

A probabilistic method for the estimation of residual risk in donated blood

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SUMMARY

The residual risk (RR) of transfusion-transmitted infections, including the human immunodeficiency virus and hepatitis B and C viruses, is typically estimated by the incidence/window period model, which relies on the following restrictive assumptions: Each screening test, with probability 1, (1) detects an infected unit outside of the test's window period; (2) fails to detect an infected unit within the window period; and (3) correctly identifies an infection-free unit. These assumptions need not hold in practice due to random or systemic errors and individual variations in the window period. We develop a probability model that accurately estimates the RR by relaxing these assumptions, and quantify their impact using a published cost-effectiveness study and also within an optimization model. These assumptions lead to inaccurate estimates in cost-effectiveness studies and to sub-optimal solutions in the optimization model. The testing solution generated by the optimization model translates into fewer expected infections *without* an increase in the testing cost.

Keywords: Blood donation; Incidence/window period model; Optimization; Risk estimation.

1. INTRODUCTION

Even with stringent post-donation screening in place in the United States for human immunodeficiency virus (HIV) and hepatitis B and C viruses (HBV and HCV), there remains a *Residual Risk* of a transfusion-transmitted infection, i.e. “probability of having a potentially infectious donation released into the blood supply” (Busch and others, 2005). This risk mainly stems from testing errors due to infectious donations within the donor's *window period*, i.e. the time between the development of infectious viremia and reactivity by the screening test (Busch and others, 2005), as well as random and systemic technical or human errors. The *incidence/window period* (IWP) model estimates the Residual Risk considering only the risk

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coming from infectious window period donations, and under the assumptions that each test always fails to detect a window period donation and is perfectly reliable outside of the window period, considering a common window period for all donors; and that each test has a false positive probability of zero (Lackritz and others, 1995; Schreiber and others, 1996; Kleinman and others, 1997; Jackson and others, 2003; Busch and others, 2005; Van Hulst and others, 2009). Accurately estimating the Residual Risk is essential for assessing the safety of donated blood and for important policy decisions, such as whether or not it is cost effective to adopt a highly reliable but expensive blood testing technology.

In reality, the time when the markers of an infectious donor become reactive to a certain test depends on the donor's physiological characteristics (Weusten and others, 2002). On the other hand, the test's window period is typically reported in the transfusion literature in terms of an *average* duration post-exposure after which the test becomes highly reliable. Due to variations in individual window periods, however, screening tests do identify a small fraction of infections within their reported window period (Weusten and others, 2002). Moreover, screening tests are not perfectly reliable outside of their reported window period, mainly due to random and systemic technical or human errors and individual variations, which could lead to infected blood being cleared for transfusion or infection-free blood being falsely discarded (Preiser and others, 2000). Relaxing these assumptions will have an impact on the Residual Risk, hence on cost-effectiveness results. Further, reducing the amount of blood wasted in post-donation screening is also important for the sustainability of the blood collection system, as demand for blood far exceeds, and will continue to exceed, the supply worldwide (e.g. Greinacher and others, 2007; Orfinger, 2010; Xie and others, 2012).

From a computational perspective, it is common in the transfusion literature to perform cost-effectiveness analysis separately for each “scenario” (a particular test or a test set). This, however, requires the analyst to determine upfront the scenarios of interest and brings in computational inefficiencies. These issues are important to address, because as population characteristics and testing budgets change, and new tests and infections emerge, it becomes necessary to reevaluate the testing strategy. Further, testing solutions for the various infections are often linked through common constraints, such as the screening budget, or economies of scale for sharing of equipment, laboratory space, staff, transportation plans. Hence, significant benefits can be achieved by constructing the testing solution *jointly* for all infections that require screening, considering common constraints that apply. An optimization-based model can overcome these computational inefficiencies in that it does not require an upfront listing of the scenarios: It evaluates *all* feasible testing scenarios in a highly effective manner and reports the “best” scenario (with respect to a given objective, e.g. minimization of Residual Risk or maximization of quality-adjusted life years (QALY) gained or healthcare savings due to infections averted).

Our objectives in this study are 2-fold: (1) to derive accurate expressions for the Residual Risk and Waste when the aforementioned assumptions of the IWP model are relaxed and (2) to study the impact of these assumptions on the Residual Risk for each test, as well as on the *optimal* (i.e. Residual Risk minimizing) testing strategy. Toward the second goal, we use an existing cost-effectiveness study of post-donation screening strategies (Jackson and others, 2003); and also extend the optimization model from our earlier work (Bish and others, 2011) and run it with published data. To improve the presentation, we relegate all derivations and some background information to the Appendix (see supplementary material available at *Biostatistics* online).

2. NOTATION AND MODEL

2.1 Notation

Let Ψ denote the set of infections for which donated blood must be screened, and Ω^i , $i \in \Psi$, denote the set of food and drug administration (FDA)-approved blood screening tests for infection i , with $\Omega \equiv \bigcup_{i \in \Psi} \Omega^i$.

Let WP_j denote the reported window period of test j , $j \in \Omega$, and \mathcal{T} denote the minimum allowable inter-donation period (the minimum period between a donor's successive donations). Let DT denote the random donation time, from time of infection, of an infected donor. Following the transfusion literature, we model DT as a continuous uniform random variable in $[0, \mathcal{T}]$ (e.g. [Weusten and others, 2002](#); [Yasui and others, 2002](#); [Busch and others, 2005](#); [Van Hulst and others, 2009](#)). However, our model is general, and allows for any continuous distribution for DT . Since DT is continuous, the probability that DT belongs to an open interval (WP_j, WP_{j+1}) and to a closed interval $[WP_j, WP_{j+1}]$ are equal. To simplify the notation, we express all time intervals as closed intervals. Let S^i denote the set of tests selected, among the tests in Ω^i , to administer for infection i , with $S \equiv \bigcup_{i \in \Psi} S^i$.

Note the difference between a donor's "individual window period," which varies among donors and is therefore stochastic, and the "test's reported window period" (WP_j), which is the deterministic value reported in the literature; see [Remark 1](#) and the subsequent discussion.

When multiple tests are administered for the same infection, a decision rule is needed to classify the blood unit as infected versus infection-free when test results are not in agreement. A commonly used decision rule in US Blood Centers, due to its conservative nature, is the *Believe the Positive (BP)* rule, which we also use. Under the BP rule, the blood unit is classified as infected if at least one test in the selected test set provides a positive result; equivalently, it is classified as infection-free only if all tests provide negative results ([Bish and others, 2011](#); [Pepe, 2003](#)).

Consider a random blood unit. We define the following events.

Events:

$A^i +$, $i \in \Psi$:	event that the blood unit is infected by infection i
$T_j^i +$, $j \in \Omega^i$, $i \in \Psi$:	event that test j provides a positive result for infection i , indicating that infection i is present in the blood unit
$T^i + (S^i)$, $S^i \subseteq \Omega^i$, $i \in \Psi$:	event that the blood unit is classified as infected by infection i using the tests in set S^i under the BP rule, that is, $T^i + (S^i) = \bigcup_{j \in S^i} T_j^i +$
$T + (S)$, $S \subseteq \Omega$:	event that the blood unit is classified as infected using the tests in set S , that is, $T + (S) = \bigcup_{i \in \Psi} T^i + (S^i)$

We let $A^i - \equiv \overline{A^i +}$, $T_j^i - \equiv \overline{T_j^i +}$, and $T - (S) \equiv \overline{T + (S)} (= \bigcap_{i \in \Psi} T^i - (S^i))$, respectively, denote the complements of these events. Similar to the transfusion literature, we assume that events $A^i +$, $i \in \Psi$, are mutually exclusive, that is, co-infection possibility in the donor population is negligible, e.g. [Busch and others \(2005\)](#), [Jackson and others \(2003\)](#), and [Weusten and others \(2002\)](#).

Residual Risk (RR) and Waste (W) for any test set $S \subseteq \Omega$ can be written as follows:

$$RR(S) = \Pr \left(\bigcup_{i \in \Psi} A^i +, T - (S) \right), \quad (2.1)$$

$$W(S) = \Pr \left(\bigcap_{i \in \Psi} A^i -, T + (S) \right). \quad (2.2)$$

2.2 An overview and discussion of the IWP model

Under the IWP model, the RR of infection i when test j is used (denoted by $RR^i(\{j\})$) reduces to the following expression (e.g. [Yasui and others, 2002](#); [Jackson and others, 2003](#); [Busch and others, 2005](#);

Van Hulst and others, 2009):

$$\begin{aligned}
 \text{RR}^i(\{j\}) &= \Pr(A^i +, T_j^i -) \quad (\text{from (2.1)}) \\
 &= \Pr(A^i +) \Pr(T_j^i - | A^i +) \\
 &= \Pr(A^i +) [\Pr(T_j^i - | A^i +, \text{DT} \in [0, \text{WP}_j]) \Pr(\text{DT} \in [0, \text{WP}_j] | A^i +) \\
 &\quad + \Pr(T_j^i - | A^i +, \text{DT} > \text{WP}_j) \Pr(\text{DT} > \text{WP}_j | A^i +)] \\
 &= \hat{I}^i \times \mathcal{T} \times \left[\left(1 \times \frac{\text{WP}_j}{\mathcal{T}} \right) + \left(0 \times \frac{(\mathcal{T} - \text{WP}_j)}{\mathcal{T}} \right) \right] = \hat{I}^i \times \text{WP}_j, \quad (2.3)
 \end{aligned}$$

where \hat{I}^i denotes the incidence rate estimator of infection $i \in \Psi$. (We have that $\Pr(A^i +) = \hat{I}^i \times \mathcal{T}$, see Brookmeyer, 2009; Van Hulst and others, 2009; and the Appendix in supplementary material available at *Biostatistics* online.)

Equation (2.3) assumes that DT is uniformly distributed in $[0, \mathcal{T}]$, and also relies on the following additional assumptions. (To simplify the notation, we drop infection and test indices.)

ASSUMPTION A1 Each test fails with probability one to detect an infectious donation during the window period, i.e. $\beta \equiv \Pr(T - | A+, \text{DT} \in [0, \text{WP}]) = 1$; and each test is perfectly reliable outside of the window period, i.e. $\alpha \equiv \Pr(T - | A+, \text{DT} > \text{WP}) = 0$.

As discussed above, due to variations in individual window periods, Assumption A1 does not hold in reality because a donor's window period may be smaller or larger than the test's reported window period, WP. Moreover, when tests are administered for multiple infections (as required in the United States), the RR expression in the IWP model also requires the following assumption.

ASSUMPTION A2 The test's false positive probability is zero, i.e. $\Pr(T + | A-) = 0$.

Assumption A2, which implies that no blood is wasted ($\text{W}(S) = 0$, $S \subseteq \Omega$), is also not realistic because technical and human errors are possible.

2.3 Model

We develop a methodology for determining RR and Waste when Assumptions A1 and A2 are relaxed, that is, for each test j , $j \in \Omega$, we allow $\beta_j < 1$, $\alpha_j > 0$, and $\Pr(T_j^i + | A^i -) > 0$. All derivations are relegated to the Appendix (see supplementary material available at *Biostatistics* online).

Equations (2.1) and (2.2) can be equivalently expressed as follows:

$$\begin{aligned}
 \text{RR}(S) &= \Pr \left(\bigcup_{i \in \Psi} A^i +, T - (S) \right) \\
 &= \left(\prod_{k \in \Psi} \Pr(T^k - (S^k) | A^k -) \right) \left(\sum_{i \in \Psi} \Pr(A^i +) \frac{\Pr(T^i - (S^i) | A^i +)}{\Pr(T^i - (S^i) | A^i -)} \right), \quad (2.4)
 \end{aligned}$$

$$\begin{aligned}
W(S) &= \Pr\left(\bigcap_{i \in \Psi} A^i -, T + (S)\right) = \Pr\left(T + (S) \mid \bigcap_{i \in \Psi} A^i -\right) \Pr\left(\bigcap_{i \in \Psi} A^i -\right) \\
&= \left(1 - \prod_{k \in \Psi} \Pr(T^k - (S^k) \mid A^k -)\right) \left(1 - \sum_{i \in \Psi} \Pr(A^i +)\right). \tag{2.5}
\end{aligned}$$

Equations (2.4) and (2.5) require false negative and true negative probabilities to be derived for each possible test set. Toward this end, we link these probabilities to individual test sensitivity (true positive probability = $\Pr(T + \mid A +)$) and specificity (true negative probability = $\Pr(T - \mid A -)$) values and infection prevalence/incidence rates, whose estimates are available in the literature. In particular, FDA labeling regulations require the performance data to be reported for all FDA-approved tests (Burd, 2010). When a gold standard test is available, test sensitivity and specificity values can be obtained by case control or cohort studies, or two-stage designs (the latter is used when the gold test involves an expensive or invasive procedure); see Pepe (2003, Section 1.2). When a perfect gold standard test is not available, various statistical methods can be used, including the Bayesian latent class model or composite reference standards method; see Joseph and others (1995), Limmathurotsakul and others (2010), Trikalinos (2012), van Smeden and others (2013); and Pepe (2003, Section 7.3).

2.3.1 Deriving the false negative probability of a test set. For any test set $S^i = \{1, 2, \dots, n^i\} \subseteq \Omega^i$, order the tests in S^i in non-decreasing order of their window periods, i.e. $WP_{(1)} \leq WP_{(2)} \leq \dots \leq WP_{(n^i)}$, and let $WP_{(0)} \equiv 0$. Using the law of total probability, we can write:

$$\begin{aligned}
\Pr(T^i - (S^i) \mid A^i +) &= \sum_{j=1}^{n^i} \Pr(T^i - (S^i) \mid A^i +, DT \in [WP_{(j-1)}, WP_{(j)}]) \Pr(DT \in [WP_{(j-1)}, WP_{(j)}]) \\
&\quad + \Pr(T^i - (S^i) \mid A^i +, DT \in [WP_{(n^i)}, T]) \Pr(DT \in [WP_{(n^i)}, T]) \\
&= \sum_{j=1}^{n^i} \Pr(T_{(1)}^i -, T_{(2)}^i -, \dots, T_{(n^i)}^i - \mid A^i +, DT \in [WP_{(j-1)}, WP_{(j)}]) \\
&\quad \times \Pr(DT \in [WP_{(j-1)}, WP_{(j)}]) \\
&\quad + \Pr(T_{(1)}^i -, T_{(2)}^i -, \dots, T_{(n^i)}^i - \mid A^i +, DT \in [WP_{(n^i)}, T]) \Pr(DT \in [WP_{(n^i)}, T]). \tag{2.6}
\end{aligned}$$

REMARK 1 The expression in (2.6) corresponding to the false negative probability of test set $S^i \subseteq \Omega^i$, $i \in \Psi$, does not require the various assumptions used in the IWP model. Of particular interest is the relaxation of the following assumptions. Equation (2.6):

- (1) applies when DT follows any general continuous distribution;
- (2) allows the false negative events, occurring for window period donations, for the different tests (corresponding to the same infection) to be dependent;
- (3) implicitly incorporates the variations in individual window periods by allowing the false negative probabilities in any donation interval (i.e. the terms, $\Pr(T^i - (S^i) \mid A^i +, DT \in [WP_{(j-1)}, WP_{(j)}])$) to differ from zero or one. (These probabilities can be derived from the distribution of individual variations; see Section 4 of the Appendix in supplementary material available at *Biostatistics* online.)

Part (1) of Remark 1 is obvious and Part (3) is detailed in the Appendix (see supplementary material available at *Biostatistics* online). In the following, we further discuss Part (2). It is well-established in the literature that the different markers appear sequentially following an infection (e.g. viral copies, followed by antibodies) (Busch and Satten, 1997; Fiebig and others, 2003; Ganem and Prince, 2004). In probabilistic terms, when a more sensitive test (with a smaller window period) fails to detect an infection, the probability that a test with a larger window period will fail to detect this infection may change (and often increase) from $\beta_{(k)} = \Pr(T_{(k)}^i - | A^i +, DT \in [0, WP_{(j)}])$ to $\gamma_{(k)(j)} \equiv \Pr(T_{(k)}^i - | T_{(j)}^i -, A^i +, DT \in [0, WP_{(j)}])$ for $k, j \in \Omega^i, k > j$. Toward this end, we allow $\gamma_{(k)(j)}$ to differ from $\beta_{(k)}$. While it is often the case that $\gamma_{(k)(j)} > \beta_{(k)}$, we make no such restrictions in the model.

Due to limited data availability on the conditional false negative probabilities, we make two assumptions, both of which can be relaxed should such data become available. First, we assume that $\gamma_{(k)(j)}$ and $\gamma_{(l)(j)}, j, k, l \in \Omega^i, k > j, l > j, i \in \Psi$, are jointly independent given test j 's negative outcome. This is a reasonable approximation, as it allows us to model the dependence among the tests without further complicating the expression. Secondly, we assume that once outside of the test's window period, false negative results occur mainly due to technical or human errors, and hence, they should not affect the performance of other tests. This assumption, formally given as Assumption B1, is reasonable because test window periods reported in the literature are often conservative in that individual window periods of most donors do not exceed the test's reported window period. That is to say, most testing errors outside of the window period occur due to technical and human errors.

ASSUMPTION B1 $\Pr(T_{(k)}^i - | T_{(j)}^i -, A^i +, DT \in [WP_{(j)}, WP_{(k)}]) = \beta_{(k)}, k > j, j, k \in \Omega^i$.

When DT is uniform in $[0, T]$, (2.6) reduces to the following:

$$\begin{aligned} \Pr(T^i - (S^i) | A^i +) &= \beta_{(1)} \left(\prod_{k=2}^{n^i} \gamma_{(k)(1)} \right) \frac{WP_{(1)}}{T} + \sum_{j=2}^{n^i-1} \left(\prod_{k=1}^{j-1} \alpha_{(k)} \right) \beta_{(j)} \\ &\quad \times \left(\prod_{k=j+1}^{n^i} \gamma_{(k)(j)} \right) \frac{(WP_{(j)} - WP_{(j-1)})}{T} \\ &\quad + \left(\prod_{k=1}^{n^i-1} \alpha_{(k)} \right) \beta_{(n^i)} \frac{(WP_{(n^i)} - WP_{(n^i-1)})}{T} + \left(\prod_{k=1}^{n^i} \alpha_{(k)} \right) \frac{(T - WP_{(n^i)})}{T}. \end{aligned} \quad (2.7)$$

Example 1 illustrates the impact of Assumption A1 on a test set's false negative probability.

EXAMPLE 1 Consider two tests, Tests 1 and 2, and suppose, without loss of generality, that $WP_1 < WP_2$. Under Assumption A1 (i.e. $\beta_j = 1$ and $\alpha_j = 0, j = 1, 2$, and $\gamma_{12} = 1$), we derive the false negative probability for Test 1 only, Test 2 only, and Tests 1 and 2 combined.

From (2.7), for $S = \{1\}$, $\Pr(T - (\{1\}) | A+) = 1(WP_1/T) + 0((T - WP_1)/T) = WP_1/T$.

Similarly, for $S = \{2\}$, $\Pr(T - (\{2\}) | A+) = \Pr(T_2 - | A+) = WP_2/T$.

On the other hand, for $S = \{1, 2\}$:

$$\begin{aligned}\Pr(T - (\{1, 2\})|A+) &= \Pr(T_1 - , T_2 - |A+) = \Pr(T_1 - , T_2 - |A+, DT \in [0, WP_1]) \Pr(DT \in [0, WP_1]) \\ &\quad + \Pr(T_1 - , T_2 - |A+, DT \in [WP_1, WP_2]) \Pr(DT \in [WP_1, WP_2]) \\ &\quad + \Pr(T_1 - , T_2 - |A+, DT \in [WP_2, T]) \Pr(DT \in [WP_2, T]) \\ &= 1 \cdot \frac{WP_1}{T} + 0 + 0 = \frac{WP_1}{T},\end{aligned}$$

that is, $\Pr(T - (\{1, 2\})|A+) = \Pr(T - (\{1\})|A+)$.

Thus, the “effective” window period corresponding to any test set S^i is given by $j \in S^i_{\min}\{WP_j\}$, $i \in \Psi$, leading to

$$\Pr(T - (S^i)|A^i+) = \frac{j \in S^i_{\min}\{WP_j\}}{T}. \quad (2.8)$$

Therefore, Assumption A1 implies, unrealistically, that adding a second test with a larger window period to the test set will *not* impact the false negative probability, and hence the RR (see (2.4)). That is, under Assumption A1, there are no benefits of administering multiple tests for the same infection (“orthogonal testing”), as the RR will be dictated by the test having the smallest window period.

Example 2 evaluates the false negative probability when Assumption A1 is relaxed and replaced by Assumption B1, with a value of $\gamma = 1$.

EXAMPLE 2 Consider the HIV test set, comprised of the individual donation Nucleic Acid Test (ID-NAT) and the antibody test (Ab), that is, $S^{\text{HIV}} = \{\text{ID} - \text{NAT}, \text{Ab}\}$, with respective window periods of 5.6 and 20.3 days (from Busch and others, 2005). Then, considering whole blood donations, for which $T = 56$ in the United States, and assuming that $\beta = 0.97$ and $\alpha = 0.0005$ for each test, the false negative probability of set S^{HIV} can be evaluated as (see (2.7)):

$$\begin{aligned}\Pr(T - (S^{\text{HIV}})|A^{\text{HIV}}+) &= \beta \left(\frac{WP_{\text{ID-NAT}}}{T} \right) + \alpha\beta \left(\frac{WP_{\text{Ab}} - WP_{\text{ID-NAT}}}{T} \right) + \alpha^2 \left(\frac{T - WP_{\text{Ab}}}{T} \right) \\ &= 0.97 \left(\frac{5.6}{56} \right) + (0.0005)(0.97) \left(\frac{20.3 - 5.6}{56} \right) \\ &\quad + (0.0005)^2 \left(\frac{56 - 20.3}{56} \right) = 0.097.\end{aligned}$$

On the other hand, under Assumption A1, the false negative probability of test set S^{HIV} is given by $\Pr(T - (S^{\text{HIV}})|A+) = \min\{5.6, 20.3\}/56 = 5.6/56 = 0.10$ (see (2.8)).

Thus, relaxing Assumption A1 leads to an incentive to perform orthogonal testing, as this reduces the false negative probability (hence the RR) of the test set.

2.3.2 Deriving the true negative probability of a test set. For any $S^i = \{1, 2, \dots, n^i\} \subseteq \Omega^i$:

$$\Pr(T^i - (S^i)|A^i-) = \Pr(T_1^i - , T_2^i - , \dots, T_{n^i}^i - |A^i-). \quad (2.9)$$

Equation (2.9) requires data on the joint specificity of all possible test combinations. As these data are not typically available in the medical literature, we propose the following bounds.

Table 1. *RR expressions for the single-infection single-test case*

RR for infection i ($RR^i(\{j\})$)	Single-infection single-test case
The IWP Model: under Assumptions A1 and A2	$\Pr(A^i+) \frac{WP_i}{T}$
Only Assumption A1 relaxed	$\Pr(A^i+) \left(\beta_j \frac{WP_i}{T} + \alpha_j \frac{(T-WP_i)}{T} \right)$
Only Assumption A2 relaxed	$\prod_{k \in \Psi \setminus \{i\}} \Pr(T^k - (S^k) A^k-) \Pr(A^i+) \frac{WP_i}{T}$
Assumptions A1 and A2 relaxed	$\prod_{k \in \Psi \setminus \{i\}} \Pr(T^k - (S^k) A^k-) \Pr(A^i+) \left(\beta_j \frac{WP_i}{T} + \alpha_j \frac{(T-WP_i)}{T} \right)$

COROLLARY 1 For any $S^i \subseteq \Omega^i$ and infection $i \in \Psi$, we have

$$\prod_{j \in S^i} \Pr(T_j^i - |A^i-) \leq \Pr(T^i - (S^i) | A^i-) \leq \prod_{j \in S^i} \Pr(T_j^i - |A^i-).$$

For $|S^i| = 1$, upper and lower bounds (UB and LB) in Corollary 1 are tight, and equal $\Pr(T^i - (S^i) | A^i-)$.

EXAMPLE 3 Consider, as in Example 2, that $S^{\text{HIV}} = \{\text{ID-NAT}, \text{Ab}\}$. Assume that the specificity of ID-NAT and Ab are, respectively, 0.997 and 0.990. Then, by Corollary 1, the specificity of set S^{HIV} can be bounded by $0.997 \times 0.990 = 0.987 \leq \Pr(T - (S^{\text{HIV}}) | A^{\text{HIV}}-) \leq 0.990$.

On the other hand, under Assumption [A2](#), the specificity of set S^{HIV} is 1, which is unrealistic as discussed above.

2.3.3 *Deriving the RR.* Equation (2.7), along with Corollary 1, can be used to derive RR and Waste in (2.4) and (2.5) for any test set S when Assumptions [A1](#) and [A2](#) are relaxed.

For the special case where a single test is administered for infection i , RR for infection i ($RR^i(\{j\})$) under the various assumptions discussed above is summarized in Table 1 (see (2.3), (2.4), and (2.7)). Observe that even when the test is perfectly reliable outside of its window period ($\alpha = 0$), the RR obtained by relaxing Assumption [A1](#) is lower than that in the IWP model. This is in line with [Satten \(1997\)](#), which shows, for the setting where DT and WP follow continuous distributions, $\alpha = 0$, and under Assumption [A2](#), that the RR for the single-infection single-test case is bounded from above by WP_j/T , and approaches this limit only when the number of donations by a donor increases to infinity.

3. NUMERICAL RESULTS

We study the impact of Assumptions [A1](#) and [A2](#) on the cost-effectiveness analysis (on RR and QALYs gained due to infections averted) in [Jackson and others \(2003\)](#), and on the optimal testing solution. When relaxing these assumptions, the data we use (i.e. β , α , and test specificity values) are representative of the possible values, and is intended to give the reader a general idea on their implications. In addition, due to lack of data, we use $\gamma_{(k)(j)} = 1$, $k > j$, $j, k \in \Omega^i$, $i \in \Psi$. As discussed in Section 2.3.1, this assumption is reasonable, as it indicates that if the marker for a test with a smaller window period has not yet developed to the level detectable by the more sensitive test, then the markers for the less sensitive tests will not have developed to their detectable levels either. We consider whole blood donations, for which $T = 56$ in the

Table 2. *Window period, QALY, and incidence data from Jackson and others (2003)*

Infection	Incidence (in 10^5 person-years)	Window period (days)			QALY (per infection averted)
		Ab	MP-NAT	ID-NAT	
HIV	1.86	16.0	11.0	7.00	7.10
HCV	2.70	70.0	10.0	7.00	0.60
HBV	3.62	45.0	39.0	20.0	0.16

United States (US-FDA, 2011). The “base case” refers to the setting where Assumptions A1 and A2 are used. The following abbreviations are used:

Ab : Antibody screening, Ag : Antigen testing,

NAT : Nucleic Acid Testing, ID-NAT (MP-NAT) : Individual Donation (Mini-pool) NAT.

3.1 Impact on an existing cost-effectiveness study

Table 2 reports the data used in Jackson and others (2003). When relaxing Assumption A1, we consider that the probability of not detecting a window period donation (β) lies in $[0.970, 0.999]$ (Weusten and others, 2002), and of not detecting an out-of window period donation (α) is 0.0005 (Preiser and others, 2000). The first part of Table 3, taken from Jackson and others (2003), reports the RR under Assumptions A1 and A2 for each of the nine tests considered in Table 2; and the second part of the table reports the RR when Assumptions A1 and A2 are relaxed, individually as well as jointly, using the equations in Table 1.

Relaxing Assumption A2 always reduces the RR over the base-case; see Table 1. On the other hand, relaxing Assumption A1 yields a lower RR than the base-case only if $\alpha \leq ((1 - \beta)WP)/(\mathcal{T} - WP)$. Then, for $\alpha = 0.0005$, relaxing A1 yields a lower RR for all values of β in $[0.97, 0.99]$, but a higher RR for $\beta = 0.999$. In conclusion, RR is generally overestimated in the transfusion literature under Assumptions A1 and A2. For example, a comparison of the base-case to the case where Assumptions A1 and A2 are relaxed shows a 5.98% reduction in the QALYs gained for administering ID-NAT over the antibody test for all infections (see Table 3). Similarly, there is a reduction in the QALYs gained when one of the two assumptions is relaxed, indicating that the effectiveness of the testing strategies is generally overestimated in the transfusion literature.

3.2 Impact on the optimal solution

We next study the impact of Assumptions A1 and A2 on the optimal testing strategy using the test characteristics and incidence data provided in Table 4. The optimal testing strategy is obtained by solving the RR Minimization (RRM) model, which is an extension of the optimization model developed in our earlier work (Bish and others, 2011) to increase model realism. In particular, RRM is expanded to: (1) allow for concave functional form of the testing cost and (2) disallow certain test combinations (e.g. mixed-platform solutions); see the Appendix in supplementary material available at *Biostatistics* online for details. Below we elaborate on the need for each extension.

In reality, it is often the case that a testing lab will have the platform/equipment for performing MP-NAT or ID-NAT, but not both. That is, a testing solution that calls for MP-NAT for some infections and ID-NAT for some other infections will likely not be feasible to implement in practice. We represent this

Table 3. *Impact of Assumptions A1 and A2 on the RR and QALYs gained*

RR (in 10 ⁶ donations)												
Infection	Under Assumptions A1 and A2 [†]			Assumption A1 relaxed			Assumption A2 relaxed			Assumptions A1 and A2 relaxed		
	Ab	MP-NAT	ID-NAT	Ab	MP-NAT	ID-NAT	Ab	MP-NAT	ID-NAT	Ab	MP-NAT	ID-NAT
HIV	0.815	0.561	0.357	0.792	0.545	0.347	0.799	0.553	0.355	0.776	0.537	0.345
HCV	5.178	0.740	0.518	5.022	0.719	0.504	5.075	0.729	0.515	4.922	0.709	0.501
HBV	4.463	3.868	1.984	4.330	3.753	1.926	4.374	3.814	1.972	4.244	3.700	1.914
QALYs gained												
	Under Assumptions A1 and A2 [†]			Assumption A1 relaxed			Assumption A2 relaxed			Assumptions A1 and A2 relaxed		
	Ab to MP-NAT	Ab to ID-NAT	MP-NAT to ID-NAT	Ab to MP-NAT	Ab to ID-NAT	MP-NAT to ID-NAT	Ab to MP-NAT	Ab to ID-NAT	MP-NAT to ID-NAT	Ab to MP-NAT	Ab to ID-NAT	MP-NAT to ID-NAT
HIV	23.9	43.0	19.1	23.2	41.7	18.5	23.1	41.7	18.6	22.4	40.4	18.0
HCV	35.2	36.9	1.8	34.1	35.8	1.7	34.4	36.1	1.7	33.4	35.0	1.6
HBV	1.3	5.2	4.0	1.2	5.1	3.9	1.2	5.1	3.9	1.1	4.9	3.8
Total	60.3	85.1	24.8	58.4	82.5	24.1	58.7	82.9	24.2	56.9	80.3	23.4

[†]From Jackson and others (2003).

Table 4. *Window period and incidence data*

Infection	Screening test	Window period (days) [†]	Incidence (in 10 ⁵ person-years) [‡]	Specificity [§]
HIV	HIV ID-NAT	5.60	2.16	0.997
	HIV MP-NAT	9.00		0.993
	HIV Ab	20.3		0.990
HCV	HCV ID-NAT	4.90	2.80	0.997
	HCV MP-NAT	7.40		0.993
	HCV Ab	58.3		0.990
HBV	HBV ID-NAT	20.6	3.43	0.997
	HBV MP-NAT	38.3		0.993
	HBsAg	38.3		0.990

[†]From [Busch and others \(2005, Figure 1\)](#).

[‡]From [Busch and others \(2005, Table 2\)](#).

[§]Specificity values used when relaxing Assumption [A2](#).

in RRM by a platform constraint that disallows this type of mixed-platform NAT solutions. Further, from [Jackson and others \(2003\)](#), we estimate the NAT cost by the following concave functions: For MP-NAT (ID-NAT), the unit cost of testing for any one infection is \$10 (\$15); any two infections is \$20 (\$30); and all three infections is \$25 (\$35). Finally, we consider that per unit costs of HIV Ab, HCV Ab, and HBsAg are \$4 each ([Jackson and others, 2003](#)). In our numerical study, we consider budget levels between \$23 and \$60, varying in \$1 increments.

Table 5 reports, under various assumptions, the optimal testing solution, budget range over which this solution remains optimal, actual RR (calculated with Assumptions [A1](#) and [A2](#) relaxed with $\beta_j = 0.97$ and $\alpha_j = 0.0005$, $j \in \Omega$), and Waste (in %). Even when Assumptions [A1](#) and/or [A2](#) are used in RRM, we still report the *actual* RR, as this is the risk the system will face. When multiple tests are administered for an infection, Corollary 1 is used to derive an LB and an UB on RR and Waste.

Part 1 of Table 5 reports the optimal solution for the base case. As discussed above, under Assumption [A1](#) there are no benefits of orthogonal testing; hence, all optimal solutions in the base case are comprised of one test per infection, independent of the budget. The optimization model can be modified to overcome this restriction by imposing “test pairing” constraints. Part 2 of Table 5 reports the new optimal solution under the requirement that each NAT test must be paired with an antibody or an antigen test.

We next relax Assumption [A1](#) with $\beta_j = 0.97$ and $\alpha_j = 0.0005$, $j \in \Omega$, see Part 3 of Table 5. Now multiple tests are selected by the optimization model at certain budgets to reduce the RR, as the false negative probability of a test set is now a function of all selected tests. Thus, there is no need to *a priori* couple and force test pairs. (Observe that the actual RR corresponding to the optimal solution for \$32 in Part 3 of Table 5 is lower than that for \$33; this is because the optimization model considers the RR with only Assumption [A1](#) relaxed.) Finally, Part 4 of Table 5 reports the optimal solution when both Assumptions [A1](#) and [A2](#) are relaxed. The optimal testing solution remains unchanged over Part 3 of Table 5 for all budgets but \$33; hence we only report the solution for \$33.

To put these results in perspective, consider, for example, a budget of \$33. Under Assumptions [A1](#) and [A2](#), the optimal solution is to select MP-NAT for both HIV and HCV, and HBsAg for HBV, resulting in an RR of 4.454 infections in one million donations (Table 5, Part 1). When antigen/antibody tests are force-paired with NAT, Ab screening is added for HCV, and MP-NAT is added for HBV, but at the expense of switching from MP-NAT to Ab for HIV, increasing the RR to a range of (4.985, 5.055) (Table 5, Part 2). Thus, forcing test pairs leads to a sub-optimal solution. On the other hand, when the actual expression on

Table 5. *The optimal test set under various assumptions*

Part 1: optimal test set—under Assumptions A1 and A2					
Budget range	HIV	HCV	HBV	Waste (%)	RR (in 10 ⁶ donations) Assumptions A1 and A2 relaxed
\$23	HIV Ab	ID-NAT	HBsAg	2.28	4.910
\$24–\$33	MP-NAT	MP-NAT	HBsAg	2.38	4.454
\$34	HIV Ab	ID-NAT	ID-NAT	1.59	3.358
\$35–\$60	ID-NAT	ID-NAT	ID-NAT	0.90	2.546
Part 2: optimal test set—under Assumptions A1 and A2 and with Ag/Ab coupled with NAT					
	HIV	HCV	HBV	Waste (%) (LB, UB)	RR (in 10 ⁶ donations) Assumptions A1 and A2 relaxed (LB, UB)
\$23–\$26	HIV Ab	HCV Ab	MP-NAT and HBsAg	(2.97, 3.65)	(8.502, 8.562)
\$27–\$31	HIV Ab	HCV Ab	ID-NAT and HBsAg	(2.97, 3.26)	(6.977, 6.998)
\$32–\$36	HIV Ab	MP-NAT and HCV Ab	MP-NAT and HBsAg	(2.97, 4.32)	(4.985, 5.055)
\$37–\$46	MP-NAT and HIV Ab	MP-NAT and HCV Ab	MP-NAT and HBsAg	(2.97, 4.99)	(4.333, 4.425)
\$47–\$60	ID-NAT and HIV Ab	ID-NAT and HCV Ab	ID-NAT and HBsAg	(2.97, 3.84)	(2.468, 2.491)

Continued

Table 5. *Continued*

Part 3: optimal test set— Assumption A1 relaxed					
	HIV	HCV	HBV	Waste (%) (LB, UB)	RR (in 10 ⁶ donations) Assumptions A1 and A2 relaxed (LB, UB)
\$23	HIV Ab	ID-NAT	HBsAg	2.28	4.910
\$24–\$27	MP-NAT	MP-NAT	HBsAg	2.38	4.454
\$28–\$31	MP-NAT and HIV Ab	MP-NAT	HBsAg	(2.68, 3.36)	(4.408, 4.439)
\$32	MP-NAT and HIV Ab	MP-NAT and HCV Ab	HBsAg	(2.97, 4.32)	(4.364, 4.426)
\$33	MP-NAT and HIV Ab	MP-NAT	MP-NAT and HBsAg	(2.68, 4.03)	(4.377, 4.439)
\$34	HIV Ab	ID-NAT	ID-NAT	1.59	3.358
\$35–\$38	ID-NAT	ID-NAT	ID-NAT	0.90	2.546
\$39–\$42	ID-NAT and HIV Ab	ID-NAT	ID-NAT	(1.59, 1.89)	(2.519, 2.527)
\$43–\$46	ID-NAT and HIV Ab	ID-NAT	ID-NAT and HBsAg	(2.28, 2.87)	(2.493, 2.508)
\$47–\$60	ID-NAT and HIV Ab	ID-NAT and HCV Ab	ID-NAT and HBsAg	(2.97, 3.84)	(2.468, 2.491)
Part 4: optimal test set—Assumptions A1 and A2 relaxed					
	HIV	HCV	HBV	Waste (%) (LB, UB)	RR (in 10 ⁶ donations) Assumptions A1 and A2 relaxed (LB, UB)
\$33	MP-NAT and HIV Ab	MP-NAT and HCV Ab	HBsAg	(2.97, 4.32)	(4.364, 4.426)

Table 6. Comparison of the RR and testing cost at a budget of \$33

Assumptions	RR (in 10^6 donations)	Waste (%)	Testing cost
Under Assumptions A1 and A2	4.454	2.28	24
Under Assumptions A1 and A2 and Ab/Ag coupled with NAT	(4.985, 5.055)	(2.97, 4.32)	32
Assumption A1 relaxed	(4.377, 4.439)	(2.68, 4.03)	33
Assumptions A1 and A2 relaxed	(4.364, 4.426)	(2.97, 4.32)	32

RR is used (by relaxing Assumptions A1 and A2) and when there is no need to *a priori* force test pairs, the solution becomes MP-NAT and Ab for HIV; MP-NAT and Ab for HCV; and HBsAg for HBV (Table 5, Part 3), with an RR range of (4.364, 4.426), lower than those in Parts 1 and 2 for \$33. This underscores the value of the optimization model that uses the actual RR function (with Assumptions A1 and A2 relaxed), and of having the optimization model decide the test selection rather than forcing it to choose test pairs.

Table 6 summarizes the impact at the budget level of \$33. The optimal test set obtained by relaxing Assumption A1 reduces the actual RR by 0.608 to 0.616 infections in one million donations (with all of \$33 used) over the optimal test set under Assumptions A1 and A2 and forced Ab/NAT pairs (with \$32 of the allocated \$33 used), see Table 6. Further relaxing Assumption A2 leads to an additional reduction of 0.013 infections in one million donations, highlighting again that coupling of the tests outside of the optimization model leads to sub-optimal solutions. Finally, when both Assumptions A1 and A2 are relaxed over the base-case (with no forced coupling), the RR reduces by 0.03–0.09 infections in one million donations. In conclusion, relaxing one or both of these assumptions leads to a *better* testing scheme with a lower RR *at the same budget level*.

4. DISCUSSION, CONCLUSIONS, AND FUTURE RESEARCH DIRECTIONS

We propose a new probabilistic method for computing the Residual Risk in donated blood after post-donation screening when two restrictive assumptions, commonly used in the IWP model, are relaxed. By mathematically modeling the Residual Risk with these assumptions relaxed, our model closes the gap between the actual probabilistic expression of Residual Risk and the expression used in the IWP model. This probability model can be used for assessing the safety of blood transfusion, evaluating the cost-effectiveness of new screening technologies, or within an optimization-based model to jointly determine the “best” testing strategy for multiple infections, considering common constraints. Assumptions A1 and A2 lead to an overestimation of the Residual Risk, hence to inaccurate estimates in cost-effectiveness studies and to sub-optimal solutions in the optimization model. The optimal testing solution translates into fewer expected infections, hence savings in healthcare expenses, *without* a corresponding increase in the testing cost. This is significant, because the transfusion-transmitted infections considered in this paper have potentially severe consequences, both from an individual and from a societal perspective. These are our main contributions.

Our results come with certain limitations. To keep the probability model tractable, easy to use, and in alignment with the data available, we have made certain modeling choices. For example, by modeling the donor arrival process as a uniform distribution over a fixed interval, as in the IWP model, we make the implicit assumption that the two stochastic processes, of donor arrival and infection occurrence, are stationary and independent, that is, donors do not alter their inter-donation period following risky behavior. However, donors engaged in risky behavior may display “test seeking” or “test aversion” tendencies, see [Gonzalez and others \(2006\)](#), [Satten \(1997\)](#), and [Yasui and others \(2002\)](#). Further, from a data availability perspective, our model requires robust estimates of various joint and conditional test performance measures (specificity and sensitivity). Since all these data are not available in the medical literature, approximations

needed to be made, including Assumption B1 and Corollary 1. On the positive side, if these data become available, then the models developed in this paper still apply. Therefore, this is a data availability, and not a modeling, issue. We hope our model motivates the medical researchers to put more effort into accurately estimating these data, closing the bridge between model requirements and data availability.

Despite the limitations discussed above, this methodology is simple enough to use and the data needed can be estimated using available data (as we do here). Consequently, this model can be an integrated component of cost-effectiveness studies and can help the decision-maker choose an optimal screening strategy in a budget-constrained environment. An important future research direction is to relax some modeling assumptions to further increase the realism of the model. This includes more realistically modeling the behavior of donors engaged in risky behavior, and incorporating prevalence/incidence rate uncertainty into the model and constraining the fraction of blood wasted by an upper limit.

SUPPLEMENTARY MATERIAL

Supplementary Material is available at <http://biostatistics.oxfordjournals.org>.

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REFERENCES

- BISH, D. R., BISH, E. K., XIE, S. R. AND SLONIM, A. D. (2011). Optimal selection of screening assays for infectious agents in donated blood. *IIE Transactions on Healthcare Systems Engineering* **1**(2), 67–90.
- BROOKMEYER, R. (2009). Should biomarker estimates of HIV incidence be adjusted? *AIDS* **23**(4), 485–491.
- BURD, E. M. (2010). Validation of laboratory-developed molecular assays for infectious diseases. *Clinical Microbiology Reviews* **23**(3), 550–576.
- BUSCH, M. P., GLYNN, S. A., STRAMER, S. L., STRONG, D. M., CAGLIOTI, S., WRIGHT, D. J., PAPPALARDO, B. AND KLEINMAN, S. H. (2005). A new strategy for estimating risks of transfusion-transmitted viral infections based on rates of detection of recently infected donors. *Transfusion* **45**(2), 254–264.
- BUSCH, M. P. AND SATTEN, G. A. (1997). Time course of viremia and antibody seroconversion following human immunodeficiency virus exposure. *The American Journal of Medicine* **102**(5), 117–124.
- FIEBIG, E. W., WRIGHT, D. J., RAWAL, B. D., GARRETT, P. E., SCHUMACHER, R. T., PEDDADA, L., HELDEBRANT, C., SMITH, R., CONRAD, A., KLEINMAN, S. H. and others (2003). Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. *AIDS* **17**(13), 1871–1879.
- GANEM, D. AND PRINCE, A. M. (2004). Hepatitis B virus infection: natural history and clinical consequences. *New England Journal of Medicine* **350**(11), 1118–1129.
- GONCALEZ, T. T., SABINO, E. C., MURPHY, E. L., CHEN, S., CHAMONE, D. A. F. AND MCFARLAND, W. (2006). Human immunodeficiency virus test-seeking motivation in blood donors, São Paulo, Brazil. *Vox Sanguinis* **90**(3), 170–176.

- GREINACHER, A., FENDRICH, K., ALPEN, U. AND HOFFMANN, W. (2007). Impact of demographic changes on the blood supply: Mecklenburg–West Pomerania as a model region for Europe. *Transfusion* **47**(3), 395–401.
- JACKSON, B. R., BUSCH, M. P., STRAMER, S. L. AND AUBUCHON, J. P. (2003). The cost-effectiveness of NAT for HIV, HCV, and HBV in whole-blood donations. *Transfusion* **43**(6), 721–729.
- JOSEPH, L., GYORKOS, T. W. AND COUPAL, L. (1995). Bayesian estimation of disease prevalence and the parameters of diagnostic tests in the absence of a gold standard. *The American Journal of Epidemiology* **141**(3), 263–272.
- KLEINMAN, S., BUSCH, M. P., KORELITZ, J. J. AND SCHREIBER, G. B. (1997). The incidence/window period model and its use to assess the risk of transfusion-transmitted human immunodeficiency virus and hepatitis C virus infection. *Transfusion Medicine Reviews* **11**(3), 155–172.
- LACKRITZ, E. M., SATTEN, G. A., ABERLE-GRASSE, J., DODD, R. Y., RAIMONDI, V. P., JANSSEN, R. S., LEWIS, W. F., NOTARI, E. P. AND PETERSEN, L. R. (1995). Estimated risk of transmission of the human immunodeficiency virus by screened blood in the United States. *New England Journal of Medicine* **333**(26), 1721–1725.
- LIMMATHUROTSAKUL, D., JAMSEN, K., ARAYAWICHANONT, A., SIMPSON, J. A., WHITE, L. J., LEE, S. J., WUTHIEKANUN, V., CHANTRATITA, N., CHENG, A., DAY, N. P. J. and others (2010). Defining the true sensitivity of culture for the diagnosis of melioidosis using Bayesian latent class models. *PLoS One* **5**(8), e12485.
- ORFINGER, B. (2010). Red Cross calls national blood shortage a disaster. <http://www.redcross.org/news/inthenews/00/7-12a-00.html>, Accessed in July 2010.
- PEPE, M. S. (2003). *The Statistical Evaluation of Medical Tests for Classification and Prediction*. Oxford: Oxford University Press.
- PREISER, W., BRINK, N. S., HAYMAN, A., WAITE, J., BALFE, P. AND TEDDER, R. S. (2000). False-negative HIV antibody test results. *Journal of Medical Virology* **60**(1), 43–47.
- SATTEN, G. A. (1997). Steady-state calculation of the risk of HIV infection from transfusion of screened blood from repeat donors. *Mathematical Biosciences* **141**(2), 101–113.
- SCHREIBER, G. B., BUSCH, M. P., KLEINMAN, S. H. AND KORELITZ, J. J. (1996). The risk of transfusion-transmitted viral infections. *New England Journal of Medicine* **334**(26), 1685–1690.
- TRIKALINOS, T. A. (2012). Options for summarizing medical test performance in the absence of a “gold standard”. *Journal of General Internal Medicine* **27**(1), 67–75.
- US-FDA. (2011). *Maintaining a safe and adequate supply of donated blood during a severe emergency*. Blood Products Advisory Committee.
- VAN HULST, M., HUBBEN, G., SAGOE, K., PROMWONG, C., PERMPIKUL, P., FONGSATITKUL, L., GLYNN, D. M., SIBINGA, C. T. S. AND POSTMA, M. J. (2009). Web interface-supported transmission risk assessment and cost-effectiveness analysis of postdonation screening: a global model applied to Ghana, Thailand, and the Netherlands. *Transfusion* **49**(12), 2729–2742.
- VAN SMEDEN, M., NAAKTGEBOREN, C. A., REITSMA, J. B., MOONS, K. G. M. AND DE GROOT, J. A. H. (2013). Latent class models in diagnostic studies when there is no reference standard: a systematic review. *The American Journal of Epidemiology*, kwt286.
- WEUSTEN, J. A. M., VAN DRIMMELEN, H. A. J. AND LELIE, P. N. (2002). Mathematic modeling of the risk of HBV, HCV, and HIV transmission by window-phase donations not detected by NAT. *Transfusion* **42**(5), 537–548.
- XIE, S. R., BISH, D. R., BISH, E. K., SLONIM, A. D. AND STRAMER, S. L. (2012). Safety and waste considerations in donated blood screening. *European Journal of Operational Research* **217**(3), 619–632.
- YASUI, Y., YANAI, H., SAWANPANYALERT, P. AND TANAKA, H. (2002). A statistical method for the estimation of window-period risk of transfusion-transmitted HIV in donor screening under non-steady state. *Biostatistics* **3**(1), 133–143.

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