Title

Phased Implementation of Pathogen-Reduced Platelets in a Health System Facilitates Scaling-Up of Manufacturing at the Blood Center

Authors

Allen, Elizabeth S
Vincent, Colleen
Reeve, David Angus
et al.

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Phased implementation of pathogen-reduced platelets in a health system facilitates increased manufacturing at the blood center

Elizabeth S. Allen[1] *Colleen Vincent,*[2] *David A. Reeve,*[3] *and Patricia M. Kopko*[1]

BACKGROUND: Pathogen reduction treatment (PRT) reduces the risk of transfusion-transmitted infections from established and emerging organisms. Manufacturing, however, is complex. In our university health system, we phased in pathogen-reduced platelets (PR PLTs) by patient population. We then assessed the implementation strategy and investigated factors in the supply chain that prevented us from meeting the goal of providing greater than 90% PR PLTs within 6 months.

STUDY DESIGN AND METHODS: In Phase 1, PR PLTs were provided in the outpatient cancer center. Phase 2 added inpatients undergoing bone marrow transplantation, and Phase 3 included all patients. In Phase 4, the blood center implemented manufacturing optimization strategies. Product supply and usage during the first 23 months after implementation were evaluated. Investigation of the supply chain included analysis of (1) the number of in-state hospitals receiving PR PLTs; (2) the fraction of products eligible for PRT before and after manufacturing improvements.

RESULTS: During Phases 1 and 2, PR products comprised 44% and 53% of PLTs transfused in the phased-in areas. At 6 months, 41% of PLTs were PR, and at 23 months, 92%. The fraction of PR PLTs transfused in our system correlated logarithmically with the number of in-state hospitals receiving them ($R^2 = 0.71$) and the number of PR PLTs sold to those hospitals ($R^2 = 0.80$).

CONCLUSION: Phased implementation is a practical and ethical way to introduce PR PLTs in a health system and facilitates scalability at the blood center. Widespread availability of PR products may require collective action and can be increased by optimization strategies during manufacturing.

Apheresis platelet (PLT) components carry a risk of contamination from bacteria, viruses, and parasites. Interventions at all stages of the collection process, including donor screening questions, donor skin preparation,[1] use of a diversion pouch,[2,3] donor infectious disease testing, and bacterial culture of the product,[2,3] have attempted to mitigate that risk. Nevertheless, infectious organisms, particularly bacteria, have remained a significant source of transfusion-related morbidity and mortality.[3–5] Furthermore, new transfusion-transmissible pathogens, particularly arboviruses, continue to emerge and cause epidemics.[6] Cold-stored PLTs and cryopreserved PLTs[7] are in development and may decrease the risk of bacterial contamination, but neither is in widespread use. Recognizing the persistent threat posed by PLT transfusion, the US Food and Drug Administration (FDA) has recently issued new draft guidance regarding further mitigation strategies.[8]

ABBREVIATIONS: BMT = bone marrow transplant; CMV = cytomegalovirus; FDA = US Food and Drug Administration; LIS = laboratory information system; PR PLTs = pathogen-reduced platelets; PRT = Pathogen reduction treatment; SOPs = standard operating procedures; UCSD = University of California San Diego.

From the [1]Department of Pathology, University of California San Diego, La Jolla, [2]The American Red Cross, Pomona, California; and the [3]The American Red Cross, Rockville, Maryland.

Address reprint requests to: Elizabeth S. Allen, MD, Department of Pathology, University of California San Diego, 200 West Arbor Drive, MC 8720, San Diego, CA 92103; e-mail: esallen@ucsd.edu.

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Pathogen reduction treatment (PRT) provides a means to address these threats. Although several methods are being investigated,[9] only one PRT system (INTERCEPT; Cerus Corporation) is currently approved by the FDA. Intercept uses amotosalen and ultraviolet A irradiation to crosslink DNA and prevent replication of many pathogens and T cells. The technology is effective[10] with no evidence of transfusion-transmitted infections,[11,12] suggesting that it prevents septic transfusion reactions and provides a proactive approach to address emerging pathogens.

The PRT process, however, brings new complexities to collection and manufacturing. The apheresis product volume and number of platelets must fall within the FDA-approved input guardbands. Eligible products are sterile docked to kits containing amotosalen and are placed in an illuminator, exposing them to ultraviolet light, within 24 hours after collection. An adsorption device then removes any residual amotosalen.[13] The products are then transferred to final storage containers and are ready for inspection and labeling. Bacterial culture is not required.

It was expected that not all collections would be eligible for PRT. Early estimates that only 75% to 85% of single collections and 40% to 45% of double collections would meet requirements for PRT raised concern.[14] An integrated kit for collecting and treating triple products does not exist; it was later determined that although triples cannot be processed as such, they can be split into doubles and singles for PRT. One recent model showed that with optimal collection procedures, 66% to 82% of products can be treated.[15] Consequently, the inventory of pathogen-reduced (PR) PLTs was anticipated to be considerably smaller than conventional apheresis PLTs. It was clear that blood centers needed time to practice, scale up, and optimize collection and manufacturing processes, yet they needed hospitals to accept PR PLTs to begin production and have it be economically viable. Thus, a mixed inventory was inevitable. Transfusion services—particularly early adopters—need to be prepared to implement PR PLTs in a way that accommodates the mixed inventory and the scaling-up process.

In light of these challenges, we sought an ethical and pragmatic implementation strategy in our university health system at the University of California San Diego (UCSD). We undertook phased implementation by patient population, starting with those in the outpatient cancer center. We subsequently expanded usage to include the inpatient bone marrow transplant (BMT) ward, and then the entire health system population. Phased implementation prioritized patients who were immunocompromised and at highest risk of a septic transfusion reaction based on previous studies. Hong et al.[16] found that five of five confirmed septic transfusion reactions occurred in patients with hematologic disorders, and patients who developed symptomatic reactions had lower WBC counts than those who received bacterially contaminated units and did not develop reactions. Of the five reactions, four resulted from outpatient transfusions, and all had delayed onset, occurring 9 to 24 hours after transfusion.[16]

Based on these data, most patients in the cancer center and BMT ward appear to be at increased risk of septic transfusion reactions. Furthermore, should a septic reaction occur, outpatients do not have access to the immediate advanced critical care of the inpatient environment. If they have already been discharged home, they also lack the monitoring of the infusion center caregivers. From a practical standpoint, this approach defined an initial population of patients for PR PLTs who were easily identified by their location. The PR PLT inventory and usage could be expanded over time as manufacturing capabilities increased.

We evaluated the phased implementation strategy by analyzing the number of PR PLTs received from the blood center, adherence to the strategy, and ability to meet our goal of providing greater than 90% PR PLTs within 6 months. When that goal was not met, we investigated factors that influenced the fraction of PR PLTs supplied.

MATERIALS AND METHODS

Pre-implementation

Approval and funding were obtained from the hospital quality council and administration 1 year in advance of the change. Specialists in hematopoietic stem cell transplantation were educated and agreed to the change 6 months in advance.

Our laboratory information system (LIS; SoftBank version 25.5.2.1.22, Soft Computer) was updated to include the relevant product codes. As PRT obviates the need for irradiation and cytomegalovirus (CMV) serology, the LIS was modified to recognize the equivalency of PRT to these common attributes. Two new attributes, "IRRPR" and "CMVPR" were developed to describe products that were either irradiated or PR, and either CMV seronegative or PR, respectively. Patient records containing restrictions for irradiated and/or CMV-negative products were manually updated to IRRPR and CMVPR restrictions. Thus, the LIS was able to interchange PR PLTs with conventional irradiated and CMV-seronegative PLTs, while preventing erroneous transfusion of an inappropriate product.

Six standard operating procedures (SOPs) were updated, and staff reviewed and acknowledged the changes. Two of the SOPs related to the LIS (adding an attribute to a unit and adding special messages for patients). Four SOPs related to transfusion service policies (receiving blood components, irradiation, neonatal transfusion, and PLT transfusion).

Laboratory staff received live, small-group training about the mechanism and efficacy of PRT. Nurses in the outpatient cancer center and the inpatient BMT ward also attended small-group training sessions. These groups were chosen because they were the first areas to receive PR PLTs and because they are accustomed to working with irradiated products. All nurses and physicians received an e-mail communication describing PR PLTs and the plan for phased implementation (Fig. S1, available as supporting information in the online version of this paper) via the health system's standard change notification process.

Our university health system serves two hospitals (750 inpatient beds) and an outpatient cancer center, and

transfuses 9500 apheresis platelets annually. The patient population includes only adults and neonates; other pediatric patients are seen at a pediatric hospital with a separate transfusion service. Because the use of PR PLTs in pediatric populations is controversial, an effort was made to educate and discuss the issue with the neonatal intensivists, who agreed to use PR PLTs.

Implementation

In Phase 1, PR PLTs were intended for distribution only to the outpatient cancer center. In Phase 2, PR PLT distribution was expanded to include the inpatient BMT ward. In Phase 3, restrictions were lifted so PR products could be used throughout the health system. In Phase 4, the blood center implemented manufacturing optimization strategies, and transfusion practices remained the same.

Post-implementation

Per our usual practice, we monitored inpatient census and platelet usage and adjusted orders with the blood center accordingly. We monitored our quality improvement reporting system and informal communications with other departments for any concerns or complaints related to PR PLTs. In the sixth month after implementation, just 41% of transfused PLTs at our institution were PR. Because the target of greater than 90% was not reached, factors affecting the supply chain were investigated.

Supply chain investigation

The American Red Cross initially implemented PRT in March 2015 in Puerto Rico under a clinical study. Routine PRT was implemented at select sites in July 2016 and in California in February 2017. We examined two factors that may have played a role in PR PLT availability.

First, we determined the number of hospitals in California accepting PR PLTs over time, and we examined the number of PLTs sold to those clients. We hypothesized that when very few hospitals accepted PR PLTs, the blood center could not afford to manufacture potentially excess supply. As more hospitals accepted PR PLTs, it would give the Red Cross more flexibility to move inventory where it could be used, facilitating greater production overall.

Second, we considered the effect of manufacturing optimization strategies to increase the proportion of collections eligible for PRT. Beginning in February 2018, the Red Cross made two procedural changes to maximize eligibility: 1) optimizing the settings on the Amicus PLT collection devices to ensure that volume and yield were compatible with PRT and 2) identifying eligible double and triple platelet products to be split into two or three single products before PRT.[17] We hypothesized that the implementation of these procedures would correlate with an increased fraction of PR PLTs at UCSD. We compared the fraction of PLTs eligible for PRT before (25 days in February 2017) and after (April through August 2018) implementing the optimization strategies. The shorter time frame for data collection in the preoptimization phase was due to the data being collected manually.

Data collection and analysis

UCSD inventory and transfusion data for the first 23 months after implementation (February 1, 2017 through December 31, 2018) were collected. PLTs that were manufactured into multiple aliquots (n = 70) were excluded from the usage/discard analysis. Standard descriptive characteristics were performed. In the supply chain analysis, potential correlations between the proportion of PR PLTs at UCSD and factors affecting the supply chain were evaluated graphically and using the Fisher's exact test and Spearman's rank correlation, with p less than 0.05 representing statistical significance.

RESULTS

Supply and transfusion

Phase 1 began on February 10, 2017, and lasted for 6.5 weeks. During that time, we requested 31 PR PLTs weekly (five on weekdays and three on weekends), and the blood center provided an average of 23 (range, 9-33). PR products constituted 44% of PLT transfusions in the outpatient cancer center. Phase 2 began on March 27, 2017, and lasted for 2 weeks. During that time, we requested 91 PR PLTs weekly (15 on weekdays and eight on weekends) and the blood center provided an average of 57 (range, 44-69). PR products constituted 53% of PLT transfusions in the phased-in areas (Fig. 1).

Phase 3 began in month 3 (on April 10, 2017), when we began using PR PLTs throughout our health system. Our standing order fluctuated from 18 to 24 PLTs daily and we ordered additional supplies as needed. We requested that our orders be filled with as many PR PLTs as possible, with conventional products to complete the order. The blood center provided an average of 82 PR PLTs weekly (range, 33-136) and PR PLTs constituted 53% of all PLT transfusions. Phase 4 began in month 13 (February 2018) when the Red Cross implemented manufacturing optimization strategies. Our ordering practices remained the same, but the blood center provided an average of 153 PR PLTs weekly (range, 59-215) and PR PLTs constituted 80% of all PLT transfusions (Fig. 1). Overall, during the first 23 months after implementation, PR PLTs constituted 10,822 (63.8%) of the total 16,945 PLT units transfused. No transfusion-transmitted infections from PR or conventional PLTs were identified.

PLT transfusions increased over time (Fig. 1), from an average of 677 per month in 2017 to 791 per month in 2018 (p = 0.004, t test). However, the health system has also grown: the number of patient bed days increased by 9.4% from fiscal year 2017 to 2018, and a 6.1% increase is predicted for fiscal year 2019. Additionally, the number of allogeneic BMTs increased by 28% from 2017 to 2018.

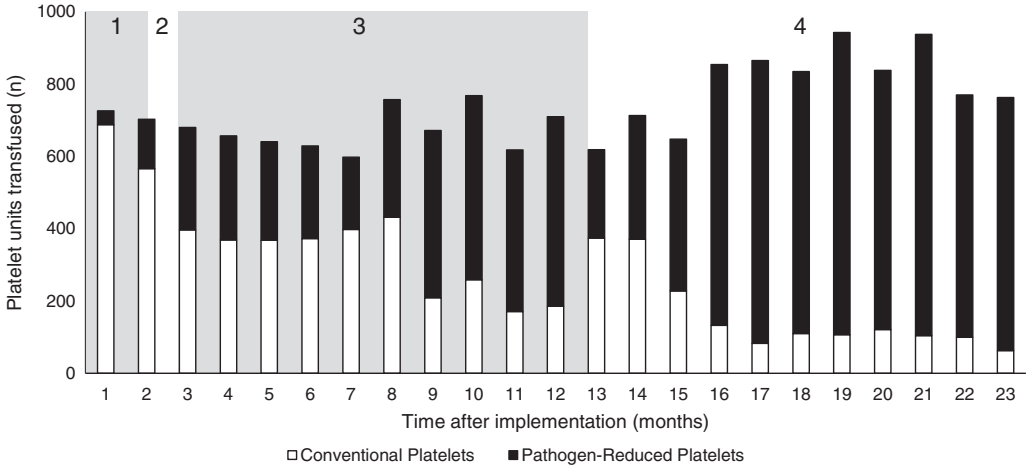

Fig. 1. Conventional and PR PLTs provided by the blood center during the 23 months after implementation. PR PLTs were introduced on February 10, 2017. During the study period, the transfusion service used an average of 737 PLTs monthly. A total of 16,945 PLTs were transfused, of which 63.4% were PR. Numbers at the top of the shaded and unshaded regions correspond to the phases.

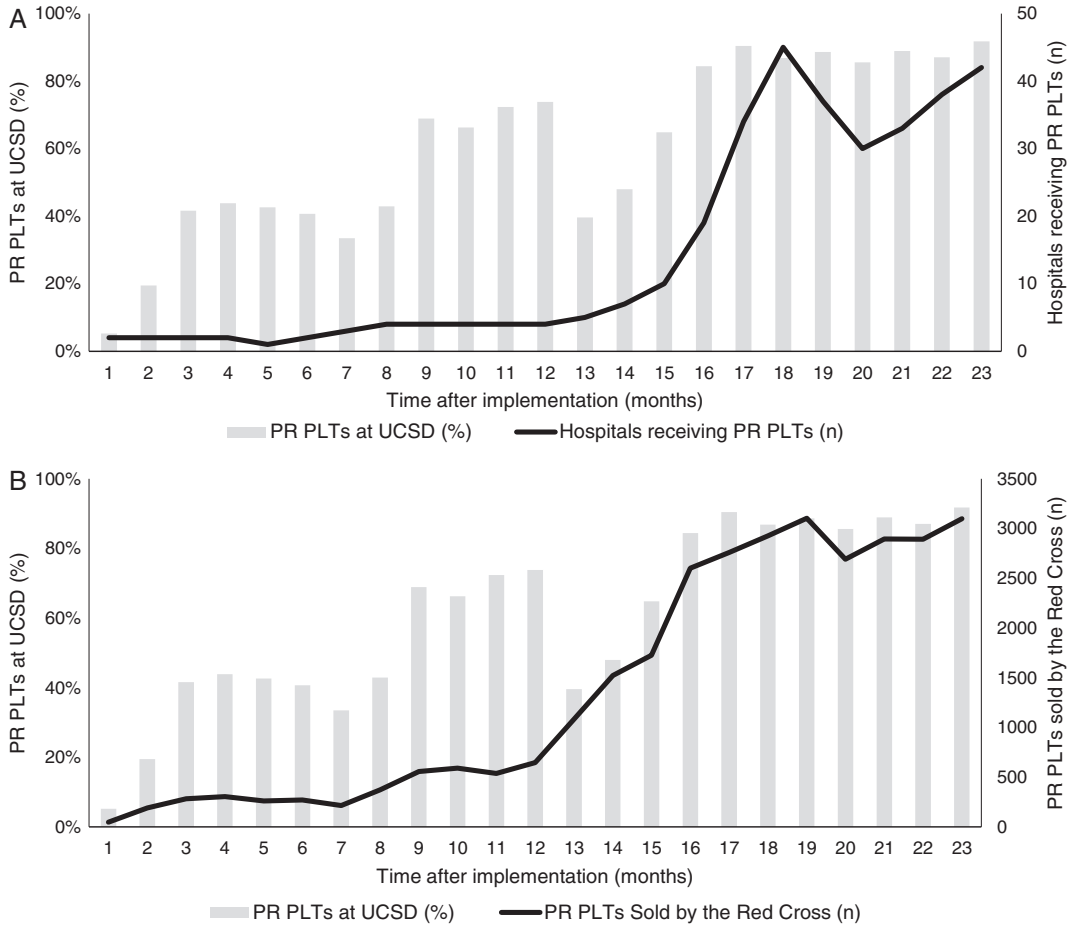

Fig. 2. Fraction of PR PLTs transfused at UCSD, and supply-chain factors affecting the blood center. The fraction of PLTs transfused at UCSD that were PR ranged from 5% in month 1 to 92% in month 23 (A and B, bars). The fraction at UCSD was then compared to the number of in-state hospitals receiving PR PLTs (A, line) and to the number of PR PLTs purchased by those hospitals (B, line).

Discarded products

During the study period, 875 of 17,820 PLTs received (4.9%) were not transfused: 680 (77.7%) expired, 68 (7.7%) were unacceptable due to broken containers, temperature, or visual inspection, 66 (7.5%) were returned to the blood center, seven (0.8%) were recalled, and three (0.3%) were spiked but not transfused. Of the untransfused units, 393 (44.9%) were PR; 328 of those expired.

Adherence to strategy

During Phases 1 and 2, laboratory technologists sometimes noted that more PR PLTs were present in inventory than they anticipated using in the phased-in areas. When this occurred, PR PLTs were issued to areas not yet phased in, to avoid wastage. An average of 1.3 PR PLTs daily (range, 0-6) were issued in this manner. Clinicians' acceptance of the product was presumed because they had been notified of the plan for implementation.

Implementation goal

The goal of achieving greater than 90% PR PLTs within 6 months was not reached. At month 6, PLT transfusions were 41% PR. At month 12, PLT transfusions were 74% PR. At month 17 (June 2018), PLT transfusions reached 90.4% PR, and then hovered in the 80% to 90% range until month 23 (December 2018), when they reached 91.7% PR.

Supply chain investigation

The number of California hospitals supplied by the Red Cross who had adopted PR PLTs grew from two to 73 during the study period. The subset of hospitals actually receiving PR PLTs each month ranged in number from two to 45 (Fig. 2A, line). The number of PR PLTs manufactured by the Red Cross and sold to these clients grew from 48 per month to 3099 per month (Fig. 2B, line). These metrics each correlated graphically ($R^2 = 0.72$ and $R^2 = 0.80$, respectively; Fig. 3) and statistically ($r = 0.84$ and $r = 0.90$, respectively; $p < 0.001$ for both, Spearman's rank correlation) with the fraction of PR PLTs at UCSD.

Manufacturing optimization strategies were deployed in the blood center in month 13 (February 2018), and manufacturing was reduced for several days while staff were trained. Before the optimization strategies, 124 of 753 units (16.5%) were eligible for PRT, and 60.5% of the eligible units underwent PRT. After implementation, 15,835 of 23,848 units (66%) were eligible, and 76.6% of the eligible units underwent PRT, representing a statistically significant increase in units eligible for PRT ($p < 0.001$, Fisher's exact test).

Initially, the optimization strategies correlated with a *decrease* in PR PLTs at UCSD, which likely resulted from a combination of reduced PRT during training and a simultaneous sharp increase in PR PLT use at other hospitals (Fig. 2B, months 12-13). The decrease, however, was followed by an upward trend in the percentage of PR PLTs at UCSD, which remained above 80% from months 16 to 23. Overall in Phase 3, 3568 of 6,730 (53.0%) PLTs transfused were PR, whereas in Phase 4, 6992 of 8786 (79.6%) were PR—a statistically significant increase ($p < 0.001$, Fisher's exact test). As manufacturing increased, the fraction of PR PLTs that the Red Cross sold to UCSD dropped from 85% to 23%, and remained in the 20% to 30% range for the remainder of the study (Fig. 4, dashed line). Yet even as UCSD became a smaller piece of the market, internal use of PR PLTs increased, illustrating that widespread adoption combined with increased manufacturing facilitated increased use.

Institutional acceptance

No relevant comments or complaints were received through our quality improvement reporting system or personal communication. At 18 months after implementation, nine physician stakeholders (six hematology/oncology physicians, one transplant surgeon, one trauma surgeon, and one neonatal intensivist) were surveyed. Only two responses were received, both of which suggested that the change was unobtrusive. As an example, one physician stated, "Thank you for bringing this change to our attention. ... It was happening in the background, but now that I am aware, I am happy that you implemented this product."

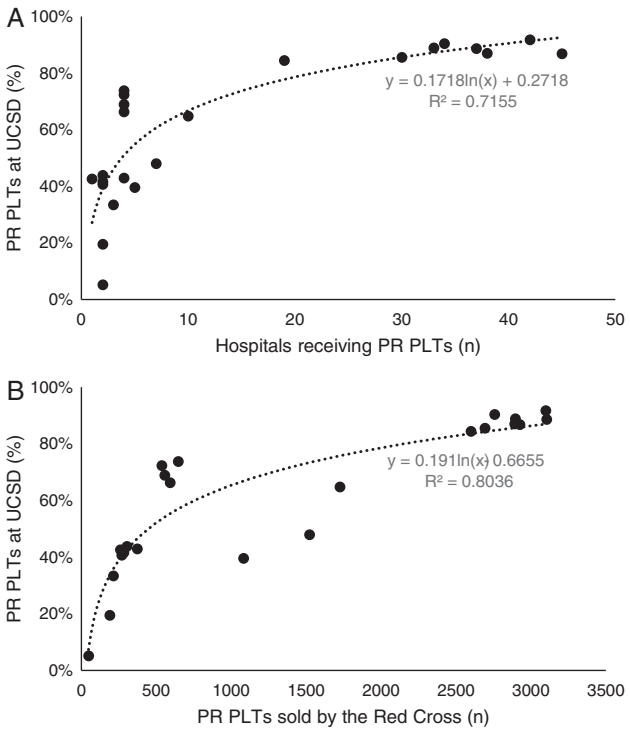

Fig. 3. Correlation over time between the fraction of PR PLTs at UCSD and other in-state hospitals accepting PR PLTs. The fraction of PR PLTs transfused at UCSD each month correlated logarithmically with the number of in-state hospitals receiving them (A, $R^2 = 0.72$) and with the number of PR PLTs purchased by those hospitals (B, $R^2 = 0.80$).

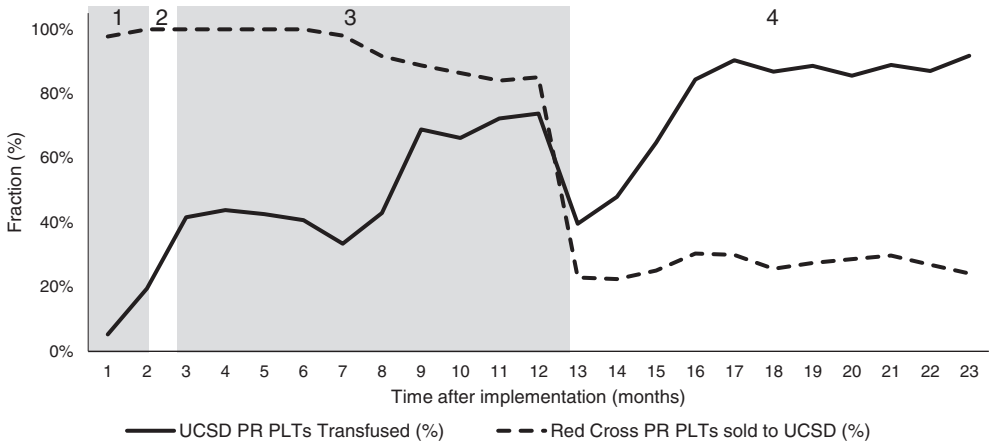

Fig. 4. Fraction of PR PLTs transfused at UCSD, and fraction sold to UCSD by the blood center. The fraction of PR PLTs sold by the Red Cross to UCSD plummeted in month 13 after manufacturing optimization strategies were implemented and new customers came on board. Yet the fraction of PLTs transfused at UCSD that were PR increased in Phase 4. Rather than increasing competition for a static resource, adoption by other institutions and improved manufacturing facilitated increased use in our health system. Numbers at the top of the shaded and unshaded regions correspond to the phases.

DISCUSSION

PRT addresses a wide array of bacteria, viruses, and parasites, as well as emerging infectious organisms; it provides safer blood products.[12,18] The collection and manufacturing processes, however, introduce new complexities. Phased implementation by transfusion services is a practical, ethical way to bring this product to patients while providing blood centers with the time and clients needed to initiate and advance manufacturing. We phased in PR PLTs by patient group, starting with those in our outpatient cancer center and expanding to the inpatient BMT ward and finally the entire health system. No complaints were received. Reaching the goal of providing greater than 90% PR PLTs took longer than expected, about 23 months, demonstrating that blood centers may need time to scale up and adapt their procedures to implement PRT without significant decreases in inventory. Optimization strategies at the blood center ultimately improved the fraction of PLTs eligible for PRT. Additionally, the increasing number of in-state hospitals accepting PR PLTs correlated with the increasing fraction in our inventory. These data suggest that implementing PRT requires collective action of the transfusion medicine community.

Phased implementation is practical because it enables a client to accept PR PLTs while the blood center's manufacturing processes are initiated and evolve. From the transfusion service perspective, PR PLTs can be used earlier, without waiting for the blood center to perfect its procedures. Our approach delineates specific populations for PR PLTs who are at risk of clinically significant septic transfusion reactions and who can be easily identified based on their location. Although concerns have been raised that providing PR PLTs for certain populations may be overly complex or lead to delays,[19] we did not experience any such difficulties.

Ethically, the main case for phased implementation is that it provides a safer product to as many patients as possible. One might counter that providing a safer product to some patients but not others violates the ethical principle of justice. The logical conclusion of such an argument, however, is that PR PLTs should be implemented only if they can be provided to all patients. From a practical standpoint that may be impossible, particularly in these early years of PRT. Thus, to follow this argument dogmatically means delaying or avoiding implementation entirely, which then violates the principle of nonmaleficence. Within the constraints of feasibility, providing a safer product to some patients rather than none appears to be the most ethical choice. Furthermore, providing PR PLTs to some patients facilitates increased manufacturing, enabling the product to be provided to more patients over time and eliminating the initial problem.

Phased implementation by patient population is also ethical because it is logical and evidence-based. It provides the product to patients who are at greatest risk of harm if a septic reaction should occur, abiding by the principle of justice. Certainly, it is possible there are other patients who could also be at high risk, for example, an individual who is immunosuppressed but not being treated at the outpatient cancer center. While our strategy may not cover every high-risk patient, it was evidence-based, rational, and feasible. Moreover, Phases 1 and 2 were relatively short, and within 2 months we began using PR PLTs throughout our health system.

Other institutions have adopted different implementation strategies, including converting directly to 100% PR PLTs (National Institutes of Health Clinical Center, personal experience) or employing secondary testing (culture or point-of-issue testing) on conventional PLTs during the conversion.[19] At UCSD, our blood supplier could not convert directly from

0% to 100%. We had previously tried secondary point-of-issue testing[20] and found that it was not optimal for our health system. Our priority was to obtain PR PLTs for as many patients as possible, as soon as possible. Nevertheless, the varied approaches demonstrate that a diverse set of strategies can be successful, and implementation strategies must be tailored to the institution.

Phased implementation inherently involves the challenge of maintaining a mixed inventory. In Phases 1 and 2, significant numbers of PR PLTs were issued to areas that were not yet phased in, an effort to avoid wasting them and simultaneously illustrating the unpredictability of PLT usage. In addition, the mixed inventory generated questions from technologists about how to prioritize PR PLTs. For example, for a BMT patient, should the technologist select a PR PLT that was near expiration or a conventional PLT of the preferred ABO group? We opted to avoid wasting PR PLTs, but there is no clear answer. Moving into Phase 3 and obtaining more PR PLTs over time alleviated most of these challenges in the laboratory. Transfusing professionals throughout the hospital also had to use both conventional and PR PLTs, but we did not receive any questions or complaints from them; fortunately, the product containers appear similar and are administered in the same way.

The mixed inventory was necessary to provide time for the blood center to scale up PRT. Investigation into the supply chain revealed a correlation between the number of other hospitals using PR PLTs, the number they purchased, and our own fraction of PR PLTs. Importantly, this analysis was not exhaustive, and other factors such as time and practice likely also play a role and affect availability of PR PLTs. Nevertheless, the correlation was strongly positive. There may be a tipping point, either in number of hospitals or their volume, which facilitates mass production and use. Remembering the adage of necessity as the mother of invention, perhaps necessity drove the manufacturing optimization strategies that ultimately made it feasible to manufacture more PR PLTs. Our fraction of PR PLTs hovered around 70% for several months, and only after the blood center implemented its changes did we reach our goal of 90%. The number of facilities accepting PR PLTs, however, appears to be the key factor. Even after the optimization strategies were implemented, the blood center still performed PRT on only 76.6% of the eligible products. These data suggest that if the transfusion community works collectively to implement PRT across more institutions, it may ultimately result in more PR PLTs becoming available for everyone.

Here, we reported our experiences as an early adopter, but our thoughts now shift to the next phase of PR PLT use. Can we obtain 100% PR PLTs at UCSD, and how? What will other institutions experience? Transfusion services adopting PR PLTs now may find that they obtain larger amounts of PR PLTs more quickly. On the other hand, if many facilities implement at the same time, demand could exceed supply. If all clients of the Red Cross requested 100% PR PLTs, there would be instant and intense competition. The next challenge in PLT manufacturing is how to approach conventional platelets or how to make 100% of collections eligible for PRT. Of note, other countries have achieved the latter.[12]

This hypothetical situation may soon be a reality. The FDA draft guidance recommends that PLTs undergo either PRT, secondary culture, or secondary point-of-issue testing.[8] PRT provides a transfusion-ready product for those wishing to avoid any secondary testing (as well as primary culture). Demand may increase considerably once these or similar requirements are codified in an FDA guidance.

PRT was approved by the FDA in December 2014 and is gaining traction in blood centers and transfusion services. PR PLTs are not a perfect product; there is evidence, for example, that they generate lower increments than conventional PLTs.[21,22] Nevertheless, they provide numerous benefits to patients. Although they are more expensive, we agree with others[19] that patient safety supercedes cost. Avoiding implementation because PR PLTs are too expensive or cannot be provided to all patients raises ethical concerns. The experiences at UCSD and other institutions[19] demonstrate multiple successful ways to phase in PR PLT use. Collective action of numerous transfusion services may be needed to enable widespread availability. Phased implementation provides a practical, ethical way to implement PR PLTs in a health system, while facilitating manufacturing improvements at the blood center.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

WEB RESOURCES

Fisher's Exact Test, http://www.langsrud.com/fisher.htm.
VassarStats: Web site for Statistical Computation, http://vassarstats.net/.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Fig. S1. Electronic message from the laboratory to the medical staff regarding the implementation of pathogen-reduced platelets. Following a standard format used at our institution for all laboratory communications, we explained the rationale and implementation plan for PR PLTs.