

Emerging viral threats to the Australian blood supply

Abstract

Objectives: To assess the risk to the Australian blood supply posed by emerging or re-emerging viral infections.

Method: A review was undertaken of the English-speaking literature on the potential for emerging viral threats to human health in Australia, the future implications of virus ecology, climate change and population movement and the implications for blood transfusion.

Results: Published data confirm that Australia's blood supply is among the safest in the world for currently screened viral pathogens as a result of rigorous surveillance, donor selection and state-of-the-art processing and laboratory testing. However, Australia has a number of other viral pathogens with the potential to threaten the safety of the blood supply such as the Ross River, Barmah Forrest, Kunjin, Japanese Encephalitis, Murray Valley Encephalitis and dengue viruses. Of these, dengue is currently of most concern to blood safety because; it can cause fatalities, there are regular seasonal outbreaks in Northern Australia and, in contrast to other viruses mentioned above an overseas case of transfusion transmission has already been documented. Notably, despite the lack of a suitable dengue screening test the ARCBS already implements supplementary measures to protect the blood supply during outbreaks.

Conclusion: Current interventions have proven extremely effective in minimising transfusion transmission in Australia of recognised viral pathogens. The threat posed by emerging viral pathogens to the safety of blood transfusion emphasises the need for global collaboration and consideration of further intervention strategies on a country by country basis including options such as nucleic acid testing and pathogen reduction technologies.

Key Words: arboviruses, infection, interventions, transfusion-transmission, blood transfusion, emerging infectious diseases, viruses.

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The war against infectious diseases is far from being won. We continue to recognise new infections and new and virulent strains of existing agents.^{1,2} The geographic ranges and prevalence rates of well-known infectious agents are expanding. These phenomena are collectively termed emerging infections and are attracting a great deal of attention, particularly from the blood transfusion community.^{3,4}

In this review, we examine a number of emerging viral infections that are relevant to the safety of the blood supply, in Australia. We also discuss some examples of viral infections that have not yet been shown to be a problem for the Australian blood supply.

By definition, a truly emerging infectious agent would be one that has newly entered a population and is not simply an established agent that has been detected for the first time. An agent can emerge either *de novo* by mutation or by crossing a species barrier to enter the human disease chain. HIV is an example of a truly emergent infectious agent. Alter⁵ noted the distinction between emerging infectious agents and emerging problems. Pre-existing bacteria emerged as problems when the frequency of platelet transfusions increased and when room temperature storage conditions for optimal platelet survival created a fertile environment for bacterial growth. The rapid spread of West Nile Virus [WNV] across North America is

an example of a re-emerging agent. It is an organism that has been known for a long time, but represented a distant and minimal transfusion risk. This changed rapidly with possible reasons including; environmental conditions exposing its mosquito vector to a large, susceptible population and the introduction of a more virulent form of the virus than that currently circulating.⁵

Methods

Information included in this review was extracted by means of a computerised (Medline) search of all recorded English literature from the year 2000 onwards. Subsequently, a manual review of bibliographies from selected articles was undertaken to identify any additional pertinent information.

Australian arboviruses and their transmission cycles

Arboviruses (an abbreviation of arthropod-borne viruses) is a term used to classify the vector-borne viruses that regularly cause human disease in Australia. These viruses are transmitted between blood-feeding arthropod vectors (mosquitoes in the Australian region) and susceptible vertebrate hosts and undergo a replicative cycle in both. The viraemia in the host usually only lasts for a few days or weeks, after which the host normally develops life-long immunity to the virus.⁶

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More than 65 arboviruses have been reported from countries in the Australasian zoogeographic region, but only a few have been implicated in human disease and only one (dengue virus) where transfusion transmission has been reported.^{6,7} Six of the viruses are of particular concern and their characteristics and potential for transfusion transmission are summarised in Table 1.

Ross River virus [RRV] belongs to the alphavirus genus. Each year it causes hundreds of cases of a debilitating and frequently persistent disease known as epidemic polyarthritis throughout Australasia. Barmah Forest virus (BFV), another alphavirus, causes a similar disease to RRV and has recently emerged as an increasing cause of human disease on mainland Australia.⁶

The genus, flavivirus includes Murray Valley encephalitis virus [MVEV] and Kunjin virus [KUNV] that are the aetiological agents of rare but potentially lethal encephalitic diseases known as Australian encephalitis, and Kunjin encephalitis, respectively.⁶

Another flavivirus of the JE sero-group is West Nile virus (WNV). Phylogenetically, it is closely related to the Australian KUNV. Until recently, WNV was endemic in a large part of Africa, Southern and South-eastern Europe, the Middle East, and the Western part of the Indian subcontinent where it periodically resulted in large, but generally geographically restricted, outbreaks. In those areas, it would not qualify as an emerging infection. However, in 1999, an outbreak of WNV infection occurred in New York City with 66 human cases and 22 deaths.⁸ By 2002, the disease had spread to most US states and into Canada, with 4,156 human cases and 284 deaths that year. Notably, the number of reported cases would have significantly underestimated the true infection rate since; a) reporting of symptomatic cases was likely incomplete, and b) most infections are asymptomatic.

By the end of 2002, more than 60 suspected transfusion-transmitted cases of WNV had been reported and 23 of these were

confirmed. Changes to donor screening programs were rapidly introduced and by July 2003, nucleic acid testing (NAT) for routine screening of blood donations in small pools was in place throughout the US and Canada. At the peak of the epidemic, the estimated population infection rate in some US states (inferred retrospectively from the incidence of WNV NAT positive donations) was as high as 3/1,000.⁹

Transfusion transmission of WNV is rare to absent outside North America and Australian virologists have speculated that KUNV exposure would offer some degree of protection in Australia.¹⁰ However, it is not inconceivable that a problem could occur with KUNV and/or MVEV in Australasia.

Dengue Flavivirus (DENV), particularly serotypes 1-4, are the most important arboviruses of humans, infecting 30-70 million individuals annually in tropical and subtropical regions, including Australasia.¹¹ Most DENV infections lead to dengue fever, a self-limiting febrile disease, but in some cases patients develop severe and sometimes fatal complications known as dengue hemorrhagic fever or dengue shock syndrome (DHF/DSS).

DENV are probably not endemic in Australia but have caused increasingly frequent outbreaks in north-eastern Australia following re-introduction of the viruses in viraemic travellers.

The first outbreak of Japanese encephalitis virus (JEV) in Australia occurred in the Torres Strait of northern Australia in early 1995. This flavivirus causes more than 50,000 clinical cases annually in eastern and southern Asia, with a 25% case-fatality rate. Recent serosurveys indicate that JEV may also be regularly active in PNG. The geographic range of JEV has increased significantly over the last three or four decades.⁶

Other arboviruses such as the alphavirus, Sindbis, the flaviviruses, Alfuy, Edge Hill, Kokobera and Stratford and the bunyaviruses, Gan Gan and Trubanaman have not been included

Table 1: Potential arboviral threats to the Australian blood supply (Adapted from⁶).

Genus	Virus	Major Vectors	Suspected hosts	Distribution in Australasia	Asymptomatic viremia in humans?	Transfusion Transmissibility
Alphavirus	Ross River	Aedes, Culex mosquitoes	Marsupials (particularly macropods)	Australia, PNG+, Pacific Islands	Yes	Unknown – No documented case
	Barmah Forrest	Aedes, Culex mosquitoes	Unknown, possibly marsupials, Birds	Mainland Australia	Unknown	Unknown – No documented case
Flavivirus	Murray Valley encephalitis	Cx annulirostris	Waterbirds	Northern Australia, occasionally south-eastern Australia	Unknown	Unknown – No documented case
	Kunjin	Culex mosquitoes	Waterbirds	Northern Australia, occasionally south-eastern Australia	Unknown	Unknown – No documented case
	Dengue (serotypes 1-4)	Aa egypti	Humans	Queensland, PNG, Pacific Islands	Yes – recently demonstrated in blood donors for Brazil/Honduras ^a	Known – Single documented case in Hong Kong ^b
	Japanese encephalitis	Culex mosquitoes	Wild and domestic birds and animals (particularly pigs)	Torres Strait Islands, Cape York Peninsula	Unknown	Unknown – No documented case

Notes:

(a) Linnen, JM et al. Dengue viremia in blood donors from Honduras, Brazil and Australia. *Transfusion* 2008, In Press.

(b) Lin, CK. First documented case of transfusion transmitted dengue virus infection. 23rd NRL Workshop on serology. Melbourne, Australia 2006

in this review as they appear to cause only mild symptoms and are therefore of less concern in Australia.¹² They are all found in Australia. Sindbis is the most common arbovirus isolated from mosquitoes but only very rarely infects humans. Alfuy is moderately common in northern Australia but does not cause human disease. Edge Hill is fairly rare, and has only once been implicated in human disease. Kokobera is not as rare as some of the others and has been found in widely different areas from Cape York to south-west WA and even PNG. It has been implicated with occasional human cases of fever with some polyarthralgia. Stratford and a third member of the Kokobera serogroup, New Mapoon, are rarer and not known to cause human disease. Gan Gan has occasionally been associated with human disease but Trubanaman hasn't, and they are both fairly rare.

Another alphavirus, Chikungunya also causes widespread epidemics, most recently in Mauritius and Reunion Island and spreading to the Seychelles and India. Chikungunya causes an arthralgic disease which until recently was not associated with severe morbidity or mortality. Recent outbreaks have demonstrated a potential for symptoms to range from mild to severe, with 237 deaths implicated among some 265,000 clinical cases in the 2006 Reunion outbreak.¹³ To date there have been no documented Australian cases of autochthonous Chikungunya infection, but there are an increasing number of imported cases.^{14,15} Given Chikungunya is commonly spread by *Aedes* mosquito genera already present in Australia, as with WNV, there is the potential (albeit remote) for it to establish itself in Australia (via a blood meal from a viraemic individual). Unlike WNV which is proven to be 'transfusion transmitted', to date there have been no reported cases of transfusion transmission associated with Chikungunya.

Other viruses

Viral Haemorrhagic Fevers (VHF) are a group of highly infectious and usually fatal diseases caused by several different viruses. Four VHF [Ebola, Marburg, Crimean-Congo and Lassa] are quarantinable diseases in Australia. The viruses are usually transmitted to humans by the bite of infected ticks and animals (including monkeys) and then the infection is transmitted between humans through body fluids and airborne droplets. They are not considered a major transfusion risk in Australia because of their rarity and the rapidity with which symptoms develop and death occurs.¹⁶ However, serological evidence of asymptomatic infection has been reported with Ebola,¹⁷ so transmission by blood transfusion could potentially occur. There has never been a case of VHF infection reported in Australia. In each Australian capital city there is an appropriately equipped medical facility for treatment of persons with a VHF. The National High Security Quarantine Laboratory in Melbourne, can test for VHF.

Two members of the paramyxovirus group of viruses, Hendra and Nipah, have been transmitted to humans via horses and pigs, respectively. Four people in Australia, have been infected by Hendra virus and two died.¹⁸ A Nipah virus outbreak in Malaysia in 1999, was characterised by severe fever, malaise and encephalopathy and killed 30% of 270 people. No human-to-human transmission was observed.¹⁹

A novel arenavirus isolated from a single donor who subsequently died of a brain haemorrhage was transmitted to three organ transplant recipients in Victoria in early 2007 (all three of whom died).^{20,21} This previously unknown virus appears to be related to lymphocytic choriomeningitis virus (LCMV), a member of the genus Arenavirus of the Arenaviridae family of the bipartite genome RNA viruses. Rodents are the reservoir hosts of almost all arenaviruses and, accordingly, LCMV infection in humans may occur in regions of high rodent density. Although transplantation transmission of this distinct, as well as prototype LCMV appears to be well established, it is unclear whether these viruses are 'passengers' or directly responsible for tissue-rejection illness and death. Although transfusion transmission has not been implicated to date, the close correlation between organ and blood transmission of many other viruses (e.g. WNV, HIV, HCV) is reason for due concern.

There is evidence that the highly contagious Severe Acute Respiratory Syndrome [SARS] virus, which emerged in November 2002, did have a viraemic phase, at least during symptomatic disease.¹⁶ However, there is no evidence (from past studies, checking donors/donations against SARS patient registries and surveillance of blood donor populations for SARS antibody) that SARS was transmissible by blood transfusion. Nevertheless, the WHO has made recommendations for blood deferral in relation to SARS and in Australia, the ARCBS donor screening questionnaire includes questions that should identify (symptomatic) donors. It is not known whether SARS will re-emerge.

Similarly, the H5N1 avian influenza virus that has spread globally since 2003 is unlikely to be an arbovirus but there is evidence that it has a short viraemic phase while symptoms are present. Transmissibility studies are under way in the US but the risk of asymptomatic H5N1 viraemia or infection with other influenza viruses novel to humans remains unknown.²²

Finally, three novel viruses were identified as a result of molecular viral discovery programs searching for the agents responsible for unexplained cases of hepatitis. HGV (hepatitis G virus, or GB virus type C), TT-virus and SEN virus have all subsequently demonstrated the ability to be transmitted by blood products and their prevalence in various populations ranges from 1.8 to 36%.^{23,24} Initially all three were proposed as possible agents for non A-E hepatitis. Comprehensive clinical studies have so far failed to demonstrate that any of these agents cause human hepatitis and they are considered to be 'agents searching for a disease'.²⁵ Accordingly, no measures to protect the blood supply from these agents have been implemented.

Surveillance

Surveillance is fundamental to the prevention and control of communicable diseases. Human cases of arbovirus infection are monitored through the National Notifiable Diseases Surveillance System (NNDSS).²⁶ States and Territories each maintain separate jurisdictional surveillance, but they all report their results, using common case definitions, to the Commonwealth Department of Health and Ageing.

The viral diseases monitored are those caused by RRV and BFV, MVEV and KUNV, DENV (all serotypes) and JEV. Table 2 shows disease notification data for 2007 compared with their five-year average rates are extracted from the NNDSS. Again, it should be noted that the number of reported cases would have significantly underestimated the true infection rate since reporting of symptomatic cases was certainly incomplete. Notifications for each disease are also regularly analysed and reported in the Department's quarterly, *Communicable Diseases Intelligence*.²⁷

More up-to-date statistics are available from the Communicable Diseases Australia website.²⁷ Complementing these data, fortnightly teleconferences by state and territory epidemiologists with their national counterparts allow recent and local disease outbreaks to be discussed and monitored.

Flavivirus sero-conversion is detected in sentinel chicken flocks in four Australian States/Territories. Flocks in Western Australia (30 flocks), Victoria (10), New South Wales (7) and the Northern Territory (9) are used to provide an early warning of increased levels of MVEV and KUNV activity in the region. During the 2003/04 season, low levels of flavivirus activity were detected in Northern Australia with both MVEV and KUNV virus activity detected in the Kimberley and Pilbara regions of Western Australia and in the Northern Territory. These programs are funded by the state health departments. Flocks are sampled regularly for antibody testing with a sensitive enzyme immunoassay. Each state has a contingency plan in the event of an outbreak.

Australia also maintains a sentinel pig program for JEV, with pig herd in northern Queensland, the Northern Territory and the Torres Strait Islands (TSI). In addition to the TSI outbreak detected in 1995 (and in most years since), an outbreak was also detected on mainland Australia in 1998.²⁸

In 2005, there were two cases of MVEV infection reported, the first in a 30-year-old male from Normanton, Queensland, and the second in a 3-year-old boy from a NT community who was treated at Royal Darwin Hospital. The latter displayed mild illness and completely recovered. His community was located near an extensive freshwater wetland with numerous water birds and frequent high numbers of common banded mosquitoes *Culex annulirostris* and *Culex palpalis*: two vectors of MVEV.²⁹

Arbovirus transmission cycles are complex and poorly understood in Australasia, particularly with regard to the role of the environment. Thus, the public health response to the threat of increased activity of these viruses must include further research into the ecologies

of these viruses, their known and potential vectors and hosts and environmental conditions that predispose to outbreaks.

Climate

The transmission of arboviruses is certainly influenced by environmental conditions that enable breeding and survival of, and interaction between, vertebrate hosts and arthropod vectors as well as virus replication (extrinsic incubation) in the vector. Rainfall, tides and sea level, temperature, humidity and wind all play a part in Australia. Consequently, changes in the climatic conditions may significantly alter the ecology and epidemiology of arboviruses and thus their potential to cause outbreaks of human disease.⁶

Expected climatic changes resulting from the 'greenhouse effect', such as increased rainfall with subsequent flooding and rising sea levels (with greater tidal penetration of coastlines), are likely to enhance breeding of mosquito vectors. Major outbreaks of RRV disease have been linked to extreme rainfall events and short-term rises in sea level. MVEV activity has also been associated with heavy rainfall and flooding. The potential for more regular and more southerly MVEV activity, following southward movement of the summer rainfall zone, is of particular concern. Outbreaks of Australian encephalitis (the disease caused by MVEV) in south-eastern Australia might be expected to increase in frequency.

Increases in temperature may accelerate vector life cycles and shorten extrinsic incubation of arboviruses. This would mean vectors would become infectious more quickly. These conditions are expected to lead to higher levels of virus activity and greater exposure of humans to the viruses. However, other influences such as increased evaporation associated with higher temperatures, or higher levels of immunity in vertebrate host populations following more frequent outbreaks, may help to moderate virus activity.

Climate change may also extend the range of known vectors and/or hosts or increase the receptiveness of a region for exotic vector species. Therefore, surveillance for further spread of other dangerous arboviruses such as JEV and DENV in the Australasian region is imperative.

Surveillance strategies should be expanded and co-ordinated nationally, particularly for regions receptive to spread of these viruses or incursion of exotic vectors or viruses. Other important responses include public education programs about mosquito avoidance and prevention of mosquito breeding as well as consideration of the threat of these viruses during planning of future residential, agricultural or industrial developments.⁶

Table 2: Arboviral disease notification data for 2007 compared with their five-year average rates extracted from the Communicable Diseases Australia website.²⁷

Virus	Number of Notifications		Notif. rates per 100,000 pop	
	2007	last 5 year mean	2007	last 5 year mean
Barmah Forest virus	1,695	1,366	8.1	6.7
Dengue Flavivirus	318	358	1.5	1.8
Flavivirus [NEC]	23	51	0.1	0.3
Japanese encephalitis [JE]	0	1	0	0
Kunjin	0	9	0	0
Murray Valley encephalitis virus	0	2	0	0
Ross River virus	4,143	3,513	19.7	17.3

NEC: Not elsewhere classified.

Apart from climate change, there are also other reasons why viral pathogens might arrive in Australia or expand their geographical distribution, such as increased international travel, increased international animal and bird movement, and deforestation.

Transmission by transfusion

A number of infectious agents are known to be transmissible by blood transfusion and vigorous effort goes into preventing or minimising such transmission. Classically, blood services have been concerned with a number of transfusion-transmitted viruses (TTV) that exhibit the following characteristics:³⁰

- 1) Cause mild or asymptomatic infections such that infected potential donors would present (and be accepted) for donation (e.g. Hepatitis A)
- 2) Have clinical latency (incubation) periods of years to decades (e.g. hepatitis B and C (HBV, HCV), human immunodeficiency virus (HIV), human T-cell lymphotropic virus (HTLV))
- 3) Might cause a 'carrier' state of infection (e.g. HIV, HBV and HCV)
- 4) Might cause a 'latent' state of infection in host cells by incorporating their own DNA in the host's DNA (e.g. HIV, HTLV and cytomegalovirus (CMV))
- 5) Would be present in blood components (e.g. HIV either in plasma as RNA or as proviral DNA in leukocytes)
- 6) Would be stable under the conditions at which blood components are stored.

Historically, almost all infections transmissible by transfusion have been characterised by a prolonged, silent carrier state with the infectious agent circulating in the blood but not causing symptoms. However, some infections with very short period of infectivity in the blood (i.e., a few days) have been transmitted via transfusion.¹⁶ Indeed, Kleinman highlights that, "WNV represents a prototype of a class of pathogens not previously recognised as a transfusion threat".³¹ These pathogens cause acute, short-term viraemia in asymptomatic potential blood donors with consequent rapid spread via localised epidemics which are temporally and geographically restricted. The transmission of WNV by blood transfusion in North America highlighted the potential of other arboviruses, e.g. dengue, to pose a similar threat to blood safety.

Nonetheless, the overall picture is that the main risk of transfusion-transmitted infections (TTI) arises from persistent infections. Because of this persistence, the presence of detectable antibody to the agent generally indicates the likelihood of continuing infection (and infectivity by transfusion), rather than clearance of the virus. With some exceptions (e.g. Hepatitis B) the detection of antibodies to infectious agents has formed the basis for the classical serological approaches to the routine testing of donated blood for TTV.

In Australia, all blood donations are routinely screened for the following viruses: HIV-1 and 2, Hepatitis B and C, and HTLV-I and II.³² Selected donations are also screened for CMV antibodies to provide CMV seronegative blood components for transfusion to immunocompromised patients at risk of severe and occasionally life-threatening complications. In addition, blood services internationally screen for a number of other transfusion

transmitted viruses including human Erythrovirus (formely Parvo B19), Hepatitis A virus and West Nile Virus.³³

Increasingly sensitive screening tests in concert with a rigorous donor questionnaire to exclude donors engaging in high-risk activities has substantially reduced the risk of transfusion transmitted HIV, HBV, HCV and HTLV in Australia.³⁴ The most recent advance in donor screening in Australia was the implementation in 2000 of nucleic acid testing (NAT) for HCV and HIV-1 RNA.³⁵ Risk modelling conducted by the ARCBS subsequent to this estimated the residual risk (i.e. the probability of releasing an infectious unit) for these viruses to be extremely low, ranging from approximately 1 in 1 million (HBV) to 1 in 7.6 million (HIV).³² This confirmed that Australia has one of the safest blood supplies in the world in terms of these pathogens. However, as the rapid emergence of WNV demonstrated, there is no room for complacency.

Indeed the challenge is to harness modern techniques against potential threats. The response of the US and Canadian Blood Services to the threat of WNV demonstrates the rapidity with which the blood transfusion fraternity in developed nations is capable of responding to a new agent and how quickly new molecular-based screening tests can be introduced.³⁶

The major risk for the ARCBS from a significant new viral disease outbreak in Australia may not be from TTI but rather the effect it would have on the maintenance of adequate staffing levels and eligible blood donors. An example might be the emergence of pandemic influenza strain that could severely compromise the ARCBS' ability to maintain an adequate blood supply.³⁷ The ARCBS has commenced dialogue with the relevant Australian Government agencies to develop a comprehensive response plan. Some priorities of this plan include: the continued protection of the health and wellbeing of staff and donors, enhanced infection control measures for blood collection facilities and modifications to donor selection criteria to boost eligible donor numbers.

Interventions

The risk of transfusion from emerging infections needs to be managed systematically. In general, a systematic approach should include a broad mechanism of surveillance to identify emerging infections, followed by a process to assess whether the agent could be transmitted by transfusion. Likely candidate agents should be prioritised for further study, both on the basis of public health importance and public concern.³⁸ Should time permit, it would be highly desirable to assess the prevalence (and ideally, the incidence) of infection in the exposed donor population. This is currently being undertaken for DENV in Australia (ARCBS unpublished). Finally, appropriate interventions should be implemented where necessary. Ideally, such interventions should be continuously evaluated for efficacy.

The range of sophisticated, incremental (and increasingly expensive) interventions to reduce microbial risks are: 1) education and selection of voluntary donors; 2) sensitive and specific serological testing; 3) leukodepletion of all blood components; 4) viral inactivation of fractionated products and, as a possible option for the future; 5) pathogen reduction for blood components; 6)

introduction of 'blood substitutes'; 7) vaccination of donors and 8) blood conservation strategies.^{3,30}

Currently available interventions include: measures based on selection of epidemiologically safe populations from which donors are drawn; measures based on a history elicited from the donor, leading to permanent or temporary deferral; and test methods designed to detect evidence of infection or infectivity with the agent in question. These measures need to be constantly reviewed as the strain on maintaining, managing and financing the blood supply increases.

A recent ARCBS report affirms the effectiveness of stringent donor selection criteria in reducing the risk of TTI. In the report, the prevalence of HIV, HCV, HBV and HTLV in accepted blood donors was 50-350 times less than in the Australian population.³⁴ In the absence of validated screening tests targeted donor questioning can also be an effective measure to minimise the TTI risk. A good example of this is the use of geographically based exclusion of donors during seasonal dengue outbreaks in Northern Australia. Subsequent to a declared dengue outbreak, all ARCBS donors are questioned and if they have travelled to the affected area they are temporarily disallowed from donating fresh blood components (although they may donate plasma for further manufacture that includes highly effective viral inactivation procedures). Once the epidemic is declared over, donor restrictions are lifted and dengue specific questioning is curtailed.

Technology advances continue to provide the potential to refine testing practices and reduce the overall risk of TTI. For example, new automated NAT systems have evolved from first generation 'semi-automated' systems.³⁹ These have expanded the existing capacity to screen for HIV and HCV RNA to include Hepatitis B DNA in a 'triplex' assay format. As well as providing the mechanism to further reduce the risk of transfusion transmitted HBV particularly in high prevalence populations, they offer improved process control (virtually eliminating 'human' errors) and improved cost effectiveness. A number of countries have implemented these triplex assays with the aim of reducing the risk of window period HBV infection and/or occult HBV infection.⁴⁰

Microarray technology offers perhaps the most promising 'next generation' blood testing platform. Petrik and co-workers describe microarrays as 'miniaturised solid phase assays of high multiplexing power'.⁴¹ These have the potential to screen for multiple agents on a single tailored 'chip' although currently the hurdle of combining protein and nucleic acid targets is an elusive goal. Developed to their full potential, microarrays could revolutionise blood screening offering rapid and inexpensive tailored testing for infectious disease markers (both protein and nucleic acid) in parallel with blood grouping antigens.

Pathogen reduction methods have been used widely in the manufacture of pooled plasma derived proteins reducing the risk of infection from these products to near zero.⁴² Physicochemical pathogen reduction techniques for individual blood components have been under development for some time but despite significant recent progress particularly with plasma and platelets, they have yet to be widely applied.⁴³ The key advantage of these techniques is

their potential to reduce or eliminate the risk of known pathogens as well as those that might emerge in the future. Despite their immense potential there are several limitations with the currently available methods that have to date precluded any from being implemented in either Australia or North America. First, no single method can be applied to all blood components. Second, existing 'safety' levels in voluntary donors are very high as a result of current risk reduction strategies (e.g. donor selection, testing and surveillance for known/emerging pathogens). Third, some methods are unable to inactivate certain pathogens including prions, spores and non enveloped viruses. Fourth, there are continuing concerns over the toxicity of residual chemical agents used in some methods. Finally, there is a perception that available techniques may well lack cost effectiveness when compared with other available interventions to address non infectious transfusion threats.⁴⁴

Despite these challenges the potential to remove all infectious agents with a single processing step remains a compelling driver to continue development of these methods.²⁵ Undoubtedly, blood services worldwide will continue to monitor the progress of pathogen reduction techniques with keen interest.

Infectious diseases in the context of today's 'global village' know no boundaries. The frequency and rapidity of international travel provide an efficient transport mechanism for existing, and perhaps more significantly novel agents. This new paradigm was well demonstrated during the 2002 SARS outbreak with a novel virus rapidly spreading from its epicenter in China, initially to Canada and subsequently threatening the remainder of the globe.¹ Clearly such challenges warrant global collaboration which thankfully emerged during the SARS outbreak on an unprecedented scale. A co-ordinated international response which brought to bear the combined resources of many jurisdictions as well as the United Nations and the WHO effectively minimised the global impact of the outbreak. The international blood banking community urgently assessed the threat posed by SARS and in the absence of a screening test rapidly implemented donor screening measures to safeguard the blood supply against the unknown potential for transfusion transmission. Although donor numbers understandably declined in the affected countries, ultimately the supply of blood and blood products was not compromised and reassuringly to date there have been no reported cases of transfusion transmission.

The lessons learned during the SARS outbreak have been further honed and applied to the current threat of influenza pandemic posed by the epizootic avian influenza A (H5N1) virus. These include the need for:

- transparent and timely outbreak reporting;
- unfettered sharing of relevant clinical and scientific data including access to genetic material;
- regular international conferences/forums to address emerging disease threats; and
- comprehensive national and international response plans for significant threats such as HIV/AIDS, and pandemic influenza.

By acting 'globally' the likelihood of success in mitigating the myriad of infectious risks is undoubtedly optimised but history reveals that man is seldom a match for nature!

Conclusion

Despite the obvious potential for blood transfusion to act as an efficient vehicle for transmitting viruses, current microbial safety interventions have proven to be extremely effective in preventing infection with recognised viruses. As risks from new agents are identified (usually after transmission is demonstrated), where available, interventions may be implemented if justified by the level of risk. If it is considered necessary to prevent such risks prospectively (rather than retrospectively) then 'catch-all' interventions such as pathogen reduction may have to be considered. Finally, the risk of emergence of transfusion-transmissible infectious diseases emphasises the need for countries to work together to help each other maintain their blood supplies during epidemics and pandemics. This is particularly important should a major infectious disease pandemic occur in different countries at different times.

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