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Transfusion-Transmissible Infection Monitoring System (TTIMS): A Tool to Monitor Changes in Blood Safety

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What would later become known as the first case of documented transfusion-transmitted HIV in the United States occurred in 1982, and the implicated donor was a man who reported having sex with other men (MSM).(1) The emergence of Acquired Immune Deficiency Syndrome (AIDS) and the recognition that it could be transmitted by blood and blood products in the early 1980s had profound effects on the US and international blood systems.(2, 3) Even before HIV was identified as the etiologic agent or tests developed to screen for antibodies in donated blood, donor deferral was the first successful strategy to prevent transfusion-transmission, and it had a dramatic impact, reducing the risk by nearly 90% in some cities.(4)

Since late 1983, the US Food and Drug Administration (FDA) has recommended the deferral of individuals at higher risk of HIV infection. From September 1985, FDA has recommended that males with MSM history, even one time, since 1977, be deferred indefinitely from donating blood.(5) In 1992, FDA issued a more comprehensive advisory memo, containing updated recommendations for donor deferral for MSM as well as for other persons with behaviors associated with high rates of HIV exposure including commercial sex workers and injection drug users. At each step, FDA Guidance was based on scientific understanding at the time related to risk factors for HIV exposure.

Efforts to evaluate, re-evaluate and modify blood donation eligibility criteria continue. The indefinite deferral of MSM in the US has now been changed to allow donation from MSM whose last sexual contact with another man was at least one year before donation.(6) This change to a time-limited deferral of MSM parallels changes made in some other countries over the last 10 years. Much can be learned from studies that have evaluated whether a change in MSM deferral policy affects the number of HIV-positive donations interdicted

and, indirectly, the residual risk of transfusion transmission. In this issue of TRANSFUSION two articles report on assessments of the rate of HIV positive donations by MSM before and after implementing time-limited deferrals for donation by MSM. Each of these studies deserve comment because the results of the analyses provide important documentation of the experience outside the US, and may provide clues as to what might happen once the 1-year deferral for MSM is fully implemented by blood centers in the US.

The first article, by Germain, compares predicted versus actual number of HIV-positive male donors when MSM deferral was changed from indefinite to a temporary deferral.(7) In this analysis, four existing models with different numerical assumptions were applied to Australia, the United Kingdom and Canada to derive predictions of the potential impact of a change from indefinite to a 1-year or 5-year deferral. The modeled results were compared to actual post-change data in these countries. The models predicted between a 73% to 3400% increase in the rate of HIV in the male donor pool in the three countries after the change in deferral policy. In reality, the actual average annual number of HIV positive collections in male blood donors remained the same or decreased in each of the three countries following the policy change. Thus, none of the models accurately predicted what was observed. However, it is unknown if HIV-positive rates in male donors will remain consistent over time because changes in donor demographics, HIV epidemiology, and rates of compliance with deferral policies may occur. Donor behavior may also change with time as younger donors, in particular, may be unfamiliar with the history underpinning the previous deferral policy and might not comply. The Germain article demonstrates that, for unexplained reasons, these models appear to have been overly conservative with respect to the impact of changing the MSM deferral on HIV-positive rates in donated blood in these countries. Given these observations, the authors suggest that predictions of residual risk (due to window period donations) might also be overestimated in these models.

The change from a permanent to a 5-year deferral for MSM in Canada was implemented in July 2013. In the second article, by O'Brien and colleagues, the observed effect of the policy change is reported for Canadian Blood Services.(8) An array of related studies was conducted evaluating HIV-infection rates, assessing risk behaviors disclosed by donors, surveying the donor population to understand compliance before and after the MSM policy change, among other topics, and assessing the impact on blood supply availability. No discernable change in HIV-positive rates or MSM risk history was observed, albeit in a country with a relatively low rate of HIV-infected blood donors. Specifically, for the 3.5 years before change (2010-July 2013), 8 HIV-positive males were identified of 12 total HIV-positive donors; for the subsequent 2-year time period (through July 2015), 4 HIV-positive males were identified of 7 total HIV-positive donors. The HIV rates were not significantly different in the two time periods ($p=0.8$). In addition, of male blood donors anonymously surveyed before implementation of the change, 0.67% reported noncompliance with the existing policy (MSM ever since 1977), whereas 0.37% would have been non-compliant with a 5-year policy. The non-compliance rate following the policy change to 5-year deferral for MSM did not change significantly, at 0.44% ($p=0.54$). O'Brien and colleagues also report that only 112 formerly deferred donors (106 male and 6 females) were re-instated in the two years after policy change, and that 500 newly eligible donors are estimated to have presented to donate. These are minimal numbers by any standard, reflecting no

substantial increase in the total number of units in the supply of blood as a result of reinstating formerly deferred donors for MSM behavior. It is not reported whether there was a broader impact on donations in settings that may have not have allowed blood drives, such as university campuses, because of the previous indefinite deferral policy. It is possible that other individuals who may not have donated in protest of the previous MSM policy (since 1977) may now be donating. These data would be difficult to obtain, except at the level of reporting established or re-established blood drives at sites which had formerly not allowed them. Even with low numbers of reentered donors following the MSM policy change, reentry remains a very important process for blood centers considering the current focus on collection from donors with specific blood types to meet transfusion needs within the changing landscape of blood usage. Regardless, the most important finding remains, that at least in first 2-years, no increase in risk of transfusion-transmitted HIV appears to be evident in Canada following the end of the indefinite deferral of MSM based on absence of a change in the rate of HIV positive donations among men and in the rate of non-compliance with a 5 year deferral.

An important and perhaps overlooked consideration is the data reported for these countries. The studies by Germain, and O'Brien and colleagues could not have been done without the presence of funded monitoring systems in the included countries to obtain actual rates or numbers before and after policy change. The results reported in these papers show that predicting or projecting policy impact requires assumptions that may not be borne out in actual experience. Thus, prospective monitoring of actual rates of transfusion-transmissible infections among donors is necessary to understand the real consequences of policy change, and to provide a basis for estimation of residual risk.

In the US, prior studies that have estimated TTI incidence and prevalence in the US have not been designed prospectively to monitor changes in blood safety over time, including the effects of policy changes. Using data from American Red Cross (ARC), the residual risk of HIV in the US blood supply is currently estimated to be between one per 1.5 – 2 million units transfused.(9) Thus, the collection of broadly representative national data are required to be of sufficient magnitude to detect even minor changes in the residual risk of infections for which the blood supply is currently screened.

To enable such monitoring in the US, the National Heart Lung and Blood Institute funded (NHLBI) Retrovirus Epidemiology Donor Study-II (REDS-II) embarked on a large pilot study that combined donor and donation data from the ARC, Blood Systems, Inc. (BSI) and New York Blood Center (NYBC) into a consolidated dataset representing approximately 50% of blood collections in the country during the years 2011 – 2012. This pilot project also conducted risk factor interviews to establish the current behavioral risk factors associated with HIV, HCV, HBV or HTLV infection among blood donors, with OneBlood also participating in the interview part of the study, discussed below.(9) These data were integral in providing evidence to inform the debate and the decision with respect to modifying the indefinite MSM deferral in the US. Furthermore, this project demonstrated the feasibility of an ongoing monitoring system in the US and provided recent data on TTI marker rates in US donors as a baseline for future comparison. A new approach to monitoring the safety of the blood supply developed from this pilot project.

Transfusion-Transmissible Infection Monitoring System

In 2013, the Department of Health and Human Services (DHHS) Blood, Organ, and Tissue Senior Executive Council (BOTSEC), which includes representation from Department of Health and Human Services, Office of the Assistant Secretary of Health (DHHS/OASH), Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), Centers for Medicare & Medicaid Services (CMS), Health Resources Services Administration (HRSA), Food and Drug Administration (FDA), HHS-Assistant Secretary for Planning and Evaluation (ASPE), HHS-Assistant Sercetary for Preparedness and Response (ASPR), and Agency for Healthcare Research and Quality (AHRQ), unanimously voted to enhance monitoring of TTIs in the US.(10)

Building on the success of the REDS-II pilot study, in September 2015 the FDA and NHLBI launched the Transfusion-Transmissible Infections Monitoring System (TTIMS) program designed to establish an integrated, comprehensive blood donor and donation monitoring system for TTIs in the US. TTIMS is intended to monitor TTI prevalence and estimate residual risks for at least 50% of the US blood supply. The development of this system is particularly important at this time as a number of changes in blood donor eligibility policies are in process as well as undoubtedly other changes in the future. One such change includes the May 23, 2016 implementation of the FDA's final rule *Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use* (11) and the FDA's final guidance *Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products*.(6) The *Revised Recommendations* specifically reference TTIMS as a vehicle "to facilitate monitoring of the safety of the US blood supply for a variety of different pathogens", and for FDA to "use TTIMS to further investigate and refine blood safety screening measures over the coming years."

TTIMS is a five-year collaboration between the FDA, NHLBI, HHS/OASH, CDC and 4 large blood centers – ARC, BSI, NYBC and OneBlood. TTIMS is both a monitoring program and an opportunity to deploy research tools to understand HIV, HBV, HCV infections in US blood donors and donated blood. TTIMS has two closely synchronized components, a Donation Database Coordinating Center (DDCC) led by the ARC, and a Laboratory and Risk Coordinating Center (LRCC) led by Blood Systems Research Institute (BSRI). The DDCC will assemble standardized demographic and test result data from all donations given to participating centers into a centralized monitoring database. The DDCC will be responsible for establishing and analyzing this consolidated database to allow for monitoring of infectious disease marker prevalence, estimating incidence of HIV, HBV, and HCV based on NAT yield infections and other incidence estimation methods, and characterizing the demographics of donors with these infections. More importantly, the DDCC will also evaluate the data in an ongoing fashion in order to determine whether there are detectable changes in infection rates over time, geography and donor demographics, thereby providing information about the impact, if any, of policy changes on blood safety. Any significant changes in the frequency of donor infections may reflect the impact of changes in donor management and selection, and could act as a signal for further evaluation and, potentially, the need for corrective action.

The LRCC will be responsible for leading risk factor interviews of donors with specific infections focused primarily on HIV and newly acquired HBV and HCV infections to identify behavioral factors associated with donor infections. In addition, a subset of donors who do not have infections will also be interviewed to assess the risk behaviors in uninfected donors, representing a key component of monitoring following any policy change. These interview data will be compared to previously collected risk factor data such as that from the REDS-II study. Donor testing using research HIV recency assays will be conducted on samples from HIV-seropositive donors to establish whether a donor has a recently acquired versus long-standing infection.(12, 13) In addition, the TTIMS LRCC will assess viral lineages in all HIV-positive donations and donations from donors with recently acquired HCV or HBV infections so as to monitor the frequency of different genetic clades/genotypes/subtypes of donor infections because these changes can affect diagnostic assays and therapeutic interventions. This work is a continuation of another REDS-II study demonstrating that genetic monitoring of HIV, HCV, and HBV infections detected through large-scale routine blood donor screening contributes to public health and complements molecular surveillance studies of highly exposed populations.(14) The LRCC will also establish a sharable biospecimen repository of plasma aliquots from donors with viral infections meeting TTIMS inclusion criteria, allowing researchers and test developers to access contemporary viral strains currently circulating in the US for viral evolution and related studies. Since the DDCC and LRCC contracts were awarded, both programs of TTIMS have been actively engaged in developing the processes needed to collect, analyze and report data.

Evidence-based policy requires systems to be in place to capture, analyze, and interpret data not only to assess the impact of changes in donor eligibility criteria, but as well, other changes in transfusion-transmitted infectious disease agents, known and emerging, that could affect blood safety. TTIMS represents an important first step to advance donor biovigilance in the US. The recent changes in donor deferral policies for HIV raise many questions and TTIMS is poised to assess whether the experience reported in other countries is reproduced in the US. TTIMS is a robust and dynamic system that will be able to monitor evidence of change, and if change is evident, to examine the source of that change. Scientific data from TTIMS, and equally importantly, the collaboration between blood collection organizations and government agencies focused on monitoring and understanding rates of TTI infection and associated risk factors are a new opportunity to enhance transfusion safety in the US.

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