

Nucleic Acid Amplification Testing and Blood Safety: What is the Paradigm?

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Over the past 2 decades the pendulum of blood safety policy has swung wide and hit hard. Intense criticism of delayed responses to the early clues of the transfusion AIDS epidemic and of tolerance to the long standing problem of post-transfusion hepatitis has had enormous repercussions.(1) Blood collection systems in a number of countries have been completely restructured. Policy makers and physicians have gone to jail. Over the past five years the working paradigm has shifted toward “the precautionary principle” and the elusive mirage of a “zero risk” blood supply. However, recent commentary on the precautionary principle suggests that even this conservative approach must not seek zero risk or involve disproportionate responses, but rather should incorporate scientific data, consistency with comparable situations, and cost-benefit analyses into precautionary decision making.(2) In this issue of **Transfusion**, a number of papers on Nucleic Acid Amplification Testing (NAT) for infectious agents, illustrate some of the very different drivers that have influenced the formulation of blood safety policy: perception, science, ethics, international politics and economics. A review of the data and issues raised in these papers presents the opportunity to discuss recent evolution of blood safety decision making, and thus attempt to answer, or better yet influence, the question posed in the title of this editorial.

NAT testing of whole blood donations has been in place in the United States since early 1999. In this issue, Stramer, Caglioti and Strong (3) report the results of testing small minipools (MP) of 16-24 plasma samples under IND (Investigational New Drug Application) clearances from the FDA. As of June 2000, the major programs in the US have tested a total of 16.3 million donations for HCV RNA, and 12.6 million for HIV RNA. A total of 62 donations (1:263,000 screened units) were confirmed to be positive for HCV RNA and negative in serological testing. Similarly, 4 HIV-RNA positive, serologically negative donations (1:3,150,000) were identified. Each of these donations could well have infected 2 to 3 recipients. Although many of the participating blood centers were operating in “phase I “ conditions (i.e., components could be issued prior to the availability of NAT results), only one (HCV) NAT positive component was transfused. With regard to specificity, the false positive rate (i.e., unconfirmed NAT reactive donations) was only 1 in 15, 800 units, better than even the best of serological screening assays.

Thus, despite fears to the contrary, the phase-in of NAT screening has occurred efficiently and without compromise to the availability of the blood supply. This is truly remarkable when one recognizes that implementation of NAT required the building of specially designed and equipped NAT laboratories and the development of new procedures to obtain donor consent and collect and rapidly transport specimens to regional NAT laboratories. Additionally, technologists were trained in molecular biology techniques; complex new data management systems for sample pooling, resolution and supplemental testing of reactive pools were developed; and NAT results were integrated into donor screening and inventory management systems. It also required NAT

manufacturers with limited prior experience in the blood screening arena, to scale up instrument and reagent production capacity and technical support services to support the testing and release of approximately 50,000 donations per day in the U.S. It is hard to escape the conclusion that this program represents an enormous accomplishment and that the benefits of accelerated implementation of NAT have outweighed the risks. Furthermore, data are emerging that show that the yield of MP-NAT has been entirely consistent with projections derived from incidence-window period model based estimates (3-8). These observations should enhance our confidence in the ability of modeling strategies to estimate the current risk of the blood supply, and to predict the yield of individual donation (ID) NAT over MP-NAT and the yield of NAT assays for HBV and for other infectious agents in the future.

Nevertheless, Sherman (9) raises a number of ethical concerns and cautions about the US NAT programs, cogently reminding us that “no harm, no foul” is not an appropriate position to take when medical ethics are considered. He questions whether the approach of essentially universal introduction of NAT while the assay was unlicensed was justified, given the very low projected yield of the tests and the complex ramifications of this unprecedented implementation process. He raises a number of ethical and medical-legal concerns, including issues around donor and recipient informed consent and cost-reimbursement for an unlicensed procedure. He is particularly critical of the “phase I” testing during which cellular components have been released into hospital inventories based on licensed serological test results prior to completion of NAT. While some of his points may be arguable, or even incorrect (e.g., the NIH Office of Protection from Research Risks formally ruled that recipients of NAT screened blood are not research subjects and do not require specific informed consent), he rightly points out that the interpretation lies in the eye of the beholder. What he did not discuss is the difficulty inherent in the collection of whole blood to provide both transfusable components and plasma for further manufacture. The challenge was to implement a program to limit the contamination of manufacturing pools (as required by international regulatory bodies) in a way that provided maximum benefit to the recipients of components. We should acknowledge the vision and flexibility of FDA and the blood systems in identifying a new, albeit imperfect paradigm for rapid implementation of an entirely new approach to donor testing.

Sherman’s critique is an interesting juxtaposition to the article by Legler et al. encouraging accelerated transition from MP to ID-NAT (10), and to the workshop summary by FDA scientists which applauds the rapid implementation of MP-NAT and addresses the issues impacting the probable need to move to ID-NAT and to add Hepatitis B and Parvovirus B19 DNA detection to NAT screening systems in the near future.(11) These perspectives reflect the domino effect that has permeated NAT screening at the national and international levels. However, these articles fail to recognize the growing pressure to control the escalating costs of medical care in general, and of blood transfusions in particular. Although blood safety has had a relatively high level of political and financial support over the past decade, there are clear signs that additional reimbursement for blood safety initiatives will have to be established if the

crusade for the holy grail of “zero risk” is to continue. As recommended by Sherman, perhaps this is a good time for “positive retrospection”.

The current debate over MP- versus ID-NAT presents an opportunity to try to bring evidence-based decision making back to the blood safety arena, and thus hopefully tug the pendulum back toward equilibrium. The implementation of NAT using minipools was a necessary compromise in light of the cost and complexity of NAT technologies and the massive scope of blood screening. The article by Legler et al. demonstrates that assay systems that have the throughput capacity to perform NAT on individual donation specimens can and are being built. Such assays have the theoretical advantage of enhanced sensitivity since performing MP NAT results in a dilution of viremic samples proportionate to the pool size. A recent study suggests that this dilution factor can impact detection of infectious donations, and hence ID NAT may be required to interdict rare window phase donations with very low viral load (12). On the other hand, another recent case report (13) demonstrates that even ID NAT may not detect all infectious units since only a small sample of plasma is tested relative to the volume of transfused blood components.

The fact that ID NAT is possible and may prevent exceedingly rare cases of viral transmission does not necessarily mean that it is warranted or justified. Policy discussions and decision-making regarding blood testing should be based on accurate estimates of the performance characteristics and incremental yield of proposed new procedures. To address this need, a collaborative group (the NAT Study Group) has been established under the auspices of the National Heart, Lung and Blood Institute-sponsored Retrovirus Epidemiology Donor Study. A key objective of this study group is to develop quantitative data on the dynamics of viremia during the early phases of HIV, HCV and HBV infections, with particular focus on the issue of the relative capacity of MP and ID-NAT to interdict infectious window-phase donations. These studies involve characterization of the performance of quantitative and donor-screening NAT assays on serial donations from several hundred source plasma donors who seroconverted or were detected during the viremic pre-seroconversion phase by NAT screening in that setting. (14) New statistical models are being developed and employed to use these data to estimate the duration of the pre-serconversion window phase detected by MP- versus ID-NAT.(15) Additional studies are also planned using animal models and recipient lookback strategies to determine the infectivity of early window phase donations.(12-14,16) Updated donor incidence rates have also been calculated in order to project the incremental yield of infectious donations interdicted by MP vs. ID NAT.(7,17) These data can then be incorporated into cost-effectiveness analyses to quantify recipient disease prevented (infections avoided or quality-adjusted life-years gained) to balance against the cost (financial and donor loss) of each procedure under consideration.(18-20)

Preliminary results from these studies indicate that the incremental window period closure and yield of ID over MP-NAT for HIV and HCV will be very small, and will come at a very high cost.(21-24) For HIV, ID NAT will close the viremic window period by approximately 4 extra days, yielding perhaps 3 additional (MP-NAT-negative) infectious donations per year among 12 million screened U.S. blood donations. Similarly,

ID NAT for HCV RNA will probably shave only 4 additional days off the HCV pre-seroconversion window period, and yield 3 to 4 viremic donations that would be missed by MP-NAT on an annual basis. Based on preliminary cost estimates of \$8 per donation for MP-NAT and \$15 per donation for ID-NAT, the cost per case detected is estimated at \$1.7 million for MP-NAT and \$2.7 million for ID-NAT, with corresponding costs per quality adjusted life year of \$1.27 million and \$1.79 million, respectively (20,23).

Despite high cost and low yield, the current political, regulatory and medical-legal environment in the U.S. and other developed countries has dictated implementation of MP-NAT, and will likely drive introduction of further safety initiatives such as ID-NAT and NAT for additional agents. But hopefully our effort to generate relevant data and rationally analyze the yield and cost effectiveness of these measures will have served a purpose – we will regain the public’s trust in our ability to oversee the safety of the blood supply and reshape the landscape on which future decisions will be made. We should also recognize the ancillary benefits of NAT screening in areas such as donor counseling and reinstatement (25,26) and elucidation of a number of research questions including the epidemiology of incident infections in low risk populations and the viral and immunological characteristics of primary infection. We should also remember that, having implemented NAT, a system is now in place to allow for a rapid response to a new/emerging agent that threatens blood safety. It should allow us to move to a more rational screening portfolio in the future, with deletion of non-specific serological tests. Also, as vaccines for HIV (and HCV) evolve, NAT will be the only way to discriminate infected from vaccinated subjects who may present as donors.

Perception has driven us to seek zero risk and we have made a creditable attempt to get there. In doing so, we have followed science and adopted new technologies. Further, we have explored a new paradigm but, in doing so, have raised ethical questions. Science tells us we could do more, but with ever diminishing incremental yield and increasing marginal cost. The ultimate need may be for a rational decision system to define the extent to which blood safety should be incremented. Such a decision process must be international in scope, since blood policies, like the viruses we are trying to avoid, ramify globally. Recent efforts by the World Health Organization to develop a “Global Collaboration for Blood Safety”, which includes an objective framework for policy debate and decision making, is a major step in the right direction.

Finally, we must recognize that those of us responsible for maximizing blood safety in wealthy countries have a responsibility to assure that basic screening measures are available for all blood donations, including those in developing countries.(27) It is estimated that up to 45% of donations in developing countries (10 to 20 million units per year) are not routinely screened using basic serological assays for HIV, HBV or HCV.(28) Given the high viral prevalence and incidence rates in these same regions, transfusions of unscreened units probably result in hundreds of thousands of infections each year. The infectious windows may be sealed shut in wealthy nations, but they remain wide open in many poor and developing countries. Perhaps this is where the real ethical burden lies, should we choose to face it.

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