Transfusion and risk of infection in Canada: Update 2006

Canadian Paediatric Society

In Canada and other developed countries, many steps are taken to minimize the risk of infection from 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 2005 note (3) and may be helpful to practitioners in discussions with patients and parents for informed consent before blood or blood product administration. The changes in this note include new Canadian data on risk of adverse transfusion events (ATEs), including risk of bacterial infection. Transfusion-related acute lung injury and major allergic or anaphylactic reactions are more common than serious infections (4).

STEPS IN THE PREVENTION OF INFECTION WITH BLOOD TRANSFUSION

Restrictive transfusion policies and effective blood conservation programs

A crucial step in enhancing safety is to carefully assess whether the patient will likely benefit from the administration of the blood or blood product (ie, that the potential benefit outweighs the potential risks) (5). Studies in both adults and children in critical care settings have shown that a restrictive transfusion policy is at least as effective as a liberal transfusion strategy in terms of outcomes (6-8). Blood conservation programs – ie, use of alternatives to transfusion – are also effective in minimizing blood and blood product use (9).

Effective evidence-based policies for donor selection, screening, product collection, testing and infusion

While any infectious agent that has a blood phase has the potential to be transmitted by the transfusion of blood or blood products, the probability of infection in the recipient depends on a number of factors, including the following (6,10,11):

- the prevalence of the agent in the blood of the donor population;
- the tolerance of the agent to blood handling, storage and manufacturing processes;
- the infectivity and pathogenicity of the agent;
- the recipient's health and immune status;
- the effectiveness of donor screening or donor testing for the agent; and
- the effectiveness of the aseptic technique used in collecting the blood or blood product from the donor and in infusing the product into the recipient.

In Canada, the infectious disease risks associated with transfusion are minimized through multiple steps, including blood collection from unpaid volunteer donors; donor interview and selection procedures; careful aseptic techniques for collection and infusion; diversion of the first 40 mL of blood collected into a diversion pouch (12); donor screening by serological and other tests, including bacterial detection in platelets (Table 1); viral inactivation procedures included in the manufacturing of plasma-derived products (Table 2) (13-15); and leukocyte-reduction techniques that reduce the infection transmission risk of white blood cell-associated viruses, such as cytomegalovirus (16). Unfortunately, the solvent or detergent and heat viral inactivation procedures noted in Table 2 cannot be used on red blood cells or platelets because neither can withstand these vigorous processes.

Table 3 identifies specific inactivation steps in the manufacturing of different plasma-derived products that decrease viral infection risks. Of note, the majority of factor VIII and factor IX used in Canada are recombinant products, not plasma-derived, and, hence, do not have the infectious risks of a blood product.

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

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

**Personal communications: Dr Gilles Delage, Héma-Québec, and Dr Heather Hume; †While the PRISM 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; ‡Héma-Québec carries out bacterial culture testing of all platelet products and CBS does this for apheresis platelets. CMV Cytomegalovirus; HBc Hepatitis B core antigen; 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*

Correspondence: Dr Noni MacDonald, Department of Paediatrics, IWK Health Centre, 5840 University Avenue, Halifax, Nova Scotia B3J 3G9. Telephone 902-470-8799, fax 902-470-7812, e-mail noni.macdonald@dal.ca

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, HBV, 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; 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 preinactivation process(es)	Pools screened for HIV, HCV, HBV and HTLV type I/II*	Further virus inactivation steps
Cryoprecipitate (a blood component, not a fractionation product)	++	Yes	None†
Factor VII	+	Yes	Heat inactivation ± solvent/detergent
Factor VIII‡	+	Yes	Heat inactivation ± solvent/detergent
Factor IX‡	+	Yes	Heat inactivation, solvent/detergent, chromatography, ultrafiltration
Antithrombin concentrates	+	Yes	COHN fractionation, heat inactivation, chromatography
Albumin	+	Yes	COHN fractionation, heat inactivation
IVIG products	+	Yes	COHN fractionation, ± hydrolase, ± solvent/detergent, ± heat inactivation, ± chromatography, nanofiltration, ± caprylate
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; †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; ‡Very few patients in Canada are treated with plasma-derived factor VII or factor IX; §Includes hepatitis B (HBV) immune globulin, tetanus immune globulin, rabies immune globulin and Rh (D) immune globulin. HCV Hepatitis C virus; IMIG Intramuscular immunoglobulin; IVIG Intravenous immunoglobulin*

Bacterial contamination of platelets is greater than that with red blood cells because platelets are stored at room temperature (22±2°C), which supports bacterial pathogen multiplication (17,18). Various strategies have been developed to try to minimize the risk of transfusion-associated sepsis, including enhanced aseptic collection and handling procedures, pretransfusion bacterial detection systems, processing and storage enhancement procedures and pathogen inactivation techniques (19,20). While the use of closed, multicomponent, plastic blood pack collection systems has helped to decrease the problem, bacterial contamination of platelet concentrates is still a concern (20). The risk of bacterial contamination of frozen components, such as fresh frozen plasma and cryoprecipitates, is now 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, it was usually due to contamination of the water bath used to thaw the product (21). The use of microwave techniques or appropriate plastic covering specifically designed for this purpose minimizes this risk.

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 organisms, 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 five days	Skin flora (eg, *Staphylococcus epidermidis*, *Streptococcus* species, Diptheroids) *Salmonella* species *Escherichia coli* *Enterococci* species *Clostridium* species *Serratia marcescens*
Plasma	Frozen, once thawed can be held at 1°C to 6°C for 24 h	*Staphylococcus aureus* *Pseudomonas aeruginosa*

ATEs IN CANADA

The Transfusion Transmitted Injuries Surveillance System (TTISS) in Canada began as a pilot project in four provinces in 1999 to look for serious adverse events with receipt of blood or blood product infusions. TTISS is now a national program in various stages of implementation in all provinces and territories (4). This program has led to an

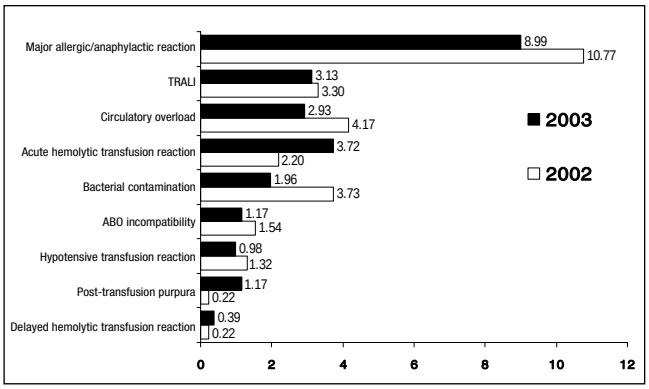

Figure 1) *Comparative rates of adverse transfusion events per 100,000 units of blood transfused in Canada in 2002 and 2003. TRALI Transfusion-related acute lung injury. Reproduced from reference 4*

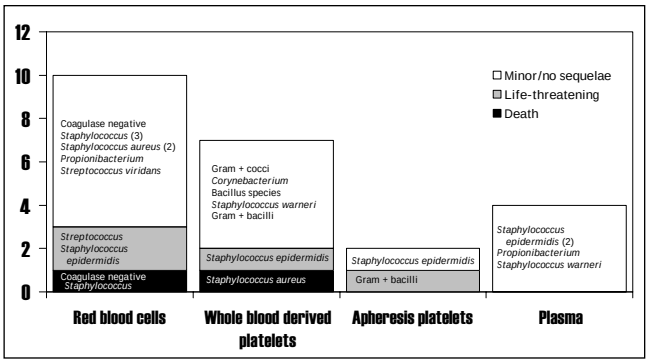

Figure 2) *Cases of bacteria identified in blood product cultures in Canada in 2002 and 2003. Reproduced from reference 4*

improvement in the quality and timeliness of risk estimates for ATEs.

The latest TTISS program report (4), covering the years 2002 and 2003, notes that a total of 1,629,684 units were transfused in the participating hospitals; 512 ATEs were reported, 296 (57.8%) of which met the surveillance case definitions. Of these, 36 (12.2%) occurred in those younger than 17 years. Overall, 51.3% of the ATEs were life threatening (rate 8.4 per 100,000 units) (4). As shown in Figure 1, the most common reported ATEs were major allergic or anaphylactic reactions (36%; rate 5.9 per 100,000 units). Bacterial contamination was the reported ATE in 10.1% (rate 1.7 per 100,000 units) (see Figure 2 for microbe types) (4). Of the 27 cases of bacterial contamination, 10 (37.0%) were related to red blood cells, 10 (37.0%) to whole blood-derived platelets, two (7.4%) to apheresis platelets and five (18.5%) to plasma (4). Of the 11 case fatalities related to transfusion (two definite, seven probable and two possible; overall rate one per 100,000 units and definitely related rate one per 483,245 units), bacterial contamination was involved in three (one definite and two probable). The incidence of ATEs by type of blood component in 2003 is shown in Table 5.

Thus, the TTISS program has verified that there is a high degree of safety in the Canadian blood system, with only small risks of bacterial contamination, and that allergic or anaphylactic reactions remain as the major concern.

ESTIMATED PER UNIT RISKS OF BACTERIAL, PARASITIC AND VIRAL CONTAMINATION OF BLOOD AND BLOOD PRODUCTS

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 6 and 7. Where Canadian data were not available, data from the United States and other countries have been included (5,10,11,14,22-24). As the data in Tables 6 and 7 show, the risks in Canada of transmitting infectious agents by blood, especially by plasma-manufactured products, are extremely low. To put it into context, a one in 3,000,000 risk is similar to that of being hit by lightning.

TABLE 5
Incidence in Canada of adverse transfusion events by blood component transfused in 2003

	Blood component					
		Whole blood-derived platelets				
Adverse transfusion event	Red blood cells (n=326,903)	Units (n=155,944)	Pools of five (n=31,189)	Apheresis platelets (n=11,694)	Plasma (n=98,914)	All products* (n=511,364)†
Major allergic or anaphylactic reaction	1:23,350	1:19,493	1:3889	1:2339	1:6182	1:11,117‡
TRALI	1:46,700	1:77,972	1:15,595	–	1:19,783	1:31,960‡
Circulatory overload	1:32,690	–	–	–	1:32,971	1:34,091‡
Acute hemolytic transfusion reaction§	1:18,161	1:155,944	1:31,189	–	–	1:26,914
Bacterial contamination	1:65,381	1:155,944	1:31,189	1:5847	1:49,457	1:51,136
ABO incompatibility	1:108,968	1:77,972	1:15,595	–	1:98,914	1:85,227
Hypotensive transfusion reaction	1:108,968	–	–	–	1:98,914	1:102,273‡
Post-transfusion purpura	1:108,968	1:155,944	1:31,189	–	–	1:85,227‡
Delayed hemolytic transfusion reaction	1:163,452	–	–	–	–	1:255,682
Other	1:108,968	–	–	–	–	1:170,455
Total	1:4953	1:11,139	1:2228	1:1671	1:3533	1:4091

**Include cryoprecipitate and granulocytes; †Whole blood-derived platelets were counted as pools of five; ‡Includes adverse transfusion events to multiple components, no single unit being related to the event; §Includes three cases of ABO incompatibility resulting in acute hemolytic reactions. TRALI Transfusion-related acute lung injury. Data from reference 4*

TABLE 6
Estimated risk of infectious agent blood or blood products

Agent or product	Transfusion-transmitted	Pathogenic	Canadian estimated risk of contamination*
Viruses for which all blood donors are tested			
HIV†	Yes	Yes	Less than one in 4,000,000
HCV†	Yes	Yes	Less than one in 2,800,000
HBV†	Yes	Yes	One in 82,000 to one in 275,000
HTLV† type I/II	Yes	Yes	Less than one in 1,000,000
WNV	Yes	Yes	No reported cases in Canada since screening introduced in 2003‡
Other viruses tested on occasion			
CMV	Yes	Yes	Risks vary with donor and recipient but are rare§
Parvovirus B19	Yes	Yes	One in 5000 to one in 20,000
GBV-C†	Yes	Unknown	One to two in 100; not known to be pathogenic
TTV†	Yes	Unknown	One in 100; rarely pathogenic
SEN-V†	Yes	Unknown	One in 100; not known to be pathogenic
HHV-8†	Unknown	Yes	Unknown
Parasites			
Malaria	Yes	Yes	Four cases reported in Canada in past 10 years
Chagas (*Trypanosoma cruzi*)	Yes	Yes	Two cases reported in Canada in past 15 years
Babesiosis (*Babesia microti*)	Yes	Yes	One case reported in Canada in past 15 years
Prion			
vCJD	Unknown	Yes	Risk unknown, extremely rare less than one in 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 residual risk calculations published by Canadian Blood Services and Héma-Québec; ‡West Nile virus (WNV) not tested in Quebec in winter; §Cytomegalovirus (CMV) infection risk is decreased by leukoreduction procedures (see text). HBV Hepatitis B virus; HCV Hepatitis C virus; HHV-8 Human herpes virus 8; HTLV Human T-lymphotropic viruses; GBV-C Formerly named hepatitis G virus; TTV Transfusion-transmitted virus; vCJD Variant Creutzfeldt-Jakob disease*

IMPORTANCE OF DOCUMENTATION OF TRANSFUSION

Experience gained from hepatitis C and HIV trace-back and look-back programs, where authorities have tried to trace transfusion recipients, have shown that many patients are unaware that they actually received a transfusion. No national electronic record of transfusions exists to facilitate any potential future tracing programs for a new transmissible 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.

RESOURCES FOR MORE INFORMATION ON INFECTIOUS DISEASES TRANSFUSION RISKS

Expanded discussion on infectious diseases risks of transfusion of blood and blood products can be found at the following Web sites:

Canadian Blood Services: Transfusion Medicine. <www.transfusionmedicine.ca>

Héma-Québec: Circular of information: For the use of Labile Blood Products, June 2005 Edition. <http://www.hema-quebec.qc.ca/media/anglais/publications/notice_ANG_complet.pdf>

Public Health Agency of Canada: Transfusion Transmitted Injuries Section About Risks of Blood Transfusion. <www.phac-aspc.gc.ca/hcai-iamss/tti-it/risks_e.html>

TABLE 7
Estimated risks of infectious agents in manufactured plasma-derived products

Agent	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 than one in 10,000,000
HCV	Yes	Yes	Less than one in 10,000,000
HBV	Yes	Yes	Less than one in 10,000,000
HTLV type 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, one in 100,000 to one in 1,000,000
WNV	No	Yes	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 one in 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; HTLV Human T-lymphotropic viruses; vCJD Variant Creutzfeldt-Jakob disease; WNV West Nile virus*

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Principal authors: *Dr Noni MacDonald, Dalhousie University, Halifax, Nova Scotia; JW Scott, Department of Health, Halifax, Nova Scotia; Ms Nancy McCombie, Transfusion Transmitted Injuries Section Blood Safety Surveillance and Health Care Acquired Infections Division, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada; Dr Pierre Robillard, Transfusion Transmitted Injuries Section Blood Safety Surveillance and Health Care Acquired Infections Division, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada; Dr Antonio Giulivi, Hematology and Transfusion Medicine, The Ottawa Hospital, Ottawa, Ontario*

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. Internet addresses are current at time of publication. This article has also appeared in a previous issue of *Paediatrics & Child Health* (Paediatr Child Health 2006;11:158-62).