



# Emerging threats to the blood supply: West Nile virus and beyond

It is now more than 40 years since Sir Macfarlane-Burnet announced to the world that "one can think of the mid-20th century as marking the virtual elimination of infectious disease as a significant factor in life" (1962). Along similar lines, Jesse Steinfeld, at the beginning of his reign as US Surgeon General, famously said that it was "time to close the book" on the problem of infectious diseases (1969).

With the hindsight of experience, we now know how spectacularly wrong they were in making these bold statements. Indeed, we are more resigned than ever to the inevitability of the continuing emergence and re-emergence of infectious diseases in our communities. This state of affairs has arisen through a combination of many factors, including a general lack of political will to seriously address emerging infectious disease as a genuine threat (to some extent SARS was a wake-up call on this front); our own changing interactions with and growing impact on our environment; economic globalisation and associated changes in human demographics; an explosion in international tourism that provides ideal opportunities for global dissemination of emerging diseases; and finally, but by no means least, a general weakening

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and, in some cases, breakdown in effective public health measures.

In addition to the direct impact emerging diseases have on the world's population, these agents may also pose a threat to recipients of blood transfusions<sup>1</sup>. However, not all will be transmissible via this route. Infections of most concern to transfusion safety are those that cause disease with an extended asymptomatic period during which the virus is present in the blood.

There are numerous examples of emerging potential threats to the blood supply (Table 1), including those that pose known risks such as new HIV variants, new hepatitis agents and West Nile virus, and those that pose a theoretical risk such as human herpes virus type 8 (HHV8), variant Creutzfeldt-Jakob disease (vCJD), SARS virus and Dengue virus.

The continued maintenance of transfusion safety will require timely action and a coordinated response to all newly emerging disease threats. This will involve the combined efforts of an efficient public health surveillance programme as well as the rapid implementation of effective screening measures to minimise the risk of emerging disease transmission.

Viral threats to the safety of blood and blood products are certainly not new phenomena. Monitoring of blood donations for potential virus contamination began in the early 1970s with serologically based tests for the detection of hepatitis B virus (HBV). The introduction of these tests lead to a dramatic decrease in the incidence of transfusion-associated hepatitis.

Nevertheless, the fact that there were a significant number of transfusion recipients still succumbing to hepatitis despite the absence of markers for HBV lead to the realisation that an additional agent or agents were contaminating the blood supply. These were collectively referred to as non-A non-B hepatitis, reflecting the absence of markers to these viruses.





Donor history and surrogate markers of liver disease, such as elevated transaminase levels were used in order to minimise the introduction of these agents into the blood supply. However it wasn't until 1989 that the first, and most important, of these agents was identified as a virus belonging to the Flaviviridae family, hepatitis C virus (HCV). With the development of sensitive serological assays for HCV and their swift introduction in 1990 into the testing of blood donations, transfusion related hepatitis was again markedly reduced.

The continued persistence of a small number of transfusion associated

hepatitis cases and the fact that about one in five community acquired hepatitis infections do not have a defined etiology, indicates the existence of additional causative agent/s. Over the last decade, the application of molecular techniques has identified several candidates present in blood; these included Hepatitis G virus (HGV), another member of the Flaviviridae and TT virus (TTV), a small DNA virus with a circular genome belonging to the Circoviridae. Subsequent studies have provided fairly convincing evidence, however, that these two viruses are not associated with hepatitis in humans<sup>2</sup>.

The current flavour of the month, SEN virus (up to eight different subtypes designated A-H have so far been identified) is another virus belonging to the same family as TT virus and has been put forward as the long-awaited agent of non A-E hepatitis. But the jury is still out on this candidate, with many studies reporting contradictory findings<sup>3,4</sup>. It is likely that the blood-borne agent responsible for non A-E hepatitis will remain elusive for a little while longer.

Perhaps the most dramatic example of an emerging disease threat that has had a significant impact on the issue of blood safety is HIV. When it first appeared in the

Table 1. Viral threats to the blood supply (adapted<sup>1</sup>).

Agent	Disease	Transmission*	History†	Screening markers
HBV	Parenterally transmitted hepatitis	Known	DH, risk	HBsAg
HCV	Parenterally transmitted hepatitis	Known	DH, risk	Antibodies to HCV HCV RNA
HIV1-2	AIDS	Known	DH, risk	Antibodies to HIV-1 and HIV-2 HIV-1 RNA
HTLV I/II	T-cell lymphoma – leukemia Hairy cell leukemia	Known		Antibodies to HTLV I
CMV	Infectious mononucleosis Interstitial pneumonia	Known		Antibodies to CMV
SEN virus	Parenterally transmitted hepatitis?	Theoretical		
HHV 8	Kaposi's sarcoma	Theoretical		
vCJD	Spongiform encephalopathy	Theoretical	DH, travel	
SARS virus	Respiratory disease	Theoretical	Travel, risk	
West Nile virus	Encephalitis	Known	Travel, symptoms	
Dengue virus	Dengue fever	Theoretical	Travel	
<p>• <i>Transmission:</i>  <i>Known = multiple documented reports</i>  <i>Theoretical = known to be viremic but no reported cases.</i></p> <p>† <i>History</i>  <i>DH = donor is asked about any history of disease.</i>  <i>Risk = donor is asked about risk factors or behaviours that may expose them to the agent.</i>  <i>Symptoms = donor is asked about the presence or recent presence of symptoms associated with the agent.</i>  <i>Travel = donor is asked about residence in or travel to a location known to present a risk of infection.</i></p>				



early 1980s, HIV infected a relatively small number of individuals. But the early recognition of the grim consequences of infection with this agent triggered an intense effort to develop serologically based tests that could be used to exclude it from the blood supply. Their introduction has been extremely effective at minimising the risk of transfusion-associated transmission of HIV. Over the intervening years, the sensitivity of these antibody assays have improved substantially, resulting in a reduction in the window period between infection and detection of seroconversion from about 3 months to just 22 days.

The potential for transmission of HIV by blood taken from a donor during this window period became an unfortunate reality with the infection of a Melbourne schoolgirl in 1999 from a blood transfusion. When this tragic story broke, it became a media and political hot potato, given that the issue of the implementation of more sensitive nucleic acid testing (NAT) was at that time under consideration.

Then Federal Health Minister, Michael Wooldridge, had already gone on record as being critical of more expensive testing in a climate of limited health resources and others in the scientific community were also questioning the cost-benefits of the additional expenditure<sup>5</sup>. However, it was not long before the introduction of NAT was approved and testing began in April 2000. NAT for both HIV and HCV has now reduced the window of infection to detection to 11 days for HIV and from 82 to 23 days for HCV. It was estimated that, across Australia, NAT may detect one extra HIV infected donor per annum<sup>5</sup>. The cost for this extra level of safety for our blood supply is approximately \$15 million annually.

At the other end of the spectrum of perceived risk is cytomegalovirus (CMV). CMV infection of immunocompetent adults is relatively mild and, given that approximately 50% of the population is CMV positive, their exclusion as potential donors would significantly impact on the country's blood supply. Instead, a limited amount of CMV seronegative blood and/or leukocyte reduced blood

components is generated for use in those patients most at risk from serious disease following CMV infection, such as low birth-weight infants, immuno-compromised individuals and those undergoing bone marrow transplantation.

Another herpes virus, human herpes virus 8 (HHV8), is of potentially greater concern. The etiological agent of Kaposi's sarcoma (KS), HHV8 has been endemic in parts of southern Africa and Europe for some time, but its 'elevation' into emerging status has come from an increased presentation through its association with HIV. Given the exclusion of these patients from donating blood, it is not likely to enter the blood supply this way and, although it has been reported in a blood donation from an otherwise healthy donor<sup>6</sup>, there has been no compelling evidence of transmission by blood transfusion<sup>7</sup>. Nevertheless, the potential risk of this agent will need to be monitored through individual case reports and other surveillance mechanisms.

Once an emerging disease has been identified as a potential threat, the most effective immediate response in order to exclude its introduction into the blood supply, is often a simple refinement of donor history screening and selection. A well constructed questionnaire can be extremely effective in removing potentially infectious blood donations.

The Therapeutic Goods Administration (TGA) formulate these changes in full consultation with the Australian Red Cross Blood Service. For most of the recent examples of emerging agents that have been identified as potential risks to blood safety in Australia, this has been the major response so far adopted. These agents include vCJD, SARS virus, West Nile virus and Dengue virus. The manner in which these threats are/were managed provides an insight into how the balance between the supply of essential blood and blood products to the community is maintained while ensuring that the threat of disease transmission is minimised.

Creutzfeldt-Jakob disease (CJD) is a spongiform encephalopathy thought to be caused by an unconventional pathogenic agent referred to as a prion,

an aberrant form of a naturally occurring host cell protein. Cases are sporadic and most often associated with a history of genetically inherited susceptibility. However, a new form of this disease, variant CJD or vCJD emerged in the human population in 1996 in the UK apparently as a consequence of the introduction into the human food supply of meat products contaminated with bovine spongiform encephalopathy (BSE). The BSE epidemic in the UK is thought to have originated in the early 1980s from the inclusion of scrapie (another prion agent) infected sheep carcasses in bone meal fed to cattle. The long disease incubation period saw this epidemic persist in the cattle population into the mid 1990s, despite the removal of the source of the contamination much earlier.

It is unlikely that CJD is transmissible by blood transfusion<sup>8</sup> and there is currently no compelling evidence of transmission of vCJD by this route either. However, the demonstration in small animal models that agents of spongiform encephalopathies may be detected in blood has meant that a deferral policy has been introduced as a precautionary measure against the theoretical risk of transmission by transfusion. Currently, individuals who lived in the UK or Ireland between 1980 and 1996 for 6 months or more are, for the time being, no longer eligible to be blood donors.

Severe acute respiratory syndrome (SARS), a disease caused by a newly identified coronavirus, exploded into the human population in southern China in late 2002. In the following months this highly contagious pathogen was rapidly disseminated around the world generating immense public health concern. Unparalleled efforts were undertaken to contain the spread of this disease; this included measures to reduce the potential risk of transmission by transfusion.

Australia was extremely fortunate to not be on the SARS itinerary, however, it was important that the TGA adopt precautionary measures against its introduction via the blood supply given that an asymptomatic viremic phase had



been established. Following the trend of other authorities overseas, they instigated a deferral policy for potential donors who had recently visited a country affected by SARS. This deferral was only for a limited period, which was meant to allow any infected donors to develop clinical signs of disease. While SARS has receded as an immediate threat to the human population, continued surveillance is in place to detect its re-emergence.

West Nile virus and its disease potential in humans has been known for many decades. It was first recognised in the West Nile region of Uganda in 1937 and is endemic in parts of Africa, countries bordering the Mediterranean, the Middle East and India. We in Australia have our own native version of this virus, Kunjin virus, an apparently non-pathogenic West Nile related sub-type.

The natural life cycle of the virus is in birds with transmission predominantly via culicine mosquitoes. Humans are essentially dead-end hosts for WNV, primarily as a consequence of the relatively low viremia levels generated during infection. In 1999, an unusual outbreak of WNV occurred in New York City, which resulted in a significant number of deaths. In subsequent years, the virus has established itself throughout North America, spreading to the west coast of the US, north through Canada and south through Mexico.

Given that the virus has a viremic phase, the potential for transmission through transfusion became a recognised risk<sup>9</sup>. Ironically, the first cases of transfusion acquired WNV infection were reported only weeks after the publication of that paper. Blood collection agencies in the US immediately began a policy of alerting donors to report any symptoms of WNV infection after donation.

By the end of the 2002 WNV epidemic, 23 people had acquired WNV infection after receipt of blood components from 16 WNV viremic blood donors. It is thought that approximately 500 viremic donations might have been collected<sup>10</sup>. Within 6-8 months of the recognition of the need to monitor the presence of this virus, suitable NAT procedures were in place<sup>11</sup>.

In Australia, the exclusion of WNV from the blood supply is achieved through a 3 week deferral policy for travellers returning from North America before they are eligible to donate blood.

Dengue virus belongs to the same family of viruses as WNV and is also mosquito transmitted. The world has experienced an explosion in Dengue virus epidemics over the last few decades with its re-introduction into many countries from which it had earlier been eradicated through concerted vector control programmes. It is estimated that up to 100 million human infections occur annually.

Since the early 1980s Dengue fever epidemics have been regularly seen in northern Australia, particularly around Cairns and Townsville, and in recent years these epidemics have been increasing in size and duration. There is a fear that this virus may be re-establishing itself in an endemic form in Australia.

The TGA has recognised the potential hazard of transmission by blood transfusion and has directed the blood service to not use fresh blood components from donors resident or visiting affected areas during an epidemic period. Collected plasma can still be used to manufacture derivatives, a measure designed to ensure minimal risk of transmission, while at the same time maintaining the blood bank in North Queensland.

It is now a certainty that emerging and re-emerging viruses will continue to pose a threat to the safety of our blood supply. Effective public health surveillance, coupled with an administrative and management framework that can rapidly implement appropriate intervention strategies, are vital to the maintenance of what has so far been an enviable safety record.

As molecular methods and technology platforms evolve, there will be improvements and cost reductions in NAT that may lead to the implementation of single donor testing instead of the current approach of mini-pool testing as well as the potential testing for a wider range of agents.

Perhaps the next phase in guaranteeing blood safety may not even be in improvements in detection but rather in developing generic technologies for inactivation of any contaminating viruses and/or in cost-effective methods for their complete separation and removal from blood components and blood products.

What is certain is that the public expectation of risk-free blood transfusion will necessitate ongoing efforts that ensure that blood donations do not become a source of transmission for emerging viral disease.

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