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A statistical method for the estimation of window-period risk of transfusion-transmitted HIV in donor screening under non-steady state

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SUMMARY

Human immunodeficiency virus (HIV) can be transmitted by transfusion of blood even if the blood unit is test-negative for HIV. This is largely due to a time period following an infection, called the window period, during which antibodies against HIV are not detectable. Window-period risk refers to the probability for a test-negative blood unit to be infectious because of its donation during the window period. Estimation of window-period risk is important in public health for evaluating the safety of donated blood. The standard method for this estimation problem has been based on so-called incidence/window-period (IWP) models in which blood-donation and HIV-infection processes are assumed to be stochastically stationary and independent. Here we propose a new approach in which we relax this key assumption of the IWP models. We estimate window-period risk for each unit of donated blood using a given distribution of window-period risk. The proposed method utilizes the actual observed donation intervals including those of seroconversions, thereby relaxing the assumption that may not be met in practice. Bootstrap is used to compute confidence intervals without specifying the complex dynamics of the donation and infection processes. A simulation study illustrates the usefulness of the proposed method over the IWP method in scenarios where the IWP assumptions do not hold. A real application of the proposed method is presented using blood bank data from a province of northern Thailand. Advantages and limitations of the proposed method are discussed and compared with the IWP models.

Keywords: Blood bank; Blood donation; Blood safety; Bootstrap incidence/window-period models; Stationary assumption.

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1. INTRODUCTION

Transmission of human immunodeficiency virus (HIV) by blood transfusions is a major public health concern. To minimize the risk of transfusion-transmitted HIV, blood banks screen out donors who appear to be at high risk for HIV infection (e.g. injecting drug users) and test every unit of donated blood for the virus. Even if maximum caution is exercised at blood banks, however, the risk of transmission cannot be eliminated completely. This is largely due to a time period following an HIV infection, called the 'window period,' during which HIV antibodies are undetectable (Petersen *et al.*, 1994). Specifically, if an HIV-infected person donates blood during his/her window period, the donated blood unit is HIV-antibody negative (HIVAb−) but infectious for HIV. 'Window-period risk' refers to this probability for an HIVAb− blood unit to be HIV infectious because of its donation in the window period.

Estimation of window-period risk is important for evaluating the safety of donated blood units for transfusion. The estimate also provides the basis for making health policy decisions on whether to implement a new detection method for routine screening. The average window-period length differs by the detection method: methods that cost more to perform tend to have shorter window periods. Benefits by shortening the average window-period length, thereby lowering the risk of transfusion transmission, can be quantified by the reduction in window-period risk and evaluated against higher costs required for the implementation and use of a new detection method.

This paper considers statistical methods for estimating window-period risk. A typical setting for which the methods are useful would be a blood bank where the donation time and HIV-antibody status of every donation are recorded. Let t_{ij} and x_{ij} be the donation time and HIV-antibody status, respectively, for ith donor's jth donation at the blood bank in a defined study time-period. Our goal is to estimate window-period risk during the study period for the blood bank using observed data, $\{(t_{ij}, x_{ij})\}$.

Previous estimates of window-period risk have been derived from so-called 'incidence/window-period (IWP) models' (Lackritz *et al.*, 1995; Schreiber *et al.*, 1996; Sawanpanyalert *et al.*, 1996; Kleinman *et al.*, 1997). We review the approach of IWP models in Section 2, explaining why we considered an alternative approach. In Section 3, we propose a new method for estimating window-period risk. The relationship of the proposed estimate to the IWP estimate is given under simplified conditions. A simulation study in Section 4 compares the proposed estimate with the IWP estimate for three different underlying scenarios: one in which the assumptions of the IWP models are met and two in which they are violated. An application of the new method is illustrated in Section 5 using data from a blood bank in a province of northern Thailand as an example.

2. ESTIMATION OF WINDOW-PERIOD RISK USING THE IWP MODELS

The approach of the IWP models initially estimates the incidence rate of HIV infection using 'repeat donors' who donated blood *at least twice* during the study period. The incidence rate estimate is the number, N_+, of repeat donors who made HIV-antibody positive (HIVAb+) donations during the study period divided by the total number of person-time at risk. The person-time at risk for ith repeat donor is $t_{i(n_i+1)} - t_{i1}$, the time between the donor's first donation at time t_{i1} and last donation at time $t_{i(n_i+1)}$ in the study period, where $(n_i + 1)$ denotes the number of donations from ith repeat donor in the study period. (Note that, for repeat donors who seroconvert during the study period, the person-time at risk is less than $t_{i(n_i+1)} - t_{i1}$. Since seroconverters are rare, however, we will not consider this modification of the person-time at risk for the conciseness of the presentation.) No donation is accepted from a donor whose previous donation was HIVAb+. The HIV-infection incidence rate, I, therefore, is estimated by

the maximum likelihood estimate for a constant hazard of Poisson process and given by

$$\hat{I} = \frac{N_+}{\sum_{i=1}^{N} (t_{i(n_i+1)} - t_{i1})}$$

where N is the number of total number of repeat donors in a study period at the blood bank of interest.

Noting that the incidence of HIV window period is equal to the incidence of HIV infection, the well known epidemiologic formula, Prevalence = Incidence × Duration, gives an estimate of the *prevalence* of HIV window period under a steady-state assumption on the infection dynamics. This *prevalence* of HIV window period is used as an estimate of the window-period risk, $\hat{\pi}_0$. Thus, the IWP model estimates the window-period risk by

$$\hat{\pi}_0 = \hat{I} \times \overline{w} = \frac{N_+}{\sum_{i=1}^{N} (t_{i(n_i+1)} - t_{i1})} \times \overline{w} \tag{2.1}$$

where $\overline{w}$ is the average length (duration) of HIV window period for the blood bank of interest.

Several important assumptions are made in deriving an estimate using the IWP model (see, for example, Kleinman *et al.* (1997)):

ASSUMPTION 1 Single-time donors and repeat donors have the same incidence rate of HIV infection.

ASSUMPTION 2 The stochastic process of donation behavior and that of HIV infection occurrence are stationary and independent.

Assumption 1 justifies the estimation of window-period risk using only the repeat donors' data. Lackritz *et al.* (1995) considered an approach that relaxes this assumption by the use of an incidence ratio between the single-time and repeat donors (see Brookmeyer & Quinn (1995), Brookmeyer *et al.* (1995), and Janssen *et al.* (1998) for methods that enable the estimation of the incidence ratio). Assumption 2 implies (2a) the donation behavior is unchanged by an occurrence of HIV infection and (2b) donation frequencies are independent of donor's risk for HIV infection. The implication (2a) is important for the unbiasedness of the estimator because donations may, for example, become more frequent specifically for checking HIV status after donors engage in a high-risk activity, in which case $\hat{\pi}_0$ would underestimate the true risk. The significance of the implication (2b) can be seen clearly in the following example. Consider two hypothetical blood banks, A and B, with an identical HIV-infection incidence rate in their respective donor populations. Intuitively, they can have different window-period risks if, for example, the blood bank A satisfies the condition of the implication (2b) while, at the blood bank B, donors with lower risk for HIV donate more frequently. Since blood bank B results in a higher proportion of HIV-uninfected blood units, its window-period risk becomes lower than A's, given everything else being equal. Equation (2.1) does not account for such donation frequencies. In the next section, we propose a new method for estimating window-period risk in which Assumption 2 is relaxed.

3. THE PROPOSED ESTIMATE OF WINDOW-PERIOD RISK

Let H_i be the number of HIV-infected but HIVAb-negative donations of ith donor, an unobservable quantity. We consider the pairs (H_i, n_i)s to be independent and identically distributed (iid) according to a probability law with a parameter π, the window-period risk, which is defined by $E[H_i - \pi\, n_i] = 0$. If H_i's were observable, we could solve an estimating equation, $\sum_i (H_i - \hat{\pi}\, n_i) = 0$, to obtain a consistent estimate of π. Since H_is are not observable, however, we propose to estimate the estimating function unbiasedly with observable variables and use $\sum_i (E[H_i | x_{i(n_i+1)}, t_i] - \hat{\pi}\, n_i) = 0$, where $t_i =$

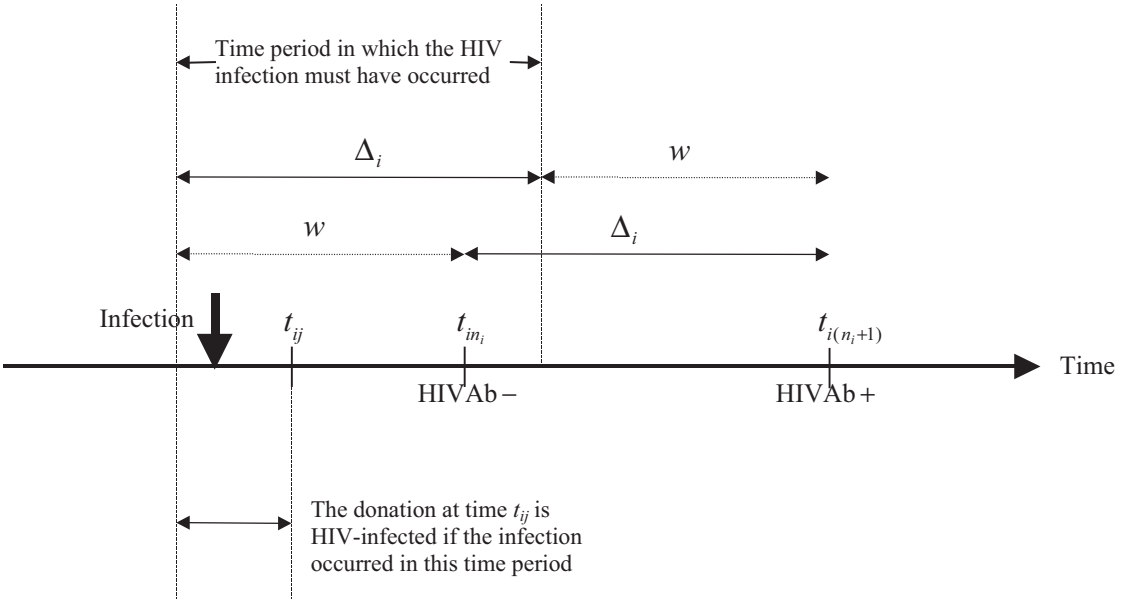

Fig. 1. An illustration of a window-period donation. A donor made HIVAb− donations at time t_{ij} and time t_{in_i} and then made an HIVAb+ donation at time $t_{i(n_i+1)}$. The infection must have occurred after time $t_{in_i} - w$, where w is the length of window period, but no later than time $t_{i(n_i+1)} - w$. For the HIVAb− donation at time t_{ij} to be HIV-infectious, the infection must have occurred before time t_{ij}.

$(t_{i1}, t_{i2}, \ldots, t_{i(n_i+1)})$. The resulting new estimator is, therefore, given by

$$\hat{\pi} = \frac{\sum_{i=1}^{N} E[H_i | x_{i(n_i+1)}, t_i]}{\sum_{i=1}^{N} n_i} = \frac{\sum_{i=1}^{N} \sum_{j=1}^{n_i} E[H_{ij} | x_{i(n_i+1)}, t_i]}{\sum_{i=1}^{N} n_i} \tag{3.1}$$

where H_{ij} is the indicator variable of HIV-infection status for the ith donor's jth donation.

To specify $E[H_{ij} | x_{i(n_i+1)}, t_i]$, consider ith donor's jth donation at time t_{ij}, where $j < (n_i + 1)$, and suppose ith donor's last donation at time $t_{i(n_i+1)}$ was HIVAb+ (Figure 1). Conditioned on the unobservable length of window-period w for this HIV infection, the HIV infection must have occurred after time $t_{in_i} - w$, but no later than time $t_{i(n_i+1)} - w$. For the HIVAb− donation at time t_{ij} to be HIV-infectious, the infection must have occurred before time t_{ij}. Thus, conditioned on both w and the last donation being HIVAb+, the probability for ith donor's jth donation to be HIV-infected is given by

$$E[H_{ij} | w, x_{i(n_i+1)} = 1, t_i] = G_i(t_{ij} - (t_{in_i} - w)),$$

where G_i is defined in the following assumption.

ASSUMPTION 3 Within the possible infection time period of $\Delta_i = t_{i(n_i+1)} - t_{in_i}$ from time $t_{in_i} - w$ to time $t_{i(n_i+1)} - w$, the conditional probability distribution of the time at which ith donor became infected is given by a known distribution G_i, given the observed data $(x_{i(n_i+1)}, t_i)$.

Note that the distribution G_i can vary across seroconverted donors and its specification may utilize information elicited from each seroconverted donor. It can also be studied systematically using a newly

proposed assay strategy (Janssen *et al.*, 1998). In the absence of such data, one may assume a uniform distribution for G_i:

$$E[H_{ij}|w, x_{i(n_i+1)} = 1, t_i] = \left\{ \frac{w - (t_{in_i} - t_{ij})}{t_{i(n_i+1)} - t_{in_i}} \right\}_{01}$$

where $\{X\}_{01}$ is equal to X if $0 \leqslant X \leqslant 1$, 0 if $X < 0$, and 1 if $X > 1$ (Petersen *et al.*, 1994; Satten, 1997). Note that the uniform distribution does not imply the steady-state assumption nor the independence between the blood-donation and HIV-infection processes. Suppose, for example, the blood-donation process changes, resulting in shorter (or longer) interdonation intervals, after the donor starts engaging in high-risk behaviors for HIV infection. This is certainly of practical importance since donors who start engaging in high-risk behaviors may start donating blood more frequently if they use the donation as a test for HIV, or less frequently if they fear the possibility of transmitting the virus or finding out their infection status. Then, the steady-state/independence assumption of the IWP model does not hold, while the uniform-distribution assumption of G_i is tenable unless additional information indicates that the risk of HIV infection changed within the possible infection time period (Figure 1). We will use the uniform distribution for G_i throughout this paper.

Since the length of window-period w is not a constant, we consider its distribution function F_w and apply it to remove the conditioning on w:

$$E[H_{ij}|x_{i(n_i+1)} = 1, t_i] \quad = \int_0^\infty \left\{ \frac{w - (t_{in_i} - t_{ij})}{t_{i(n_i+1)} - t_{in_i}} \right\}_{01} \mathrm{d}F_w.$$

Setting $E[H_{ij}|x_{i(n_i+1)} = 0, t_i] = 0$ for donors with their last donations being HIVAb− (Assumption 4 below), Equation (3.1) gives an estimate of window-period risk.

ASSUMPTION 4 Donors without an HIVAb+ donation in the study period did not have an HIV infection before their last donations at time $t_{i(n_i+1)}$ (i.e. for all i and j, $E[H_{ij}|x_{i(n_i+1)} = 0, t_i] = 0$).

Note that the last donation of each donor is not counted in the numerator or denominator of (3.1). This is natural for the last donations that are HIVAb+ because the window-period risk is a quantity defined for HIVAb− donations. The last donations that are HIVAb− are also excluded, however. This is because they do not have any subsequent donations that are necessary for estimating their window-period risk, the same reason that the single-time donors' donations are excluded.

An approach to statistical inference

Consider a random vector $Y_i = (x_{i(n_i+1)}, t_i)$ for $i = 1, \ldots, N$. We assume that the Y_i are iid samples from a distribution function F_Y. This is an assumption on the donation dynamics between donors. Our new estimator $\hat{\pi}$ of window-period risk is a function of realizations $y_i s : \hat{\pi}(y_1, y_2, \ldots, y_N)$. This perspective justifies statistical inference on the window-period risk based on nonparametric bootstrap samples from $\hat{F}_y$. We propose to construct confidence intervals (CIs) and perform hypothesis testing on window-period risk based on the bootstrap method (Efron & Tibshirani, 1993).

Relationship to the IWP estimate

We now present an intuitive understanding of the new estimate under a highly simplified setting. The highly simplified setting refers to (A2), (A3) of the following three conditions.

(A1) Assumptions 1, 3 and 4 are met with G_i being uniform distribution.

(A2) A seroconversion occurs $\overline{w}$ days after an HIV infection.
(A3) No inter-donation interval is shorter than the window period of $\overline{w}$ days.

Under the condition (A2), a window-period donation occurs only if the donor is infected within $\overline{w}$ days prior to the donation. Given $x_{i(n_i+1)} = 1$ (HIVAb+), Assumption 3 implies

$$E[H_{in_i}|x_{i(n_i+1)}, t_i] = \overline{w}/(t_{i(n_i+1)} - t_{in_i}).$$

For $j \leqslant n_i$, (A2) and (A3) together imply $E[H_{ij}|x_{i(n_i+1)}, t_i] = 0$, a special condition permitted by the conditions (A2) and (A3) here which did not hold in the general derivation of our proposed estimator at the beginning of this section. Thus,

$$\hat{\pi}^* = \frac{\sum_{\{i:x_{i(n_i+1)}=1\}} \overline{w}/(t_{i(n_i+1)} - t_{in_i})}{\sum_{i=1}^{N} n_i}. \tag{3.2}$$

The same estimator was considered by Satten (1997) under the steady-state assumption. Note that (3.2) is a reduced form of our proposed estimator, (3.1), under the highly simplified, but non-steady-state, conditions (A2), (A3). Comparing (2.1) and (3.2), we recognize the following relationship under the highly simplified conditions above:

$$\frac{\hat{\pi}^*}{\hat{\pi}_0} = \overline{\Delta} \times \sum_{\{i:x_{i(n_i+1)}=1\}} \frac{1}{(t_{i(n_i+1)} - t_{in_i})} \Big/ N_+ \tag{3.3}$$

where $\overline{\Delta}$ is the average inter-donation interval of all donations made by the N donors in the study period. The ratio factor given by (3.3) may be used for a crude assessment of Assumption 2, the factor close to unity suggesting the appropriateness of Assumption 2 (Satten, 1997).

4. A SIMULATION STUDY

To compare the performance of the proposed method with the IWP method, a simulation study is conducted under three different scenarios with 100 iterations for each scenario: one scenario satisfying both assumptions of the IWP models, Assumptions 1 and 2, and two scenarios violating Assumption 2 in different ways. We consider a blood bank to which 100 000 individuals make blood donation. In the first scenario, the donation and HIV-infection processes are generated by independent homogeneous Poisson processes with mean intervals of 2 years and 200 years, respectively. The study period is 12 years starting the 60th year from the initiation of the processes so that some individuals enter the study period with HIV infection. We generate HIVAb data by assuming a 45-day period following an HIV infection as the window period: its length is fixed to reduce complexities of the simulation without affecting general properties of the two approaches. The 45-day fixed window period is used in the estimation by both methods. These parameters are selected so that the simulated average window-period risk is similar to the estimated level from the real example in the next section. In each iteration of the simulation, we count the number of HIV-positive/HIVAb-negative donation units and divide it by the number of HIVAb-negative units to compute the true window-period risk in the study period. The proposed and IWP estimates are obtained using the observed data of repeat donors. From a set of 100 iterations, bias and mean-squared error (MSE) were calculated for each estimation method. The two scenarios that violate Assumption 2 of the IWP method are created as follows. Scenario A considers a change in donation frequency and HIV-infection risk following donors start engaging in high-risk behaviors: the frequency of donation increases by a factor of three and the HIV infection risk increases by a factor of ten after the initiation.

Table 1. *Results of a simulation study with 100 iterations comparing bias and mean-squared errors (MSE) of the proposed and IWP estimates under three different scenarios*

IWP assumptions		True window-period risk	IWP estimate			Proposed estimate		
		Mean	Mean	Bias	MSE	Mean	Bias	MSE
Yes		6.18	6.14	−0.04	0.17	6.15	−0.03	0.14
No	Scenario A*	13.42	9.50	−3.92	15.68	13.89	0.47	0.48
	Scenario B**	1.20	2.17	0.97	0.96	1.08	−0.12	0.03

Scenario A* = The frequency of donation and the risk of HIV infection increase by factors of three and ten, respectively, after a start of engaging in high-risk behaviors

Scenario B** = One half of the population donates three times more frequently than the other half and is at no risk for HIV infection

The process for the initiation of engaging in high-risk behaviors is generated by a homogeneous Poisson processes with mean intervals of 100 years that is independent of the blood-donation and HIV-infection processes. Scenario B considers correlation between donation frequency and HIV risk, namely, one-half of the population has an increased donation rate by a factor of three but has no risk for HIV infection.

The results of the simulation study are shown in Table 1. Under the scenario that satisfies the IWP assumptions, the IWP and proposed methods give similar performances; both are nearly unbiased and have comparable MSEs. In Scenario A and B that violate the IWP assumptions, however, the proposed method performs appreciably better than the IWP method. In Scenario A with a change in the donation frequency and HIV-infection risk after starting to engage in high-risk behaviors, the IWP underestimated the true risk with bias being about 30% of the average true risk and MSE being about 33 times higher than the proposed method. In Scenario B with a group of a higher-frequency donation and no HIV risk, the IWP overestimated the true risk with bias being about 80% of the average true risk and MSE being over 30 times higher than the proposed method.

5. An example: data from a blood bank in a province of northern Thailand

As an illustration of our proposed method, we estimate the window-period risk for a blood bank in a northern Thailand province between 1989 and 1998. The population of the province was about 1.2 million in 1993, and served by several hospitals including a 720-bed government hospital where the blood bank is located. During the 10-year study period, there were 20 913 repeat donors to the blood bank who have donated a total of 101 695 units of blood and contributed a total of 64 412.49 person-year. Of those, 338 donors had their last donations in the study period tested as HIVAb+. The IWP model gave an incidence rate estimate of 52.47 per 10 000 person-years (95% Poisson-based CI 46.88–58.07 per 10 000 person-years). This resulted in an estimate of the window-period risk being 6.47 per 10 000 donations (95% CI 5.78–7.15 per 10 000 donations). To compute the window-period risk based on our proposed method, we used the log-normal distribution as the distribution of window-period length. Two parameters of the log-normal distribution were determined by two assumptions: (1) the mean window-period length was reported to be approximately 45 days for an assay method used in the Thai blood bank (Petersen *et al.*, 1994); and (2) few, if any, remain infectious and HIVAb− for longer than 6 months (Petersen *et al.*, 1994; Satten, 1995). We fixed the mean of the log-normal distribution at 45 days and considered four values for its 95th percentile: (a) 100; (b) 125; (c) 150; and (d) 174 days (Figure 2). The distribution (d) has the longest tail of the log-normal distributions with mean 45 days. Petersen *et al.* (1994) gave 95% CIs for the quantiles of the window-period length distribution using transfusion data. The four 95th percentiles

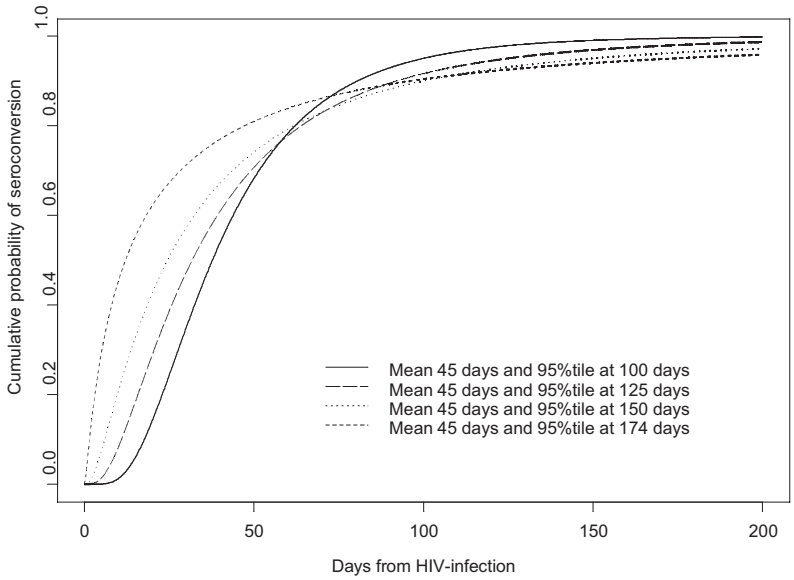

Fig. 2. Four log-normal distributions of the window-period length with a mean of 45 days and a 95%tile of 100, 125, 150, and 174 days.

(a)–(d) are consistent with the 95% CIs of Petersen *et al.*, while the median of the distribution (d) was inconsistent with their CIs: the distribution (d) gives a median of 12.2 days that is outside of the 95% CI 23.9–56.6 days given by Petersen *et al.*

Table 2 presents the window-period risk estimates by the proposed method using the four log-normal distributions. The risk estimates varied from 5.82 per 10 000 donations based on the distribution (d) to 7.30 per 10 000 donations based on the distribution (a). The distributions (a), (b), and (c), which are consistent with Petersen *et al.*'s 95% CIs, gave estimates which were 1.06–1.13 times higher than the IWP estimate. This factor is roughly consistent with the ratio factor of 1.19 given by (3.3), even though the derivation of the ratio factor (3.3) used a set of over-simplified conditions. The bootstrap-based 95% CIs for the window-period risk were (a) 6.29–8.38; (b) 6.28–8.25; (c) 5.97–7.79; and (d) 5.12–6.56 by the respective window-period length distribution.

6. DISCUSSION

We proposed a method for computing window-period risk by specifying the distribution of window-period length. This specification requires additional data/information such as those provided by Petersen *et al.* (1994). In the example in Section 5, we assessed the sensitivity of the window-period risk estimate to the specification of the distribution of window-period length and found that the three log-normal distributions that are consistent to the data of Petersen *et al.* (1994) resulted in similar estimates. Although this specification is a requirement in the proposed method, its use has certain advantages. For example, even when the detection methods are different across units (e.g. due to an introduction of a new method or selective use of a more expensive/sensitive method for donated blood units that are perceived to be high-risk), we can apply different forms of window-period length distribution according to the detection methods used for each unit and the subsequent unit. The greatest advantage of specifying the distribution of window-period length is perhaps the ability to calculate a window-period risk estimate for each

Table 2. *Comparisons of window-period risk estimates (/10 000 units) by the IWP and proposed methods with four different log-normal distributions used as the window-period length distribution. For the proposed method the window-period length is assumed to follow a log-normal distribution with mean μ (45 days) and 95%tile Q_{95} (100, 125, 150, and 174 days); 95% bootstrap confidence intervals are given in parentheses*

Methods	Window-period risk estimate
IWP	6.47
Proposed method	
$\mu = 45/Q_{95} = 100$	7.30 (6.29–8.38)
$\mu = 45/Q_{95} = 125$	7.23 (6.28–8.25)
$\mu = 45/Q_{95} = 150$	6.86 (5.97–7.79)
$\mu = 45/Q_{95} = 174$	5.82 (5.12–6.56)

HIVAb− donated unit. The estimation utilizes the actual observed donation intervals that are specific to the donor of interest, most importantly the seroconversion donation interval. In contrast, the IWP model is insensitive to the lengths of seroconversion donation intervals as we demonstrated in Sections 4 and 5.

The ability to provide an estimate of window-period risk to each HIVAb− unit opens up new possibilities for efforts towards lowering window-period risk at the blood bank. For example, the estimate of the window-period risk can be modeled by the characteristics of the donation unit, such as age, sex, the number of previous blood donations, and the length of the last donation interval. Such a model may be used at the blood bank to predict the window-period risk of each donation at the time of donation for deciding, for example, whether to use a more sensitive test for HIV detection for a particular unit or defer the donation itself. For the donors with low-risk characteristics, blood bank staff may encourage the continuation of donations in the future.

Assuming $E[H_{ij}|x_{i(n_i+1)} = 0, t_i] = 0$ for $j \leqslant (n_i+1)$ in Assumption 4 is a limitation of the proposed method, which is not necessary in the IWP method due to its Assumption 2. For some blood banks where donation intervals can be short relative to the window-period lengths of the detection method used, this zero-approximation would be untenable. The application of the proposed method must, therefore, be preceded by the comparison of donation intervals with the distribution of window-period length. The key assumption of the IWP model is Assumption 2, which implies Assumption 3 of the proposed method, and therefore, is more stringent than Assumption 3. It is, however, debatable whether Assumption 3 is entirely tenable. We believe that the conditional probability of an HIV-infection time in the possible infection period (Figure 1) given the observed data is a complex function of HIV incidence over time, donation behavior, and possible changes in donation behavior associated with potential HIV-infection activities, and unique to each seroconversion. Without any specific information for each seroconversion, we used a uniform distribution for every seroconversion. It is possible in the proposed method to use an alternative distribution, or even construct and apply a specific distribution for each seroconversion according to some information elicited from the seroconverter.

An important public health question is whether the window-period risk is declining over time, and if so, how much. A difficulty in the IWP model in answering this question is the interval-censored nature of the HIV-infection occurrence. For example, if a donor had an HIVAb− donation in 1995 and then had a subsequent donation in 1999 which was HIVAb+, it is unclear how the calculation of annual incidence rates in the IWP model should incorporate this record. The proposed method is subject to a different type of difficulty in estimating calendar-year-specific window-period risk. Specifically, the right-truncation of donation data at the end of the study period will affect the later calendar years of the study period more severely: only shorter seroconversion intervals can be observed for the later calendar years of the study period. Thus, this length-biased sampling due to right-truncation needs to be appropriately accounted for.

Finally, the window-period risks for viruses other than HIV are also of concern with respect to the safety of donated blood. For Hepatitis C virus, for example, whose window-period lengths are generally longer than those of HIV, the window-period risk has also been estimated based on the IWP models (Schreiber *et al.*, 1996; Tanaka *et al.*, 1998). It is our hope that the method proposed here would enhance the research on blood safety by serving as an alternative tool to the IWP models.

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