48]. Outbreaks in susceptible populations can reach extremely high attack rates, for example in the 2011 Lahore epidemic, there were over 500 000 suspected dengue cases (in a city of 5 million), and a dengue IgG seroprevalence of 67.9% the following year, where dengue was not endemic previously [49]. Surveillance of animals hosts, vectors and clinical cases is often inadequate [50]. Passive surveillance often results in underreporting, with an estimated expansion factor to account for underreporting of symptomatic dengue of 7.6 in South-East Asia estimated in a recent systematic analysis [51]. Limitations in surveillance also impair response to novel or re-emergent arboviruses [52]. Cross-protection between

serologically related viruses has been postulated to contribute to geographically distinct patterns of distribution with cross-neutralization studies showing variable patterns of protection in animals [53] and humans [54]. Changes in virus and vector ecologies or vaccination policies may influence arboviral (re)-emergence.

The demographic transition leading to increasing age of infection has been reported in Thailand [55] and Singapore [56]. With more young adults rather than children with arboviral infections, the risk to the blood supply will alter significantly. Urbanization, deforestation and increased travel all contribute to increasingly large arboviral epidemics year on year in the region [57]. Given the widespread endemic nature of outbreaks, and the lack of distinct seasonality in some tropical countries, spatio-temporal limitation on donation is problematic. Pathogen inactivation systems thus far are effective in plasma or platelet fractions and not whole blood or red cell components. The apparent low rate of arboviral TATs may mask a growing problem due to inadequate haemovigilance and lack of clinical recognition. While the model of WNV testing in the United States has been extremely successful, cost-effectiveness studies thus far demonstrate an incremental cost per QALY of over USD 1 000 000 for NAT screening over questionnaire-based deferral in one analysis [58] and between USD 256 000 and 1 044 000/QALY for targeted individual donation testing relative to no screening in a different model [59]. Such an approach may not be feasible given global health priorities in the less well-developed economies in South-East Asia. Even current strategies such as donor deferral require optimization and novel cost-effective strategies for pooled testing would be welcome. The threat of arboviruses, both known and emerging, remains one that requires ongoing research to delineate and manage.

Disclosure

The authors have no conflict of interest to declare.

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