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Short Report

Residual risk of HIV, HCV and HBV in Canada

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ABSTRACT

Background: Residual risk is estimated as the product of the incidence and the infectious window period, the time during which a blood donation could be infectious but the assay may not detect it. In 2011 nucleic acid multiplex testing (MPX) was implemented in 6 unit minipools (previously 24 unit minipools). MPX also included hepatitis B (HBV) NAT for the first time (complementing HBsAg screening) in addition to HIV-1 and hepatitis C (HCV) as before. We aimed to estimate window period risk-day equivalents for MPX, and the residual risk of viral infections in blood donations updated to reflect current incidence and testing.

Methods: Transmissible disease conversions of repeat donations to Canadian Blood Services within the three-year period 2012–2014 divided by person-years estimated incidence for HIV, HCV and HBV (adjusted for transient viremia). Window period risk-day equivalents for MPX were estimated using a published method. Residual risk was the product of incidence and window period risk-day equivalents. 95% confidence intervals were estimated using Monte Carlo simulation of the window period risk-day equivalents and the incidence density 95% confidence intervals.

Results: The incidence rate per 100,000 person years for HIV was 0.28, HCV 1.0 and HBV 0.26. The residual risk of HIV was 1 per 21.4 million donations, HCV 1 per 12.6 million donations and HBV 1 per 7.5 million donations.

Conclusion: The residual risk of infection is very low, similar to 2006–2009. The safety benefit of further shortening of the infectious window period is below the threshold to quantify.

1. Introduction

Monitoring infectious disease risk is essential to ensuring the safety of the blood supply. Residual risk is estimated as the product of the incidence and the infectious window period, the time during which a blood donation could be infectious but the assay may not detect it. Our previous estimates made very conservative assumptions of the window periods, specifically that one virion in a unit of blood would be infectious and that the assay would fail to detect the infection over the full window period. A more realistic approach has been described by Weusten and colleagues [1,2]. Window-period risk-day equivalents take into account the lower probability of infectiousness with low viral concentration in the early window period, and the lower probability of failing to detect a viremic unit as viral concentration rises towards the end of the widow period.

Even so, our previous estimates for HIV, HCV and HBV showed very low residual risk [3]. Since that time we have implemented the Roche Multiplex NAT assay for HIV, HCV and HBV using 6 unit minipools. Previously we were using the Roche Ampliscreen for HIV and HCV using 24 unit minipools, thus an increase in sensitivity was expected due to the smaller minipool size. In addition, we have not published our results using HBV NAT, previously relying on an HBsAg assay to detect incident infections.

We aimed to update Canadian Blood Services' residual risk estimates to reflect current incidence, current testing and more realistic window period estimates. As there are no published window period estimates for the Roche Multiplex assay, we estimated the risk day equivalents as well as the conventional widow periods. We report the incidence density of HIV, HCV and HBV as well as the estimated residual risk of infection over the three year period from 2012 to 2014.

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Table 1
Incidence and Residual Risk of HIV, HCV and HBV in Canadian Blood Services' Donations, 2012–2014.

Virus	Number of incident cases	Person-years of observation	Repeat donors Incidence rate per 100,000 person-years of observation (95% CI)	All donations Incidence rate per 100,000 person-years of observation (95% CI)	Window Period Risk-Day Equivalents (95% CI)	Residual Risk per million donations (95% CI) [1 per number of donations]
HIV	2	854,829	0.23 (0.03, 0.85)	0.28 (0.04, 1.03)	6.1 (4.4, 7.8)	0.047 (0.009, 0.168) [1 in 21.4 million]
HCV	7	854,839	0.82 (0.33, 1.69)	1.0 (0.40, 2.06)	2.9 (2.1, 3.8)	0.079 (0.030, 0.170) [1 in 12.6 million]
HBV (unadjusted)	1	854,832	0.12 (0.003, 0.65)	0.15 (0.004, 0.79)		
HBV (adjusted for transient viremia)			0.21 (0.01, 1.13)	0.26 (0.01, 1.37)	18.8 (13.3, 24.3)	0.134 (0.020, 0.665) [1 in 7.5 million]

2. Methods

2.1. Transmissible disease testing

HIV-1/2 antibody (anti-HIV-1/2), HCV antibody (anti-HCV), HBsAg, and antibody to HBV core antigen (anti-HBc) were detected using the Abbott PRISM chemiluminescent assay (Abbott Laboratories, Abbott Park, IL). Confirmatory testing for HIV was performed Western blot (Calypte Biomedical Corp., Pleasanton, CA), for HCV using a third generation recombinant immunoblot assay (RIBA, Chiron Corp., Emeryville CA) and for HBsAg using the Abbott PRISM HBsAg confirmatory assay. All donations were also tested for HIV, HCV and HBV nucleic acid using the Roche Multiplex (Roche Molecular Systems, Branchburg NJ) in 6-unit minipools. A donation was considered to be positive for HCV if NAT-reactive or if antibody confirmed positive. HIV and HBV were considered to be positive if NAT reactive.

2.2. Analysis

All allogeneic donations made to Canadian Blood Services between January 1, 2012 and December 31, 2014 were included. Incidence rates were calculated only from donors with at least two donations over three years. Person-years were calculated as the sum of all interdonation intervals of 3 years of less during the study period. For a transmissible disease positive donation, only one half of the interdonation interval was counted in the person-years calculation. For donors with a negative donation in the study period who had their previous donation in the previous 3 years but before January 1, 2012, the person-years were counted from January 1, 2012 to their donation date within the study period. For transmissible disease positive donations that occurred on the donor's first donation in the study period but there was a negative donation within the preceding 3 years, the donor was considered an incident case if the mid-point of the interdonation interval was within the study period. Incidence was then calculated as the number of positive donations divided by the corresponding person-years of observation. Ninety-five percent confidence intervals were calculated by the exact method based on the Poisson distribution assumption. The incidence rate in first-time donations was estimated by multiplying the repeat-donor incidence rate by a conversion factor of 3.2 [4]. This seroconversion factor was based on HCV NAT yield data in first-time and repeat donations in the US. In the absence of data for HBV, and given the wide confidence interval for HIV, we used the same seroconversion factor for all three viruses [3]. To adjust for transient viremia, HBV incidence was modified using the method of Korelitz et al. which was calculated for this dataset [5].

Window period risk-day equivalents were estimated using the method of Weusten et al. [1,2]. The 95% limits of detection for multiplex are included in the package inserts, but the 50% limits of detection are required for risk day equivalent estimation. These were estimated by Probit analysis using analytic sensitivity data from the package insert for each virus. Constants for the formula were as per Weusten et al. [1,2] and adjusted for 6 unit minipools. In order to compare the impact of using risk-day equivalents to estimate residual risk rather than window-periods, we also estimated the window periods using the method proposed by Busch [7] with the 50% limit of detection and doubling time [2].

Residual risk was estimated using the method originally published by Schreiber et al. [6]. The residual risk of transfusion-transmitted infection was calculated as the product of the incidence rate and the window period risk-day equivalents point estimates. Confidence intervals were estimated using a Monte-Carlo simulation to include the confidence interval for the incidence rate and the confidence interval of the window period risk-day equivalents estimate.

3. Results

The window period risk-day equivalents are shown in Table 1. Compared with those calculated with the assumption of uniform infectivity over the full window period [7,8]: HIV 8.0 (6.9–9.2) days; HCV 4.1 (3.6–4.6); HBV 22.4 (18.3–26.5), risk day equivalents are shorter by: HIV 1.9 days, HCV 1.2 days and HBV 3.6 days. There were 2,579,980 allogeneic donations between January 1, 2012 and December 31, 2014, of which 2,388,120 had 2 or more donations within 3 years and were included in the analysis. Table 1 shows estimates of the incidence rates in repeat donations and the incidence rate overall (in first time donors included). Table 1 shows the estimated residual risk of releasing a potentially infectious window period unit into the blood supply. The lowest risk is associated with HIV (1 in 21.4 million donations), and the highest with HBV (1 in 7.5 million donations). There have been two NAT-only cases during 2012–2014. Both were from male repeat donors. One was positive for HBV NAT (non-reactive for both anti-HBc and HBsAg) in 2012 and had donated 84 days previously. The other was positive for HCV NAT (negative for anti-HCV) in 2014 and had donated 182 days previously. If incident cases were defined as only those with a negative donation in the preceding 12 months, none were significantly different from those reported in Table 1 ($p > 0.05$). Residual risk estimated using window periods yields a risk of 1 in 16.3 million for HIV, 1 in 8.9 million for HCV and 1 in 6.3 million for HBV, thus only slightly higher than using window period risk-day equivalents, but each had overlapping confidence intervals.

4. Discussion

Incidence for HIV, HCV and HBV remains very low, consistent with reports in other developed countries [9–12]. Furthermore, incidence for all three viruses was not significantly different from our previous report of 2006–2009 ($p > 0.05$) [3]. Estimating incidence involves some uncertainty, particularly in the evaluation of true incident cases, in the choice of time period of assessment and approach for inclusion of first time donors. For HIV and HCV assessment of true positivity by NAT could lead to false positives, but in

all cases of HCV donations were also positive for anti-HCV (except 1 NAT-yield case) and all HIV positive donations were also positive for anti-HIV. In our previous estimates [3] we did not have HBV NAT for all donations, and relied largely upon low sample to cut-off of HBsAg to exclude likely false positives. However, we were able to assess all incident cases with HBV NAT as a screening assay for this analysis. Importantly, the addition of HBV NAT to our testing arsenal had no impact on already low incidence. In contrast, HBV NAT may reduce risk from window period infections in countries such as Japan [13] where incident infections are more frequent. We chose a three year time period to assess incidence. This time period may give a more robust estimate than a 12 month period because more incident cases can be included but theoretically longer intervals between infection and the next blood donation could over-estimate. However, because all but one incident repeat donor had a negative donation within 12 months of their positive donation this is unlikely. If incidence had changed over the period, the estimate could be less accurate, but the number of incident cases was small for all markers, and we did not observe any trend over the period [14]. Finally, incidence in first time donors is difficult to estimate. It is possible to estimate incidence based on NAT-only cases (NAT positive, antibody negative) which would include first-time donors [7,8] but such cases are extremely rare. For the study period there were only two NAT-only cases (HBV and HCV), both repeat donors. We therefore chose to adjust for first time donation incident cases mathematically, recognizing that this may slightly overestimate incidence.

Residual risk estimates are used to counsel patients about risks of transfusion, hence it has long been considered reasonable to overestimate risk with conservative assumptions. However, that was at a time when transfusion services were expected to aim for zero risk, whereas current thinking is to strive for risk as low as reasonably achievable [15]. Risk estimates are increasingly used to inform a range of policies and should be as accurate as possible. We therefore estimated and applied window period risk-day equivalents that we believe are more reflective of the true risk. To our knowledge neither window periods nor risk-day equivalents have been previously published for the Roche Cobas TaqScreen MPX assay. Our estimates show that risk-day equivalents are slightly shorter. However, even combined with an improvement in sensitivity of NAT with a smaller minipool (6 vs 24 units), our residual risk estimates are not significantly different from those of 2006–2009 after taking into account uncertainty around both the true incidence and the true risk-day equivalents. MPX was implemented largely for operational reasons, and these results highlight that in countries such as Canada that already have very low incidence, residual risk has become so low that any safety benefit of further shortening the window period is below the threshold to quantify.

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References

[1] Weusten J, Van Drimmelen J, Lelie N. Mathematic modeling of the risk of HBV, HCV, and HIV transmission by window-phase donations not detected by NAT. Transfusion 2002;42:537–48.
[2] Weusten J, Vermeulen M, Van Drimmelen H, Lelie N. Refinement of a viral transmission risk model for blood donations in seroconversion window phase screened by nucleic acid testing in different pool sizes and repeat test algorithms. Transfusion 2011;51:203–15.
[3] O'Brien SF, Yi Q-L, Fan W, Scalia V, Fearon MA, Allain J-P. Current incidence and residual risk of HIV, HBV and HCV at Canadian Blood Services. Vox Sang 2012;103:83–6.
[4] Zou S, Stramer SL, Notari EP, Kuhns MD, Krysztof D, Musavi F, et al. Current incidence and residual risk of hepatitis B infection in the United States. Transfusion 2009;49:1609–20.
[5] Korelitz JJ, Busch MP, Kleinman SH, Williams AE, Gilcher RO, Schreiber GB. A method for estimating hepatitis B virus incidence rates in volunteer blood donors. National Heart, Lung, and Blood Institute Retrovirus Epidemiology Donor Study. Transfusion 1997;37:634–40.
[6] Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. N Engl J Med 1996;334:1685–90.
[7] Busch MP, Glynn SA, Stramer SL, Strong DM, Caglioti S, Wright DJ, et al. A new strategy for estimating risks of transfusion-transmitted viral infections based on rates of detection of recently infected donors. Transfusion 2005;45:254–64.
[8] Kleinman SH, Busch MP. Assessing the impact of HBV NAT on window period reduction and residual risk. J Clin Virol 2006;36:S23–9.
[9] Zou S, Dorsey KA, Notari EP, Foster GA, Krysztof D, Musavi F, et al. Prevalence, incidence, and residual risk of human immunodeficiency virus and hepatitis C virus infections among United States blood donors since the introduction of nucleic acid testing. Transfusion 2010;50:1495–504.
[10] Zou S, Stramer SL, Notari EP, Kuhns MC, Krysztof D, Musavi F, et al. Current incidence and residual risk of hepatitis B infection among blood donors in the United States. Transfusion 2009;49:1609–20.
[11] Safe supplies: uncovering donor behaviour. Annual review from the NHS Blood and Transplant/Public Health England Epidemiology Unit, 2014, London; 2015. http://www.gov.uk/government/collections/bloodborne-infections-in-blood-and-tissue-donors-bibd-guidance-data-and-analysis. [Accessed 3 November 2016].
[12] Australia transfusion-transmissible infections in Australia: 2015 Surveillance Report. The Kirby Institute, The UNSW and Australian Red Cross Blood Service; 2015. http://kirby.unsw.edu.au/. [Accessed 3 November 2016].
[13] Taira R, Satake M, Momos S, Hino S, Suzuki Y, Murokawa H, et al. Residual risk of transfusion-transmitted hepatitis B virus (HBV) infection caused by blood components derived from donors with occult HBV infection in Japan. Transfusion 2013;53:1393–404.
[14] Brambilla DJ, Busch MP, Dodd RY, Glynn SA, Kleinman SH. National Heart, Lung and Blood Institute Recipient Epidemiology and Donor Evaluation Study – III (REDS-III). A comparison of methods for estimating the incidence of human immunodeficiency virus infection in repeat blood donors. Transfusion 2017;57:823–31.
[15] Menitove JE, Leach Bennett J, Tomasulo P, Hatz LM. How safe is safe enough, who decides and how? From a zero-risk paradigm to risk-based decision making. Transfusion 2014;54:753–7.