Transfusion and risk of infection in Canada: UPDATE 2004

Canadian Paediatric Society

In Canada and other countries, many steps are taken to minimize the risk of infection through the transfusion of blood or blood products (1). However, the infection risk can never be zero because these are biological products taken from living donors who are never 'germ free' (2). This is in contrast to drugs that can be manufactured de novo under sterile conditions in a laboratory. The present note provides an update on transfusion infection risks in Canada. It replaces the 2003 note (3), and may be helpful to practitioners in discussions with patients and parents toward obtaining informed consent before blood or blood product administration.

While any infectious agent that has a blood phase has the potential to be transmitted by transfusion of blood or blood products, the probability of infection in the recipient depends on a number of factors, including (4):

- the prevalence of the agent in the blood of the donor population;
- the tolerance of the agent to blood handling, storage and manufacturing procedures;
- the infectivity and pathogenicity of the agent;
- the recipient's health status; and
- the effectiveness of donor screening or donor testing for the agent.

The importance of these factors is well illustrated by the tale of West Nile virus (WNV). WNV has only recently been introduced into the North American bird population and, through secondary transmission via mosquitoes, to humans (5,6). Not surprisingly, given the blood phase of infection, WNV was shown in 2002 to be transmissible by blood (7), with an estimated mean risk of 2/10,000 to 5/10,000 (maximum 21/10,000) in outbreak regions in the United States (8). This resulted in rapid efforts to develop a screening test to detect WNV infection in blood donors (9). Both the Canadian Blood Services and Héma-Québec started testing for WNV infection in June 2003, using a new test that has an estimated sensitivity of 75% to 90% to detect infected donors during the WNV season. The seasonal variation in the transmission of WNV from mosquitoes to humans means that the prevalence of acute infection among blood donors varies. Surveillance through the new screening programs for blood donors last year found marked variation in the prevalence of WNV infection across the country, as well as variation in the onset of the 'season' for WNV in different regions. The background risk of WNV in unscreened blood is predicted to change over the next few years as the bird population becomes immune, resulting in decreased transmission from the avian population to mosquitoes and to people. With WNV donor screening testing now in place, the risk of contamination in blood collected from donors during a WNV outbreak is now estimated to be 1/100,000 to 3/100,000. This measure reflects the sensitivity of the test and the prevalence of infection among donors in a given region.

This past season, the blood donor WNV screening program has had the added benefit of providing public health authorities with a marker for infection rates among local and regional populations. Public health authorities in most jurisdictions now provide regular updates concerning the penetration of WNV in birds, animals and humans in Canada during the mosquito season. In the same way that Canadians monitor the Weather Channel, health care practitioners need to monitor the 'Web-based public health channels' through their local public health unit, a provincial or territorial health Web site or via Health Canada's West Nile Monitor (10), to gain a sense of the background risk for WNV in their region.

In Canada, the infectious disease risks of transfusion are minimized through multiple steps, including: blood collection from volunteer unpaid donors, donor interview and selection procedures, donor screening by serological and other tests (Table 1), and viral inactivation procedures included in the

TABLE 1
Testing of blood donors in Canada* by Canadian Blood Services (CBS) and Héma-Québec

HIV-type 1/2/0† group	Antibody/NAT
HBV	Hbs Ag, Anti-HBc‡
HTLV type I/II	Antibody
Syphilis	Nontreponemal test – Treponemal test/PK-TP
HCV	Antibody/NAT
WNV	NAT
Other§	CMV antibody on selected units only

**Personal communications: Dr Gilles Delage, Héma-Québec; Dr Heather Hume, CBS. Héma-Québec and CBS are developing bacterial culture testing for thrombopharesis platelets; †While the newer PRISM human immunodeficiency virus (HIV) antibody test does detect HIV group O, donors are still asked questions related to travel to parts of the world where HIV-O infection is prevalent, until a change in practise is approved; ‡Antibody to hepatitis B core antigen (Anti-HBc) testing has been introduced by Héma-Québec in 2003 and will be introduced by CBS in late 2004; §Héma-Québec and CBS are developing bacterial culture testing for thrombopharesis platelets. CMV Cytomegalovirus; Hbs Ag Hepatitis B surface antigen; HBV Hepatitis B virus; HCV Hepatitis C virus; HTLV Human T-lymphotropic viruses; NAT Nucleic acid testing; WNV West Nile Virus*

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TABLE 2
Specific manufacturing procedures for virus inactivation or removal

Procedure	Agents inactivated	Agents not inactivated
Inactivation by heat	CMV, HAV, HBV, HCV, HIV, WNV, Parvovirus B19	
Inactivation by solvent/detergent	CMV, HBC, HCV, HIV, WNV	HAV, Parvovirus B19, enteroviruses
Ultrafiltration using 35 nm and 15 nm filters	Removes even small viruses but also macromolecules eg, Factor VIII is decreased	
Leukocyte depletion	Decreases CMV, HTLV type I, II	Non-WBC associated viruses

CMV Cytomegalovirus; HAV Hepatitis A virus; HBV Hepatitis B virus; HCV Hepatitis C virus; HIV Human immunodeficiency virus; HTLV Human T-lymphotropic viruses; WBC White blood cell; WNV West Nile virus

TABLE 3
Manufacturing steps to decrease infectious risks of plasma preparations and plasma-derived components

Plasma preparation	Virus risk pre-inactivation process(es)	Pools screened for HIV, HCV, HBV, and HTLV type I, II*	Further virus inactivation steps
Cryoprecipitate	++	yes	none†
Factor VII	+	yes	heat inactivation ± solvent/detergent
Factor VIII	+	yes	heat inactivation ± solvent/detergent
Factor IX	+	yes	heat inactivation, solvent/detergent, chromatography
Antithrombin concentrates	+	yes	COHN fractionation, heat inactivation
Albumin	+	yes	heat inactivation
IVIG products	+	yes	COHN fractionation, ± hydrolase, ± solvent/detergent, ± heat inactivation, ± chromatography, nanofiltration
IMIG	+	yes	COHN fractionation, solvent/detergent, heat treatment, nanofiltration,± chromatography
Specific antibody products‡	+	yes	COHN fractionation or ion exchange column chromatography, solvent/detergent, filtration ± heat inactivation

**Human T-lymphotropic viruses (HTLV) type I/II are cell-associated viruses, so they are not found in manufactured plasma-derived products and serological screening of source plasma is not required. Similarily, cytomegalovirus (CMV) is primarily cell-associated and the manufacturing processes remove risk; †Hence the risk of transmission of infection from cryoprecipitate is similar to the risk from blood and blood products, and greater than from plasma-derived manufactured products; ‡eg, Hepatitis B (HBV) immune globulin, Tetanus Immune globulin, Rabies Immune globulin, Rh (D) immune globulin, etc. HCV Hepatitis C virus; HIV Human immunodeficiency virus; IMIG Intramuscular immunoglobulin; IVIG Intravenous immunoglobulin*

TABLE 4
Bacterial agents associated with acute infection during blood product transfusion

Blood component	Storage	Bacterial agent
Packed red cells	1°C to 6°C for 35 to 42 days	*Yersinia enterocolitica* Gram-negative, including *Pseudomonas* species
Whole blood	1°C to 6°C for 35 to 42 days	Gram-negative organisms
Platelets	20°C to 24°C for 5 days	Skin flora (eg, *Staphylococcus epidermidis* Diptheroids) *Salmonella* species *Escherichia coli* *Enterococci* species *Clostridium* species *Serratia marcescens*
Plasma	18°C, thawed, 1°C to 6°C for 24 h	*Staphylococcus aureus* *Pseudomonas aeruginosa*

manufacturing of plasma-derived products (Table 2) (11-14). As noted in Table 2, solvent/detergent procedures dissolve the lipid envelope of the human immunodeficiency virus, WNV, hepatitis B virus and hepatitis C virus, but are not effective against nonlipid enveloped viruses such as hepatitis A virus or parvovirus B19. Heat inactivation is effective against a wide range of viruses, including WNV, hepatitis A virus and parvovirus (14). The leukocyte reduction technique that is used by Canadian Blood Services and Héma-Québec to further improve the safety of the blood supply also reduces the infection transmission risk, particularly for cytomegalovirus (CMV) (13). Table 3 identifies specific inactivation steps in the manufacture of different plasma-derived products that decrease viral infection risks.

Unfortunately, the solvent/detergent and heat inactivation procedures noted in Table 2 cannot be used on red blood cells or platelets, because neither can withstand these vigorous viral inactivation processes. Pathogen reduction techniques suitable for these labile blood components are in development and, in some cases, being tested in clinical trials.

Almost all reported acute infectious complications arising from blood product transfusion are associated with bacterial pathogens (15,16) (Table 4). While the use of closed multicomponent plastic blood pack collection systems has helped to decrease the problem, contamination of platelet concentrates is still a concern (16). The risk of bacterial contamination of frozen components such as fresh frozen plasma and cryoprecipitates is now very low, because the usual microbes (Table 4) are killed by freezing and other storage conditions. Where plasma has been found to be the source of infection, this was usually due to contamination of the water bath used to thaw the product (17). The use of microwave techniques specifically designed for this purpose minimizes this risk.

TABLE 5
Estimated risk of infectious agent blood or blood products

Agents and products	Transfusion-transmitted	Pathogenic	Canadian estimated risk of contamination*
Viruses for which all blood donors are tested			
HIV†	Yes	Yes	<1/4,000,000
HCV†	Yes	Yes	<1/1,000,000
HBV†	Yes	Yes	1/275,000 to 1,000,000
HTLV† types I and II	Yes	Yes	<1/4,000,000
Other viruses			
CMV	Yes	Yes	risks vary with donor/recipient‡
Parvovirus B19	Yes	Yes	1/10,000 to 1/15,000
GBV-C†	Yes	Unknown	1-2 in 100; not pathogenic
TTV†	Yes	Unknown	1/100; rarely pathogenic
SEN-V†	Yes	Unknown	1/00; not pathogenic
HHV-8†	Unknown	Yes	Unknown
WNV	Yes	Yes	1-3/100,000 during outbreak§
Parasites			
Malaria	Yes	Yes	4 cases reported in Canada in last 10 years
Chagas (*Trypanosoma cruzi*)	Yes	Yes	2 cases reported in Canada in last 15 years
Babesiosis (*Babesia microti*)	Yes	Yes	1 case reported in Canada in last 15 years
Prion			
vCJD	Unknown	Yes	theoretical risk of <1/10,000,000

**Risk of contamination refers to the potential residual risk of infection from the listed organisms in blood or blood products after proper screening and manufacturing processes have occurred; †Based on 3% to 5% of the Canadian population from the 17 to 65 years age group being blood donors. Based on reported cases from Public Health. Based on sensitivity and specificity of the tests used at Canadian Blood Services and Héma-Québec; ‡Cytomegalovirus (CMV) infection risk is decreased by leukoreduction procedures (see text); §West Nile virus risk of 1-3/100,000 during an outbreak is an estimation given the sensitivity of the screening test and the prevalence of donor infection during an outbreak. HBV Hepatitis B virus; HCV Hepatitis C virus; GBV-C formerly named Hepatitis G virus; HHV-8 Human herpes virus 8; HIV Human immunodeficiency virus; HTLV Human T-lymphotropic viruses; TTV Transfusion-transmitted virus; vCJD Variant Creutzfeldt-Jakob disease; WNV West Nile Virus*

TABLE 6
Estimated risks of infectious agents in manufactured plasma-derived products

Agents	Historical evidence of transmission from plasma product	Pathogenic	Canadian estimated risk of contamination*
Viruses for which all blood donors are tested			
HIV	yes	yes	less than1/10 million
HCV	yes	yes	less than 1/10 million
HBV	yes	yes	less than 1/10 million
HTLV types I, II	yes	yes	only theoretical risk
Other viruses			
CMV	no	yes	only theoretical risk
Parvovirus B19	yes	yes	only theoretical risk if heat inactivation; otherwise 1/100,000 to 1/1,000,000
WNV	no	yes	much lower than 1/100,000, only theoretical risk
Parasites			
Malaria	no	yes	only theoretical risk
Chagas	no	yes	only theoretical risk
Babesiosis	no	yes	only theoretical risk
Prion			
vCJD	unknown	yes	theoretical risk of less than 1/100,000,000

**Risk of contamination refers to the potential residual risk of infection from the listed organisms in plasma-derived products after proper screening and correct manufacturing processes have taken place. CMV Cytomegalovirus; HBV Hepatitis B virus; HCV Hepatitis C virus; HIV Human immunodeficiency virus; HTLV Human T-lymphotropic viruses; vCJD Variant Creutzfeldt-Jakob disease; WNV West Nile virus*

The estimated per unit risks of contamination in blood, blood products and manufactured plasma-derived products in Canada for a number of viral, bacterial, parasitic, prion and tick borne agents are presented in Tables 5 and 6. Where Canadian data are not available, data from the United States and other countries have been included (4,12,18-20). As the data in Tables 5 and 6 show, the risks in Canada of transmitting infectious agents by blood, and especially by plasma manufactured products, are extremely low. For context, a 1/3,000,000 risk is similar to that of being hit by lightning.

The risk estimates for transmission of CMV remain complex (21). Although 40% to 70% of donors are CMV-positive, the risk of disease in nonimmunocompromised recipients is very low, while the risk of disease in immunocompromised patients is significant. For CMV seronegative recipients, the risk of CMV infection in solid organ transplant recipients and in bone marrow transplant recipients is 2% to 3% and 20% to 50%, respectively. This risk can be decreased with selection for seronegative donors and/or the use of leukocyte depletion filters, eg, the estimated risk for a bone marrow transplant recipient is only 2.4 % using a leukocyte depletion filter (13).

Although the risk of transmission of infectious agents through blood and plasma products is very low, the possibility of risk with a new or previously unrecognized agent is always present. Hence, a reassessment of the potential transfusion risk must be made when a new agent is discovered, as was done with the severe acute respiratory syndrome donor deferral program (22). Experience gained from hepatitis C and human immunodeficiency virus trace-back and look-back programs, where authorities have tried to trace transfusion recipients, has shown that many patients are unaware that they actually received a transfusion. No national electronic record of transfusions yet exists to facilitate any potential future tracing programs for a new transmittable agent. Therefore, it is important to make sure that transfused patients are aware that they received blood, blood products or manufactured plasma-derived products, and that the discharge or outpatient note adequately documents these transfusions and records the label code numbers for the specific products used.

Recently, a pilot project aimed at improving surveillance for adverse events with transfusion of blood and blood products (Transfusion Transmitted Injuries Surveillance System) was carried out by Health Canada and four provinces (British

Columbia, Quebec, Nova Scotia and Prince Edward Island). This pilot has demonstrated the benefits of standardized case definitions, report forms, and the added value of electronic reporting for ease and timeliness of data analysis. The Transfusion Transmitted Injuries Surveillance System program has now been extended to four other provinces and is expected to be applied nationwide by 2006. When fully implemented, this program is expected to improve the quality and timeliness of risk estimates for blood related infectious diseases and injuries.

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The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate. This article also appears in Paediatr Child Health 2004;9(3).