Risks Associated With Transfusion of Cellular Blood Components in Canada

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We provide a comprehensive review of risks associated with allogeneic red blood cell and platelet transfusions in Canada. The review focuses on clinically symptomatic noninfectious transfusion risks (acute and delayed hemolytic, febrile nonhemolytic [FNHTR], allergic, volume overload, transfusion-related acute lung injury, graft-versus-host disease, and posttransfusion purpura) and the risk of clinically significant disease from transfusion-transmitted infections. Data sources include information from Canadian Blood Services, Héma-Québec, Health Canada, and the Québec Hemovigilance System as well as published information from research studies and international hemovigilance systems. We estimate that in 2000 the aggregate risk of potentially severe reactions (excluding FNHTR and minor allergic reactions) was 43.2 per 100,000 red cell units (95% confidence interval [CI]: 38.7-48.1), affecting 337 recipients, and 125.7 per 100,000 platelet pools of 5 units (95% CI: 100.8-154.9), affecting 88 recipients. The most frequent potentially severe outcomes for red cell transfusion were hemolytic reactions and volume overload and for platelet transfusion were major allergic reactions and bacterial contamination. The current risk of human immunodeficiency virus and hepatitis C virus transmission is approximately 1 in 4 million and 1 in 3 million units, respectively. These estimates are useful for decisions concerning transfusion therapy, the informed consent process, and for evaluating efficacy of interventions to reduce risk.

PHYSICIANS' DECISIONS whether to transfuse and patients' decisions whether to consent to a transfusion depend on a balancing of the risks and benefits of the transfusion for the particular patient. This review provides a comprehensive and rigorous assessment of the risks associated with allogeneic red blood cell and platelet transfusions in Canada. The risk estimates reported are primarily focused on the occurrence of clinically identifiable adverse transfusion reactions. Estimates, expressed as rates of adverse reactions expected after transfusion, are made for each outcome separately and analyzed together at the end of the review.

We have classified potential hazards of transfusion into 6 groups categorized by the various stages of the blood donation and transfusion process as follows:

1. Inherent infectious risks from the donor (eg, viruses, bacteria, or parasites that are present in the blood of a donor).
2. Risks introduced at blood collection (eg, possible bacterial contamination of the unit due to skin plug contamination or lack of sterility).
3. Risks introduced in blood processing, often because of deviations or errors in procedure such as during testing or improper storage or labeling.
4. Risks introduced during blood administration/transfusion, often because of deviations or errors in procedure such as ordering or transfusing the wrong product or mistakes/errors in labeling.
5. Risks that are dependent on blood component–recipient interactions. Adverse outcomes in this situation can be mediated by donor characteristics (unusual antibodies that are not recognized pretransfusion and react with antigens in the recipient) or recipient factors, such as the presence of alloantibodies or the recipients' medical condition (eg, immunosuppression).
6. Risks that are dependent entirely on recipient characteristics (eg, severely compromised cardiac function that can lead to volume overload after the infusion of blood or other fluids). These are risks of transfusion but they

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are not inherent to the specific unit of red cells or platelets transfused.

Although arranging the hazards into such groups may help with the interpretation of risk estimates, it should be recognized that the specific cause of an adverse transfusion reaction is not always known (ie, the hazard cannot be identified) and the interplay between various different factors, which determines whether a hazard will result in an adverse outcome, is not always understood.

MEASUREMENT OF RISK

The simplest means of determining risk is by clinical case reporting of adverse reactions or effects* after transfusion. Unfortunately, clinical case reporting has several limitations as a source of comprehensive information about rates. The most important may be its dependence on the awareness and vigilance of physicians and other health care workers to (1) look for adverse effects, (2) report these effects, and (3) determine whether the effects could have been caused by the transfusion. It is difficult enough to identify the effects that occur within a short time of transfusion. However, the longer the time after the transfusion that the effects occur, the less likely it is that the effects will be recorded (especially if they are mild or are nonspecific) and/or linked to the transfusion. Also with case reporting, there are no denominator data for calculation of reaction rates. Despite these limitations, much of the data on risks have been gathered from case reporting.

With prospective studies, caregivers are looking for specific effects, and because the number of patients at risk is known, rates can be determined (ie, the number of cases detected is divided by the number of recipients observed). However, prospective studies are difficult to perform and if the effects are rare, the studies would need to be very large and, hence, very expensive. Retrospective studies using chart reviews can be performed, but these suffer from the limitation of variations in awareness of the caregivers and the reliability of reporting. Surveillance systems for transfusion reactions are another means of collecting data for measuring risk. However, because these surveillance systems rely on passive reporting, there may be large variations between systems in recording and reporting reactions; case definitions may vary between reporting systems and also between reporting facilities within the same system. Furthermore, surveillance systems may not provide data on the number of units or recipients transfused; without these denominator data, rates cannot be calculated.

The establishment of hemovigilance programs in France and Québec has involved the investment of significant resources to help strengthen reaction reporting. These programs increase awareness and vigilance of health care personnel, which increases the likelihood of identifying adverse reactions and linking them to transfusion through subsequent investigations. However, even in these systems, the lack of long-term follow-up limits the accuracy of risk estimates based on outcome measurements for those reactions that do not occur until several days or more after transfusion.

In some circumstances, the magnitude of a risk can be estimated from characteristics of the donated units and the recipient population. For example, we may know the frequency of certain rare antigens and antibodies in the population and can estimate the likelihood that a recipient will receive a unit that will cause an antigen-antibody reaction, which in turn may or may not produce clinical symptoms. In the case of infectious diseases for which we have screening tests, there are mathematical models that estimate the likelihood that a unit will contain an infectious agent despite routine donor screening and testing procedures.

Except in some prospective studies, data sources for the number of recipients transfused have usually been lacking and risk estimates most often have been calculated based on the number of units transfused rather than the number of patients exposed to the risk. This approach attributes a transfusion reaction in a recipient to exposure to a single unit rather than to the total number of units transfused to that recipient. This is a reasonable approach to reactions that result from attributes inherent to a unit (risks included in group 1 or 2, such as bacterial contamination) or to reactions that result from blood component-recipient reactions (eg, hemolysis because of ABO incompatibility). In the latter case (group 5 and some group

*It is more common to use the term “event” to describe the occurrence of a negative consequence from a process. However, in this review the events that we are measuring/assessing are the adverse effects of a transfusion on the recipient, so the terminology that is used is “adverse reaction” “effect” rather than “even”.

4 risks), although the specific unit itself may not be the source of the risk, it is assumed that the per unit risk estimate will accurately estimate the likelihood that a donor-recipient interaction would result in an adverse event in a similar large population of transfusion recipients. However, for reactions based solely or primarily on recipient factors (eg, group 6 risks, such as volume overload), calculating a rate per transfused blood component is somewhat problematic because the unit of risk is actually the recipient; nevertheless, such a calculation may be performed to compare these risks with other risks of transfusion that are expressed on a per unit basis.

Influence of Errors on Risks and Risk Estimates

Errors contribute to the risk of blood transfusion and reducing errors will decrease risks.[1] In cases in which we derive our estimates of risks by measuring outcomes, the effect of errors will be already incorporated into the estimate. For example, unidentified errors in "manufacturing" (eg, processing, labeling, and storage of blood) will be included in our risk estimates if they lead to a clinically identifiable reaction in the recipient. However, risk estimates derived by modeling do not always include the effect of errors. For group 1 risks, errors at blood centers could lead to the release of untested or inadequately tested units or units that had tested positive (and not been discarded). We attempted, where possible, to include these effects in our models but were limited by the small amount of data assessing error rates at blood centers. However, given the increasingly vigilant regulation of blood centers as a good manufacturing practice environment, increasing computerization, the low prevalence of samples that test positive and, for some of the infectious disease markers, the duplicate or even triplicate testing, such group 1 errors are considered to have a very minimal effect on our risk estimates.[2]

METHODS

Literature Review

The Medline database was searched using the following general and specific key terms: *transfusion reaction*, *transfusion error*, *adverse transfusion event*, *transfusion complication*, *febrile nonhemolytic transfusion reaction*, *transfusion allergic reaction*, *transfusion anaphylactic reaction*, *hemolytic transfusion reaction*, *ABO errors*, *transfusion and volume/circulatory overload*, *transfusion-related acute lung injury*, *transfusion-associated graft versus host disease*, *posttransfusion purpura*, *transfusion*, and *bacterial contamination*. The search was limited to the years 1980 to 2002. Some major articles identified in the articles retrieved through the Medline search and others cited in the book *Transfusion Reactions* edited by Mark A. Popovsky (AABB Press, 2001) were also retrieved even if dated before 1980.

Data from the literature for infectious risks of transfusion were accessed through extensive bibliographies previously prepared by one of the authors (SK). Infectious disease publications from 2000 to 2002 were selected from review of a reference list available to subscribers of an American Red Cross list server. In addition, reference lists from relevant chapters of major transfusion medicine textbooks were reviewed.

Studies were reviewed and data included in this report if all or most of the following criteria were met: (1) the studies reviewed experience with a large number of transfusions, (2) the studies were performed using a standardized protocol with clear definitions for specific transfusion reactions, (3) the data were obtained under a set of transfusion practices related to those currently in use in Canada, and (4) the studies were performed in Canada. In some cases, studies that did not meet these criteria were also included, particularly for adverse reactions for which little data were otherwise available.

Canadian Source Data

Blood collection/distribution data. Data were obtained from Canadian Blood Services (CBS) National Office and from Héma-Québec (HQ). The CBS data were for calendar year 2000 and the HQ data for fiscal year 2000 (April, 1 2000, to March 31, 2001). Data from each organization included number of units collected (allogeneic, directed, autologous, apheresis), number of components distributed (red cells, platelets, platelet apheresis), and number of components transfused or outdated or in hospital inventory (red cells, platelets, platelet apheresis). For CBS, the number of units accounted for by the hospital-based reports was approximately 5% to 10% less (depending on component type) than the number of units distributed. This shortfall presumably represents underreport-

ing of information from hospitals to CBS. For purposes of this review, the number of transfused CBS units is the number of transfused units indicated on the hospital report. CBS and HQ data were totaled and rounded, generating the following numbers that have been used as denominators in this review: (1) red cells transfused: 780,000; (2) platelets transfused: 350,000 (assumed to be 70,000 platelet pools); and (3) plateletapheresis transfused: 13,000. In 2000, approximately 960,000 allogeneic units were collected with 11% coming from first-time donors and 89% from repeat donors.

Infectious disease testing data. Data were obtained from the CBS National Testing Laboratory and from the HQ Epidemiology Unit. Data included rates of standard infectious disease screening and confirmatory assays. Data to support the calculation of incidence of human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV) in repeat donors were obtained for the years 1998 to 1999 from the Epidemiology Department of CBS. These data included number of seroconverting donors for anti-HIV, anti-HCV, and hepatitis B surface antigen (HBsAg) and person years of observation of the repeat donor population.

Adverse reaction data. Data on serious adverse reactions after transfusion were obtained from the CBS National office for the years 1999 and 2000 and from HQ for fiscal year 2000. Data from CBS and HQ for 2000 were totalled and used to represent the number of serious adverse reactions for selected categories (various noninfectious risks and bacterial contamination) that were reported by the hospitals to the Canadian blood collection agencies in that year. Data on adverse transfusion events reported to Health Canada were obtained from Health Canada for the year 2000 (P Ganz and F Hindien, 2000, written communication). In addition, a cumulative summary report of such data for the years 1993 to 1999 was also made available. Data on adverse transfusion reactions reported in year 2000 to the Québec hemovigilance system were obtained from presentations at scientific meetings.

The Québec hemovigilance system. The Québec government decided in 1998 to develop a new blood system based on regionalization of blood transfusion responsibility to what was called *designated hospitals*. These 20 hospitals are responsible for transfusion safety and quality in their region. All other Québec hospitals having a blood bank are called associated hospitals and are under the coverage of their designated hospital for transfusion activities. Transfusion safety officers were hired in the designated hospitals to investigate and report adverse transfusion reactions. A standard form was developed and implemented in all these hospitals in the year 2000. All transfusion reactions, mild or severe, are to be reported to the Québec Health Ministry where a provincial transfusion safety officer validates the data. Data analyses were performed at the Hemovigilance Research Unit of the Québec Public Health Institute. In 2000, all 20 designated and 8 of 79 associated hospitals reported reactions to the system. Overall, these 28 hospitals managed 38 blood banks representing 80% of the volume of blood components transfused in the province of Québec.[3]

Data on the number of components transfused by these participating hospitals and on the number of recipients of each type of product were obtained on a monthly basis through a report sent to HQ by the hospitals. Data for number of components and estimated number of recipients transfused in 2000 were: (1) red cells: 138,605 units and 47,343 recipients; (2) platelets: 79,875 units and 5,943 recipients; (3) fresh-frozen plasma: 35,481 units and 5,621 recipients; and (4) cryoprecipitate: 14,595 units and 480 recipients.

The number for platelets included both whole-blood–derived and apheresis platelets. However, more than 92% of platelet units transfused in Québec were whole-blood–derived platelets. Thus, for this review, the number of platelet pools in hospitals participating in the Québec hemovigilance system was calculated by dividing the total number of platelets transfused in these hospitals by 5 (the average number of units in a pool). The data on number of recipients transfused were less reliable than those for components transfused. Recipients may have been counted more than once if they had received multiple types of components or had multiple transfusion episodes in the year 2000.

The system used to grade the association of the reaction to transfusion and to grade the severity of the reaction is the same as that used in the French hemovigilance system. Only reactions with an association to transfusion ≥ 2 (ie, possible, probable, and definite) were used in the calculation of rates of adverse transfusion reactions. As expected of a new surveillance system, participation has gradu-

ally increased since implementation in early 2000, and reporting was more complete during the last 6 months than during the first 6 months of year 2000. However, a comparison between the rates for the last 6 months of 2000 and for the entire year showed no statistically significant difference. Thus, for the purpose of precision of the estimates of rates, data for the whole year were used.

International Surveillance Data

France. The term *hemovigilance* was created in France where the reporting of all transfusion reactions since 1994 has been made mandatory. Annual reports from 1994 to 1998 and data for the year 2000 were obtained directly from the head of the French Hemovigilance Unit and from presentations in scientific meetings.[4-7]

United Kingdom. In 1996, through an initiative of the UK National Blood Service and professional societies, a reporting system for serious hazards of transfusion (SHOT) was created in the United Kingdom. This system is completely voluntary and anonymous with respect not only to the patient but also to the reporting physician. Data for the United Kingdom were obtained from annual SHOT reports since 1996.[8-11]

Statistical Methods

No attempt was made to calculate confidence intervals for data reported in the literature or for data obtained from non-Canadian sources. In the Québec hemovigilance system, the denominators on components transfused allowed for the calculation of reaction and component specific rates of adverse transfusion reactions per 100,000 components transfused (unless otherwise specified) as well as 95% exact confidence intervals based on the binomial distribution (using the facility Epitable Calculator from the software EPI-INFO version 6.04).[12]

INFECTIOUS RISKS

An important aspect of assessing the infectious risks of transfusion is the distinction between the risk of transmission of the agent and that of clinically significant disease, which generally occurs only in a percentage of those who become infected. Many agents (eg, HIV, HCV, and human T-cell lymphotropic virus [HTLV]) produce clinical disease only many years after the initial infection. It is obvious that the deleterious effects of these agents will occur in fewer patients than would be predicted from per unit risk estimates of transmission. Data on long-term survival of transfusion recipients indicate that mortality at 40 months is 36% to 49% for red cell recipients and 52% to 68% for platelet recipients[13-15]; for purposes of this review, we have taken 50% as the average mortality for recipients of cellular blood products. Long-term survival has been documented to be better for younger patients (<age 40) who, however, comprise a relatively small percentage (estimated at 9% to 26% in the 2 cited studies) of transfused recipients. Concern about long-term chronic sequelae is obviously greatest for those recipients who are transfused at a young age and who have a good disease prognosis.

There are some infectious agents for which there are no data to support transfusion transmission but for which the theoretical possibility of transmission exists based on indirect epidemiologic or laboratory data and/or plausible biological evidence for a blood-borne phase in the donor and the in vitro survival of the agent in the stored blood component. In such cases, the risk is termed to be a theoretical risk.[16] For some agents with a theoretical risk (eg, variant Creutzfeldt-Jacob disease [vCJD]), the current data are insufficient to evaluate the risk; if the risk subsequently turns out to prove real, it is possible that the degree of risk may be shown to be high. In other circumstances (eg, classical Creutzfeldt-Jacob disease [CJD]), theoretical risk can be equated with a negligible or zero risk. This assessment is possible when a large amount of data documenting lack of observed transfusion transmission has been accumulated. In such cases, risk is termed theoretical rather than zero because, despite such observational data, it is virtually impossible to prove that transfusion transmission will never occur.

In contrast to agents that cause disease but have not been shown to be transfusion transmitted, other agents have been shown to be transmitted by transfusion but have never been documented to cause clinical disease. For such agents (eg, GB virus-C [GBV-C], TT virus [TTV], SEN virus [SENV]; all discussed later), it is possible to calculate a risk of transfusion transmission but nevertheless to conclude that the agent poses little or no risk of an adverse outcome to recipients.

Because transfusion-transmitted risks are currently so low in developed countries, it is exceed-

ingly difficult to directly measure these risks with accuracy. Furthermore, because symptoms related to transfusion-transmitted infection may not occur for many years, measurement of this risk is hampered by the difficulty of linking the resultant clinical disease to the previous transfusion. For these reasons, mathematical modeling, when possible, may be the best approach for estimating the risk of certain transfusion-transmitted agents.

Although each unit of donated blood is tested for evidence of HIV, HCV, HBV, and HTLV, transmission of these agents can still occur because of window-period transmissions (the primary contributor to risk for these agents), a chronic carrier state that is not detectable by screening assays, viral variants that are undetectable by current assays, and laboratory error.[17,18] When the only significant element of risk for an agent arises from the transfusion of window-period units, the mathematical model used to estimate this risk is the incidence/window-period model (described in detail elsewhere).[19,20] This model is appropriate for estimating the residual risk in Canada (after the implementation of laboratory testing and donor deferral procedures) for HIV, HCV, and HTLV and for estimating a component of risk for HBV. Incidence is calculated by using data from multiple donations from repeat donors. Incidence in first-time donors cannot be calculated by this approach but can be determined for some agents (eg, HIV and HCV) by using tests that are specific for new infection. A weighted average for incidence in the entire blood donor population can then be calculated by using the rates in first-time and repeat donors weighted by the relative frequency of donations from each type of donor.

Not all potentially infectious units will necessarily transmit infection. Therefore, the per unit risk of the unit being donated during the window period should be multiplied by the likelihood that such a potentially infectious blood component will transmit the agent to the recipient. However, despite the possibility of less than 100% transmission from window-period units (transmission risks have been estimated at 80%-90% for HIV and HCV),[21,22] the estimates in the literature have generally assumed a worst-case scenario of 100% probability of transmitting infection from a nondetected window-period unit.

HIV

In a 1997 publication, Remis et al[23] used a variation of the incidence/window-period model to estimate HIV transfusion risk in Canada.[23] Their data source was the HIV incidence rate in repeat blood donors in Montreal (which was higher than in the rest of Canada) for the years 1985 to 1993. These authors projected that the risk throughout Canada for those years was 1 in 913,000 units. Recently, HIV incidence in CBS donors for 1998 to 1999 has been estimated at 0.53 per 100,000 person years. The residual risk of HIV transfusion transmission in Canada can therefore be calculated by using the following data inputs in the incidence/window-period model: (1) incidence in repeat donors: 0.53 per 100,000 person years; (2) incidence in first-time donors: 2× repeat donor incidence (from US studies)[24]; (3) first-time/repeat donor ratio: 11%/89%; (4) window period with nucleic acid testing (NAT): 13 days; and (5) recipient risk of acquiring infection if exposed: 100% (worst-case scenario).

Using these numbers, the current risk estimate for transfusion-transmitted HIV infection in Canada is 1 in 4.7 million transfused red cell or platelet units. With regard to chronic sequelae, we conclude that all transfusion-transmitted cases may suffer serious long-term complications based on the chronicity of HIV infection and the potential for the infected recipient to either develop disease or require long-term antiretroviral therapy.

HCV

Recently, HCV incidence in CBS donors for the years 1998 to 1999 has been estimated at 0.89 per 100,000 person years. The residual risk of HCV transfusion-transmission in Canada can therefore be calculated by using the incidence/window-period model as follows: (1) incidence in repeat donors: 0.89 per 100,000 person years; (2) incidence in first-time donors: 2× repeat donor incidence (from US studies)[24]; (3) first-time/repeat donor ratio: 11%/89%; (4) window period with NAT: 12 days; and (5) recipient risk of acquiring infection if exposed: 100% (worst-case scenario).

Using these numbers, the current risk estimate for transfusion-transmitted HCV infection in Canada is 1 in 3.1 million transfused red cell or platelet units. Based on data on the natural history of HCV infection in transfusion recipients, we conclude

that 20% of HCV infected persons resolve their infection, 60% develop chronic infection without severe liver disease, and 20% develop significant liver disease such as cirrhosis.[25,26] As a worst-case scenario, we hypothesize that the 80% of HCV infected recipients who do not resolve their HCV infection are at risk for serious long-term complications (eg, development of disease or requirement for antiviral therapy).

HBV

There are 2 major sources of HBV risk from transfusion in Canada: donors in the window period of HBV infection (ie, before development of a positive HBsAg test) and donors who are chronic HBV carriers but who have undetectable levels of HBsAg.[27]

Recently, HBsAg incidence in CBS donors for the years 1998 to 1999 has been estimated at 2.85 per 100,000 person years. Because HBsAg is usually a transient marker that disappears several months after infection, measuring HBsAg incidence will underestimate true HBV incidence. Therefore, the incidence/window-period model developed by Retrovirus Epidemiology Donor Study investigators includes a statistical adjustment to calculate HBV incidence from observed HBsAg incidence.[20,28] This adjustment, when applied to the Canadian HBsAg incidence data, yields an HBV incidence of 7.59 per 100,000 person years. Using this incidence and an estimated 59-day infectious window period, the risk of acquiring HBV from a window-period transfusion in Canada can be calculated as 1 in 82,000 units (1.2 per 100,000 units).

A method to estimate the risk of HBV transmission from chronic carriers with undetectable HBsAg on blood donor screening assays has recently been applied in 2 US studies based on the assumption that HBsAg negative, HBV chronic carriers capable of transmitting HBV will test positive for anti-HBc and have detectable HBV DNA using very sensitive HBV NAT techniques.[27,29] REDS investigators estimated that 1 in 49,000 HBsAg negative, anti-HBc positive units in the early 1990s contained low levels of HBV DNA and therefore should be regarded as likely to transmit HBV infection if transfused.[29] A recent study conducted by the American Red Cross indicated a similar rate of potentially infectious units in their donor population. A third study conducted in the United Kingdom using a lookback methodology calculated a rate of potential HBV transmission from HBsAg negative chronic carriers of 1 in 52,000 units.[30] The estimated rates from the 3 studies cited earlier are likely to apply to Canada; this is supported by the observation that the rate of anti-HBc–positive Canadian blood donors in pilot studies is as high as the rate of anti-HBc–positive donors in the United States during the timeframes of the cited studies. Therefore, it seems reasonable to estimate that in Canada, where anti-HBc testing is not performed, the current risk of transfusion-transmitted HBV from chronic carriers with undetectable HBsAg may be as high as 1 in 50,000 units (2 per 100,000 units).

The overall HBV risk is a sum of the risk from window-period transmission (1.2 per 100,000 units) and from chronic carriers who lack detectable HBsAg (2 per 100,000 units). Thus, the estimated per unit risk of HBV infection in Canada may be as high as 1 in 31,000 (if all chronic carriers transmit) to 1 in 82,000 (if none transmit). In the absence of data to the contrary, it is prudent to consider that any unit with detectable HBV DNA has the potential to transmit HBV to transfusion recipients; therefore, our best estimate for HBV transfusion risk is 1 in 31,000 units (3.2 per 100,000 units). The actual risk of HBV may be lower than predicted by our estimate because a small percentage of recipients exposed to HBV by transfusion would be protected because of immunity as a result of a previous naturally occurring infection or HBV vaccination.

The large majority of adults who are infected with HBV resolve their infection. Data indicate that there is only a 5% chronic carrier rate in adults and that severe liver disease (cirrhosis and hepatocellular carcinoma) occurs in 15% to 25 % of chronically infected persons several decades after infection. These observations suggest that the serious outcome of a chronic carrier state (with or without severe liver disease) will occur at a rate that is 40-fold lower (based on 50% recipient mortality rate and a 5% carrier rate in surviving recipients) than the rate of HBV infection. This calculates to a risk of transfusion-transmitted chronic HBV disease of 1 in 1,240,000 units (0.08 per 100,000 units).

There are 2 caveats to these observations concerning the low rate of clinical disease. Firstly, it is possible that immunocompromised recipients who

acquire transfusion-transmitted HBV may have a higher chronic carrier rate and a higher rate of developing severe disease than the general adult population.[27] Secondly, it is now known that despite lack of HBsAg detection in peripheral blood, HBV DNA can persist for decades in the serum and liver of some patients. However, because clinical disease has not been shown in such persons, these latter considerations have not been taken into account in our estimates.[31]

HTLV

The HTLV group consists of 2 retroviruses (HTLV-I and HTLV-II) that are highly leukocyte associated and can cause human disease, albeit infrequently. The transmission rate, determined from lookback studies in the United States, was found to be 35% or lower from HTLV-infected cellular blood components; the rate varied with the length of storage of the blood component.[32] These data strongly suggest that the presence of viable lymphocytes is necessary for HTLV transmission by transfusion. In Canada, all cellular blood products undergo prestorage leukoreduction, which has been shown to markedly reduce HTLV viral load. This will likely prevent HTLV transmission unless the infected unit is collected from a donor with an HTLV proviral concentration in peripheral blood of $>10^5$/mL. The range of titers of HTLV in the blood of newly infected donors before seroconversion is currently unknown.[33]

Schreiber et al[34] used the incidence/window-period model applied to 1991 to 1993 US blood donor data to estimate that the risk of transfusing a unit obtained in the 51-day window period before the development of HTLV antibody was 1 in 641,000.[34] Given that only one third of cellular units transmit HTLV infection, this projects to a transfusion risk of approximately 1 in 1.9 million units. Because donor HTLV prevalence rates are lower in Canada than in the United States (12 per 100,000 first-time donors in 2000 *v* 35 per 100,000 first-time donors in the Schreiber study), it is also reasonable to assume that HTLV incidence is likely to be lower in Canada than in the United States. Given the low projected transfusion-transmitted HTLV risk in the United States and some further risk reduction provided by universal leukoreduction in Canada, it can be concluded that that the risk of transmitting HTLV infection to Canadian transfusion recipients is extremely low and the risk of clinically significant disease is even lower.

Syphilis

Before testing of donated blood for serologic evidence of syphilis and before refrigerator storage of red cells, there were approximately 150 to 200 published transfusion-transmitted syphilis cases described in the late 1930s and the 1940s. However, since 1950, there have been only 2 cases of transfusion-transmitted syphilis reported in the English language literature, one from a 1969 transfusion in the United States and one from a 1978 transfusion in the Netherlands.[35,36] Therefore, it is reasonable to conclude that the risk of transfusion-transmitted syphilis in Canada is virtually nonexistent.

Hepatitis A Virus

Hepatitis A virus (HAV) transmission by transfusion will occur only during the brief several week period of asymptomatic HAV viremia.[37] Only rare cases of transfusion-transmitted hepatitis A from blood components have been reported, with approximately 25 case reports in the literature through 1989.[38] Our review of the case reporting data would suggest a risk in the order of 0.1 per million transfused units. There has been only a single case of transfusion-transmitted HAV reported in Canada in the past 8 years. It can be concluded that the risk of HAV infection to Canadian transfusion recipients is extremely low.

Non–A-E Hepatitis

Studies have shown that approximately 20% of acute community-acquired hepatitis cases in the United States cannot be attributed to A-E hepatitis viruses or other known causes; it is inferred that these cases may be because of an as-yet undiscovered viral agent.[39] Cases of chronic hepatitis appear to be infrequently associated with this postulated agent.

The significance of transfusion-transmitted non–A-E hepatitis is less clear. Retrospective evaluation of a US study conducted in the late 1970s provided laboratory evidence that suggested that a viral agent other than HCV caused 5% to 10% of transfusion-transmitted non-A, non-B hepatitis. However, these cases were all asymptomatic and characterized by only mild alanineaminotransferase (ALT) elevations. A minority of cases showed

chronic ALT elevation but no clinical sequelae. These data suggested that this agent caused only a mild form of subclinical hepatitis that usually resolved. Several European studies also documented the presence of ALT elevations in transfusion recipients that were attributed to the non–A-E hepatitis agent.[39] More recent studies in the transfusion setting have failed to confirm these observations. For example, data from a Canadian study in the late 1980s showed that mild ALT elevations after transfusion occurred just as frequently in recipients of autologous and allogeneic units, indicating that this laboratory abnormality was unlikely to be caused by a transfusion-transmitted virus.[40]

These combined observations indicate that the current risk of transfusion-transmission of a putative non–A-E hepatitis virus resulting in clinical disease should be considered to be probably nonexistent in Canada.

Newly Discovered Transfusion-Transmitted Viruses

Two viruses, GBV-C (also called hepatitis G virus) and TTV (TT virus) have been discovered within the last 6 years as part of research programs aimed at identifying the agent of non–A-E hepatitis.[41] GBV-C viremia is present in approximately 1% to 4% of donors worldwide, with a prevalence of 1% documented in a small sample of Canadian donors.[42,43]

Subsequent to the discovery of the initial TTV isolate, research has shown that TTV consists of numerous genotypes and is closely related to other viruses that form a family of circular single-stranded DNA viruses with a high degree of genetic diversity. TTV viremia rates in donors were initially reported to range between 1% and 10% in developed countries.[41] With the development of more sensitive polymerase chain reaction (PCR) assays using conserved regions of the genome common to many TTV isolates, viremia has been documented to be as high as 90% in a recent study of Norwegian blood donors.[44]

Even though both agents are transfusion transmitted, extensive research indicates that neither agent causes hepatitis or is convincingly associated with any human disease[41,42]; therefore, they pose no known risk of adverse outcome to Canadian transfusion recipients.

Recently, specific variants of a new class of viral agents termed SENV (SENV-D and SENV-H), which are genetically related to the expanding class of TT viruses, have been hypothesized to be the causative agent of non–A-E hepatitis. Initial studies have shown an association between infection with these 2 SENV subtypes and transfusion-transmitted hepatitis cases from the 1970s.[45] However, no causal relationship has been shown. Furthermore, initial studies in patient groups with liver disease suggest that SENV does not cause such disease.[46] It has been shown that SENV is transmitted by transfusion and can establish chronic asymptomatic infection.[45] The prevalence of SENV viremia in blood donors has not yet been firmly established but has been reported to be approximately 2% for SENV D and H variants in US blood donors and 10% in Japanese blood donors.[45] Although the data are more preliminary for SENV than for GBV-C and TTV, it can be concluded that SENV currently does not pose a risk of serious adverse outcomes (eg, chronic hepatitis) to Canadian transfusion recipients.

Cytomegalovirus

Cytomegalovirus (CMV) transmission to immunocompetent hosts rarely causes clinically important consequences, whereas CMV transmission to immunosuppressed patients can result in acute, severe clinical disease manifested by pneumonia, hepatitis, and other symptoms that can lead to death.[47,48] Immunosuppressed patient groups at risk for serious CMV disease include allogeneic bone marrow transplant recipients, unborn fetuses, solid organ transplant recipients, HIV-infected patients, and patients who have conditions that are likely to require an allogeneic bone marrow transplant in the future. Other groups at somewhat lesser risk are low–birth-weight infants and autologous bone marrow transplant recipients.[47,48]

The risk of transmitting CMV by transfusion to CMV seronegative patients at high risk of serious CMV disease is reduced by providing special types of cellular blood components designated as CMV reduced-risk products.[47,48] Traditionally, these products have been supplied from CMV seronegative donors through selective screening of donations for CMV antibody. More recently, leukoreduction of cellular blood components has been accepted by some experts as a method that is as effective as CMV antibody screening for supplying CMV reduced-risk blood.[49,50]

Several studies in CMV seronegative bone mar-

row transplant patients receiving multiple blood transfusions have reported that primary CMV infection occurs in 1% to 4% of recipients of CMV reduced-risk (either CMV seronegative or leukoreduced) blood products.[50-52] However, it is important to note that in contrast to other transfusion-transmitted agents these conclusions are based on the unproven assumption that the posttransplant infections resulted from transfusion rather than from other nosocomial routes.

There are 2 possible major reasons why breakthrough transfusion-transmitted infections might occur with CMV reduced-risk products. One is a failure of the risk reduction process (eg, false-negative CMV antibody results or the failure of leukoreduction filters to adequately remove sufficient numbers of leukocytes from the transfused units). The second possibility is that transmission may occur from infected donors with plasma viremia who are in the antibody-negative window phase of infection; such units would not be interdicted by either risk reduction method. Although CMV nucleic acid sequences have been identified in plasma by sensitive PCR methods, this latter mechanism should still be regarded as theoretical because the infectivity of such units has not been shown.[51]

In Canada, where all cellular blood products are prestorage leukoreduced, recipient groups at highest risk for clinically significant primary CMV disease have the benefit of receiving units that are both CMV seronegative and leukoreduced. There are no studies that have evaluated the risk of CMV transmission when this type of blood product is transfused. The cumulative effect of these 2 interventions would be expected to mitigate the risk that might result from failure of either of these methods; however, it remains possible that the theoretical existence of a donor with cell-free viremia could result in CMV transmission despite use of both risk reduction methods.

Because of the potential marked influence of the recipient's immune system on whether CMV is reactivated from a transfused unit, the use of CMV reduced risk components for some patient populations, and the uncertainty in the data concerning breakthrough infections, it is not possible to assign a CMV risk per unit as can be done with other infectious agents.[48] However, given our current state of knowledge, it is reasonable to conclude that the risk of significant CMV clinical disease from transfusion of cellular blood components in Canada in high-risk patient groups should be low to nonexistent; however, the true risk remains unknown.

Human Herpesvirus 8

Only 1 published study has directly evaluated the possibility of transfusion-transmission of human herpesvirus 8 (HHV-8) by blood components. In this study, HHV-8 was not detected in 13 recipients of cellular components from HHV-8 antibody–positive donors.[53] Furthermore, in another study that showed an HHV-8 seropositivity rate of 3.3% in US donors, HHV-8 viremia could not be shown in 37 seropositive donors.[54] Thus, seropositivity does not appear to correlate with viremia, making the possibility of transfusion- transmission from seropositive donors unlikely. There are no data regarding seropositivity or viremia rates in Canadian blood donors. Because of the leukocyte-associated nature of the virus, universal leukoreduction of red cells and platelets in Canada should virtually eliminate any risk of HHV-8 transfusion transmission. Currently, the risk of HHV-8 transmission by transfusion in Canada should be regarded as virtually nonexistent.

Parvovirus B19

Parvovirus B19 viremia rates in blood donor populations (as detected by nucleic acid testing) have been reported to range from 0.03% to 0.1% in the United States and Scotland and to show seasonal variation.[55,56] Nevertheless, only 3 cases of clinical disease (anemia) associated with parvovirus B19 transmission by blood component transfusion have been reported in North America and Europe.[57] This low number may be because of recipient immunity from previous B19 exposure, a low rate of transmission possibly because of low B19 viral concentration in the blood donor or the lack of clinical symptoms in most persons who acquire the infection. The occurrence of so few cases worldwide indicates that the risk of symptomatic transfusion-transmitted parvovirus B19 infection in Canada should be regarded as extremely low.

Malaria

Transfusion-transmitted malaria is common in some parts of the world but is rare in North America. In the United States, there has been an average

of 2 to 3 cases of transfusion-transmitted malaria per year over the 40-year period from 1958 through 1998, for an estimated rate of occurrence during the entire period of 0.25 cases per million red cells transfused.[58,59] The overall fatality rate was 11%. In the decade of the 1990s, 71% of cases were caused by *Plasmodium falcipirum*. Transmission occurs from donors who acquired infection from foreign travel, residency, or birth and who either have become chronic long term carriers (which is rare) or who have not responded correctly to questions that are part of the blood donor screening process.[58,60] Of 70 cases in which the blood component type was known, 66 occurred after whole-blood or red cell transfusion, whereas 4 occurred after platelet transfusion. Because transfusion transmission is from the intraerythrocytic asexual form of the malarial parasite, transmissions from platelets have been attributed to the presence of small amounts of contaminating red cells.

In Canada, 3 cases (all caused by *P falcipirum*) were diagnosed in the 6-year period from 1994 through 1999. Two of these cases occurred before the revision of blood donor questioning in 1995, whereas only 1 case has occurred in the 5 years (1996-2000) since the revised criteria were adopted.[61] The risk of transfusion-transmitted malaria in Canada since revision of the blood donor screening criteria in 1995 is extremely low. Given an estimated 780,000 red cell transfusions in Canada annually, this rate can be estimated to be 0.25 per million transfused red cells (1 case in 4 million red cells transfused), which is similar to that documented in the United States.

Babesiosis

Babesia are small protozoan parasites that infect red cells. *Babesia microti,* the major pathogenic species in North America, is transmitted by the bite of a deer tick (*Ixodes scapularis*) in endemic areas, especially the northeastern United States. Although Babesia is not endemic in Canada, the possibility for an increased number of cases exists given the common border with the endemic United States. Transfusion transmission can occur from infected donors who remain asymptomatic but parasitemic for years.[62] Most transfusion-transmitted infections result in mild clinical disease but occasionally severe disease with intravascular hemolysis and renal failure will occur; 1 fatality has been reported.[62] After malaria, babesiosis is the second most commonly reported transfusion-transmitted parasitic infection in the United States, with over 40 cases reported in the literature in the last 2 decades, mostly in immunocompromised or asplenic patients.[62] Although the majority of cases involved transfusion of red cells, at least 4 cases have been attributed to the transfusion of platelets, most likely because of small amounts of contaminating red cells.[62,63]

The clinical case reporting data would suggest an incidence of approximately 0.1 per million red cell units transfused in the United States. However, multiple cases have been reported in each of the last 3 years, suggesting that the transfusion-transmission rate in the United States may be increasing and raising the possibility that transfusion risk may also increase in Canada.[64] However, only 1 case of transfusion-transmitted Babesia has thus far been documented in Canada. This occurred in 1999 in Ontario in a recipient who was not immunocompromised or asplenic. The donor had visited an endemic area in the United States. This case was both reported as an adverse reaction to Health Canada and published in the literature.[65] Based on this single case report, it is likely that the current risk of transfusion-transmitted babesiosis in Canada is extremely low.

Lyme Disease

The organism of Lyme disease is a spirochete, *Borrelia burgdorferi*. It is transmitted by several species of ticks, with the most prominent being the deer tick, *Ixodes scapularis*, the same vector that carries *Babesia microti*.[63] Lyme disease is endemic in parts of the United States but is not common in Canada. Despite the theoretical possibility of transfusion transmission, there have been no reported cases of transfusion-transmitted Lyme disease anywhere in the world, and 2 studies provide evidence against transfusion transmission. In a lookback study of 6 recipients of blood products derived from donors subsequently diagnosed as having Lyme disease, none were found to be infected.[66] A second study done in an endemic area showed no clinical or serologic evidence of transmission in 155 multitransfused cardiac surgery patients.[67] Currently, the risk of transfusion-transmitted Lyme disease should be regarded as theoretical only. If such a risk were found to exist, it should be extremely low in Canada.

Ehrlichiosis

Ehrlichia are aerobic gram-negative bacteria that infect leukocytes and are responsible for 2 acute febrile illnesses, human monocytic ehrlichiosis and human granulocytic ehrlichiosis (HGE), identified in the past 20 years in the United States. Ehrlichia are transmitted by ticks; *Ixodes scapularis,* the same tick that carries Lyme disease and Babesiosis, is the vector of HGE.[63] The prevalence of antibodies to the HGE agent is highest in the northeastern and upper midwestern US states that are in close proximity to Canada.

A single case of probable transfusion transmission of Ehrlichia with resultant HGE in a recipient occurred in the United States in 1998.[68] No cases have been reported in Canada. PCR studies indicate that Ehrlichia can be found both in leukocytes and in plasma. Because of its leukocyte tropism, leukoreduction would be expected to decrease, if not eliminate, the risk of transfusion transmission.[63] The risk of transfusion-transmitted Ehrlichia in Canada is extremely low.

Chagas Disease

Chagas disease is caused by a protozoan parasite, *Trypanosome cruzi*, which establishes a chronic, asymptomatic carrier state in most infected persons. The parasite is endemic to Mexico and Central and South America where large numbers of transfusion-transmitted cases have been documented. Since the mid-1980s, only 6 cases of acute fulminant transfusion-transmitted Chagas disease have been reported in North America, all in immunocompromised patients.[62] Platelets have been the implicated blood component in all cases in which data were available. Two of these North American cases occurred in Canada; one in 1986 and one in 2000.[69,70] In both cases, the implicated donor had lived in South America. Recently, an additional case of asymptomatic transfusion-transmitted *T cruzi* infection has been documented in the United States in a recipient transfused with a *T cruzi* seropositive platelet unit.[71] This latter case indicates that cases of asymptomatic transfusion-transmitted *T cruzi* infection may occur and not be recognized. Nevertheless, the occurrence of only 2 clinical cases in Canada over a 15-year period indicates that the risk of symptomatic transfusion-transmitted *T cruzi* infection in Canada is extremely low.

Creutzfeldt-Jacob Disease

CJD is a rare, fatal, degenerative neurologic disease with a long asymptomatic latent period. The etiologic agent of CJD is thought by most experts to be a prion. There are no reported cases of transmission of CJD by blood transfusion. Nevertheless, because of the long incubation phase of the disease (as shown from growth hormone transmissions) concern arose in the mid-1990s that CJD transmission could occur from asymptomatic donors to blood transfusion recipients. This theoretical risk led to the establishment of enhanced donor deferral policies (based on iatrogenic exposure or family history of the disease) for potential CJD carriers. Several recent epidemiologic studies have confirmed earlier studies in failing to establish a link between transfusion and transmission of CJD.[72-74] Although still regarded as a theoretical risk, there is an emerging consensus that CJD is not transmitted by transfusion.[75,76] Currently, the risk of transfusion-transmitted classical CJD in Canada should be regarded as virtually nonexistent.

Variant Creutzfeldt-Jacob Disease

Variant Creutzfeldt-Jacob disease (vCJD) is a fatal, degenerative neurologic disease newly discovered in the United Kingdom in 1996. As of early September 2002, 127 definite or probable cases have been reported in the United Kingdom with an additional 6 cases originating in France and one in Italy. Four additional reported cases have occurred elsewhere (one each in Canada, the United States, Hong Kong, and Ireland) but are assumed to have been acquired in the United Kingdom.[77,78]

It has been proven that the etiologic agent of vCJD (probably a prion) is the same agent that causes bovine spongiform encephalopathy. The spread of the agent from cattle to man and the detection of the vCJD prion protein in lymphoid tissue has raised concern that there is a biological basis for the possibility that vCJD is transmitted by peripheral routes, including blood transfusion.[79] To date, no cases of transfusion-transmitted vCJD have been reported anywhere in the world. However, because vCJD is a new disease and other transmissible spongiform encephalopathies are known to have long incubation periods, the 6-year observation period since the discovery of the disease is too short to draw firm conclusions. The biological differences between vCJD and classical

CJD are significant enough to make it unreasonable to extrapolate epidemiological data about the lack of transfusion transmission of classical CJD to vCJD.[79] Although the risk of transfusion-transmitted vCJD is currently theoretical, donor deferral policies to lower this theoretical risk have been implemented in Canada. These policies are based on length of stay in European countries in which vCJD or BSE have been documented. Currently, with these policies in place, it is reasonable to conclude that the risk of transfusion-transmitted vCJD in Canada, if it exists at all, is extremely low.

Bacterial Infection

There are at least 3 potential sources of bacterial contamination of collected blood: bacteria in the donor's blood because of an underlying condition causing donor bacteremia, skin flora introduced at the time of phlebotomy, and contamination introduced by processing.[80] Transfusion-transmitted bacterial infection (TTBI) can be asymptomatic or can present with mild to severe symptoms. To establish a definitive diagnosis of TTBI, the same bacterial species should be isolated from the transfused component and from the recipient's blood.[80] Some investigators have used more stringent criteria (eg, matching of antibiotic sensitivities or molecular profiles of the transfused component and recipient isolates), whereas others have used less stringent criteria (eg, a positive component or recipient culture but not both). These varying criteria need to be kept in mind when data concerning the frequency of symptomatic TTBI from various sources are compared.

Incidence in platelet recipients. Table 1 summarizes the results of several prospective studies conducted in platelet transfusion recipients. The clinical trigger for initiating a TTBI investigation and the criteria used to establish causality differed between studies.

Investigators from Johns Hopkins Hospital (JHH) reported their TTBI data for platelet transfusion recipients over a 12-year period from 1987 to 1998.[81] During this timeframe, they used a consistent protocol that involved a bacteriologic workup for all transfusion reactions characterized by either fever in any patient or by chills in patients on antibiotics or antipyretics. Workup was initiated if the symptoms occurred within 1 hour of the completion of platelet transfusion. The number of platelet transfusion episodes was well documented (either a transfusion of a pool of platelets, estimated to average 6 whole-blood–derived platelet concentrates per pool, or transfusion of an apheresis product obtained from a single donor). There were 23 documented TTBI cases and 4 deaths, all occurring in patients with malignancy receiving aggressive chemotherapy; such patients accounted for approximately 70% to 80% of platelet transfusions at this institution.

A 1-year study conducted at the University of Cleveland Cancer Center from 1991 to 1992 involved culturing platelet concentrates either before or subsequent to transfusion, without regard to clinical symptoms of the patient.[82] Six of 14,481 platelet concentrates (comprising 3141 pools) gave positive cultures. However, only 1 of 4 patients who received a culture-positive platelet unit developed clinical symptoms. Subsequently, by using a larger dataset, these same investigators documented that 42% of patients who received culture positive platelets over a 10-year period (1991-2000) were symptomatic.[83]

Investigators from Queen Mary Hospital in Hong Kong reported their TTBI data for 161 bone marrow transplant recipients receiving platelet

Table 1. Risks per 100,000 Platelet Pools or 100,000 Apheresis Platelets for Symptomatic TTBI

		Infections		Deaths	
Study	Years	Pools	Apheresis	Pools	Apheresis
Ness,[81] JHH, Baltimore	1987-1998	40.2	7.5	6.2	1.5
Yomtovian,[82] Cleveland	1991-1992	47.5*	0	NA	NA
Chiu,[84] Hong Kong	1991-1994	280	NA	0	NA
Bacthem,[85] France	1996-1998	7.2 (95% CI: 2.6-15.6)	3.2 (95% CI: 1.5-6.0)	0	0.7 (95% CI: 0.08-2.6)
Bacon,[86] US	1998-2000	1.1 (95% CI: 0.4-1.7)	1.0	0.2	0.2
QH[87]	2000	13-44†	NA	6.3 (95% CI: 0.0-34.9)	NA

Abbreviation: NA, not available.

*The rate of 190/100,000 positive cultures was adjusted for a 25% rate of symptomatic infection

†The lower number in the range includes only definite cases (n = 2); the higher number includes definite and probable cases (n = 7). The 95% CI for definite cases is 0.0-45.2, and the 95% CI for probable cases is 17.6-90.3.

transfusions from 1991 to 1994.[84] Almost all of these patients were neutropenic, were receiving steroids and antihistamines as premedication for transfusion, and were on antibiotics at the time of the transfusion. Platelet transfusions were given as pools with a median of 6 units per pool. Almost all platelet units were 5 days old at the time of transfusion. Febrile transfusion reactions characterized by a rise of 2°C within 24 hours of transfusion or 1°C accompanied by chills/rigors were investigated for bacterial contamination. Of 37 febrile transfusion reactions investigated, 10 were proven to be TTBI, and severe reactions of septic shock (but no deaths) occurred in 4 cases.

Table 1 also summarizes results obtained from 3 surveillance systems. Within the French hemovigilance system, a focused study on bacterial contamination (the Bacthem case-control study) provides the most thorough data on TTBI.[85] Data for this substudy were collected over a 2-year interval from November 1996 through November 1998. A total of 158 cases of possible TTBI were reported to the hemovigilance system, of which 117 were excluded from further analysis because of inadequate documentation of bacterial etiology. Of the 41 nonexcluded cases, 14 were classified as definite TTBI (positive blood culture of component and recipient with same organism and antibiotic sensitivities), 25 as probable TTBI (positive blood culture of component but no positive recipient culture), and 2 as possible TTBI (no positive blood component culture, recipient with positive culture, and no other infection source identifiable). Pooled platelets were the source of infection in 7 cases (2 patients had severe symptoms, but there were no deaths), whereas apheresis platelets were the source of infection in 9 cases (2 fatalities occurred and 5 patients had severe symptoms). In 6 of the 9 apheresis cases (67%), a gram-negative bacterium was identified. This finding is in contrast to historical data showing a predominance of gram-positive bacteria in culture-positive whole-blood–derived platelet concentrates.[80]

In the United States, a surveillance study focused on bacterial contamination of blood components (BaCon study) was conducted from 1998 through 2000.[86] The study was limited by its inability to accurately measure hospital participation rates and to determine the actual number of units transfused. The investigators used very stringent criteria for attributing a case to TTBI, requiring both a positive blood component culture and a positive recipient culture with identity of the isolates proven by molecular techniques. Of 56 cases that met at least 1 clinical criterion, 34 were judged to be confirmed cases of TTBI. Of the 34 cases, 11 were from pooled platelet concentrates (2 fatalities), and 18 cases (4 fatalities) were from single donors apheresis units.

Within Canada, adverse transfusion reactions reported to Health Canada from 1995 through 2000 revealed a mean of 6.3 reported cases of possible TTBI per year for all transfused blood components. For years in which data were available, red cell transfusions accounted for approximately 1 case annually, with platelet transfusions accounting for the remainder. Approximately 25% to 50% of cases had evidence that definitely or probably linked the reported reaction to bacterial contamination of the transfused component.

A review of cases reported to HQ and to Health Canada in 2000 revealed 5 to 7 cases (depending on stringency of criteria) of reported TTBI from platelet transfusions. CBS data showed no cases of platelet-associated TTBI. A review of the Québec hemovigilance system indicated 7 cases with a probable or definite association with transfusion. Two of these cases, including 1 fatality, were classified as definite based on culturing the same organism from the pool and the recipient; the remaining 5 were classified as probable based on the presence of organisms in the platelet pool without a positive culture result in the recipient.[87]

Using the Québec hemovigilance data, a rate of TTBI within Québec can be calculated.[87] If all 7 cases are attributed to TTBI, the rate is 8.8 per 100,000 transfused platelets or 443.8 per 100,000 platelet pools (95% confidence interval [CI]: 17.6-90.3); if only the 2 definite cases are considered, the rate falls to 2.5 per 100,000 transfused platelets or 12.5 per 100,000 platelet pools (95% CI: 0.0-45.2). The rate of fatal TTBI is 6.3 per 100,000 transfused platelet pools (95% CI: 0.0-34.9); however, this rate is based on only 1 fatal case.

Data summary and best estimate of current risk in Canada. Given that in the year 2000 the infrastructure for reporting of transfusion reactions differed in Québec and the rest of Canada, it seems reasonable to assume that there was underreporting of TTBI from hospitals outside the province of Québec. For this reason, data from the Québec hemovigilance system have been taken to represent the best estimate for the TTBI rate throughout Canada. Furthermore, the Québec hemovigilance

data are very similar to data from the JHH study. These similar results from surveillance and a well-designed observational study suggest that it is reasonable to use Québec hemovigilance data to estimate a national rate for Canada and that the best estimate for risks of TTBI is 13 to 44 per 100,000 platelet pools. The actual rate of bacterially contaminated platelet units may be higher, as it has been shown in 1 study that 58% of such units were transfused without producing clinical symptoms.[83] With regard to fatal reactions, the data are sparser but again show good correlation between Québec hemovigilance and the JHH study; the best estimate for fatal TTBI is 6.3 per 100,000 platelet pools (95% CI: 0.0-34.9). However, these fatality rates are based on only 1 death in the Québec hemovigilance data and 2 in the JHH data.

There are no Canadian data for the risk of TTBI after transfusion of apheresis platelets, which currently account for less than 15% of platelet transfusion episodes in Canada and even a lower percentage in Québec. Data from outside Canada (see Table 1) indicate that TTBI risk from apheresis platelets was lower than that from pooled platelet concentrates in 1 retrospective study but not statistically significantly different in reports of 2 surveillance-based studies.[81,85,86]

Incidence in red cell recipients. The storage of red cell units at refrigerator temperature precludes the growth of many bacterial species that can grow in platelet units stored at room temperature. Nevertheless, certain species of psycrophilic bacteria (*Yersinia enterocolitica* and selected *Pseudomonas spp* and *Serratia spp*) can grow in stored red cell units, and these organisms can result in recipient infection.[80] There are only 2 prospective studies of TTBI in red cell recipients, both performed at the Dana Farber Cancer Center in Boston, encompassing the years 1987 through 1993.[88,89] Bacterial cultures were performed on approximately one third of recipients with febrile reactions in the earliest years and subsequently from almost 100% of such recipients. Over the entire interval of both studies, 38,665 red cells were transfused. One red cell unit gave a positive bacterial culture; however, the recipient culture in this case was negative. The lack of other similar prospective studies in red cell recipients is probably because of the very large sample size required to accurately determine the rate of such reactions.

Table 2 summarizes the results of several reports of TTBI in red cell recipients. In the late 1980s and mid-1990s, public health attention was focused on *Yersinia enterocolitica* infection transmitted by red cell transfusions because of the recognition of several fatal cases. In New Zealand, 8 cases of transfusion transmitted *Y enterocolitica* infection (with 5 fatalities) were reported in 520,000 red cell transfusions from 1990 through 1996 for a rate of 1 per 65,000 units and a fatality rate of 1 per 104,000 units.[90] In the United States, 21 *Y enterocolitica* cases (11 of which were fatal) were reported in an 11-year interval from 1986 through 1996.[91] These data compute to a risk of approximately 1 case per 5 million red cell units transfused.

The Bacthem case control study in France reported 25 cases of TTBI from transfused red cells, of which 13 recipients had severe symptoms and 4 died.[85] Over 50% of the cases were associated with bacteria that were gram-negative rods, but only 1 of the 25 cases was caused by *Y enterocolitica*. A number of cases were caused by organisms not previously associated with TTBI from red cell transfusions. In the United States, the BaCon study reported 5 septic reactions (only 1 was caused by *Y enterocolitica*) and 3 fatalities to red cell transfusion in 1998 to 2000.[86]

A review of cases from HQ, CBS, Health Canada, and Québec hemovigilance in year 2000 revealed 1 definite red cell associated case from CBS, 1 definite red cell associated case from Québec hemovigilance (the patient was symptomatic and both the red cell unit and the recipient culture grew out the same organism), and 4 probable cases

Table 2. Risks per 100,000 Transfused Red Cell Units for Symptomatic TTBI

	Years	All Reactions	Deaths
Theakston,[90] New Zealand	1990-1996	1.5	1.0
US (historical)[91]	1986-1996	0.02	0.01
Bacthem,[85] France	1996-1998	0.6 (95% CI: 0.4-0.9)	0.1 (95% CI: 0.03-0.25)
Bacon,[86] US	1998-2000	0.02 (95% CI: 0.003-0.04)	0.01
QH[87]	2000	0.7-3.6*	0

*The lower number in the range includes only definite cases (n = 1), the higher number includes definite and probable cases (n = 5), and the 95% CI for definite cases is 0.0-4.1 and the 95% CI for probable cases is 0.0-8.5.

from Québec hemovigilance (positive red cell unit culture but negative recipient culture). In all 5 Québec hemovigilance cases, the patient's symptoms were mild. None of the cases were caused by gram-negative rods, and there were no endotoxin-mediated symptoms.[87]

Using the Québec hemovigilance data, a rate of red cell associated TTBI can be calculated. If all 5 cases are attributed to TTBI, the rate is 3.6 per 100,000 transfused red cells (95% CI: 0.0-8.5); if only the definite case is included, the rate is 0.7 per 100,000 transfused red cells (95% CI: 0.0-4.1).

Data summary and best estimate of current risk in Canada. The 2 data sources from the US (historical data and the BaCon study) report very low rates (approximately 0.02 cases per 100,000 red cell units transfused) of red cell associated TTBI,[86,91] whereas an older report from New Zealand and a contemporary report from France report rates that are 30- to 75-fold higher (0.6 to 1.5 cases per 100,000 red cell units transfused).[85,90] It is difficult to know how to interpret the recent French data because the majority of cases were reported as probable (not definite) TTBI cases, a high percentage of patients had mild symptoms, and the organisms isolated differed from historical reports. It is unclear whether these results are a consequence of better transfusion reaction surveillance or whether the symptoms in some of the cases have been inappropriately attributed to bacteria cultured from the transfused red cell units.

The rate calculated from Québec hemovigilance data (0.7-3.6 per 100,000 red cells transfused) is consistent with the recent French report and may represent the best current estimate for Canada. However, it should be noted that there is still a great deal of uncertainty about the Québec hemovigilance red cell TTBI data for the following reasons: the observation timeframe has been short, the cases have a variable degree of proof, and all of the few reported reactions had mild symptoms. Further data will be needed to substantiate this preliminary rate.

NONINFECTIOUS RISKS

Hemolytic Transfusion Reactions

A hemolytic transfusion reaction consists of an accelerated destruction of red blood cells because of incompatibility between the donor and the recipient. Red cell hemolysis can also occur because of nonimmunological causes like overheating of the blood unit and mechanical damage to the cells because of extracorporeal circulation devices or aging of red cell units during storage. These rare events can also cause reactions, but they are not included in this review. Hemolytic transfusion reactions are classified as acute when occurring in the first 24 hours after transfusion, or delayed, when occurring 24 hours to up to 3 weeks after transfusion (the usual is 5 to 8 days). Usually in acute reactions the hemolysis is intravascular and in delayed reactions it is extravascular.[92] Data on the incidence of acute and delayed hemolytic reactions are summarized in Table 3.

Incidence of acute hemolytic transfusion reactions. A frequently cited study done at the Mayo Clinic, Rochester, MN, in the period 1964 to 1973 reported 47 cases of hemolytic reactions (24 acute and 23 delayed) after the transfusion of 268,000 blood units.[93] Six deaths were associated with these hemolytic reactions for a mortality rate of 2.2 per 100,000 units transfused. A standard definition was used for the entire study period to ascertain all cases of hemolytic transfusion reactions, but it is not clear whether the study was prospective or retrospective. Although old, the study was well conducted and monitored with rigorous criteria, and the data were from a single institution where careful attention was paid to adverse transfusion reaction monitoring.

A later study at the same clinic involved retrospectively reviewing the records of all patients who had been transfused during the period 1974 to 1977.[94] Seven cases of acute haemolytic transfusion reactions (AHTRs) and 37 of delayed hemolytic transfusion reactions (DHTRs) were discovered from the 148,554 transfused whole blood or red cell units, an almost 50% reduced rate of AHTR compared with their previous study. The same rigorous criteria were used for defining cases.

In a study of hemolytic transfusion reactions in oncology patients performed during the period 1974 to 1981 at the M.D. Anderson Hospital and Tumor Institute in Houston, TX, Lichtiger and Perry-Thornton,[95] found 3 cases of AHTR after the transfusion of 142,957 units of red cells.[95] This study relied on the reactions reported to the blood bank; therefore, underreporting is likely and the rate is probably underestimated.

In a review of transfusion errors reported in New York State from January 1, 1990, to December 31, 1999, when a total of 9 million red cell units were transfused, Linden et al[96] identified 237 ABO-

Table 3. Risks per 100,000 Transfused Whole-Blood or Red Cells Units for Acute, Delayed Hemolytic and Delayed Serologic Transfusion Reactions

Study	Year/Patients	Product	Acute Reaction	Delayed Reaction
Pineda,[93] Mayo, US	1964-1973 all patients	Whole blood	9.0	8.6
Breandan Moore,[94] Mayo, US	1974-1977 all patients	Whole blood and/or red cells	4.7	24.9
Lichtiger,[95] TX	1974-1981 oncology patients	Red cells	2.1	0.7
Linden,[96] NY	1990-1999 all patients	Red cells	1.1 2.6 ABO errors*	N/A
Vamvakas,[97] Mayo, US	1980-1992 all patients	Red cells	NA	52.7 18.5 (DHTR) 33.4 (DSTR)
Pineda,[98] Mayo, US	1993-1998 all patients	Red cells	NA	76.9 (95%CI:65.4-90.1) 14.9 (95%CI:10.1-21.4)(DHTR) 62.1 (95%CI:51.7-74.0)(DSTR)
Ness,[99] JHH, Baltimore	1986-1987 all patients	Red cells	NA	62.3 11.0 (DHTR) 51.3 (DSTR)
French Hemovigilance[7]	2000 all patients	Red cells	3.2 1.1 ABO errors	69.1 0.7 (DHTR) 68.4 (DSTR)
QH[3]	2000 all patients	Red cells	7.9† (95%C.I.:0.0-14.3)† 7.2 (95%C.I.:0.0-13.4) ABO errors‡	39.7 (95%CI:30.0-51.8) 10.8 (95%CI:0.0-18.1)(DHTR) 28.9 (95%CI:20.7-39.4)(DSTR)

Abbreviations: DHTR, delayed hemolytic transfusion reaction; DSTR, delayed serologic transfusion reaction; NA, not available.

*Forty-three percent of ABO incompatibilities resulted in acute hemolytic reactions.

†Fifty-four percent of acute hemolytic reactions were due to ABO incompatibilities and 46% were due to incompatibilities in other antigen systems.

‡Sixty percent of ABO incompatibilities resulted in acute hemolytic reactions.

incompatible transfusions irrespective of whether hemolysis occurred. Of these, 102 (43.0%) resulted in AHTRs. Five deaths related to AHTRs were reported for a mortality rate of 0.056 per 100,000 units. These data came from a state reporting system that required hospitals to report all transfusion-associated incidents that posed a significant risk to the patient, whether or not an injury occurred. The number of reporting facilities ranged from 247 to 261 during the study period. Because this system relied on reporting from multiple sources, underreporting would be expected and the rates are probably underestimates of the real situation.

The majority of adverse transfusion events reported to the SHOT system were under the classification of incorrect blood component transfused with 81 such events in 1996 to 1997, 110 in 1997 to 1998, 144 in 1998 to 1999, 201 in 1999 to 2000, and 190 in 2000 to 2001.[8-11] The 2000 to 2001 data indicated that 139 cases were related to red cell transfusion with 26 of these being ABO incompatible transfusions; however, no rate calculation for ABO incompatibility was done and there were no data as to how many of these cases resulted in AHTRs.[11]

In 2000, the French hemovigilance system reported 78 AHTRs, of which 62 occurred with red blood cell transfusions. There were 21 ABO-incompatible transfusions because of red blood cells and 4 because of platelet transfusions.[7]

In the year 2000, there were 7 AHTRs reported to Health Canada, 1 by CBS and 6 by HQ; of these, 4 were related to ABO-incompatible transfusions. These data likely suffer from significant underreporting.

In the Québec hemovigilance system, there were

11 AHTRs (6 because of ABO incompatibilities and 5 because of incompatibilities in other antigen systems) in 138,605 red cell units transfused.[3] In addition to the 6 ABO incompatibilities resulting in acute hemolytic reactions, there were 4 additional ABO incompatible transfusions in which the patients were asymptomatic. Thus, there were a total of ten ABO-incompatible transfusions related to red cells. Two deaths occurred from acute hemolytic transfusion reactions for a mortality rate of 1.4 per 100,000 units (95% CI: 0.0-5.3).

Incidence of delayed hemolytic transfusion reactions. DHTRs are caused primarily by the presence of antibodies in patients previously sensitized by transfusions or pregnancy. The development of these antibodies may occur without clinical symptoms or laboratory evidence of hemolysis in patients after a transfusion; many authors call this a delayed serologic transfusion reaction (DSTR, also referred to as alloimmunization). Whenever this distinction is made in the literature, the rates will be presented both for delayed hemolytic and delayed serologic reactions. When no distinction is made, rates will be presented as delayed hemolytic reactions.

The data for DHTRs from the 2 Mayo Clinic studies described earlier are summarized in Table 3.[93,94] Of note is the significant increase in DHTR rate in the second study. Because the same rigorous criteria were used for defining cases in both studies, this increased rate is probably explained by improvement in identifying antibodies in transfused patients.

A further study on delayed hemolytic transfusion reactions was performed at Mayo Clinic during the period 1980 to 1992.[97] Since 1980, a standard procedure was introduced at Mayo for the diagnosis of these reactions and for their classification into DHTRs or DSTRs. The criteria for classification were very rigorous requiring strong evidence of hemolysis for the DHTRs. All records of patients who received a clinical diagnosis of DHTR or DSTR were retrospectively reviewed to ascertain their correct classification and to identify factors associated with hemolysis. A total of 296 delayed reactions occurred during the period when 562,124 red blood cell units were transfused. DHTR represented 104 and DSTR 188 of these cases (4 cases could not be classified). This is the most rigorous study in the literature on delayed hemolytic transfusion reactions.

By using the same methodology, the study was continued at Mayo for the period 1993 to 1998.[98] After every serologic diagnosis of DHTR/DSTR, each case was reviewed and considered a DHTR if there was an unexplained decrease in hemoglobin after the transfusion or clinical evidence of hemolysis. This evidence was based on the following criteria: elevation of serum indirect bilirubin level or serum creatinine level, reduction of serum haptoglobin from pretransfusion level by at least 50%, hemosiderinuria, hemoglobinuria, hemoglobinemia, an unexplained fever, or decreased urine output. The higher incidence of DSTR with respect to the previous study is probably because of better ascertainment and identification of antibodies in transfused patients.

Using rigorous criteria for case definition, Ness and colleagues[99] did a study on DHTRs and DSTRs at the Johns Hopkins Hospital in Baltimore during the period January 1986 to August 1987. A DSTR was defined on the basis of patient serologic findings pre- and posttransfusion and through a retrospective chart review of all DSTR cases for evidence of hemolysis. During that period, 54,562 red cell units were transfused, and 34 DSTR cases were identified. Of these, only 6 had evidence of hemolysis (DHTR).

In the French hemovigilance system, in 2000, there were 16 DHTRs (14 because of red cell transfusion) and 1,320 DSTRs to red cells.[7] This is an impressive capture of DSTRs from a surveillance system, showing rates comparable to well-designed prospective studies.

In 2000, 15 cases of DHTR and 17 cases of DSTR were reported to Health Canada. Because only serious adverse transfusion reactions are reported to Health Canada, these data probably do not include mild and moderate reactions and therefore cannot be used for calculation of rates in Canada.

In the Québec hemovigilance system in year 2000, there were a total of 55 delayed reactions (DHTR and DSTR) associated with red blood cell transfusions.[3] Using the same criteria as the Mayo Clinic study, 15 of those were DHTRs and 40 were DSTRs. There was one death related to a severe case of delayed reaction in a patient with multiple alloantibodies for a mortality rate of 0.7 per 100,000 units transfused (95% CI: 0.0-4.1). It must be noted that underreporting of DSTR is probably significant because many consider that alloimmu-

nization without symptoms is not an adverse transfusion reaction, especially if the patient is not to receive blood in the near future.

Incidence of hemolytic reactions after platelet transfusion. Although hemolytic reactions (acute and delayed) have been reported with other components such as platelets and plasma, the risk is substantially lower and estimates are not available in the literature. In a review of the literature by McManigal and Sims[100] and reported by Larrson et al[101] who added 1 case, 12 cases of acute hemolysis caused by the transfusion of ABO out-of-group platelets were reported between 1976 and 1999. In all cases, including 1 in Canada,[102] the donor was group O and the recipients were mainly group A but some were also group AB or B. These reactions are caused by the presence of donor antibodies (anti-A and/or anti-B) in the plasma portion of the platelets causing hemolysis of the recipient's red blood cells. This can occur when there is a high concentration of these antibodies in the donor plasma; the prevalence of group O donors with such high concentration of antibodies has been reported to range from 10% to 20% in US blood donors.[101] Hemolysis appears to occur more frequently after transfusion of apheresis platelets than pooled whole-blood–derived platelets because antibodies in the apheresis unit are not diluted by the plasma from other donors, as is the case with pooled whole-blood–derived platelets. A more frequent occurrence than hemolysis after the transfusion of ABO-incompatible platelets is the coating of recipient's red cells with donor antibody (evidenced by a positive direct antiglobulin test) in the absence of symptoms.

There was no acute but 1 delayed hemolytic and 3 delayed serologic reactions associated with platelet transfusion in the Québec hemovigilance system in 2000 (none were associated with plasma). All hemolytic transfusion reactions reported to Health Canada in 2000 were associated with red cells. However, in past years, a few such reactions were reported with platelet transfusion (1 in 1999 and 2 in 1998).

Data summary and best estimate of current risk in Canada. For AHTRs, data from Québec hemovigilance system are similar to those obtained from prospective and retrospective studies even though some of these studies are quite old. Therefore, we believe that the best data to estimate the risk of AHTR in Canada is from the Québec hemovigilance system. The risk estimate is 7.9 per 100,000 units of red cells (95% CI: 0.0-14.3). The risk estimate for transfusion of ABO-incompatible red cells is also taken from Québec hemovigilance system and is 7.2 per 100,000 units (95% CI: 0.0-13.4).

For DHTRs, data from Québec hemovigilance system are also similar to published data from prospective and well-designed retrospective studies, some of them being recent and reflecting current transfusion practices. Hence, our best estimate for the risk of DHTRs in Canada is from Québec hemovigilance data and is 10.8 per 100,000 units of red cells (95% CI: 0.0-18.1).

As for DSTRs, because such reactions are underreported in the Québec hemovigilance system, data from that system cannot be used to estimate risk. The best estimate comes from the most recent Mayo Clinic study that reflects current transfusion practices in the United States, which are very similar to those in Canada. Hence, the risk estimate is 62.1 per 100,000 red cell units (95% CI: 51.7-74.0). Based on the literature and the case-reporting data from Canada, we can conclude that the risk of hemolytic transfusion reactions because of platelet transfusion is low.

Febrile Nonhemolytic Transfusion Reactions

A febrile nonhemolytic transfusion reaction (FNHTR) is characterized by an elevation of temperature of greater or equal to 1°C near the end of or shortly after the completion of transfusion (rarely 1-2 hours after transfusion) that cannot be explained by the patient's underlying condition or another type of adverse transfusion reaction. Additional symptoms such as chills or rigors; sensation of cold and/or discomfort; and more rarely headaches, nausea, and vomiting may also be present. In some cases, the only symptoms are the presence of chills or sensation of cold and rigors without any rise in temperature; despite the absence of fever, this set of symptoms is also classified as a febrile nonhemolytic transfusion reaction.[103] FNHTRs are usually mild and have no significant sequelae. However, they cause anxiety to patients who may be reluctant to receive further transfusions

Incidence. Data on the incidence of FNHTR vary greatly in the literature. Possible reasons for this variation include differences in patient populations, differences in recording of symptoms by

nursing staff, differences in reporting mechanisms and case ascertainment, and differences in the use of pretransfusion medication to control fever. Because universal prestorage leukoreduction for cellular blood components in now standard in Canada, this review focuses primarily on studies that examined leukoreduced products. Incidence data are presented separately for red blood cells and platelets in Tables 4 and 5.

Uhlmann et al[104] conducted a retrospective analysis of transfusion reactions reported to the Barnes-Jewish hospital blood bank in St Louis to study the influence of pre-storage leukoreduction of red cells on the incidence of transfusion reactions. A FNHTR was defined as a temperature rise of 1°C or more occurring in association with transfusion without any other explanation. The study relied on reporting of reactions to the blood bank and a thorough investigation of all reported cases. In the year 1999, 31,543 nonleukoreduced red blood cell units were transfused and in the first 6 months of year 2000, 16,093 leukoreduced red blood cell units were transfused. Rates of FNHTR were 50% higher for nonleukoreduced than for leukoreduced red blood cell transfusions. These rates are, however, very low compared with other studies. This might be because of underreporting of these minor reactions to the blood bank.

Tanz et al[105] reported in an abstract a study from Johns Hopkins Hospital on the incidence of transfusion reactions after the transfusion of red cells in 2 different periods. From January 1998 to July 1999, 39.8% of red cell units were leukoreduced and from July 2000 to March 2001, 95.4% of red cell units were leukoreduced. The rate in the second period was significantly lower than in the first period ($P = .0005$). No definition of FNHTR was provided in the abstract. This study appeared to also rely on reactions reported to the blood bank and is thus subject to the same problem of underreporting as the previously mentioned study.

Heddle et al[106] conducted a prospective observational study during the early 1990s at McMaster University Hospital in Hamilton on 41 patients aged 17 to 70 years old (72% having hematologic malignancies) who received 117 red blood cell and 65 platelet transfusions. The FNHTR rate was significantly lower for red cell than for platelet transfusions and appeared to be lower for apheresis platelet than for pooled random donor platelet transfusions. There was also a tendency toward lower rates if leukoreduction was applied. This was a well-designed study with a standard definition for FNHTR and a good assessment of cases through a questionnaire administered to the patient before and after the transfusion. The sample size, however, was small as shown by the very wide confidence intervals, particularly with apheresis platelets.

Investigators at the Dana-Farber Cancer Institute in Boston, MA, reviewed all transfusion reactions that occurred in 1993 (a period when all red cell units were leukoreduced either by bedside filtration or by freezing/deglycerolization and platelet transfusions were with single donor apheresis platelets).[89] A FNHTR was defined as an elevation of body temperature of at least 1°C during or immediately after transfusion without any other cause after investigation. There were 152 FNHTRs in 7,080 RBC transfusions and 82 FNHTRs in 5,197 platelet apheresis transfusions. This was a well-designed study with standard definitions were applied by an independent reviewer.

A similar study using the same definition of

Table 4. Risks per 100 Transfused Red Cell Units for Febrile Nonhemolytic Transfusion Reactions

Study	Year/Patients	Product		Incidence (per 100 Units)
Heddle,[106] Hamilton	Early 1990s mainly oncology patients	Red cells		6.8 (95%CI:3-13)
Dzieczkowski,[89] Boston	1993 oncology patients	Red cells	LR	2.15
Federowicz,[107] Boston	1994 oncology patients	Red cells	PSLR	1.10
Uhlmann,[104] St Louis	1999-2000 all patients	Red cells	Not leukoreduced	0.12
			PSLR	0.08
Tanz,[105] Baltimore	1998-2001 all patients	Red cells (1/98-6/99)	39.8% PSLR	0.44
		Red cells (7/00-3/01)	95.4% PSLR	0.17
French Hemovigilance[7]	2000 all patients	Red cells—PSLR		0.07
QH[3]	2000 all patients	Red cells—PSLR		0.11 (95%CI:0.09-0.13)

Abbreviations: LR, leukoreduced (bedside); PSLR, prestorage leukoreduction.

Table 5. Risks per 100 Platelet Transfusions for Febrile Nonhemolytic Transfusion Reactions

Study	Year/Patients	Product	Incidence (per 100 Units)
Heddle,[106] Hamilton	(Early 1990s) all patients (mainly oncology)	Random donor	37.5 (95% CI:21-56)
		Random donor-LR	28.0 (95% CI:12-49)
		Single donor	20.0 (95% CI:0.5-72)
		Single donor-LR	0.0 (95% CI:0.0-71)
Dzieczkowski,[89] Boston	1993 oncology patients	Single donor	1.58
Federowicz,[107] Boston	1994 oncology patients	Single donor	1.73
Anderson,[108] UK	(Mid 1990s) oncology patients	Single donor	3.09
		Random donor-BC	3.80
		Random donor	17.09
Sarkodee-Adoo,[109] Baltimore	1993-1996 oncology patients	Single donor	0.94
		Random donor	2.72
Kelley,[110] Pittsburgh	1995-97 hematology, oncology, bone marrow transplant patients	Single donor	0.15-0.75
		Random donor	4.6-11.1
		Random donor ≤3 days	1.1
Heddle,[111] Hamilton	(Late 1990s) hematologic malignancies	Random donor-PR	21.3
		Random donor-PSLR	6.7
		Single donor-LR	8.3
Couban,[112] Hamilton	1994-1997 pediatric patients	Platelets Pools	12.0
		Plasma-removed	7.1
		PSLR	4.6
French Hemovigilance[7]	2000 all patients	Single donor-PSLR	0.19
QH[3]	2000 all patients	Platelet pools-PSLR	0.13 (95% CI:0.08-0.2)

Abbreviations: BC, buffy-coat method; LR, leukoreduced; PR, plasma removal; PSLR, prestorage leukoreduction; random donor, whole-blood–derived platelets that are pooled; single donor, apheresis platelets.

FNHTR was conducted in the same institution at a later period when all red cell and platelet units were leukoreduced at the prestorage stage.[107] This latter study documented 60 FNHTRs in 5,412 RBC transfusions and 59 such reactions in 3,405 platelet transfusions. The 50% lower FNHTR rate after red cell transfusions in the second study was statistically different from the rate in the previous study ($P = .0045$).

In the United Kingdom during the mid-1990s, Anderson et al[108] prospectively randomized 51 patients with hematologic malignancies to receive either apheresis platelets, whole-blood–derived platelets made from the pooled buffy-coat method, or pooled units of platelets made from the platelet-rich plasma method. They observed a higher incidence of FNHTR for the latter group. However, their randomization process appeared to have generated groups that were improperly balanced in terms of age distribution and type of cancer, but it is not clear if this influenced the outcome of their study.

In a prospective monitoring study of transfusion reactions by the nursing staff at the Marlene and Stewart Greenebaum Cancer Center in Baltimore during the period July 1, 1993, to June 30, 1996, a total of 197 transfusion reactions were observed after 4,926 platelet transfusions; of these, 119 were FNHTRs.[109] Rates were 3-fold higher for platelet pools compared with apheresis platelets. There was a clear association of reaction with the length of storage for pooled platelets but not for apheresis platelets. The definition of FNHTR was clearly stated, and the prospective design enhanced the validity of the results.

Kelley et al[110] conducted a retrospective study on FNHTR rates after platelet transfusions on a hematology/oncology/bone marrow transplant ward in a Pittsburgh hospital during each of 3 consecutive 5-month periods from November 1995 to February 1997. The first period was called baseline, and the majority (96%) of platelet transfusions were with apheresis platelets. In the following period (period A), the majority (64.3%) of transfusions were with pooled platelets aged 1 to 5 days and in the third period (period B), 50.8% of

transfusions were with pooled platelets ≤3 days old. Rates of FNHTR for apheresis platelets did not differ significantly in the 3 periods. For pooled platelets, the rate of FNHTR was significantly lower with younger age platelets (period B) than during period A. The definition of FNHTR in this study was standard, but the reporting relied on the diagnosis made by multiple physicians on the ward. Therefore misclassification of cases and underreporting could have occurred.

Heddle et al[111] conducted a randomized trial comparing plasma removal to 2 types of prestorage leukoreduction methods for preventing reactions to platelets. A total of 129 patients with hematologic malignancies were randomly assigned to plasma supernatant removed platelet transfusions, prestorage leukoreduction of whole-blood–derived platelets, and leukoreduced apheresis platelets. An FNHTR was defined in 2 different ways: an asymptomatic febrile reaction was defined as a rise in temperature that reached 38°C or higher and was ≥1°C rise over baseline with no other signs or symptoms being present; an inflammatory reaction was characterized by symptoms of rigors, chills, and sensation of cold. Rates of FNHTR for apheresis platelet transfusions were 0.6% for asymptomatic febrile and 7.7% for inflammatory, and for pooled platelet transfusions they were 0.3% for asymptomatic febrile and 6.4% for inflammatory. This is one of very few studies showing no significant difference between apheresis and pooled platelet transfusions.

In a randomized crossover trial of plasma removal for platelet transfusions in children, Couban et al[112] studied prospectively the incidence of adverse reactions including FNHTRs, defined as a temperature increase of greater than 1°C during or within 2 hours after the transfusion and/or signs and symptoms of chills, cold, and rigor, in 35 patients meeting the inclusion criteria and having given consent. They also prospectively audited 33 consecutive patients who received prestorage leukoreduced platelets during a part of the study period. In all, 226 platelet transfusions were administered to 68 children. There were respectively 9 FNHTRs to 75 standard whole-blood–derived, 6 reactions to 85 plasma-reduced, and 3 reactions to prestorage leukoreduced platelet transfusions. None of the differences were significant.

In the French hemovigilance system, in 2000, there were 1,366 FNHTRs to red blood cell transfusions for a rate of 0.07% and 1,336 such reactions to platelet transfusions for a rate of 0.19%.[7] All products were subject to prestorage leukoreduction.

In the year 2000, there were only 4 cases of FNHTRs reported to Health Canada, all associated with platelet transfusions. However, minor reactions such as FNHTRs are not designated as reportable to Health Canada so it is not surprising that this reporting system would fail to capture them.

In the Québec hemovigilance system the incidence of FNHTR is 149 cases in 138,605 red cell units transfused and 21 cases in 15,975 platelet pools transfused.[3] Many of these reactions are not reported by Québec hospitals because of their benign nature and high frequency. Hence, these data represent a substantial underestimation of the risk.

Data summary and best estimate of current risk in Canada. The rates of FNHTR in the different studies in the literature are difficult to interpret and compare because of the differential effects of underreporting (given the benign nature of the problem and the use of medication to prevent its occurrence) and overreporting (because of falsely attributing fever to a transfusion reaction instead of to the recipient's underlying condition causing fever that may be only coincidental with the transfusion) in the different studies. Thus, the rate of FNHTR for Canadian red cell recipients is difficult to estimate. Data from Québec hemovigilance system cannot be used to estimate this rate because of substantial underreporting.

The most commonly reported rates of 0.5% to 1% for FNHTR, for the general population of recipients after red blood cell transfusions, were established before the use of universal prestorage leukoreduction that has subsequently been shown to significantly reduce the rate of FNHTR.[103] Given the current practice of universal prestorage leukoreduction in Canada, it seems most reasonable to base our risk estimate on the recent studies performed in the United States cited in Table 4 with prestorage leukoreduced red blood cell transfusions. Therefore, based on the most recent study, our best estimate for the risk of FNHTR in Canada after the transfusion of red cells is 0.2%.

For platelet transfusions, rates of FNHTR have been reported mainly for oncology patients who receive the vast majority of platelet transfusions. In a majority of studies, rates are lower with single-

donor platelets obtained through apheresis and also with whole-blood–derived (random donor) platelets prepared with the buffy-coat method. However, in Canada, the vast majority of transfused platelets are whole-blood derived through a platelet-rich plasma method. These platelets, according to reports in the literature, present the highest risk of FNHTR. Our best estimate for FNHTR after platelet transfusion in Canada comes from a Canadian randomized trial that documents a rate of 6.7% for platelet pools that have been leukoreduced at the prestorage stage and given to oncology patients who have previously been heavily transfused. Although these patients are more susceptible to FNHTR than are newly diagnosed cancer patients or patients given platelet transfusions for other reasons, we believe that this estimate will only slightly overestimate the risk given that the majority of platelet transfusions are used in heavily transfused oncology patients.

Allergic Transfusion Reactions

Allergic reactions have been described under many terms in the literature: allergic, minor allergic, anaphylactoid, anaphylactic, and anaphylactic shock. An allergic reaction consists of a cutaneous manifestation characterized by one or more of the following symptoms: pruritus; urticarial lesions (wheals); erythema of the skin (localized or generalized); flushing; and, more rarely, angioedema. An anaphylactoid reaction will present, in addition to cutaneous signs and symptoms, with some degree of hypotension, dyspnea, stridor, wheezing, chest pain, or tachycardia. Severe gastrointestinal symptoms like nausea, vomiting, abdominal cramps, and diarrhea may also be present.[113] An anaphylactic reaction presents with the same features as an anaphylactoid reaction except that hypotension is severe enough to lead to shock and loss of consciousness and might result in cardiac arrest and death. For the purpose of this review, we have adopted the classification proposed by Vamvakas and Pineda.[114] According to this classification scheme, an allergic reaction will be termed a minor allergic reaction, and an anaphylactoid or anaphylactic reaction will be termed a major allergic reaction.

The mechanisms responsible for allergic transfusion reactions are multiple and complex. The classical mechanism is the presence of a preexisting immunoglobulin (Ig) E antibody in the serum of the recipient reacting with a protein (antigen) in the plasma part of the transfused blood component causing a type I hypersensitivity reaction. Because some individuals have very low levels of serum and secretory IgA and are lacking the 2 isotypic determinants of the IgA class of immunoglobulins or lack 1 of the 2 isotypic determinants (despite having normal levels of IgA), they can develop class-specific or allotype-specific anti-IgA.[115] Preexisting antibodies to serum proteins other than IgA (IgG, albumin, haptoglobin, transferrin, C3, C4, and so on) can also induce allergic reactions as can preexisting HLA antibodies and chemical, drug, or food allergens.[114,116,117]

Incidence data. Definitions of allergic transfusion reactions vary greatly in the literature, and there are few data on incidence from well-designed prospective studies in the general patient population. Data on the incidence of allergic transfusion reactions are presented in Table 6.

In a retrospective review of 10,085 consecutive whole-blood or packed red cell transfusions at the Children's Hospital in Boston in the early 1960s, Kevy et al[118] found a rate of 1.07 urticarial reactions per 100 units. At the end of each month, all transfusion records were checked for the presence of an adverse transfusion reaction. An urticarial reaction was defined as the obvious evidence of dermal allergy, wheals, or periorbital edema without fever. The cases were well ascertained but, because of the age of this study, the results may not be applicable to current transfusion practices.

Pineda and Taswell[119] reported 4 cases of reactions related to anti-IgA in recipients over a 5-year period. These are case reports, and the number of products transfused are estimates. Moore,[113] in a concise review of anaphylactic transfusion reactions done in 1985, reported a 3% rate of mild allergic reactions from the Mayo clinic, but it is not stated for which period or how this rate was calculated. A mild allergic reaction was defined as hives or localized urticarial rashes.

Table 6 includes the rates of allergic reactions reported in studies previously described in this review under FNHTR. All 7 of these studies reported varying rates of minor allergic reactions but no major allergic reactions.[89,104-107,111,112]

In the randomized trial of varying types of platelet transfusions conducted by Heddle et al,[111] an allergic reaction was defined as pruritis, urticaria, erythema, and/or flushing. The population studied

Table 6. Risks per 100 Transfusions for Minor and Per 100,000 Transfusions for Major Allergic Reactions

Study	Year/Patients	Product		Minor Reactions Risk/100	Major Reactions Risk/100,000
Kevy,[118] MD	(early 1960s) pediatric patients	Whole blood and packed red cells		1.07	
Pineda,[119] Mayo, US	(early 1970s)	All components			2.1 (anti-IgA)
Moore,[113] Mayo, US	(early 1980s)	All components		3.0	
Dzieczkowski,[89] Boston	1993 oncology patients	Red cells	bed side leukoreduction	0.51	
		Platelets	Apheresis	3.69	
Federowicz,[107] Boston	1994 oncology patients	Red cells	PSLR	0.41	
		Platelets	Apheresis	3.17	
Sarkodee-Adoo,[107] Baltimore	1993-1996 oncology patients	Platelets	All	1.26	
			Apheresis	0.59	
			Platelet pools	1.40	
Uhlmann,[104] St-Louis	1999-2000 all patients	Red cells	Not leukoreduced	0.04*	
			PSLR	0.06*	
Tanz,[105] Baltimore	1990-2001 all patients	Red cells	95.4%PSLR	0.15*	
			39.8%PSLR	0.25*	
Heddle,[111] Hamilton	2000 hematologic malignancies	Platelets	Apheresis	4.8*	
			Platelet pools (PSLR[a])	4.1*	
Couban,[112] Hamilton	1994-1997 pediatric patients	Platelets	Pools	5.3*	
			Plasma removed	5.9*	
			PSLR	7.6*	
French Hemovigilance	2000 all patients	Red cells		0.02	0.3
		Apheresis platelets		0.41	7.7
QH[3]	2000 all patients	Red cells		0.07 (95%CI:0.06-0.09)	4.3 (95%CI:0.0-9.6)
		Platelet pools		0.30 (95%CI:0.22-0.40)	62.6 (95%CI:30.0-115.1)

Abbreviation: PSLR, prestorage leukoreduced.

*The rates of reactions to these different components within each study were not statistically different.

was heavily transfused and therefore at higher risk of developing allergic reactions. Hence, the rate could be an overestimation of the risk in a general patient population.

In the study from Dana Farber by Dzieczkowski et al,[89] an allergic reaction was defined as the presence of hives or urticaria, but in the later study at the same institution by Federowicz et al,[107] the definition differed slightly with the addition of wheezing and angioedema.

In the SHOT system, an allergic reaction is defined as the presence of 1 or more of rash, dyspnea, and angioedema.[11] An anaphylactic reaction is defined as hypotension with 1 or more of rash, dyspnea, and angioedema. For the year 2000 to 2001, there were 2 allergic and 2 anaphylactic reactions reported with red cell transfusions and 1 allergic and 6 anaphylactic reactions with platelet transfusions. It must be remembered that only severe reactions are to be reported to SHOT. Data from the 2 previous years showed numbers in the same order of magnitude.

In the French hemovigilance system, in 2000, there were 5 major allergic reactions to red blood cell transfusions and 15 to platelet transfusions.[7] For minor allergic reactions, rates were low both for red blood cell and platelet transfusions. The definitions used were the same as those used in this review.

In the year 2000, there were 23 cases of allergic

reactions reported to Health Canada, 8 associated with red blood cell transfusions, 7 with pooled platelet transfusions, 1 with apheresis platelet transfusion, and 7 with plasma transfusion. Of these, 20 were related to transfusion, 2 were possibly related, and 1 was not related. None appeared to be related to the presence of anti-IgA in the recipient. No distinctions were made between minor allergic, anaphylactoid, or anaphylactic reactions. Severity of reactions was not reported. In previous years, there were 1 case reported in 1999, 11 in 1998 (including 4 anaphylactic shock and 3 anaphylactoid reactions), none in 1997, 1 in each of 1996 and 1995, and 3 in 1994 (including 1 fatality).

The Québec hemovigilance system uses the classification of minor allergic reaction and major allergic reaction (anaphylactoid and anaphylactic).[3] The incidence of minor allergic reactions in 2000 was 99 cases in 138,605 red cell units transfused and 48 cases in 15,975 platelet pool transfusions. Many minor allergic reactions are not reported by Québec hospitals because of their benign nature and large numbers. Hence, these data represent a substantial underestimation of the risk. For major allergic reactions, the incidence was 6 cases in 138,605 red cell units transfused and 10 cases in 15,975 platelet transfusions. Of these 16 major reactions, only 1 was an anaphylactic reaction, and only 1 appeared to be related to the presence of anti-IgA in the recipient.

Data summary and best estimate of current risk in Canada. The rates of minor allergic transfusion reactions most often cited in the literature are 1% to 3%, with no distinction being made between red cell, platelet, or plasma transfusions.[113,114] Given that different definitions have been used and that most studies have relied on reporting of reactions to the blood bank and not on careful review of all transfusions (thus being subject to underreporting), it is difficult to estimate a risk of minor allergic transfusion reactions after the transfusion of red cells or platelets. Data from Québec hemovigilance represent a substantial underestimation of the true rates of minor allergic reactions both for red blood cell and platelet transfusions. This is because of underreporting of this reaction, which is thought to be of no clinical significance in a majority of cases, hence not worthy of reporting by Québec hospital blood banks. Therefore, these data cannot be used to accurately estimate risk in Canada.

Given the US studies summarized in Table 6 that most closely represent current transfusion practice in Canada, our best estimate for the risk of minor allergic reactions after red cell transfusions is 0.4%. This estimate is based on the highest rate reported in the 3 most recent studies.[89] For pooled platelet transfusions, we have chosen the estimate of 4.1% from the data reported by Heddle for pooled platelets (even though patients in that study were previously heavily transfused and thus were at higher risk of allergic transfusion reactions) because the data were obtained using the current transfusion practice in Canada. This estimate is similar to those of investigators at the Dana Farber Clinic and by Heddle after the transfusion of single-donor apheresis platelets.[89,107,111] As for major allergic reactions (anaphylactoid and anaphylactic), Québec hemovigilance data are taken as the best risk estimate. For red cell transfusions, the risk is 4.3 per 100,000 units (95% CI: 0.0-9.6), and for platelet transfusions, it is 62.6 per 100,000 platelet pools (95% CI: 30.0-115.1). Although these are higher than published rates, it must be remembered that the rates in the literature are almost only for anaphylactic reactions related to the presence of anti-IgA in the recipient. This mechanism represents only a small proportion of all major allergic reactions. Hence, data from the Québec hemovigilance system probably better reflect the current risk of major allergic transfusion reactions in Canada.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is characterized by acute respiratory distress, noncardiogenic bilateral pulmonary edema and hypoxemia that occur within 1 to 6 hours (more usually within 1-2 hours) after transfusion of plasma-containing blood components.

Although the precise pathophysiology for this reaction is not agreed on, 2 types of risk factors have been suggested: (1) a donor associated risk factor (ie, plasma from multiparous female donors, which has a higher frequency of anti-HLA antibodies or antigranulocyte antibodies than plasma from other donors), and (2) a unit associated risk factor (ie, plasma that is "older," allowing for accumulation of a priming agent).

Incidence. The incidence data from the literature and surveillance systems are summarized in

Table 7. Many reviews quote the incidence of TRALI as 2 per 10,000 transfused units or 16 per 10,000 transfused patients. These estimates are based on a study by Popovsky and Moore[120] published in 1985. The study involved investigating all cases of acute respiratory distress that occurred within 4 hours of transfusion at hospitals associated with the Mayo Clinic from June 1982 to October 1984. During the study period, 194,715 units of blood products were transfused to approximately 22,292 patients. TRALI was diagnosed in 36 patients (2 died). Granulocyte antibodies were shown in the serum of at least 1 unit of donor blood in 32 of the 36 cases, and lymphocytotoxic antibodies were shown in 26 cases. The majority of cases occurred after transfusion of whole blood (21 cases); 10 cases were found after transfusion of red cells, and 5 cases were found after fresh-frozen plasma.

In a study by Clarke et al,[121] 46 of 14,602 transfusions of random-donor platelets were associated with acute severe respiratory reactions in a 2-year period (1991-1993) in a single institution. There was 1 death. Patient and product factors in the 46 cases were compared in a nested case control study with those of 225 randomly selected controls who had received random donor platelets and experienced no respiratory reactions. The data suggested that certain patients are at risk (hematological malignancies and cardiac disease), and platelet storage time has a role in pathogenesis. In a report from New Zealand by Henderson,[122] 46 cases of pulmonary edema were reported and a total of 440,000 components were transfused during the years (1981 to 1987) covered by the report. Although this report is quoted in some reviews, there is little information provided about the cases to indicate whether reliance can be placed on these data.

Table 7. Risks per 100,000 Units and 100,000 Patients for TRALI

Study	Years	Type of Component	TRALI cases	Risk (per 100,000 Units)	Risk (per 100,000 Patients)
Popovsky,[120] Mayo, US	1982-1985	Not specified*	36	20	160
Weber,[123] Mayo, US	1985-1993	Not specified*	8	NC	42
Clarke,[121] Alberta	1991-1993	Platelets†	46	320	NC
French Hemovigilance[4-7]	1995-2000‡	Not specified*	7‡	NC	1.4
	2000	Apheresis platelets	1	0.5	NC
SHOT[8-11]	1999-2000	Red cells	6	0.25§	NC
	2000-2001	Red cells	6	0.25§	NC
		Platelets‖	3	1.38§	NC
Health Canada and CBS/HQ	1999-2000¶	Red cells	8.5	0.5	NC
		Platelet pools	2.5	1.5	NC
Health Canada	1998#	Red cells	11	1.4	NC
		Platelet pools	8.5	12.1**	NC
QH[3]	2000	Red cells	1	0.7	2.1††
		Platelet pools	1	6.3**	16.8††
Goldman,[125] Quebec	1999-2000	Red cells	7	0.9	NC

Abbreviation: NC, not calculable from available data.

*Type of plasma-containing blood component transfused was not specified and could include whole blood, red cells, random donor platelets, apheresis platelets, plasma, and cryoprecipitate.

†It is assumed from the abstract that data are for random donor units rather than platelet pools.

‡These data are a yearly average of the five years of available data.

§This is based on the range for the number of red cell units transfused considering the number distributed and the proportion that went to hospitals participating in the SHOT system. The total number of units distributed was 2.7 million.

‖This represents a mix of apheresis platelets and pooled platelet concentrates.

¶Case data for 1999 and 2000 were used. Fractional cases were attributed as discussed in the text. Data on number of units transfused was for year 2000: 780,000 red cells, 70,000 platelet pools. An additional 13,000 apheresis platelets were also transfused but are not included because of the fact that the TRALI rate for recipients of this component has not been previously reported.

#Case data for 1998 were used. The data for number of units transfused in 1998 were not available; the number of units transfused in year 2000 (see footnote‖) was used instead. Although the number of units transfused in 1998 may have been slightly different from year 2000, this is not likely to have a significant effect on the rate.

**Rates are per 100,000 platelet pools.

††The accuracy of number of recipients is subject to the limitations noted in the Methods section.

Weber et al[123] in a review of quality assurance databases of 139,245 consecutive anesthesia cases at 1 hospital (whether or not they received transfusion) from 1985 to 1988 found 5 cases of TRALI as the implicated cause among 20 cases of acute fulminant pulmonary edema occurring within the first 2 postoperative hours. The diagnoses of TRALI were confirmed by detecting antigranulocyte antibodies in donor serum that were reactive with the patient/recipient's granulocytes. Subsequently, 3 more cases were identified for an incidence of 8 cases (none fatal) in 18,864 patients who received 1 or more blood products. The authors concluded that the rate of TRALI implicated as the cause of fulminant pulmonary edema in patients who received general anesthesia and 1 or more blood products was 1 in 2,358 patients. They attributed this relatively high rate to the high index of suspicion at their institution.

Palfi et al[124] in 2001 published the results of a double-blinded randomized controlled crossover study looking at the effect of plasma from multiparous blood donors on the development of TRALI. Intensive care patients anticipated to need at least 2 units of plasma were randomly assigned either to receive a unit of control plasma from a nonmultiparous donor and 4 hours later to receive a unit from a multiparous donor or to receive the 2 units of plasma in the reverse order. Five transfusion reactions were recorded in the 100 patients, four after transfusion of plasma from multiparous donors (1 diagnosed as typical TRALI). Detailed analysis of all recipients revealed that, after the transfusion of the multiparous plasma units, recipients had a significantly lower oxygen saturation and higher tumor necrosis factor α levels than after transfusion of control plasma. These differences were small but significant and considered to be physiologic signs of mild TRALI, leading the authors to conclude that plasma from multiparous blood donors may impair pulmonary function in intensive care unit patients more frequently than had been previously appreciated.

As recently reported by Rouger in an international forum, the French hemovigilance system, from 1995 onward, has recorded an average of 7 cases of TRALI a year.[125] Less than 10% of the cases were fatal. During this period, approximately 500,000 patients were transfused yearly, with an annual average of 2.3 million cellular blood products. In year 2000, only 1 case of TRALI was reported for the 195,390 platelets (almost all apheresis platelets) transfused that year.[7] In 1999 to 2000, the SHOT system had 19 cases of TRALI reported and 18 investigated.[10] There were 6 deaths reported among the cases, but only 1 was considered probably related to TRALI. (Three were possibly related, and 2 were unrelated). Most cases were associated with transfusion of a single type of component (eg, red cells or platelets). In the cases in which multiple component types were transfused, we attributed the case equally to each component type transfused. Based on this analysis, the 18 cases of TRALI were attributed as follows: 6 cases assigned to red cells, 6.5 to platelets, and 5.5 to plasma. For the year 2000 to 2001, 6 cases were reported attributed to red cell transfusions and 3 attributed to platelet transfusions.[11] Estimates of rates from these data use as denominators 2,354,487 red cells and 217,725 platelet transfusions. (These are 87% of the total number of units issued by the UK blood services because hospitals participating in SHOT received an estimated 87% of the issued blood components).

In 1999 and 2000, respectively, 11 and 9 adverse transfusion reactions reported to Health Canada were reported under the category of TRALI-like respiratory reactions. These cases appeared to be diagnosed based solely on clinical signs and symptoms, and no serological data were reported. Of the 7 definite and probable cases in 2000, 3 were associated with red cell transfusions, 1 with platelet transfusion, and 3 with plasma. Of the 9 probable cases reported in 1999, 5 were associated with red cell transfusions, 1 with platelet transfusion, 1 received both red cells and platelets, and 2 received only plasma. None of the cases from 1999 and 2000 were fatal.

In 1996 to 1998, 20 to 25 TRALI cases were reported annually to Health Canada. Of the 23 cases reported in 1998, 10 were associated with red cells, 8 with platelets, 1 with red cells and platelets, 1 with red cells and plasma, 2 with FFP, and 1 with an unknown component type. Using these data, the TRALI rate for both red cells and platelets would be significantly higher than that calculated from the 1999 to 2000 data. The higher number of TRALI cases in 1998 and preceding years is likely related to reports initiated by a single physician at one of the blood centers with a special interest in TRALI who left Canada in 1999.

In the international forum on TRALI mentioned

earlier, Goldman reported 3 possible severe TRALI reactions per year in Québec for the last 2 years for a total of 6 cases with 3.5 of these cases resulting from red cell transfusions.[125] She estimated that 190,000 red cell units were transfused annually in Québec. In the same forum, Freedman reported that at a single institution in Toronto with an annual transfusion volume of 12,000 units, there was an average of 1 case per year.

In 2000, 1 fatal case of TRALI associated with red cell transfusion was reported to the Québec hemovigilance system and 1 nonfatal case was reported associated with platelet transfusion.[3] We have noted slight differences between the data from the Québec hemovigilance system (2 cases) and those submitted by HQ to Health Canada in which 4 cases (3 considered related and 1 possibly related) were reported. These differences can be explained by the lack of full participation of Québec hospitals in the Québec hemovigilance system for the year 2000 and the difference in the reporting period.

Data summary and best estimate of current risk in Canada. The data summarized in Table 7 indicate that estimates for the rate of TRALI obtained from various data sources vary by 100-fold. The estimates of rates of TRALI from red cells and platelets derived from the Québec hemovigilance system (each based on only 1 reported case) are of the same order of magnitude as the rate that one calculates from the French hemovigilance and SHOT systems and from cases recently reported to Health Canada (if one makes assumptions about the denominators). However, these rates are all lower than those derived from the 3 specific studies cited in Table 7 performed in the 1980s and early 1990s.

The postulated mechanisms for TRALI indicate that the reaction is caused by plasma that is present in the transfused blood component. Red cells transfused in the 1980s, before the standardized use of additive storage solutions, were suspended in substantially more plasma than are current red cell concentrates. Therefore, if plasma volume influences the likelihood of TRALI developing, it would be reasonable to assume that the rate of TRALI from red cells transfused in 2000/2001 would be lower than the historical 1980s data would indicate.

In the absence of standardized definitions, standardized methods of case ascertainment, and a contemporary prospective study with a large number of recipients, it is therefore extremely difficult to select a point estimate for the rate of clinically significant TRALI in Canada. The best interpretation of the available data is that as the level of suspicion or vigilance increases, so does the recorded incidence. We believe that estimates from hemovigilance systems (including the Québec hemovigilance system) represent underestimates of the true rate of TRALI because of underrecognition and underreporting. We have therefore decided to base our best estimate on earlier (1998) Health Canada data collected at a time when we believe that vigilance for TRALI was greater, at least in 1 region of the country. The point estimates for TRALI risk calculated from these data are 1.4 per 100,000 red cell units and 10.2 per 100,000 platelet pools.

The problems of underrecognition and/or underreporting of TRALI are clearly illustrated by a personal communication that in the first 6 months of increased vigilance for adverse transfusion reactions 3 cases of TRALI have been reported at 1 hospital in Toronto (A Lima, 2001, oral communication). The issue of underreporting of TRALI is not unique to Canada and is clearly illustrated in a study by Kopko et al[126] in the United States through the use of a targeted lookback for recipients of plasma previously donated by a donor implicated (eg, antileukocyte antibody was shown in the donor's plasma) in a recent fatal case of TRALI. Of the 36 patient charts that could be reviewed, 15 recipients were found to have respiratory reactions after transfusion; 7 reactions were mild/moderate and 8 were severe. Only 7 of the reactions (5 mild/moderate and 2 severe) had been reported to the transfusion service, and only 2 (1 mild/moderate and 1 severe) were reported to the regional blood collection facility.

A report on an international forum on TRALI concluded that "the general opinion is that TRALI is significantly under-diagnosed."[125] Because of the lack of a uniformly applied set of criteria for a diagnosis of TRALI, cases may be misdiagnosed as volume overload or conversely, respiratory distress associated with other clinical conditions could be falsely attributed to transfusion. Furthermore, the randomized prospective study by Palfi et al[124] suggest that there is a spectrum of transfusion-induced lung injury ranging from physiologic effects that are not clinically identifiable, through

mild clinical effects, to severe clinically significant lung impairment, to death. It is likely that many mild cases of TRALI are not recognized.

Volume (Circulatory) Overload

Volume or circulatory overload is characterized by congestive heart failure and acute pulmonary edema and results from incapacity of the heart to adequately pump the additional blood volume through the circulation.

Incidence. Very few studies have measured or estimated the incidence of transfusion associated volume overload. The results of these and other sources of data are summarized in Table 8. In a retrospective study at 1 medical center, Popovsky and Taswell[127] found an incidence of 1 in 3,168 patients transfused with red cells for the 7-year period under review. After the initiation of a bedside consultation service at the same medical center, these investigators identified 26 cases in a 2-year period for a reaction rate of 1 in 708 patients receiving red cell transfusions. In 20% of the cases, a single unit of red cells was sufficient to precipitate acute respiratory distress, and in each of these 9 cases, there was an underlying cardiac or pulmonary disease. The mean age of patients with volume overload was 60.

A study of patients undergoing total hip or knee replacement suggested that transfusion associated volume overload is a common complication, at least in the elderly.[128] Four of 382 patients receiving transfusions developed transfusion-associated volume overload. The mean age was 87 years. It is of interest that 2 of the 4 received only autologous units. A recent study looking at the use of autologous and allogeneic blood in total hip or knee arthroplasty showed that volume overload occurred more frequently in patients receiving allogeneic transfusion than in patients who were not transfused (8% compared with 4% without transfusion).[129]

The French hemovigilance system reported 742 cases in the 6 years of reporting. Of these, there have been 27 deaths, which computes to a fatality rate of 3.6% if volume overload was the actual cause of death. For the year 2000, 167 cases were reported of the approximately 500,000 recipients who were transfused.[7]

Twenty-three cases of circulatory overload associated with the infusion of blood components were reported to the Québec hemovigilance system for the year 2000.[3] Of these, 20 cases received red cells and 1 received platelets (the other 2 cases received plasma). In the year 2000, there were approximately 47,343 recipients of red cells and 5,943 recipients of platelets at the hospitals participating in the Québec hemovigilance system.

Data summary and best estimate of current risk in Canada. The best way to express risk of volume overload is on a per recipient basis because the patient's underlying condition is the major determinant of whether the recipient will develop this particular adverse reaction to transfusion. The best estimate for risk in Canada is that estimated from the Québec hemovigilance data: 42.2 per 100,000 red cell recipients (95% CI: 25.8-65.3) and 16.8 per 100,000 platelet recipients (95% CI: 0.0-93.7). However, for the purposes of comparisons with the other risks presented in this review, we also express this risk on a per unit basis: 14.4 per 100,000 red blood cell units (95% CI: 0.0-22.5) and 6.5 per 100,000 platelet pools (95% CI: 0.0-34.9). Although it is difficult to verify the accuracy of the first year of data from the Québec hemovigilance

Table 8. Risks per 100,000 Recipients for Transfusion-Associated Volume (Circulatory) Overload

Study	Year	No. of Cases	Product	Rate/100,000 Recipients
Popovsky,[127] Mayo, US	1975-1982	(mean 2.75/yr)	Red cells	31.6
	1983-1984	26	Red cells	141
Audet,[128] MA	1992-1993	4	Red cells	1047*
Bierbaum,[129] US	1996-7	270	Total red cells	6220†
		150	autologous	5280†
		120	allogeneic	8000†
French Hemovigilance[7]	2000	167	Cellular components	33.4
QH[3]	2000	20	Red cells	42.2 (25.8-65.3)
		1	Platelet pools	16.8 (0.0-93.7)

*These were considered patients at higher risk (elderly, mean age, over 77 years).

†Recipients were elderly patients (mean age: 67 years) undergoing total hip or knee arthroplasty.

system, it is somewhat reassuring that the 95% confidence intervals for the rate of volume overload from the Québec hemovigilance system encompass the rate found in the French hemovigilance system.

These Canadian risk estimates are for all transfused patients irrespective of their underlying medical condition. As indicated by studies referenced in Table 8, the risk of volume overload may be as high as 1% to 8% of transfused recipients in susceptible patient groups, and this risk may occur even from low volume (eg, single unit) transfusions. There are no Canadian data that allow for calculation of risk in specific patient groups.

Posttransfusion Purpura

Posttransfusion purpura (PTP) is a rare syndrome characterized by sudden onset of severe, but usually self-limiting, thrombocytopenia usually occurring 5 to 10 days after transfusion. It is generally accepted that the reaction is caused by antiplatelet antibodies in the recipient that cause in vivo destruction not only of the donor platelets (antigen positive) but also of the recipient's own platelets (antigen negative).

Incidence. No prospective studies to determine the incidence of PTP have been performed, and there are no agreed on or routinely quoted estimates of risk. McFarland[130] notes that by 2001 there had been approximately 300 cases reported in the literature. She described a model to estimate the likelihood of PTP occurring (ie, 3% of North American whites do not express human platelet antigen-1a [HPA-1a] on their platelets and 28% of those are estimated to have the appropriate immune response gene to produce HPA-1a antibodies). With about half the population being women, half estimated to have been pregnant, and 4 million transfusion episodes/year in the United States, McFarland estimated that there could be 8,000 to 9,000 cases of PTP annually in the United States. She observed that this is far higher than the number of cases reported. One reason for this discrepancy may be that there are many mild cases (and perhaps some that are more severe) that are not recognized. However, it is more likely that because the exact causative mechanism of PTP is unknown, there may be other immune factors determining whether the presence of platelet antibodies will cause PTP in a person receiving antigen-positive platelets.

The number of cases of PTP reported to the SHOT system in the United Kingdom for the past 5 years (1996/97-2000/2001) has been 11, 9, 11, 6, and 3 per year, respectively, with only 1 death.[8-11] The authors of the SHOT reports believe there is not major underreporting of clinically recognized cases of PTP in the United Kingdom. To obtain a very approximate estimate of risk from these data, we averaged the number of cases from these 5 years (8 cases per year) and divided by 87% of the total number of red blood cell units (2.7 million) distributed in United Kingdom for each of the last 2 years (1999-2001). We estimated that the cases reported in United Kingdom represented a risk of 0.34 per 100,000 units of red cells.

Since 1993, there have been no cases of PTP reported to Health Canada. In the year 2000, 1 case was reported to the Québec hemovigilance system for a rate of 0.7 per 100,000 red cell units (95% CI: 0.0-4.1).[3]

Data summary and best estimate of current risk in Canada. Based on the 1 case reported to Québec hemovigilance for the year 2000, our best risk estimate for PTP is 0.7 cases of PTP per 100,000 units. Obviously, the confidence intervals on this estimate are very wide. This estimate is consistent with the estimate calculated from the SHOT data (0.34 cases per 100,000 units). However, it is far smaller than the approximately 70 cases per 100,000 units that would be derived if McFarland's mathematical model were applied to Canada. Even though there may be significant underrecognition and underreporting of cases in Canada, the experience in other countries (the United States, France, and the United Kingdom where the reported cases have also been orders of magnitude lower than the modeling predicts) indicates that the model should not be considered an accurate predictor of risk.

Transfusion-Associated Graft-Versus-Host Disease

Transfusion-associated graft-versus-host disease (TA-GVHD) manifests as a complex of symptoms including fever, skin rash, diarrhea, liver dysfunction, and bone marrow failure typically occurring 7 to 10 days after transfusion.[131] The condition is considered to be 90% fatal and not responsive to immunosuppressive therapy. The cause is the engraftment of donor lymphocytes, their proliferation, reaction to, and destruction of host (recipient) tissues.

For TA-GVHD to develop, there are 3 necessary conditions[132]: (1) differences in HLA antigens between donor and recipient, (2) presence of immunocompetent cells in the graft, and (3) inability of the host to reject the immunocompetent donor cells.

A recipient may not be able to reject lymphocytes that are HLA distinct (different), if he/she is severely immunocompromised or if he/she is immunocompetent but receiving a transfusion from a donor who is homozygous for major HLA antigens for which he/she is heterozygous. In this latter case, the recipient cannot recognize the donor cells as foreign, but the donor cells do recognize the recipient cells as foreign. The likelihood that this will occur varies dramatically depending on the source of the donated blood. For recipients of directed donations from first- or second-degree relatives, in which the chances of shared haplotypes is high, the risk of TA-GVHD is much higher than for recipients receiving unrelated allogeneic blood. The level of risk in this latter situation can be computed by considering the heterogeneity of a given population for HLA antigens. Most of the case reports of TA-GVHD in this category are from Japan where the population is relatively less heterogeneous.[133]

The recognition that severely immunocompromised patients are at increased risk for TA-GVHD led to the implementation of preventative measures (ie, when these patients are to be transfused, the components are irradiated with 25 Gy gamma radiation). Because no breakthrough cases have been described using this technique, it is assumed to be effective at preventing donor lymphocytes from engrafting and/or reacting against the recipient's tissues. In addition, because recipients of directed donations from first- or second-degree relatives are considered to be at high risk, such donations are irradiated in Canada and in many other countries.

Incidence. The literature contains individual case reports and summaries of reported cases, but no incidence data have been reported from any country.[134] Various authors have published estimates of the probability of shared HLA haplotypes between individuals within different countries. Using data derived from serologic HLA typing techniques, Ohto et al[135] estimated the likelihood of a recipient receiving a unit from a donor homozygous for a shared HLA haplotype in Canadian whites (and being at risk of GVHD) to be 1 in 154 in parent-to-child directed donations and 1 in 1,664 in unrelated allogeneic transfusions. Another similar independent estimate of 1 in 185 in Canadian whites for directed donations from first- and second-degree relatives has been quoted by Hume and Preiksaitis.[136]

Wagner and Flegel[137] estimated the likelihood of a shared haplotype in different populations using data from more sensitive DNA-based, high-resolution HLA typing. These estimates are the most commonly quoted in the literature. Their risk estimate for Canadian whites of 1 in 2,893 to 1 in 21,157 is considerably higher than their estimate for US whites (1 in 17,682 to 1 in 39,034) but lower than their estimate for Japan (1 in 1,612 to 1 in 7,981).

Yasuura et al[138] reported in 2000 on a retrospective review of patients having undergone cardiac surgery at a hospital in Japan. They showed an incidence of 1 in 212 (4 cases in 847 patients) of TA-GVHD in recipients of fresh (less than seven days old) allogeneic blood from unrelated donors and noted that this is equivalent to the incidence estimated from haplotype frequencies in Japan. This and the observation that a high proportion of the case reports of TA-GVHD in the literature are from Japan support the general principle that the less diverse the racial backgrounds of donors and recipients the higher the risk of TA-GVHD.

A more recent report by Roshansky et al[139] showed that to cause TA-GVHD, donors need to be homozygous for HLA class I antigens but could be heterozygous for class II antigens. The authors claimed "the theoretical chances of TA-GVHD in immunocompetent patients may be greater than calculated on the basis of homozygous HLA haplotypes in the population." These authors estimate an incidence of 1 in 2,000 of shared class I HLA haplotypes in the United States but note that this is much higher than the number of reported TA-GVHD cases.

For the most recent year of published data, no cases of TA-GVHD have been reported to the French hemovigilance system, and only 1 case has been reported to SHOT. There were 4 cases of TA-GVHD reported to SHOT annually for each of the first 3 years of the program (1996-1999).[8-11] All 12 cases were fatal. Eight cases had some degree of immunocompromise (5 cases had B-cell malignancy, 2 had congenital/acquired immunodeficiency, and 1 had an autoimmune condition),

whereas 4 cases were not considered to be immunocompromised; 3 of the latter were cardiac surgical patients, who are considered by some authors to be at increased risk. None of the 12 patients had received irradiated components because none of the patient's clinical diagnoses fulfilled the criteria in use at the time for provision of irradiated components. One case received leukocyte-reduced units.

There have only been 2 cases of TA-GVHD reported to Health Canada since 1992. However, a report of 2 fatal cases of TA-GVHD at 1 hospital in Alberta was presented at a Canadian Society of Transfusion Medicine meeting in 2000. To our knowledge, at least 1 and possibly both of these cases were not reported to Health Canada. Both cases were in young infants; 1 infant was on chemotherapy, whereas the other was only 2 days old and was retrospectively diagnosed with an immunodeficiency syndrome. Both were transfused with nonirradiated components.[140] No cases of TA-GVHD were reported to Québec hemovigilance system in the year 2000.

Data summary and best estimate of current risk in Canada. Because persons in the 2 highest risk groups (highly immunocompromised and patients receiving directed donations from close relatives) are well identified and because irradiation is effective at preventing TA-GVHD, irradiation is the standard of practice in Canada for blood transfusions to these 2 groups. Based on this practice, we conclude that the risk is close to zero in these groups. However, there are 3 reasons why cases could still occur:

1. There is no universal agreement on all conditions that lead to the level of immunocompromise that puts recipients at high risk of TA-GVHD (and hence to be identified as needing irradiated units).[141] This explains many cases reported to the SHOT system in the United Kingdom in previous years.
2. Patients may not yet be diagnosed with conditions that cause immunosuppression. This appears to be the reason for at least 2 cases in young infants in Canada.
3. Procedural errors may occur such that a high-risk recipient will get an unirradiated unit by mistake. Although this type of error has been documented, it has not, to our knowledge, been the cause of any of the recently reported cases.[10]

Risk is considered very low for immunocompetent recipients receiving transfusions from unrelated donors. Modeling to estimate the magnitude of this risk in the Canadian population estimated the risk to be between 1 in 2,893 and 1 in 21,157. Even the minimum estimate of risk using this mathematical model is much higher than the number of cases that have been reported. Possible reasons for this include:

1. Serious underreporting and/or underrecognition of the disease because of comorbidity, late onset, or the similarity of the symptoms to other conditions (drug reactions and viral infections). Because the disease is 90% fatal, it seems unlikely that many cases would go unrecognized. However, it is possible that cases are not reported.
2. The more likely explanation is that lymphocytes in the transfused unit(s) are no longer viable or capable of mounting an immune response in the recipient (ie, much of the blood transfused is greater than 7 days old, and the lymphocytes are no longer able to engraft, be stimulated, and mount an immune response). This hypothesis is supported by (1) most case reports note that the blood was fresh, (2) Yasuura et al's data[138] showed all cases in their study were recipients of blood that was stored for less than 7 days, and (3) experimental data showing that leukocytes in units stored greater than 5 days have lost their capacity to be stimulated in mixed lymphocyte cultures.[142,143]
3. Leukoreduction may decrease the risk of TA-GVHD by decreasing the number of immunocompetent lymphocytes so that there are insufficient numbers to mount an immune response. While possibly decreasing the risk, leukoreduction does not prevent the development of TA-GVHD. There are reports of three cases of TA-GVHD in recipients of leukoreduced blood.[10,144,145]
4. The multiracial nature of the Canadian population (donors and recipients) was not taken into consideration when the mathematical model was applied. Hence, the risk estimate from modeling is likely to overestimate actual risk.

Therefore, the best estimate for recipients in Canada developing TA-GVHD is based on observed and reported clinical cases. This risk is considered

Table 9. Risks of Clinically Symptomatic Adverse Noninfectious Reactions Associated With the Transfusion of Cellular Blood Components in Canada

	Risk of Reaction per 100,000 Units		Source of Data		Predicted Annual No. of Cases†		
Type of reaction	RBCs	Platelet Pools	Primary	Corroborative*	RBCs	Platelet	Total
AHTR	7.9 (0.0-14.3)‡		QH	Lit	62	≪1	62
		Ext low	Lit	HC			
DHTR	10.8 (0.0-18.1)‡		QH	Lit	84	≈1	85
		Low	HC	QH			
FNHTR	200		Lit	QH	1,560	4,690	6,250
		6,700	Lit				
Allergic minor	400		Lit		3,120	2,870	5,990
		4,100	Lit				
Allergic major	4.3 (0.0-9.6)‡		QH		34	44	78
		62.6 (30-115.1)‡	QH				
TRALI	1.4		HC	QH	11	8	19
		12.1	HC	QH			
Volume overload	14.4 (0.0-22.5)‡		QH	French HV	112	4	116
		6.3 (0.0-34.9)‡	QH				
PTP	0.7 (0.0-4.1)‡	None	QH	SHOT	5	0	5
GVHD	Low or ext low	Low or ext low	Lit	HC			<1

NOTE. For many risks, data were insufficient to make quantitative estimates. In these cases, risk categories were assigned as follows: low, estimated as greater than one per million (0.1 per 100,000); ext low, extremely low: estimated as less than 1 per million (0.1 per 100,000).

Abbreviations: AHTR, acute hemolytic transfusion reaction; DHTR; delayed hemolytic transfusion reaction; FNHTR, febrile nonhemolytic transfusion reaction; GVHD, graft-versus-host disease; PTP, posttransfusion purpura; TRALI, transfusion-related acute lung injury.

QH Québec hemovigilance system; CBS, Canadian Blood Services; HC, Health Canada; Lit, International and Canadian medical literature; SHOT, Serious Hazards of Transfusion; French HV, French hemovigilance system.

*Data sources that provide additional corroborative information. These do not necessarily provide the same point estimate but support that the estimate in the table is of the right order of magnitude.

†Based on 780,000 annual red cells transfused and 70,000 platelet pools: apheresis platelets are not included in this calculation.

‡Confidence intervals are given when data are derived from the Québec hemovigilance system.

to be very low, probably less than 1 per million units transfused.

SUMMARY OF RISKS OF TRANSFUSION IN CANADA

The risks of clinically symptomatic noninfectious and infectious adverse reactions in Canada are summarized in Tables 9 (non-infectious risks) and 10 (infectious risks). The far right-hand columns of these tables project the annual number of cases of each reaction that are expected to occur in Canada assuming 780,000 red cell units and 350,000 platelets (70,000 platelet pools) are transfused annually.

The noninfectious risk estimates in this review were taken either from the published literature or from direct data sources that we reviewed. Our direct data source estimates for many adverse reactions (eg, hemolytic reactions, major allergic reactions, and volume overload) tended to be at the high end or higher than published risk estimates. The 1 major exception was the risk of TRALI, where most experts agree that all available estimates probably underestimate its actual occurrence, especially if mild cases are considered.

The HIV, HCV, and HBV risk estimates have been generated by mathematical modeling.[19,20] The incidence/window-period model used to generate these estimates has been widely used in various countries in the last decade and has been partially validated by its demonstrated ability to predict the yield of newly introduced assays.[20] The input data for our estimates were obtained from CBS and then generalized to all of Canada; a comparison of infectious disease marker rates between CBS and HQ suggests that this does not introduce any major inaccuracies.

It was not possible to generate quantitative risk estimates for most of the infectious agents in Table 10. Based on our review of the literature and its relevance to Canadian geography and transfusion practice, we have classified many of these agents

Table 10. Risk of Transfusion-Transmitted Infection and Resultant Clinical Symptoms or Chronicity Associated With the Transfusion of Cellular Blood Components in Canada

	Risk per 100,000 Units			Predicted Annual No. of Cases of Clinically Significant Disease[a]		
Type of Reaction	Risk of Infection[b]	Risk of Acute Clinically Symptomatic Infection[c]	Risk of Chronicity[d]	RBCs	Platelet	Total
Bacterial infection-platelets[e]	5.9-21[f,g]	2.5-8.8[g]	None	NA	9-31[g]	
Bacterial infection-RBCS	Unk[h]	0.7-3.6[g]	None	6-28[g]	NA	15-59[g]
HBV	3.2[i]	1.6[j]	0.08	0.62	0.28	0.90
HCV	0.032[i]	Virt N/E	0.014	0.1	0.05	0.15
HIV	0.021[i]	Virt N/E	0.012	0.09	0.04	0.13
Malaria[k]	0.025	0.025	None	0.20	≪1	0.20
Babesiosis	Ext low	Ext low	None			≪ 1
Chagas disease	Ext low	Ext low	Unk[l]			≪ 1
HAV	Ext low	Ext low	None			≪ 1
Parvo B19	Unk[m]	Ext low	None			≪ 1
Ehrlichiosis	Ext low	Ext low	Ext low			≪ 1
Non A-E hepatitis	Probably N/E	Probably N/E	Probably N/E			≪ 1
SENV	Common	Probably N/E[n]	Probably N/E[n]			≪ 1
CMV[p]	Unk:dependent on patient group and type of blood product					Unk[o]
HTLV I-II	Virt N/E	Virt N/E	Virt N/E			None
Syphilis	Virt N/E	Virt N/E	Virt N/E			None
HHV-8	Theor; virt N/E	Theor; virt N/E	Theor; virt N/E			None
CJD	Theor; virt N/E	Theor; virt N/E	Theor; virt N/E			None
vCJD	Theor	Theor	Theor			None
Lyme disease	Theor	Theor	Theor			None
GBV-C	Common	None	None[p]			None
TTV	Common	None	None[p]			None

NOTE. For many agents, data were insufficient to make quantitative estimates. In these cases, risk categories were assigned as follows: Common, risk probably above 1%; Low, estimated as greater than 1 per million (0.1 per 100,000); Ext low, extremely low: estimated as less than 1 per million (<0.1 per 100,000); probably N/E, probably nonexistent: data are incomplete but existing data suggest that the phenomenon does not occur; virt N/E, virtually non-existent: although an extremely low risk might exist, Canadian transfusion practices should virtually eliminate this risk; Theor, theoretical: transfusion transmission has never been documented but is theoretically possible; None, available data allow a conclusion of no (zero) risk.

Abbreviations: Unk, unknown (no data available or data not interpretable); NA, not applicable.

[a]Based on 780,000 annual red cells transfused and 350,000 platelets in 70,000 platelet pools: apheresis platelets are not included in this calculation.

[b]Includes asymptomatic and symptomatic infections.

[c]Symptomatic infection only.

[d]Chronicity (chronic carrier state with potential for disease) is calculated based on the assumption that 50% of recipients do not survive long enough to develop chronic effects. Of surviving recipients, 100% of those infected with HIV, 80% of those infected with HCV, and 5% of those infected with HBV are estimated to become chronic carriers.

[e]The estimate in this table is given per 100,000 platelets so as to be comparable to other agents in the table. Note that the estimate given in table 1 and in the text is per 100,000 platelet pools and is therefore five fold higher.

[f]This is a calculated number for all (symptomatic and asymptomatic) TTBI from platelet pools. The adjustment, based on data from Yomtovian et al showing that only 42% of platelet associated TTBI cases were symptomatic, has been applied to the symptomatic reactions detected in the QH system.

[g]Estimate is a range based on probable and definite cases.

[h]There are no data to calculate the number of asymptomatic bacterial infections from red cell transfusions.

[i]Determined from the incidence/window period model using 1998-1999 CBS data as the primary data source.

[j]Based on 50% of HBV infections resulting in symptoms.

[k]Estimate is for risk from red cells. Risk from platelets is much lower.

[l]A chronic carrier phase of Chagas exists, but has not been reported for transfusion-transmitted infection.

[m]No systematic studies of transfusion-transmitted parvovirus B19 infection have been performed and thus asymtomatic transmissions cannot be ruled out.

[n]To date, data have shown no acute symptoms or chronic disease with SEN-V infection. More data need to be accumulated to completely rule out these possible outcomes.

[o]CMV infections may occur at an unknown rate (perhaps as much as 1% per recipient, depending on underlying diagnosis) in recipients of leukoreduced, products who do not receive CMV seronegative units. However, clinically significant disease is not expected to occur in these groups. For immunosuppressed patient groups in which clinically significant disease could occur, transfusions are with leukodepleted, CMV seronegative units. Therefore, the annual number of cases of clinically significant disease should be extremely low. Although CMV can produce chronic latent infection, the risk of clinically significant disease because of reactivation is thought to be extremely low. See text for further details.

[p]Although the chronic carrier state for these agents has been documented, it is not known to cause any disease.

Table 11. Overall Risks and Expected Annual Number of Clinically Symptomatic Adverse Transfusion Reactions in Canada*

	Red cells		Platelets		Total
	Per 100,000 Units (95%CI)	Expected No. of Cases per Year	Per 100,000 Pools (95%CI)	Expected No. of Cases per Year	Expected No. of Cases per Year
All reactions	643.2 (625.6-661.2)	5,017	10,925.7 (10,695.5-11,159.2)	7,648	12,665
Potentially severe reactions					
All†	43.2 (38.7-48.1)	337	125.7 (100.8-154.9)	88	425
Infectious	3.7 (0.0-5.3)	29	44.3 (30.1-62.9)	31	60
Non infectious	39.5 (35.2-44.2)	308	81.4 (61.7-105.5)	57	365

*Excludes reactions after transfusion of apheresis platelets because of the lack of data for several types of potentially severe adverse reactions and the relatively small fraction (approximately 15% in 2000) of platelet transfusion doses supplied by platelet apheresis.

†These estimates were calculated by taking the higher of the 2 risk estimates for bacterial infection (see text). If the lower risk estimates are used, the aggregate risk estimates for all potentially severe reactions do not change significantly. The rate for red cells would be 40.4 per 100,000 units (95%CI: 36.1-45.1) and for platelets would be 94.3 per 100,000 platelet pools (95%CI: 72.9-119.9).

as having extremely low risk, defined as a risk of less than 1 per million transfused units. For some agents with extremely low risk, the risk is probably even much lower. Other agents are classified as having a risk that is virtually nonexistent (based on interventions in Canada that lower the risk) or theoretical but not proven.

Using the data from Tables 9 and 10, it is possible to generate an overall estimate for transfusion risk in Canada. This estimate is presented in Table 11 in the following ways: (1) for all clinically symptomatic transfusion reactions and (2) for noninfectious, infectious, and all reactions with the potential for severe outcomes (this excludes FNHTRs and minor allergic reactions). Note that not all adverse events tabulated as potentially severe reactions will result in such severe outcomes.

Given the risks presented in Table 11, a total of 12,665 adverse transfusion reactions per year would be expected to occur in Canada related to the transfusion of red cells and whole-blood–derived platelets; of these, 425 would have the potential for a severe clinical outcome. Although the rate of potentially severe reactions is 2.9-fold higher for platelet pools than for red cells (125.7 per 100,000 platelet pools *v* 43.2 per 100,000 red cells), the relative rates are reversed if the platelet risk is expressed on a per unit rather than a per platelet pool basis (25.1 per 100,000 individual platelet units vs 43.2 per 100,000 red cells; ratio of 0.58). This greater per unit risk for red cells and the larger amount of red cell units transfused explain why 79% (337 of 425) of the potentially severe reactions are associated with red cell transfusion.

For platelet transfusions, the 2 reaction categories with the highest rates are minor allergic reactions and FNHTRs. Both of these reactions, although frequent, are of limited clinical significance to the patient. Major allergic reactions and bacterial infection are the next most common reactions to platelets with, respectively, 44 and 9 to 31 recipients projected to be affected annually in Canada. These reactions may cause severe outcomes, including death, in some affected recipients. TRALI, GVHD, and hemolytic transfusion reactions from passively transfused antibody in platelet products are rare.

For red cells, minor allergic reactions and FNHTRs are also the 2 most frequent reactions. The next most common is volume overload, with 112 cases projected. This projection is highly dependent on the characteristics of the recipient population, and such data on recipient susceptibility are lacking. Delayed and acute hemolytic reactions with, respectively, 84 and 62 annual expected cases are the next most common reactions to red cells. If the 2 categories of hemolytic reactions are aggregated, then 146 cases of clinical transfusion reactions because of red cell incompatibility would be expected, making this the most prominent category of potentially severe outcomes associated with red cell transfusion. All 3 of these reaction categories (volume overload, acute hemolytic, and delayed hemolytic) can be lethal.

Several risks are higher with pooled platelet transfusions than with red cells: the risk of FNHTR is 34-fold greater, the risk of major allergic reaction is 15-fold greater, and the risk of bacterial infection is approximately 12- to 19-fold higher. However, if the platelet risk were to be expressed

on a per platelet basis (rather than for a pool of 5 platelets), then the difference in rates narrows.

There are only 2 transfusion-transmitted infectious agents (bacteria and HBV) that carry a risk to Canadian transfusion recipients of greater than 0.1 per 100,000 transfused units (ie, a risk greater than 1 in a million). The risk of symptomatic transfusion reactions because of bacterial contamination may be as high as 13 to 44 per 100,000 transfused platelet pools and 0.7 to 3.6 per 100,000 transfused red cells. However, many of these reactions are predicted to result only in mild symptoms. Furthermore, it is highly probable that an even larger number of recipients is transfused with bacterially infected platelet units without developing any reported symptoms. In the case of HBV, the risk of transfusion-transmitted infection (approximately 3.2 symptomatic and asymptomatic cases per 100,000 units) is estimated to be 40-fold higher than the risk of chronic HBV infection (approximately 0.08 per 100,000 units). We project that approximately 1 clinically significant case of HBV transmission will occur annually.

The current risk of transfusion transmission of the 2 viruses (HIV and HCV) of most concern to the public is approximately 1 in 4 million transfused units for HIV and 1 in 3 million transfused units for HCV. We project that a clinically significant case of transfusion-transmitted HIV would occur once in 7 to 8 years, and a clinically significant case of HCV would occur once in 6 to 7 years. Despite this low level of risk, concern about transmission of these agents is understandable because long-term, potentially lethal, chronic sequelae may occur in recipients transfused at a young age who have a good disease prognosis. An additional concern is the potential for secondary transmission of infection from the transfusion recipient to other individuals.

With regard to transfusion transmission of agents such as malaria, babesiosis, or Chagas disease, it is possible that clinical cases may go unrecognized under current systems for monitoring and reporting of adverse transfusion outcomes. Furthermore, lack of recognition or underreporting might also limit the identification of clinical cases that might result from a new infectious agent entering the blood supply.

The best available current data indicate that some infectious transfusion risks in Canada approach zero (HTLV, syphilis, non–A-E hepatitis), whereas other risks are theoretical (CJD, vCJD, HHV-8, Lyme). Finally, although there are newly discovered viruses (GBV-C, TTV) that are frequently transmitted by transfusion, careful study has not shown any disease associated with these agents and they are of no apparent risk to transfusion recipients.

Comparison to Other Sources of Data on Transfusion Risks

Our risk estimate for reactions with potential for severe outcomes can be compared with a similar type of aggregate estimate provided in a 1997 US publication by the Government Accounting Office (GAO).[146] One significant difference between these 2 studies is our ability to access primary data sources (hemovigilance systems from Québec, France, and the United Kingdom as well as adverse reaction reporting to the blood operators and Health Canada) to estimate the noninfectious risks of transfusion. These sources were unavailable to the GAO report authors who instead relied on review articles in the medical literature.

The aggregate risk estimate for potentially severe reactions provided in the GAO report was 80 per 100,000, which was comprised of an estimate for infectious risks of 50 per 100,000 transfused units and an estimate for noninfectious risks (which included the following 4 risks: ABO incompatibility, TRALI, volume overload, and anaphylaxis) of 30 per 100,000. This can be compared with our lower risk estimate of 43.2 per 100,000 for potentially severe reactions because of red cell transfusion and 25 per 100,000 for individual platelet units (125.7 per 100,000 platelet pools). Our estimate for noninfectious risks, which included the additional categories of major allergic reactions, all acute hemolytic reactions (not just those caused by ABO incompatibility), delayed hemolytic reactions, PTP, and GVHD, was 39.5 per 100,000 red cell units, which was somewhat higher than the GAO estimate of 30 per 100,000. The major difference in the risk estimates between the GAO report and the estimates in our review is for infectious risks; the GAO estimate was 50 per 100,000 transfused units as compared with our estimate of 3.7 per 100,000 transfused red cell units. Our lower infectious risk estimate is partly a reflection of improved testing for HCV and HIV and partly a consequence of the methodology used by the GAO authors. When multiple estimates of a

transfusion risk were available, the GAO authors chose the highest estimate to construct a worst-case scenario; this resulted in their choice of a very high-risk estimate for HCV (data in the last 5 years have shown this to be incorrect), which affected their overall infectious risk estimate.

Fatalities From Transfusion in Canada

From 1993 to 2000, there were 1 to 5 transfusion-related fatalities per year (mean of 2.5) reported to Health Canada. In addition, there were 1 to 4 fatalities per year that were reported in association with transfusion but which, when assessed, were found not to be related to transfusion. In 2000, 8 deaths after transfusion were reported to Health Canada, of which 4 were assessed to be transfusion-related. These 4 transfusion-related deaths were all from Québec and were also captured by the Québec hemovigilance system. Three of these were after the transfusion of red cells (1 AHTR because of an ABO error, 1 AHTR not related to an ABO error, and 1 DHTR) for a rate of 2.2 per 100,000 units (95% CI: 0.0-6.4), and one was after platelet transfusion (bacterial sepsis) for a rate of 6.3 per 100,000 platelet pools (95% CI: 0.0-34.9).[3]

Although possible, it is unlikely that there were zero transfusion-related deaths in the rest of Canada in 2000. The most likely conclusion from these year 2000 data is that, even for transfusion associated deaths, there is underreporting by hospitals outside of Québec to CBS and therefore to Health Canada.

Comparison to Other Sources of Data on Fatal Outcomes From Transfusion

The most current reported rates of death caused by acute hemolytic transfusion reactions are much lower than the 1 in 69,300 red cell units from the Québec hemovigilance system. In the 1940s to the 1970s, rates varied from 1 in 915 to 1 in 33,500 units. In the 1980s and 1990s, they varied from 1 in 230,000 to 1 in 800,000 units.[1] With regard to fatalities related to ABO errors, the most current published figure of 1 in 1,800,000 red cell units for the period 1990 to 1999 in New York State[96] is 13-fold lower than the rate of 1 in 138,000 from the Québec hemovigilance system. The reasons for such a discrepancy are unknown. It is probably a combination of differences in reporting systems, differences in underreporting rates, and the fact that estimates from the Québec hemovigilance system are based on only 1 year of data.

The fatality rate from platelet-induced sepsis of 6.3 per 100,000 platelet pools is very similar to that reported from an observational study done at a large US hospital but higher than that reported from other surveillance systems in France and the United States.[81,85,86]

In a review of 355 deaths reported to the US Food and Drug Administration from 1976 to 1985 done by Sazama,[147] 148 (44.5%) transfusion-related deaths were because of acute hemolytic reactions, 26 (7.3%) were because of delayed hemolytic reactions, and 26 because of bacterial contamination (7.3%). Other causes included non-A, non-B hepatitis (11.8%), acute pulmonary edema (8.7%), and hepatitis B (7.3%). Although the data from the Québec hemovigilance system are thus far very limited, it is of interest that the relative frequency of causes of death is consistent with the major categories reported to the FDA.

Use of Québec Hemovigilance System Data as the Basis of Many Noninfectious Risk Estimates

The data used for many of the estimates of noninfectious risks in this review have been taken from the Québec hemovigilance system during its first year of implementation and generalized to the rest of Canada.[3] There are several reasons why such projections should be valid. In most cases, estimates from the Québec hemovigilance system data are similar to those reported in the literature from carefully performed focused prospective or retrospective studies or similar to those extrapolated from data collected by other surveillance systems (France and the United Kingdom). Although this similarity in findings does not ensure accuracy, it suggests that the Québec hemovigilance system captures adverse effects of transfusion better than any other mechanism currently in place in Canada. In addition, given that transfusion practices are not systematically different in Québec than in the rest of Canada, there is no reason to believe that adverse transfusion reactions would be expected to occur at any greater frequency in Québec. Nevertheless, the precision of some of the risk estimates generated from these data is limited (and hence the confidence intervals are wide) for 2 reasons. Firstly, there are a relatively small number of observed adverse outcomes in this system for some of the rarer types of transfusion reactions and

for lethal events. Secondly, the system has tracked the outcomes of only a relatively small number of units (138,605 red cells and 15,975 platelet pools).

The data from Québec hemovigilance system cited in this review were collected in a startup phase of the system in which reporting is highly likely to be incomplete. Most surveillance systems report a greater incidence of events after the system is operational for several years. Despite the fact that a number of smaller Québec hospitals did not participate in the Québec hemovigilance system in the year 2000, the system captured data from hospitals transfusing approximately 80% of components in Québec. Although the outcomes of the remaining 20% of transfusions given in nonparticipating hospitals could not be tracked, it is unlikely that reaction rates will be substantially different when these hospitals become part of the reporting system.

Another limitation of these initial Québec hemovigilance system data is the inability to verify the accuracy of reporting with regard to recording of symptoms, appropriate classification of reactions, and linkage of symptoms with transfusion. This limitation is somewhat mitigated by the careful review of all transfusion reaction reports (with the exception of many FNHTR and minor allergic reactions) by a physician at the Québec Public Health Institute who was able to adjust the reaction classifications if an inappropriate assessment had been made by the reporting hospital.

Anticipated Changes in Transfusion Risk in the Future

Multiple factors including changes in the risks associated with the biological properties of blood components, the characteristics and susceptibility of transfused recipients, and modifications in transfusion practice may influence whether these current risk estimates will apply in future years. This can be shown by observing how risk has changed in the recent past. Over the last 2 decades, there has been a major decrease in the risk of transfusion-transmitted viral infections, whereas the risk of other serious and potentially fatal outcomes of transfusion (e.g. AHTR, DHTR, TRALI, bacterial infection) has not appeared to significantly decrease.

Recent experience has also shown that new or emerging pathogens are continually being identified.[16] Occasionally, these agents have been introduced into the blood supply, and, when that happens, the risk of transfusion may increase significantly, as was the case with HIV. It is not possible to predict if such a scenario will recur.

Currently, a great deal of attention is being focused on identifying errors in the transfusion process. It is possible that this increased attention will lead to improvements (eg, increased computerization by blood operators and hospital transfusion services, application of blood standards in hospital transfusion services, and of quality management systems throughout the hospital) that will reduce risk.[1]

In the area of infectious disease, laboratory testing methods not currently used in Canada for detection of bacterial contamination and detection of HBV infection (eg, HBsAg assays with enhanced sensitivity, minipool HBV NAT, and anti-HBc assays) are available or in development and the feasibility and desirability of their implementation will need to be assessed.[27,148]

The development of newer types of blood products (pathogen inactivated platelets or red cells, oxygen carrying substitutes, red cells rendered nonimmunogenic either by stripping off A or B antigens or by masking [blocking] multiple red cell antigens) may reduce some of the known risks of transfusion.[149-152] However, it must be recognized that other, as yet unquantifiable, risks could be introduced by the use of such products (eg, allergic reactions to the added chemical agent, unanticipated toxic reactions, and so on). If such risks are rare, long term, or specific to certain groups of susceptible recipients, it is unlikely that they would be detected in clinical trials. It will require close observation of large numbers of transfused recipients to detect whether new unanticipated risks are introduced.

Interpretation of Risk in the Context of Benefit

This review has assessed risk without consideration of the benefits that result from transfusion. The decision to transfuse must balance the risks of transfusion against the benefits and must do so in the context of the particular clinical situation involving the particular patient. The classification of risk presented in this review may make it easier for physicians (and patients) to assess the risk to an individual patient by recognizing that some risks are inherent to the blood itself, whereas others are highly dependent on recipient susceptibility factors. This risk information then can be interpreted in light of the potential benefits for that particular

patient and whether there are any alternative treatments that would have a better risk-benefit ratio. Furthermore, by providing an accurate assessment of the risks of clinically significant adverse outcomes from transfusion of cellular blood products in Canada in 2000 and beyond, this review may serve as a useful resource for policy makers who are considering the pros and cons of introducing further measures to decrease the risks of transfusion.

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