How safe is safe enough, who decides and how? From a zero-risk paradigm to risk-based decision making

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Health care costs have risen to 17.4% of US gross domestic product, and health care economists urge a reversal of this unsustainable trend.[1] In response, providers find themselves entangled in a transition from "volume" to "value," moving away from payment tied to utilization toward reimbursement linked to patient outcomes. As transfusion medicine practitioners, we see this direction reflected most starkly in the adoption of patient blood management programs aimed at optimizing transfusion therapy (largely by driving down use) and reducing adverse events.

Patient blood management programs address volume and promote value as documented in pivotal, randomized controlled trials (e.g., TRICC, FOCUS) demonstrating that outcomes are no better with liberal transfusion strategies, and some outcomes may be improved with restrictive approaches. Red blood cell (RBC) utilization in the United States has decreased from 49.4 units per 1000 population in 2008 to an estimated 39.6 per 1000 currently (R. Benjamin, American Red Cross, personal communication, 2013) and estimates trend to less than 30 units per 1000 population in the Netherlands, Canada, and Australia. Because US community blood collection facilities are structured to provide high volumes of components, evolving restrictive transfusion practices mean that revenues are falling and centers have excess capacity, remediation of which leads to reductions in blood program staffing. At the same time, hospitals concerned about the uncertainty of health care financing under health care reform demand price reductions. Reduced staffing and falling revenues make it difficult for blood programs to maintain continuous improvement initiatives and surge capacity for unexpected demand. Meanwhile the public, many physicians, professional standard-setting organizations, and regulatory agencies seem committed to a zero-risk blood supply paradigm with inadequate attention to its associated costs. These trends create a perfect financial storm of major impediments for blood centers wishing to maintain high standards of quality and patient service, much less to innovate. The larger health care sector struggles with the pressures for reform by focusing on coordinating service delivery in constructs like accountable care organizations and by enhanced competition through price transparency.[2] These efforts encounter resistance when the public perceptions of risk and of cost-effectiveness analyses come into play.[3] In the United States, the Food and Drug Administration (FDA), by statute, addresses blood safety largely independent of resource considerations. Professional standard-setting organizations in the United States and elsewhere issue standards that focus on product safety without a comprehensive or transparent consideration of cost-utility or cost-effectiveness especially relative to more global patient safety initiatives. A narrow focus on product safety, which has diminishing returns after major issues are mitigated, can divert limited resources from higher-impact patient safety concerns. Neglected initiatives may include prevention of inappropriate transfusions and mitigation of common risks associated with appropriate transfusions (not to mention diversion of limited resources from more global risks outside transfusion such as health care-associated infections and medication errors).

The current paradigm, with its foundations firmly rooted in our experience of HIV and hepatitis, was described in a November-December 1987 **TRANSFUSION** editorial. "Looking back on the year this volume spans

ABBREVIATIONS: ABO = Alliance of Blood Operators; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RBDM = risk-based decision making.

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leaves one uneasy about the apparent reinforcement of the public policy that only a blood supply with zero risk to recipients is politically acceptable. A corollary of this policy has also emerged: if anything can be done to reduce the risks of transfusion, without regard to its position in the ranking among the other risk-reduction efforts society demands of medicine, it should be done. Thus, a *de minimis* risk stands on equal footings with major health hazards."[4]

This stringent precautionism is in stark contrast to the risk analysis approach employed during the previous decade when mathematical calculations were used to estimate harm after introduction of new technologies whose risks could be measured but was problematic in addressing hazards that were quantitatively uncertain.[5] By 1995, the Institute of Medicine report on AIDS' entry to the blood supply and the response to it[6] included 14 recommendations urging action despite ambiguity. For example, Recommendation 6 stated "where uncertainties or countervailing public health concerns preclude completely eliminating potential risks, the FDA should encourage, and where necessary require, the blood industry to implement partial solutions that have little risk of causing harm." In Canada, the 1997 Krever Commission report stated "if there is a risk, no matter how small, the (blood) operators should seek to mitigate that risk . . . in the absence of evidence, precautionary steps should be taken."[7] This rigid application of the precautionary principle requires that those developing policies prove the negative, that risk is not accrued. The transfusion medicine embrace of this approach is intimately tied to how we addressed the threats of that time, that is, HIV and HCV. It is legitimate to ask what could have been accomplished if the current laser focus on transfusion-transmitted infections, without transparent concern for resource use, had been directed to more appropriate transfusion or at some of the medical errors to which the Institute of Medicine has ascribed a far higher mortality burden.[8]

Even in the face of restricted resources many of us (both physicians and our professional organizations) are nearly incapable of looking beyond individual patient decisions to a population-based perspective:[9] namely, a contemporary discussion of the "tension between population health and individual health care." Traditionally, US health care principles involve treating each patient strictly as an individual. The observation that higher health care spending in the United States does not translate into even equal outcomes compared to other countries supports a change in focus from individual clinical decision making toward a population health approach that promotes community wellness. This transition envisions a system prioritizing aggregate outcomes and aligning resource allocations with them. It explicitly recognizes that some patients will be disadvantaged who now receive essentially unlimited diagnostic and therapeutic procedures and limited resources that might provide more benefit for the community may be diverted.

In this climate, cost-utility analyses show some blood product safety initiatives cost more than 10 times the currently accepted threshold of up to $100,000/quality-adjusted life-year (QALY) gained for other of medical interventions.[10] Will the emphasis on "outcomes" by payers and practitioners extend to the blood community and will we, the public, and our regulators reexamine any zero-risk expectations we hold? Can a new strategy, risk-based decision making (RBDM), emerge to handle these growing issues of concern?

The current blood safety decision-making process is complex, difficult to explain, and not obviously proportional to risk and leads to dissatisfaction among blood operators, reimbursement or funding agents, industry, patients and patient groups, governments, regulators, and others. As we move to value-based care delivery, one might conclude that a formal, rational plan for explicit decision making (and for paying for our decisions) would resonate with transfusion medicine. This development has not been the case. Instead of integrating blood safety within a societal perspective of patient outcome priorities, the blood community's practices appear to be siloed in our very narrow discipline, with regulatory and professional standard-setting processes for making safety policy decisions reflecting the 1980s experience with HIV and HCV—certainly not ideal for addressing less titanic problems. This holdover 20th-century approach with its political, medicolegal, and governance underpinnings leads to safety measures aimed at maximal safety without defining "tolerable risk," invoking and potentially misapplying the precautionary principle. In the absence of an appropriate, more rigorous decision-making framework, the pursuit of zero or de minimis risk can create an atmosphere where no intervention is too expensive.

A decision-making process is needed that maximizes recipient and donor outcomes, that integrates from a *societal* perspective, the science of blood safety, the ethics, social values, economics, public expectations, and historic context in which we live, with the priorities of health care. A possible framework for moving in this direction was articulated during the 3-day International Risk-based Decision-making for Blood Safety Consensus Conference in Toronto in October 2010.[11] An independent 12-person panel of professionals with experience in the risk industry and health care concluded: "Although the public often appears to expect that all risks can be eliminated from their lives, zero risk is an unattainable goal."

After the consensus conference, the Alliance of Blood Operators (ABO) began a Risk-based Decision Making Project (to which the authors are contributing) "to develop an integrated, internationally applicable framework, entrenched in donor safety and optimal patient out-

comes, to guide major policy and operational change." ABO is a global network of blood operators that includes America's Blood Centers; the American Red Cross; the Australian Red Cross Blood Service; Blood Systems, Inc.; Canadian Blood Services; the European Blood Alliance; and National Health Service Blood & Transplant (United Kingdom). Ad hoc partners on this project include AABB and Héma-Québec. Currently in Phase I, the ABO project is developing an overall framework to structure more formal transfusion safety decision making. The project is focused on four areas: 1) the development of the framework itself, 2) methods for assessment of health economics and outcomes targeted to the blood safety context, 3) best practices for the engagement of stakeholders in RBDM, and 4) the creation of a Web portal that will provide access to RBDM tools, where risk data and decisions may be shared. Under discussion are risk management principles, communication and consultation policies, risk tolerability criteria, and policies for conduct of natural and social science assessments. The framework will include guidance regarding issue identification and problem formulation, assessment, evaluation, and decision making and follow-up. Blood safety health economics and outcomes tools are intended to support the decision-making process.

This issue of **TRANSFUSION** contains seven articles that raise questions about how we might approach various aspects of transfusion safety. Each demonstrates a hazard and potential interventions to mitigate risk. Each would benefit from the application of a formal RBDM process.

O'Brien and coworkers[12] describe an analysis in Canada of a risk question-based *Trypanosoma cruzi* testing strategy. They estimate that 0.71 to 4.38 seropositive donations were missed in 2012—not zero risk and explicitly judged to be tolerable. There is no description of the process that led to that judgment.

Eder and colleagues[13] isolated *Clostridium perfringens* from an apheresis platelet (PLT) associated with a febrile reaction and from a cocomponent. The aerobic bottle routinely used for early in-process culture of PLTs did not support growth of this anaerobe, and a point-of-transfusion test missed it. Some may argue that we should routinely use anaerobic culture bottles and that point-of-transfusion tests should be reconfigured to address these organisms. The authors, appropriately in our view, "acknowledge that policy should not be based on a single anecdote," but do not address the question of risk thresholds for changing policy, from where to get the resources that would be consumed by intervening further or assessing the societal interest being addressed by intervention.

Garson and coworkers[14] demonstrate that a nucleic acid testing–based screen for 16S ribosomal DNA is too insensitive, compared to a culture-based test, for bacterial screening of PLTs early in storage. They found seven of 2050 expired PLTs to be repeatedly reactive by their polymerase chain reaction (PCR) test, none of which was confirmed with culture of frozen, stored aliquots. They conclude that "rapid PCR assays such as this may be suitable for a strategy of late or prerelease testing," despite identifying only 17.6% (3/17) of the culture-positive units. How does one decide that this or another level of performance is appropriate when selecting strategies to mitigate PLT-associated sepsis? Vollmer and colleagues[15] evaluated a flow cytometric method of bacterial detection in RBCs, suggesting that, while room temperature–stored PLTs may have a higher per-unit risk, because of the much large number of RBC transfusions compared to PLTs, we might consider the assay to be a "basic tool for studying bacterial contamination of RBCs, potential screening strategies, and the clinical outcome of RBCs prepared for transfusion." How do we decide if they are correct and that the morbidity associated with sepsis from RBCs justifies the effort?

De Kort and coworkers[16] recognize the donor history questionnaire as a series of tests susceptible to analysis using standard test performance metrics, including cost-effectiveness. Under their assumptions, and with current testing protocols, the transfusion-transmitted infections queries studied are not cost-effective, with an incremental cost-effectiveness ratio (ICER) of almost €700,000 per QALY. We suspect that the donor questionnaires used in the United States are similarly cost-ineffective and would enthusiastically participate in an evaluation of their continued use in their present forms. Were we to agree to suspend interventions at some ICER threshold in the United States, one can speculate about the impact on donor deferral and counseling and regulatory reporting burdens (e.g., investigation, remediation, and biologic product deviation reports associated with postdonation information).

Simon and colleagues[17] conclude that universal screening with *Babesia microti* antibody of donors for infection in endemic regions "is appropriate from an economic perspective based on the societal willingness to pay for preventing infectious threats to blood safety" with ICER estimates of $760,000/QALY. The authors base their judgment on the observation that we have implemented interventions costing this much and more for other infectious threats. Is their rationale sound in a RBDM framework that integrates resource-constrained priority setting from a societal perspective?

The risks from transfusion of hepatitis E virus (HEV) transmission have provoked much recent discussion.[18] Ren and colleagues[19] in the People's Republic of China describe a donor HEV antigen prevalence of 0.06% (6/10,741), half of whom harbored viral RNA. Is this sufficient, in and of itself, to justify screening in their country, and if not, what further epidemiologic, transmission, and clinical data are needed to make such a decision—questions we will face in North America soon?

These articles reinforce something we already recognize. Clinical vigilance drives the continuous improvement of transfusion safety. Accepting this reality, can we develop an objective case for support of a robust (mandatory?) biovigilance program that will identify and quantitate emerging risks and even monitor clinical outcomes related to transfusion? We argue that a transition to RBDM is the optimal approach and that the appropriate point of view for RBDM is a societal perspective for priority setting, not what we see from the bottom of the transfusion medicine "silo."

Another example we will be considering in the very near future—the long anticipated availability of photochemically treated blood components (pathogen reduction)—provides an opportunity to apply RBDM to guide our thinking and arrive at a rational decision. We will be challenged to weigh the risks, benefits, and costs of these new technologies, in a nuanced assessment that incorporates scientific and economic factors, including the cost and value of existing safety interventions in the context of broader societal priorities. A report analyzing the cost-utility of pathogen reduction in Canada estimated a cost of $1.3 million/QALY for whole blood pathogen reduction and $1.4 million/QALY for PLTs and plasma.[20] In a qualitative risk-benefit analysis focused on pathogen-reduced apheresis PLTs in the United States, the authors (including an employee of a company developing pathogen reduction technologies) concluded there was a "favorable risk-benefit profile for the implementation of pathogen-inactivated platelets."[21] Reduced bacterial contamination, amelioration of emerging infectious agent transmission, and transfusion transmission of cytomegalovirus were quantified benefits. Nonquantified benefits were protection against transfusion-associated graft-versus-host disease, reduction of febrile nonhemolytic transfusion reactions and alloimmunization, and the possibility of eliminating some testing and administrative costs. The conclusions of these two studies exemplify the complexity and criticality of the assumptions used to evaluate changes in the transfusion safety regime. They highlight the utility of a structured approach to decision making and, critically, a transparent process for identifying and engaging stakeholders who will have to "sign off" on assumptions used for modeling and the tolerability of the risks estimated. We must ask if it is appropriate for the blood community to commit resources of the magnitude required to implement pathogen reduction without such a process to inform the decision making and ultimately justify the resources needed if implementation is judged appropriate.

Ultimately, the decisions required of the blood community, including our regulators, are not solely ours to make. That is a major benefit of the evolving conception of RBDM—the foundational engagement of a broader audience in decision making than has been included historically. We think RBDM reflects an appropriate broad view of the health care universe. It ultimately allows us to pursue the initiatives that add a threshold value to the delivery of our services, to maintain risk levels as low as reasonably achievable when current scientific, social, and economic factors are taken into account and it demands subsequent review and revised decisions in light of new information and technology. The alternative is to continue on our current course—in our opinion too narrowly. We can choose the latter, but it is not clear that this paradigm is financially sustainable without rethinking the value proposition of maintaining a safe and adequate blood supply. If we choose to move toward the former, we must prepare to defend social utility decisions that tell patients and their advocates when the decision is that some specific safety or quality initiatives "are not worth it." May we all live in interesting times.

CONFLICT OF INTEREST

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