

REVIEW ARTICLE

The Relative Safety of Pooled Whole-Blood-Derived Platelets Prepared by the Buffy-Coat Method Versus Single-Donor (Apheresis) Platelets

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SUMMARY

Conversion to a single-donor (apheresis) platelet inventory in Western Europe and other countries that provide similar health care to the US but rely on buffy-coat pooled whole-blood-derived platelets will confer the benefit of a ≥ 2 -fold reduction in the risk of all emerging transfusion-transmitted infections (TTIs). In Europe, this benefit will include a ≥ 2 -fold reduction in the risk of acquiring variant Creutzfeldt-Jakob disease (vCJD) from platelet transfusion. In countries that use buffy coats from first-time donors to produce platelet pools, there will also be a ≥ 2 -fold reduction in the risk of human immunodeficiency virus, hepatitis B virus, and hepatitis C virus infections. Conversion to a single-donor inventory collected from male donors (or female donors without a history of pregnancy or shown not to have white-blood-cell antibodies) should also reduce the risk of transfusion-related acute lung injury, although this prediction is based on theory and may not materialize or prove hard to document. Because conversion to a single-donor inventory can effect a ≥ 2 -fold reduction in the risk of all TTIs without incurring any risk, it is a more advantageous risk-reduction strategy for emerging TTIs compared with the introduction of pathogen-reduction systems for platelets. The latter cannot protect from vCJD and potentially also from some other emerging TTIs; moreover, they have recently been associated with an increased risk of bleeding. (Clin. Lab. 2010;56:263-279)

INTRODUCTION

To procure a platelet dose that could have been collected from a single plateletapheresis donor, pooled whole-blood-derived (PWBD) platelets pool donations from 4 to 6 whole-blood donors—each one of whom could be a source of a transfusion-transmitted infection (TTI). The relative safety of PWBD platelets prepared by the platelet-rich plasma (PRP) method versus single-donor (apheresis) platelets transfused in the US was recently reviewed¹. The conclusions of that review¹ may not pertain to countries other than the US where PWBD platelets prepared by the buffy-coat (rather than PRP) method are used².

PRP and buffy-coat pooled platelets differ, as emphasized by the recent meta-analysis¹ which identified one clinically-important difference between them: only the PRP (as opposed to the buffy-coat) PWBD platelets were associated with a higher (5.6-fold; $p < 0.05$) risk of transfusion-associated sepsis (TAS)—most likely secondary to bacteria contaminating the collected compo-

nent from the donor's skin during venipuncture. Since PWBD platelets, whether prepared by the PRP or the buffy-coat method, involve 4 to 6 (or more) venipunctures—compared to 1 venipuncture for single-donor platelets—we would expect both types of pooled platelet components to be associated with an approximately 5-fold increase in the risk of TAS compared with apheresis platelets. However, the meta-analysis (conducted separately for PRP or buffy-coat platelets collected in the US or Europe and integrating the odds ratios [ORs] of bacterial contamination in PWBD versus single-donor platelets) did not find an increase in the odds of bacterial contamination of buffy-coat PWBD versus apheresis platelets¹. A theoretical justification for a lower bacterial risk associated with buffy-coat (versus PRP) PWBD platelets has been advanced³.

Although a higher risk of TAS apparently does not result from buffy-coat PWBD (compared with single-donor) platelets, the other infectious risks of pooled (ver-

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sus single-donor) components require careful consideration. Importantly, any comparison of buffy-coat PWBD versus apheresis platelets may warrant different conclusions in countries like the Netherlands where the incidence of known TTIs is extremely low and, in addition, blood from first-time donors (who have a several-fold higher risk of known TTIs compared with repeat donors⁴) is not used for transfusion; countries like Germany and Canada where the incidence of known TTIs in blood donors is extremely low, but blood from first-time donors (who have not been prescreened for the known TTIs and may be experiencing a window-period infection) is used for transfusion; and countries like South Africa⁵ (and perhaps also Spain^{6,7}) that have a higher risk of transfusion-transmitted human immunodeficiency virus (HIV) infection compared to North America and the rest of Europe. Such considerations (incidence of known TTIs in blood donors and use of blood from first-time donors for transfusion) render the comparison of the relative safety of buffy-coat PWBD versus single-donor platelets more complex than what was assumed by Devine et al² and Schrenzenmeier and Seifried⁸. This review will therefore examine the relative safety of buffy-coat PWBD versus single-donor platelets in terms of: (i) known TTIs, that is, HIV, hepatitis C virus (HCV), and hepatitis B virus (HBV) infections; (ii) emerging TTIs, including variant Creutzfeldt-Jakob disease (vCJD), West Nile Virus (WNV) infection, and others; and (iii) transfusion-related acute lung injury (TRALI).

In addition, unlike the earlier review¹ whose scope was restricted to the US—where pathogen reduction technologies for platelet concentrates are not licensed for use by the Food and Drug Administration (FDA)—the current review will pertain to countries that often offer blood operators the option to use pathogen reduction technologies as an alternative to single-donor platelets for the purpose of reducing the infectious risks of transfusion. Accordingly, a discussion of this alternative (omitted from the previous review¹ of the safety of PRP platelets used in the US) will be included here.

PRP VERSUS BUFFY-COAT PWBD AND SINGLE-DONOR PLATELET CONCENTRATES

In the US, only 12.5 % of therapeutic platelet doses transfused in 2006 were transfused as PRP PWBD platelets⁹ (Table 1). Thus, the feasibility of exclusive reliance on single-donor platelets can be considered established in the US where: 1) 87.5 % of all platelet doses are already transfused as single-donor platelets⁹; and 2) owing to the large size of the inventories, maintenance of two platelet manufacturing methods is not needed for meeting platelet supply needs. Platelets were prepared from 16.9 % of allogeneic whole-blood units in 2006 compared with 30.3 % in 2004⁹. An even larger reduction in the proportion of platelet pools had been realized between 2002 and 2004 indicating that—had there been

a mandate to do so—blood operators could have replaced the remaining pools with single-donor components by 2009.

In Europe, there is an approximately 50:50 split between the use of PWBD versus single-donor platelets¹⁰. Denmark, Finland, and the Netherlands prepare 85 % to 95 % of transfused platelets as buffy-coat PWBD platelets, demonstrating that a national platelet supply can be derived almost entirely from collected whole blood and very little reliance upon plateletapheresis collections.

Quebec provides 80 % of transfused platelet doses as single-donor platelets and 20 % as buffy-coat PWBD platelets. The Quebec blood operator felt that—given the size of its inventory which serves a 7.5-million population—maintenance of two platelet manufacturing methods was necessary for its always being capable of meeting platelet supply needs. In the rest of Canada (population of 24.5 million served by one blood operator), 70 % of platelet doses are transfused as buffy-coat PWBD platelets¹¹. In that part of the country, a move from PRP to buffy-coat PWBD platelets was made gradually between 2004 and 2008 in an effort to both introduce bacterial-culture testing of platelet pools and realize some perceived logistical advantages¹² that the buffy-coat production method might offer (e.g., overnight storage of collected whole blood and procurement of 30–75 mL/unit of additional recovered plasma). Before PRP PWBD platelets could be pre-pooled and cultured,^{13,14} the *cardinal* advantage of buffy-coat (compared with PRP) platelets was that—much like the apheresis platelets—buffy-coat platelets could be pre-pooled and cultured¹⁵. In 2004, when the AABB (formerly, American Association of Blood Banks) required that blood establishments limit and detect bacterial contamination in all platelet components, automated bacterial-culture systems were available in North America only for single-donor platelets. Accordingly, to implement bacterial culture of as many transfused platelets as possible, the US and Quebec moved toward single-donor platelets, while the rest of Canada moved from PRP to buffy-coat PWBD platelets.

Another advantage of the buffy-coat method (important before universal white-blood-cell [WBC] reduction was introduced) was that—compared with the PRP method—it resulted in up to a 1-log fewer WBCs per red-blood-cell (RBC) component. This advantage had to be weighed against the disadvantage of losing 20 mL (approximately ≥ 10 %) of the donor's RBCs because of the mechanics of the buffy-coat production method¹⁶. Although the conferred advantage vis-à-vis WBC content is at this point moot in Europe and Canada, the disadvantage remains. In theory, for every 10 (or fewer) units of RBCs required by a massively-transfused patient, an 11th RBC unit (entailing an additional allogeneic-donor exposure) can be needed for achieving the same hemoglobin target if the buffy-coat production method is used.

To render the expected decrease in the therapeutic efficacy of the prepared RBC component acceptable, it

Table 1. Preventable allogeneic-donor exposures in the US owing to the continued transfusion of pooled whole-blood-derived platelets.

10.388 million whole-blood-derived-equivalent platelet units transfused in the US in 2006†:
—9.092 million (87.5%) transfused as single-donor platelets
—1.296 million (12.5%) transfused as pooled whole-blood-derived platelets
For platelet doses transfused as pooled whole-blood-derived platelets:
—1.296 million whole-blood donors were used
—these patient needs could have been met instead by 216,000 donors of single-donor platelets
—thereby avoiding 1.080 million exposures of transfusion recipients to allogeneic donors

†The median number of whole-blood-derived platelet concentrates per platelet pool was observed to be 6 (range, <5 to >10) for US hospitals⁹.

has been postulated that buffy-coat PWBD platelets may have superior efficacy compared with PRP PWBD platelets¹⁷. PRP platelets are centrifuged against the platelet container, while buffy-coat platelets are centrifuged against the cellular elements of the whole-blood unit. This may lead to less platelet activation during buffy-coat-pool preparation compared with PRP-pool preparation. Platelet activation is one mechanism of platelet loss during storage¹⁷. If fewer platelets are lost during the storage of buffy-coat (compared with PRP) pools, transfusion recipients should receive a higher effective platelet dose, resulting in a higher corrected count increment (CCI) following transfusion of buffy-coat (rather than PRP) pools prepared from an equal number of platelet donors.

Recently, Schrezenmeier and Seifried⁸ presented a review of the laboratory studies that had compared a variety of quality-control variables between buffy-coat PWBD and single-donor platelets. They found that the available studies had not demonstrated that one of the products was consistently better than the other for the variables tested. However, they concluded that—given the inter-donor variability in platelet function—pooling before transfusion should reduce the variation in platelet function among platelet components released for transfusion⁸.

Neither this expected superiority of the platelet components manufactured by the buffy-coat method (in terms of more standardized platelet function⁸ or increased post-transfusion CCI¹⁸), nor the aforementioned expected inferiority of the RBC components manufactured by the buffy-coat method (in terms of post-transfusion hemoglobin increment^{16,19}) has hitherto been documented by clinical studies showing a reduction (or increase) in the number of platelet doses (or the number of RBC units) transfused to patients receiving platelets (or RBCs) prepared by the European (versus the US) method. In the absence of such superiority or inferiority findings from clinical studies, this review will assume that buffy-coat PWBD and single-donor platelets have equivalent therapeutic efficacy (that is, they can achieve the same therapeutic effect when transfused to patients who are not alloimmunized to HLA antigens). There-

fore, a decision on whether to transfuse one versus the other component should be based solely on considerations of safety¹⁸.

Given the recent discussion of the ethics of relying on buffy-coat PWBD versus single-donor platelets,⁸ it is important to consider at the outset why the ethical arguments for: 1) not “wasting” the donor’s “gift” of buffy-coat (but using it instead to produce platelets for transfusion); and 2) not exposing donors to the “additional” risk of plateletapheresis (which is unnecessary or incremental, since all of a country’s platelet transfusion needs can be met by using [already available] buffy-coat pools),⁸ should not influence the decision whether to transfuse buffy-coat pools versus apheresis concentrates. Modern apheresis technology permits us to collect all components needed for transfusion (RBCs, platelets, and plasma) without utilizing more donations compared to when we used to rely on whole-blood donations for making blood components²⁰. This is because, in addition to collecting platelets and (2 or more) units of plasma, modern apheresis technology permits us to collect “double” RBCs, as well as RBCs *along with* platelets and/or plasma²⁰⁻²².

In a recent series of moderate and severe donor reactions (based on 793,293 allogeneic whole-blood and apheresis donations made in 2007 in the US),²¹ the reaction rate per 10,000 donations was 52 for whole blood (2,872/552,183), 17 for platelet-/plasmapheresis procedures (93/54,841), 15 for collections of “double” RBCs (21/164,179), and 45 for collections of RBCs along with platelets and/or plasma (2/18,790). The type of collection (each of the aforementioned types of apheresis collections versus whole-blood donation) was not associated with any increase in the frequency of moderate or severe donor reactions. On the contrary, compared with whole-blood donations, platelet-/plasmapheresis collections were associated with a significant ($p < 0.05$) reduction (OR=0.54; 95 % confidence interval [CI], 0.34-0.85) in the frequency of donor reactions in a multivariate analysis,²¹ confirming the univariate association reported previously for collections made between 2004 and 2006²². In the previous series,²² the frequency of moderate and severe reactions was 0.47 % for whole

blood versus 0.15 % for plateletapheresis collections ($p < 0.05$).

The current US experience^{21,22} thus directly contradicts the current German experience and the historical literature on reaction rates reviewed by Schrenzenmeier and Seifried⁸. Even if plateletapheresis procedures were associated with a higher reaction rate in Germany today than whole-blood collections, the rights of transfusion recipients supersede any (perceived) rights of platelet donors²³. Donors have given informed consent to undergo plateletapheresis after having been informed of the risks of the procedure. Therefore, the duty of both blood establishments and transfusion services is to maximize the safety (and efficacy) of the transfused platelet component for the benefit of transfusion recipients.

RISK OF TTIs ASSOCIATED WITH BUFFY-COAT PWBD VERSUS SINGLE-DONOR PLATELET TRANSFUSION

If the prevalence of the next TTI to emerge in blood donors is p , we can assume that: 1) a particular transfusion recipient has a negligible probability of receiving more than 1 infectious unit (i.e., each distributed blood component contaminated with the new pathogen will infect a different transfusion recipient and will therefore represent a new case of a TTI); 2) all transfusion recipients are at risk, that is, there is a negligible probability of an infectious component's being given to a transfusion recipient who is already infected; and 3) the probability of at least one's of 4 or 6 donors in a pool of 4 to 6 WBD platelets being infectious (i.e., $1 - [1 - p]^4$ or $1 - [1 - p]^6$, respectively) approximately $4p$ or $6p$.

In the case of an emerging transfusion-transmitted virus similar to HIV or WNV, infectivity in blood or plasma (number of infectious copies per ml) is so high that any patient transfused with even a few mL of blood or plasma could contract infection. Thus, if the next major TTI had the characteristics of HIV or WNV, pools of 4 or 6 platelet concentrates would have 4 or 6 times the transmission risk associated with a single-donor platelet concentrate, no matter what manipulations are attempted during the manufacturing process to minimize plasma pooling by the 4 or 6 donors contributing to the platelet pool (i.e., manipulations to remove as much of the plasma from each buffy coat as possible and to re-suspend the platelets in a platelet additive solution). Therefore, the incremental risk from platelet pools would apply equally, whether PRP pools with approximately 50 mL of plasma from each donor are transfused in the US, or buffy-coat pools with (ideally) ≤ 10 mL of plasma from each donor are transfused in Canada or Europe (with the remainder of donor plasma replaced by a platelet additive solution).

The same probability (i.e., a $4p$ or $6p$ probability of a recipient's being infected from a pool of 4 or 6 platelets if the incidence of an infection in blood donors is p versus

a probability p of a recipient's being infected following receipt of single-donor platelets) applies to TTIs with the classical transfusion-transmitted viruses (HIV, HCV, and HBV) in countries that follow the same regulations as the US (e.g., Canada or Germany), thereby transfusing blood from first-time donors⁴. The incremental risk of HIV, HCV, and HBV in association with platelet pools (compared with single-donor platelets) may be virtually zero for countries like the Netherlands that do not transfuse blood from first-time donors and also test donors for HIV nucleic acid, HCV nucleic acid, and antibody to the hepatitis B core antigen (anti-HBc), in addition to testing them for antibody to HIV, antibody to HCV, and hepatitis B surface antigen (HBsAg).

Whether a pool of 4 or 6 platelets is associated with a $4p$ or $6p$ probability of infecting a transfusion recipient (compared with a probability p for a single-donor platelet concentrate) has been disputed. Schrenzenmeier and Seifried⁸ proposed that pools of 4 to 6 platelets are associated with no increase in risk compared with single-donor platelets, because the estimates of the increase in risk with platelets pools have been derived from mathematical models rather than observational studies. However, differences in risks as small as the risks of TTIs cannot possibly be documented by such studies unless hundreds of thousands of transfusion recipients are included. Even hemovigilance methods are not suited for monitoring rare TTIs²⁴. Unless an emerging agent is associated with extremely low infectivity (i.e., an extremely low number of infectious copies per mL), so that few mL of blood or plasma do not suffice to transmit infection, it is *biologically implausible* to suggest that exposure to 4 to 6 donors would carry the same risk as exposure to 1 donor.

Magnitude of the increase in risk

Although the fact that a pooled product is associated with a higher risk of TTIs than a single-donor product is intuitively obvious, the precise magnitude of the increase in risk in association with a buffy-coat pool (to which 4 to 6 different donors have contributed) compared with a single-donor concentrate is hard to estimate because competing assumptions (Table 2) are involved¹. Vamvakas¹ presented the two extremes of the plausible range (i.e., the best-case versus the worst-case scenario) for the difference in risk. For countries relying on buffy-coat PWBD platelets, the best-case scenario minimizes the difference in risk between pooled and single-donor concentrates; conversely, the worst-case scenario maximizes this difference. Given the 4 sets of competing assumptions listed in Table 2, the two extremes of the plausible range correspond to a 2-fold (best-case) versus 6-fold (worst-case) difference in risk. More specifically, if pools of 4 WBD platelet concentrates were used and all single-donor concentrates were split (with the concentrates split into 3 components compensating for any unsplit collections), there would be a 2-fold difference in risk between PWBD and sin-

Table 2. Competing assumptions entering the estimation of the magnitude of the increase in the risk of TTIs in association with the receipt of buffy-coat PWBD versus single-donor platelets¹.

Best-case scenario*	Worst-case scenario†
Pools of 4 WBD platelets	Pools of 6 WBD platelets
No recipient of a pooled (or single-donor) concentrate receives a 2nd or 3rd platelet dose owing to inadequate CCI	Recipients of a pooled (or single-donor) concentrate may receive a 2nd or 3rd platelet dose owing to inadequate CCI, as dose escalation is the usual approach to non-immune causes of platelet refractoriness
≥64 % ⁹ of single-donor platelets represent split products (so that an infected apheresis donor can infect 2 or even 3 recipients)	Split or “double”-split apheresis components (transfused sequentially to the same patient when needed) <i>further</i> reduce the number of donor exposures to which recipients of single-donor platelet concentrates are subjected ¹⁸ (see text) Transfusion of single-donor platelets together with (if needed) the RBCs and/or plasma obtained from the same multicomponent apheresis procedure to the same patient <i>further</i> reduces the number of donor exposures to which multi-transfused patients are subjected ²⁰ (see text)
An infected apheresis donor can donate more than once during the window period of HBV infection	There is a 6- to 25-fold difference (p<0.05) in the prevalence of HIV, HCV, and HBV infection between plateletapheresis and whole-blood collections ²⁷ (Figure 1)

* Corresponding to a 2-fold increase in risk (lower extreme of the plausible range).¹

† Corresponding to a 6-fold increase in risk (upper extreme of the plausible range).¹

gle-donor concentrates. Conversely, if: 1) pools of 6 WBD platelet concentrates were used; 2) there were a further 2-fold reduction in the number of donor exposures to which recipients of apheresis concentrates are subjected for the reasons given in the 2nd and 3rd row of Table 2 (2nd column); and 3) all single-donor concentrates were split (same as in the aforementioned best-case scenario); there would be a 6-fold difference in risk between PWBD and single-donor concentrates¹.

Thus, in countries employing the same donor-screening tests as the US, transfusion of pooled concentrates would be associated with a ≥2-fold difference in the risk of known TTIs (i.e., HIV, HCV, and HBV infection) compared with transfusion of single-donor concentrates (if these countries, like the US, used platelets from first-time donors to produce platelet pools). When—as in the USA—HIV nucleic acid, HCV nucleic acid, and *anti-HBc* testing is performed (in addition to HIV and HCV antibody and PRISM HBsAg testing),²⁵ the window period of HIV, HCV, and HBV infection (in days, along with the associated 95 % CI) is, respectively, 9.5 (8.2-10.8), 8.0 (6.8-9.2), and 38.3 (33.0-43.7). Testing for HBV nucleic acid is not required in the US, although part of the US blood supply (like part of the German blood supply) is further tested for HBV nucleic acid, resulting in a further reduction of the window period by 5 to 8 days. Whether HBV nucleic acid testing is performed or not, it is possible that a plateletapheresis donor may make more than 1 infectious donation if s/he donates during the window period of an incident HBV

infection. There have been reports of such occurrences,²⁶ although they have happened in environments not performing testing for anti-HBc.

In countries using platelets from first-time donors to produce platelet pools, the greater prevalence of known TTIs (i.e., HIV, HCV and HBV infection) in whole-blood compared with (non-double-RBC) apheresis collections²⁷ (Figure 1) must be weighed against the concern about a donor’s with an incident HBV infection making more than one platelet donation during the window period of her/his infection. Zou et al²⁷ did not demonstrate corresponding differences in the incidence of (new) HIV, HCV, and HBV infections between (non-double-RBC) apheresis (including plateletapheresis) and whole-blood collections, because: 1) new HIV, HCV, and HBV infections in repeat US blood donors are exceedingly rare; and 2) overall prevalence of HIV, HCV, and HBV infection does not consistently reflect the corresponding incidence⁴. By the same token, however, for blood systems testing for anti-HBc, there is no estimate of the risk of a second or third plateletapheresis collection’s being made during the window period of an incident HBV infection. Although concern about this possibility does exist, concern about the possibility that donors with a 25-fold higher prevalence of HBV infection could have a higher risk of incident infection exists as well. Accordingly, these two concerns likely cancel each other out.

Although an infected apheresis donor could infect 2 or even 3 recipients (because ≥64 %⁹ of single-donor

platelets represent split products), judicious use of split or “double-split” apheresis platelets in the future could compensate for the effect of split products from an infected donor. As shown by the Prophylactic Platelet Dose on Transfusion Outcomes (PLADO) RCT,²⁸ it is safe to transfuse platelets prophylactically to hemato-oncology patients with hypoproliferative thrombocytopenia—when the 10,000/ μ l platelet transfusion trigger is reached—at a dose half the customary dose. Although a dose equal to half the standard dose was as effective as the standard dose in preventing bleeding (Figure 2), patients who received half the standard dose needed platelet transfusion more often. For this reason, the difference in the total transfused dose of platelets received by the half-the-standard-dose versus the standard-dose arm—albeit significant—was small (9 %). Because patients in the low-dose arm received platelet transfusions every few days, it should be possible to devise an inventory management practice whereby the second half of a single-donor platelet concentrate is administered to the same patient when the subject is an in-patient and requires a second platelet transfusion within the shelf life of the product¹⁸. In this manner, the small reduction in total number of transfused platelets observed in the PLADO RCT²⁸ could translate into a clinically-significant reduction in the number of donor exposures for hemato-oncology patients supported with prophylactic platelet transfusions at half the dose currently regarded as “standard”.

Multicomponent apheresis collections (as performed in the US²⁰⁻²²) could reduce the number of donor exposures to which multiply-transfused platelet transfusion recipients are subjected in yet another way. Since it is possible to collect single-donor platelets along with RBCs and/or plasma from the same donor in the course of one donation, and since RBC and/or plasma transfusions are often needed by patients receiving platelets, the RBCs and/or plasma from the same apheresis collection as the platelets (components with a longer shelf life than the platelets) could be held for transfusion to the same transfusion recipient as the platelets. In addition to reducing the number of allogeneic-donor exposures for the prevention of TTIs, such a strategy would also decrease the number of exposures to donor plasma potentially containing circulating WBC antibodies (see below in the section on TRALI). In this way, multicomponent apheresis collections—if reserved in the future for transfusion to the same transfusion recipient—could reduce the risk of both TTIs¹⁸ and TRALI²⁰.

Emerging TTIs

In contrast to the preceding discussion of the risk of a transfusion-transmitted HIV, HCV, and HBV infection, whether a blood system uses platelets from first-time donors to produce platelet pools (or not) does not impact on the difference in risk for emerging TTIs between buffy-coat PWBD and single-donor platelets. First-time and repeat donors carry the same risk of an emerging TTI, because repeat donors have not been

“pre-screened” for the new pathogen. Table 3 shows the number of cases of an emerging TTI that could be prevented each year in the US if the remaining 12.5 % of platelet doses still transfused as pools⁹ were transfused as single-donor concentrates.

Two scenarios are considered: 1) that the next emerging agent will have a long incubation period measured in years (like HIV), thereby accumulating over time in the donor population before becoming recognized; and 2) that the next emerging agent will be present for a short period in the donor’s circulation, during acute (rather than chronic) infection as was the case with WNV. Because of the surveillance systems put in place since the emergence of HIV, it is assumed that the next “HIV-like” agent to emerge will be recognized faster than HIV. For this reason, although HIV infection had reached a prevalence higher than 1 per 1,000 in US blood donors in 1984 (the year before testing for HIV infection was introduced), it is assumed that the next “HIV-like” agent will have reached a prevalence of only 1 per 10,000 in blood donors during the year before testing commences. Concerning the next “WNV-like” agent to emerge, it is assumed that it will replicate the events that took place in the US during the 2002 WNV epidemic. During the summer and fall of 2002 (the year before testing was introduced), 380 WNV-infectious donations are estimated to have been made in the US²⁹. Countries using buffy-coat PWBD platelets are at significantly higher risk from emerging TTIs than the US, because they usually rely on pools for the majority of platelet transfusions. This (higher than in the US) risk can be illustrated by the projections for the rest of Canada (outside Quebec) where 70 % of platelet doses (compared with 20 % in Quebec) are transfused as buffy-coat pools. Under the assumptions of the best-case scenario (Table 2), if—as expected from the difference in population—12 times fewer platelet doses were transfused annually in Canada (outside Quebec) than in the US, and the proportion of platelet doses transfused as buffy-coat PWBD platelets in Canada (outside Quebec) were 5 times greater than in the US, the continued transfusion of buffy-coat PWBD (rather than single-donor) platelets in Canada (outside Quebec) would result in 15 or 4 *additional* (i.e., preventable) transmissions of the next HIV-like or WNV-like agent to emerge in the future. These estimates pertain (as the estimates under the “best-case scenario” in Table 3) to the peak year of the agent’s accumulation in the blood donor population before testing is introduced (for the next HIV-like agent), or the first major seasonal epidemic (for the next WNV-like agent)³⁰.

Although the population of Canada (outside Quebec) is 12 times smaller than the US population, as many as 15 (compared with 36) additional cases of the next HIV-like agent and as many as 4 (compared with 10) additional cases of the next WNV-like agent would be expected. This (proportionately higher than in the US) number of additional cases from platelet transfusion highlights the vulnerability to emerging TTIs of coun-

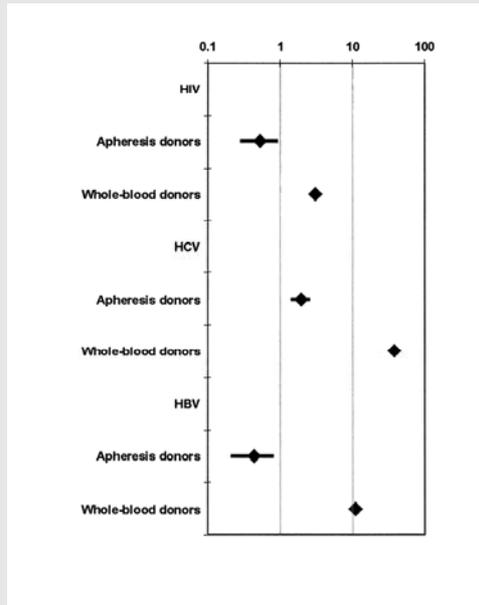


Figure 1. Prevalence of infectious disease markers among (non-double-RBC) apheresis versus whole-blood collections (2004 through 2008) in the American Red Cross²⁷. For each virus (HIV, HCV and HBV) the prevalence (per 100,000 collections) is depicted, surrounded by its 95 % CI. The prevalence of HBV infection is based on the results of HBsAg testing. There is a 6-to 25-fold, statistically significant (p<0.05) difference in the prevalence of infectious disease markers between (non-double-RBC) apheresis (including plateletapheresis) and whole-blood collections for all 3 viruses: the corresponding 95 % CIs do not overlap.

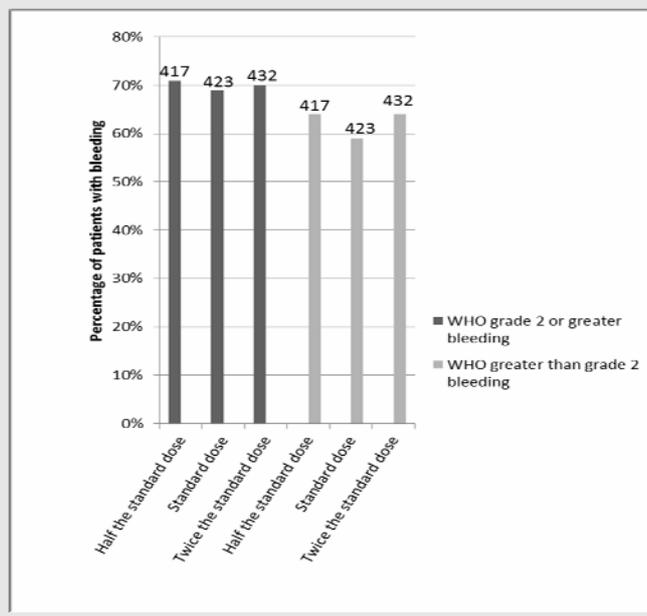


Figure 2. Comparison of the proportion of patients bleeding following random allocation to the half-the-standard dose, standard-dose, and twice-the-standard-dose arm of the Prophylactic Platelet Dose on Transfusion Outcomes (PLADO) RCT²⁸. The number of subjects allocated to each arm is shown above each column. All randomized patients received at least 1 platelet transfusion. Whether the endpoint was bleeding of WHO (World Health Organization) grade 2 or greater or bleeding greater than grade 2, the same proportion of patients developed bleeding, whether they were allocated to receive half the standard dose, the standard dose, or twice the standard dose of platelets—that is, respectively, 1.1×10^{11} platelets/ m^2 , 2.2×10^{11} platelets/ m^2 , or 4.4×10^{11} platelets/ m^2 , corresponding to half a single-donor concentrate, one single-donor concentrate, or two single-donor concentrates (or an equivalent dose of pooled whole-blood-derived platelets).

Table 3. Annual decrease in the number of transmissions of emerging TTIs from platelet transfusions in the US¹.

Emerging TTI	Prevented if 100% (from 87.5%) of doses are transfused as single-donor (rather than PRP PWBD) platelets+	
	Best-case scenario ¹	Worst-case scenario ¹
Next HIV-like pathogen to emerge in the future*	36.1	108.2
Next WNV-like pathogen to emerge in the future†	9.9	29.7

+ See calculation of the number of preventable allogeneic donor exposures in Table 1.

* Reaching a prevalence of 1 per 10,000 blood donors (10 times less than the 1984 HIV prevalence).

† Causing 380 transfusion transmissions in its first seasonal epidemic (as was the case with WNV in 2002)²⁹.

Table 4. Randomized controlled trials of amotosalen-HCl/UVA-treated platelets.

RCT (year of publication) (sample size)	Pathogen-reduced platelets were associated with:
EuroSPRITE³⁶ (2003) (n = 103)	No difference in transfusion efficacy BUT: Compared to platelets stored in plasma, platelets stored in platelet additive solution (PAS) II have a 20% lower CCI Approximately half of the control platelets were stored in PAS-II (rather than plasma)
SPRINT³⁷ (2004) (n = 645)	Lower post-transfusion platelet count increment Reduced transfusion interval Increased rate of transfusion failure
Janetzko et al³⁸ (2005) (n = 43)	Borderline significant reduction in transfusion efficacy endpoints

tries that still transfuse buffy-coat PWBD platelets. Despite the fact that a move toward single-donor platelets (like in the US and Quebec) is a fail-safe approach to decreasing the risk of emerging TTIs from platelet transfusion without incurring any increase in risk, an alternative approach that is presently debated is the introduction of pathogen-reduction systems for platelet concentrates.

The agreement on the appropriateness of introducing pathogen-reduction technologies for platelets³¹⁻³³ when the technologies become licensed by the US FDA¹⁸ underscores the current concern of the transfusion-medicine community about emerging TTIs. Recently, the AABB³⁴ prioritized 68 potentially or actually transfusion-transmitted agents based on both the existing evidence of their transmissibility by transfusion and their potential for severe clinical outcomes. Four priority categories were assigned to convey a particular agent's significance: white, yellow, orange, and red. The "red" agents were the vCJD prions, dengue-fever

virus, and *Babesia* species. The "orange" agents were *Leishmania* species, *Plasmodium* species, *Trypanosoma cruzi*, Chikungunya virus, and St. Louis encephalitis virus. With the exception of the last two agents, for which the concern was that they have the potential to replicate the WNV experience of transfusion transmission, all other "red" or "orange" agents have been shown to be transfusion-transmitted. Further emerging transfusion-transmitted agents of significant concern (such as the xenotropic murine leukemia-related virus [XMRV]³⁵) have continued to be reported after the publication of the AABB compendium³⁴.

Although the introduction of pathogen-reduction systems for platelets in countries like South Africa⁵ (and perhaps also Spain^{6,7}) is justified because of a higher risk of HIV transmission by transfusion compared to North America and the rest of Western Europe, the implementation of pathogen reduction of platelets in Switzerland illustrates the concern of regulators about emerging TTIs. While such concern is both realistic and

appropriate,¹⁸ it is noteworthy that European and Canadian regulators have not given precedence to the risk-reduction strategy of moving from buffy-coat PWBD to single-donor platelets over the strategy of adopting the (not yet FDA-licensed) pathogen-reduction systems for platelets. A digression is thus warranted here to examine whether this alternative risk-reduction strategy may be more appropriate for Western Europe and Canada than moving toward a single-donor platelet supply.

ARE PATHOGEN-REDUCTION SYSTEMS THE MOST ADVANTAGEOUS APPROACH TO PROTECTING PLATELET TRANSFUSION RECIPIENTS FROM EMERGING TTIs TODAY?

Table 4 summarizes the results of the 3 previous randomized controlled trials (RCTs) of platelets treated with amotosalen-HCl/ultraviolet-A light versus non-treated platelets³⁶⁻³⁸. With the exception of the small EuroSprite Trial,³⁶ for whose results—as indicated in Table 4—the effect of having stored platelets in platelet additive solution (PAS) II may have been an alternative explanation, both other trials^{37,38} showed either a statistically significant reduction in³⁷ or a trend toward reduced efficacy³⁸ for the treated platelets. Until recently,¹⁸ the inferior efficacy data from these 2 RCTs^{37,38} were considered to have been due to mere loss of platelets secondary to the photochemical treatment process. Such a loss of platelets would result in a reduced effective platelet dose and thus a reduced post-transfusion CCI, which could be overcome by increasing the number of transfused platelet concentrates. Because such transfused platelets are pathogen-reduced, the associated increase in the number of donor exposures was not viewed with particular concern. Stated another way, the advantages of the pathogen-reduction technology were thought to exceed the disadvantages^{18,31-33}. Observational studies that followed the introduction of the technology in some countries^{39,40} reinforced this interpretation of the data. Not only did they not observe any increased bleeding among the recipients of the treated platelets but also they did not document an increase in the platelet transfusion requirements of the transfusion recipients^{39,40}.

Adverse effects of pathogen-reduction systems for platelets

The publication of the findings of the (Dutch) Sanquin RCT of Kerkhoffs et al⁴¹ necessitated a re-consideration of this interpretation of the data concerning the therapeutic efficacy of pathogen-reduced platelets. In the Sanquin trial,⁴¹ not only were the laboratory indicators of therapeutic efficacy reduced for the treated platelets, but patients receiving treated platelets suffered more bleeding as well. This was the case ($p < 0.05$) whether all bleeding or only bleeding greater than or equal to grade 2 was considered (Figure 3). In either case, there were approximately twice as many bleeding episodes when

treated platelets were transfused—a sizable and clinically-important difference that could not be ascribed only to platelet losses secondary to the treatment process (i.e., the kind of adverse effect that had been assumed previously to be overcome by simply increasing platelet dose). To account for the increased risk of bleeding in their patients receiving treated platelets, Kerkhoffs et al⁴¹ proposed that platelets may suffer a functional platelet impairment from the treatment process. Damage of platelet mitochondrial nucleic acids by the treatment process might not only result in loss of viability of a proportion of the treated platelets, but could also impair their hemostatic capacity⁴¹. It should be noted that, in the extended safety report of the SPRINT trial, the frequency of grade 2 or greater bleeding was also significantly higher in patients receiving pathogen-reduced platelets than in controls (43 % versus 34 %; $p = 0.02$)⁴². The RCT of Kerkhoffs et al⁴¹ controlled for the effect of platelet additive solution (Figure 3), was conducted in an unselected hematology population, and was also conducted independently by the Dutch Blood Services (i.e., without involvement of the manufacturer). Amotosalen-HCl/ultraviolet-A light is the only platelet pathogen-reduction technology that has hitherto undergone clinical trials. Therefore, given the magnitude of the infectious risks of platelet transfusion in Europe and North America today, the disadvantages from adopting this technology to prevent emerging TTIs exceed the advantages. Further developmental work is needed before the pathogen-reduction technologies for platelets are ripe for implementation.

vCJD

When we consider specifically the European context, there is a second reason why the risk-reduction strategy of introducing pathogen reduction of buffy-coat PWBD platelets is inferior to the risk-reduction strategy of moving from buffy-coat PWBD to single-donor platelets. Emerging pathogens are *unpredictable*: a fact of which the transfusion-medicine community has been made poignantly aware after the emergence of the vCJD prions. Pathogen-reduction systems, however, are always validated against pathogens that are already known. For this reason, they may—or may not—protect patients from the next major emerging TTI, and *for sure* they will not protect European transfusion recipients from vCJD.

Platelets contain no vCJD infectivity. The current opinion held by the UK Spongiform Encephalopathy Advisory Committee (SEAC)⁴³ is that, based on data from animal models, vCJD infectivity in human blood is likely to be partitioned between plasma and WBCs and to be only minimally associated with RBCs and platelets. With regard to platelet concentrates—whether buffy-coat PWBD or single-donor—minimization of plasma pooling and resuspension in additive solutions rather than plasma would likely reduce the amount of residual plasma to 80-90 ml⁴⁴. This amount of plasma would contain more than enough infectivity to transmit infec-

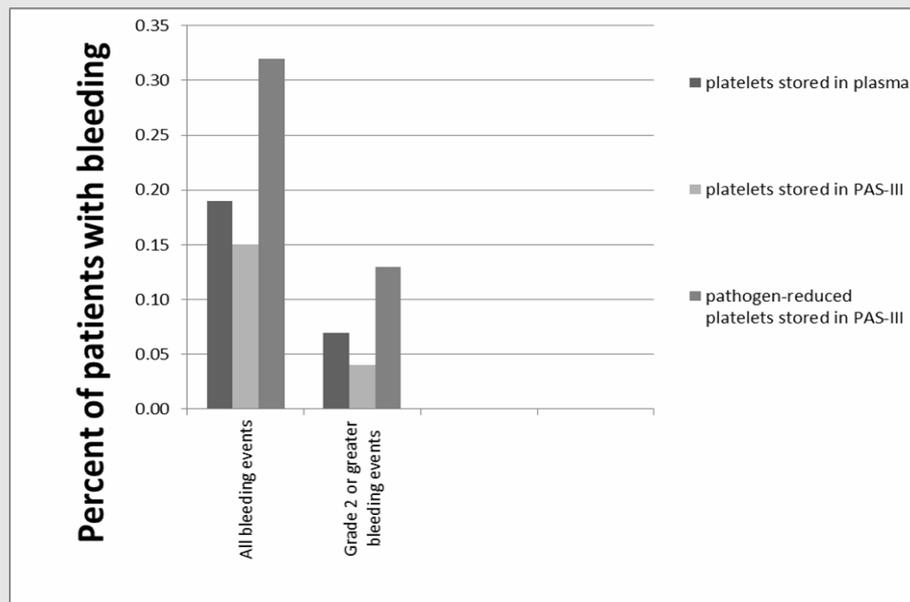


Figure 3. Randomized comparison of the proportion of patients suffering any bleeding event, or a grade 2 or greater bleeding event, while being supported by platelets stored in plasma, platelets stored in platelet additive solution (PAS) III, or pathogen-reduced platelets stored in PAS-III. Two hundred seventy-eight patients were randomized into 3 treatment arms. Patients receiving pathogen-reduced platelets suffered more bleeding, whether all bleeding events ($p = 0.034$) or bleeding events of grade 2 or greater ($p = 0.044$) were considered.

Table 5. Systematic review of studies diagnosing TRALI based on the Canadian consensus criteria⁵⁷ in settings transfusing both single-donor and PRP PWBD platelets¹.

Study (design)	Risk of TRALI in association with pooled whole-blood-derived versus single-donor platelets
Robillard et al ^{58†} (passive surveillance)	1 per 40,452 platelet pools versus 1 per 46,996 single-donor platelets
Gajic et al ⁵⁹ (nested case-control study within observational study)	Cases received 10 single-donor platelets and 6 platelet pools Controls received 3 single-donor platelets and 3 platelet pools (The cases received more platelet transfusions than the controls but the type of platelet concentrate did not differ)
Eder et al ⁶⁰ (passive surveillance*)	1 per 279,805 transfused platelet pools ¹ versus 1 per 285,630 transfused single-donor platelets ¹

† The figures in this article⁵⁸ were reported separately for 2004 and 2005; because experience with the use of the Canadian consensus criteria⁵⁷ matured between 2004 and 2005, the 2005 figures⁵⁸ are given in the Table. In 2004, platelet pools and single-donor platelets were also associated with a similar risk of TRALI.

* Analysis limited to fatal TRALI cases.

tion to transfusion recipients under even optimistic infectivity assumptions⁴⁴. Thus, efforts to minimize the plasma volume of platelets through replacement with platelet additive solutions are likely to be ineffectual,⁴⁴ and the UK is in the process of converting its platelet supply from buffy-coat PWBD to single-donor platelets. Prion-reduction filters are not currently applicable to platelets. More specifically, the reason why minimization of plasma pooling and resuspension in additive solutions should be ineffectual is as follows: One refers to an “infectious dose” as the minimal dose capable of transmitting infection in an animal model for the mode of contamination given⁴⁵. Studies in rodents⁴⁶⁻⁴⁸ with transmissible spongiform encephalopathy (TSE) showed infectivity of 1-10 infectious doses per mL of whole blood. About 40 % of this infectivity was distributed in the WBCs and the remainder in the plasma⁴⁸. The latter form of infectivity probably predominated, because the majority of the cell-associated infectivity was loosely bound and could be washed off⁴⁸. Although infectious prions may partition between the cellular and acellular fractions of human blood differently from the manner in which they partitioned in these rodent models, based on the findings of the animal models, it can be expected that ordinary WBC reduction through filtration (as implemented in the UK in October 1999) would remove 40-70 % of the total infectivity present in a whole-blood unit,⁴⁸ but would have little impact on the plasma-borne infectivity.

Under optimal conditions, only 10 mL of donor plasma can be left in a RBC unit prepared in an additive solution, although—under the usual conditions of manufacturing RBCs by the buffy-coat method in the UK—20 mL of plasma usually remain in the supernatant fluid. If: 1) 40 % of the infectivity resides in the WBCs and 60 % in the plasma; 2) the starting whole-blood infectivity is 10 infectious doses/mL; 3) the whole-blood unit is WBC-reduced; and 4) the residual plasma volume at the completion of all manufacturing steps is 10 mL; 110 infectious doses would be left in a RBC unit released for transfusion⁴⁴. In a similar manner, even if only 5 mL (or less) of plasma from each donor contributing to a buffy-coat pool were left in the transfused component, this small amount of plasma would contain sufficient infectivity to infect transfusion recipients.

Elsewhere in Europe, outside the UK and by the end of 2009, there had been 41 cases of vCJD; remarkably, there has not yet been a case in Germany⁴⁹. Nonetheless, the description in other countries—such as Spain and Saudi Arabia—of vCJD patients who had been blood donors in the past suggests that the problem has already taken on an international dimension,⁴⁵ warranting proportional responses from outside the UK as well. If we accept the prevalence of subclinical vCJD in the UK to be 1 per 10,000,⁵⁰ from the relative incidence of clinical disease between each particular country and the UK, we can expect the prevalence of subclinical vCJD in Europe to be: 1 per 60,000 in Ireland, 1 per 70,000 in France, 1 per 150,000 in the Netherlands, 1 per 150,000

in Portugal, 1 per 250,000 in Spain, and 1 per 1,000,000 in Italy⁵¹.

In the UK, *PRNP* gene codon-129 methionine homozygotes may have a risk as high as 1 per 100,000 to develop a fatal disease following exposure to vCJD through transfusion if they survive for ≥ 5 years after the transfusion⁵¹. Such would be the risk of transfusion-acquired *clinical* disease if: 1) ordinary WBC reduction (as practiced in the UK today) did not prevent transmission of vCJD; 2) the probability of developing clinical disease after receiving blood from a donor who later developed vCJD were 23 % (i.e., the same as the in the small cohort that we have so far studied: 3 cases of vCJD among an estimated 13 methionine homozygotes among 32 patients hitherto surviving for ≥ 5 years post-transfusion; 3) the prevalence of subclinical disease in the UK population were approximately 1 per 10,000 (the latest estimate from tonsil samples⁵⁰); and 4) 40 % of donors with subclinical disease could transmit infection to transfusion recipients, as was the case in the completed sheep scrapie experiment⁵².

A risk of this magnitude warrants preventive measures to protect recipients from a fatal transfusion-acquired disease, and the move in the UK from buffy-coat PWBD to single-donor platelets for the prevention of transfusion transmission of vCJD is necessary. For the same reason, a move from buffy-coat PWBD to single-donor platelets would also be warranted in Ireland (where the risk of contracting vCJD for methionine homozygotes surviving for ≥ 5 years post-transfusion could be approximately 1 per 600,000), as well as in France (risk of 1 per 700,000). Both of these risks are of a magnitude similar to other infectious risks of transfusion (e.g., the risk of HIV transmission when the US blood supply was screened for HIV by means of HIV antibody and p24 antigen), which were deemed in the past to be of a magnitude sufficient to warrant implementation of additional preventive measures (e.g., HIV nucleic acid testing).

WOULD CONVERSION TO A SINGLE-DONOR PLATELET SUPPLY AFFECT THE RISK OF TRALI?

Contrary to what had been postulated,⁵³ the higher risk of TTIs in association with PRP PWBD (compared with single-donor) platelets in the US is most likely not offset by a higher risk of TRALI from single-donor platelets^{1,54}. A WBD platelet concentrate contains 4 to 6 times less plasma from any *individual* donor (who may be a female donor alloimmunized to paternal WBC antigens during a previous pregnancy and having circulating antibodies potentially directed to the transfusion recipient's WBC antigens). However, each of the 4 to 6 donors in a pool can be a female multiparous donor with circulating WBC antibodies whose ≤ 20 mL of plasma suffice to cause TRALI^{55,56}. The higher probability of exposure to ≤ 50 mL of plasma from each such

alloimmunized donor in a US platelet pool probably carries as much TRALI risk on average as the receipt of ≤ 300 mL of plasma from a single donor who may be similarly alloimmunized^{1,18}. The studies comparing the risk of TRALI (diagnosed based on the Canadian consensus criteria⁵⁷) from PRP PWBD versus single-donor platelet concentrates (transfused simultaneously to the same patient population) thus showed a similar risk of TRALI from both components¹. These studies⁵⁸⁻⁶⁰ are shown in Table 5.

The lack of any empirical support for a difference in the risk of TRALI between PRP PWBD and single-donor platelets (Table 5) notwithstanding, as recently as in August-September 2009, 22 % of US blood centers responding to a questionnaire from an AABB-appointed TRALI Working Group stated that they endeavored to increase production of PWBD platelets in an effort to mitigate the risk of TRALI from single-donor platelets. Eight of 10 blood centers proffering this response as a TRALI risk-reduction strategy were increasing production of PWBD platelets regardless of the gender of donors contributing to a platelet pool⁶¹. This tendency to produce more PWBD platelets (in a misinformed^{1,54} effort to reduce the risk of TRALI from a platelet transfusion) may unfortunately well be reflected in the—soon to be released—2009 US platelet utilization survey data (which were collected in 2008).

Fortunately, on the other hand, the most frequently implemented policy for TRALI risk reduction has been to increase the proportion of apheresis platelet collections from male donors, either by collecting more individual products from male donors or by achieving a higher split rate⁶¹. HLA antibody testing (of female donors with a history of pregnancy) had been implemented by 43 % of the responding institutions⁶¹. However, triage criteria for HLA screening varied greatly. Two blood centers screened all female donors while 18 blood centers required a given number of pregnancies to initiate screening. Moreover, no blood center was screening female donors for granulocyte antibodies⁶¹.

All available data⁵⁸⁻⁶⁰ directly comparing the risk of TRALI between PWBD versus single-donor platelets (Table 5) pertain to PRP rather than buffy-coat platelets. For the US PRP PWBD platelets, we can postulate that—since their risk of TRALI does not differ from that of single-donor platelets transfused in the studies⁵⁸⁻⁶⁰ listed in Table 5 (i.e., single-donor platelets collected without regard to the donor's gender and without screening of the female donors for a history of pregnancy or for WBC antibodies)—their risk of TRALI should be *higher* than that of *future* US single-donor platelets (to be collected from male donors or from female donors without a history of pregnancy or shown not to have WBC antibodies)¹⁸. Based on this theoretical prediction, reliance on a 100 % single-donor platelet inventory collected from male donors or screened female donors can be an important national TRALI risk-reduction strategy for the US¹⁸. As already discussed,²⁰ reserving the RBCs and/or plasma (collected along with

the single-donor platelets in the course of a multicomponent apheresis collection) for transfusion to the same transfusion recipient can further reduce the risk of TRALI in the US. The plasma contribution of each whole-blood donor to a buffy-coat pool is limited to 5-20 mL and the pooled platelets are resuspended in male plasma or in platelet additive solution. Since buffy-coat PWBD platelets contain ≤ 20 mL of plasma from each unscreened female donor (i.e., each potentially multiparous donor with circulating WBC antibodies), they should have a *lower* risk of TRALI compared with PWBD platelets (which contain ≤ 50 mL of plasma from each unscreened female donor). However, because they contain *some* plasma (5-20 mL) from each unscreened female donor, they should have a *higher* risk of TRALI compared with future single-donor platelets collected from male donors or screened female donors³⁰.

Win et al⁵⁵ and van Stein et al⁵⁶ documented TRALI occurring secondary to this minor plasma contribution from unscreened female donors to buffy-coat pools. The study of van Stein et al⁵⁶ expertly illustrates the risk of TRALI in a national blood system relying entirely on the buffy-coat production method for both platelets and RBCs (Figure 4). That series of 49 cases passively reported to the Dutch Blood Services (Sanquin) was completed in the 2.5 years immediately before the Netherlands introduced the risk-reduction strategy of transfusing male-only plasma; and, compared to earlier TRALI case-series, it had the *cardinal* advantage of performing a *complete* work-up on *all* the donors implicated in TRALI occurring in multiply-transfused transfusion recipients. By doing so, it avoided the observation bias common to most other case-series: that is, the observation bias stemming from selective work-ups of the implicated female donors (or even female donors of high-plasma volume components)¹⁸.

A *complete* work-up for TRALI⁵⁶ included both HLA- and granulocyte-antibody tests in the sera of all implicated donors, as well as a WBC-incompatibility test between each implicated donor and the recipient. The purpose of the laboratory work-up was not to make a diagnosis of TRALI—as TRALI was being diagnosed solely based on the Canadian consensus criteria⁵⁷—but to identify a subcategory of “alloimmune” TRALI. There were 10 deaths.

Had “male-only” plasma been used over the 2.5 years of the study, 2 deaths would have been prevented; had “male-only” plasma *and platelets* been used over the 2.5 years of the study, 3 deaths would have been prevented. The majority (7 of 10) of deaths were secondary to transfusion of RBCs, produced by the buffy-coat method and containing only 20 mL of residual donor plasma.

The preceding discussion presumes that WBC antibodies in the donor plasma (which are directed against WBC antigens of the recipient) have a pathogenetic role in TRALI¹⁸. Although hitherto all of our TRALI risk-reduction strategies⁶² have been based on this premise, not all available data indicate that avoidance of female

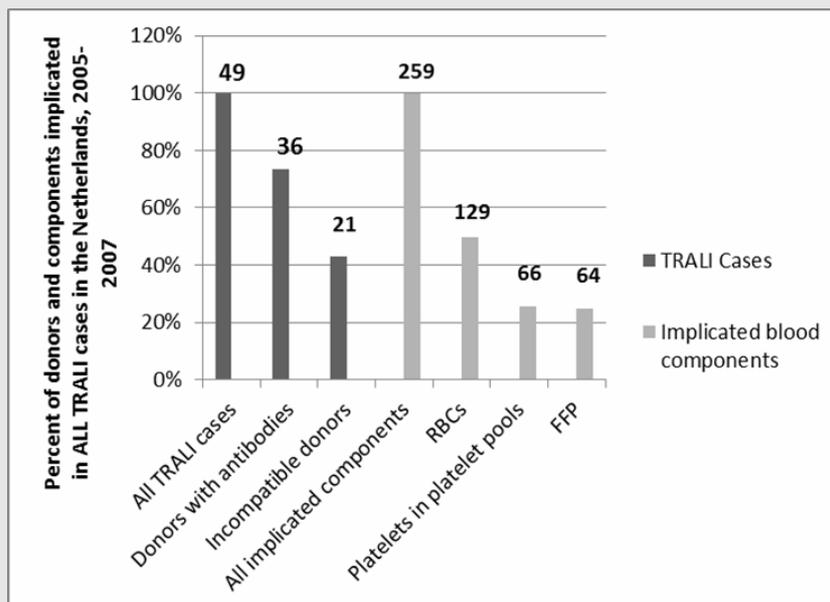


Figure 4. Forty-nine cases of TRALI diagnosed in the Netherlands between January 2005 and July 2007. In 36 (73.5 %) cases, at least one implicated donor had WBC antibodies. In 21 (43 %) cases, serologic incompatibility was demonstrated between at least one donor and the recipient (i.e., the donor’s antibody was directed against a WBC antigen of the recipient). Two hundred fifty-nine components (129 RBCs, 66 platelet pools, and 64 units of plasma) had been administered to these multiply-transfused patients. When the analysis was limited to the 21 alloimmune cases of TRALI, there were 31 components producing serologic incompatibility with the recipient; 14 (45 %) were plasma, 14 (45 %) were RBCs, and 3 (10 %) were platelets (in platelet pools).

Table 6. How small a risk defines the “as-low-as-reasonably-achievable” (ALARA) risk?

Any risk prevented by indefinitely deferring (in North America) travelers to the UK, France, and Europe

Which may (or may not) be smaller than:

Any risk prevented by indefinitely deferring (in North America) MSM who have *not* had sex with another man in the last 10 years⁶⁸⁻⁷⁰

Which is much smaller than:

The risk prevented by *not* transfusing buffy-coat pooled whole-blood derived platelets

Which is smaller than:

The risk prevented by *not* transfusing PRP pooled whole-blood derived platelets

donors results in a reduction in mortality⁶³. Although it can be postulated that a 100 % single-donor platelet supply (collected solely from male donors or screened female donors) could reduce the risk of TRALI,¹⁸ this theoretical prediction may not materialize or may be hard to document because of the observation bias and passive surveillance artifact surrounding diagnoses of TRALI reported to hemovigilance systems¹⁸. Because: 1) the hitherto-available empirical data (Table 5) show an equal risk of TRALI with PRP PWBD versus single-donor platelets; and 2) the Dutch data (Figure 4) show a risk of TRALI secondary to components containing only 20 mL of donor plasma; policy-makers deciding between a single-donor versus a buffy-coat PWBD platelet supply should base their judgment on considerations other than preventing the risk of TRALI. Stated another way, policy-makers considering this specific question could assume that buffy-coat PWBD and single-donor platelets are associated with a similar risk of TRALI.

CONCLUSIONS

Conversion to a single-donor (apheresis) platelet inventory in Western Europe and Canada (outside Quebec) will confer the benefit of a ≥ 2 -fold reduction in the risk of all emerging TTIs. In Western Europe, this would include a ≥ 2 -fold reduction in the risk of vCJD transmission through platelet transfusion. In countries that use buffy coats from first-time donors to produce platelet pools, there will also be a ≥ 2 -fold reduction in the risk of HIV, HCV, and HBV infection from platelet transfusion.

The debate over whether to introduce pathogen-reduction technologies for platelets highlights the (*most appropriate*) concern of regulators and the transfusion-medicine community about emerging TTIs. Based on the available data (Table 3 and Figure 3), however, a move toward a 100 % single-donor platelet inventory is a better strategy for reducing the risk of transfusion transmission of emerging TTIs than is the introduction of pathogen-reduction systems for platelets. Considering the magnitude of the current infectious risks of transfusion in Western Europe and Canada, the disadvantages from these technologies (Figure 3) exceed the advantages.

At least in some countries, the legacy of the HIV (and sometimes also the HCV) transfusion transmission epidemics of the 1980's produced an environment in which national blood services are expected to operate in a risk-management framework⁶⁴. The risk-management strategies, based on the precautionary principle,^{65,66} were perhaps best articulated by the Krever Commission in Canada⁶⁷: "Preventive action should be taken when there is evidence that a potentially disease-causing agent is or may be blood borne, even when there is no evidence that recipients have been affected. If harm can occur, it should be assumed that it will occur. If

there are no measures that will entirely prevent the harm, measures that may only partially prevent transmission should be taken."

A move toward a 100 % single-donor platelet inventory is precisely a "measure that will [not] entirely prevent the harm", and it is recommended because a "measure that will entirely prevent the harm" (i.e., a pathogen-reduction technology with a tolerable burden of adverse effects as well as effective against *all* emerging pathogens) is not yet available. The available pathogen-reduction technologies would completely protect us from the next HIV-like or WNV-like agent; but they would offer no protection from vCJD and potentially some other emerging TTIs as well. Moving toward a 100 % single-donor platelet inventory would effect a ≥ 2 -fold reduction in the risk of the next HIV-like or WNV-like agent *as well as* the risk of vCJD and *all* emerging TTIs; and it would confer this benefit without any increase in the risk of bleeding.

For blood systems operating within a risk-management framework,⁶⁴ a move toward a 100 % single-donor platelet inventory would thus be warranted. A valid objection is that, when inventories are not as large as US inventories, a single platelet manufacturing method may not offer operators sufficient flexibility for meeting platelet supply needs². In such situations, the correct mix of single-donor and buffy-coat PWBD platelets should weigh availability against the increased risk of emerging (and—where applicable—also known) TTIs. In this author's opinion, operators should aim for as high a proportion of single-donor platelets as feasible from the size of their inventory. The decision by the Quebec blood operator (which serves a 7.5-million population) to adopt an 80 % single-donor/20 % buffy-coat PWBD mix (by platelet dose) illustrates how national blood services can satisfy the competing mandates of safety and availability in their jurisdictions³⁰.

An alternative to this approach could be cooperation between national blood services (or independent blood centers) to increase the size of their joint inventories so as to make the maintenance of two manufacturing methods unnecessary for meeting platelet supply needs. The recent findings from the PLADO RCT²⁸ that a platelet dose equal to half the customary dose is as effective as the customary dose in preventing bleeding in patients with hypoproliferative thrombocytopenia should alleviate operators' concerns² about their being able to meet platelet supply needs after long weekends and holidays if they do not maintain two platelet manufacturing methods. In the event of a shortage, single-donor concentrates can be split by hospital transfusion services after long weekends or holidays, to meet patient needs until regular plateletapheresis collections resume and hospital inventories are replenished.

In conclusion, the incremental risks from pooled platelets have been regarded as "tolerable" in the past, because—at that time—the other tolerated risks of transfusion were greater than they are today. Important advances in blood safety were made in the 21st century,

however, regarding TRALI,⁶² TAS,^{13,14} as well as the detection of early HIV or HCV infection in blood donors by means of nucleic-acid testing and the prevention of transfusion transmission of vCJD by deferring visitors to the UK, France, and Europe from donating blood. Given the magnitude of the transfusion risks tolerated today in North America and Western Europe, buffy-coat PWBD platelets must be regarded as exceeding the “as-low-as reasonably-achievable” (ALARA) risk (Table 6)⁶⁸⁻⁷⁰. This is because the emergence of the next major trans-fusion-transmitted pathogen is the greatest threat to blood safety in Western Europe and North America today,¹⁸ and the only way for us to reduce the risk of *any* emerging TTI is by decreasing the number of allo-geneic-donor exposures. This can be accomplished through evidence-based transfusion guidelines and avoidance of pooled products (such as PWBD plate-lets)¹⁸. Accordingly, it is time for the buffy-coat PWBD platelets transfused in Western Europe and Canada to be replaced by single-donor platelet concentrates, in the same manner as the (considerably riskier) PRP PWBD platelets already have—in their vast majority—been replaced by single-donor platelets in the US.

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