International application of the Incidence Rate/Window Period model

Estimating risks of transfusion-transmitted infections (TTIs) is essential for monitoring blood safety and for helping physicians and patients make informed decisions when discussing allogeneic transfusion versus other therapeutic options. Since the 1980s and the HIV pandemic, proposed interventions to decrease TTI risks have mostly centered on reducing viral-transmission risks, with consequent implementation of increasingly stringent donor behavioral and highly sensitive laboratory screening procedures in many countries. As these measures have driven risks down, direct methods to estimate risks, such as prospective studies of transfusion recipients or testing of donor samples with sensitive research tests, have become impractical and/or prohibitively expensive due to the very large sample size required to conduct such studies.[1] This has led to the use of mathematical approaches that can be applied to a limited data set and allow for accurate estimation of risks if based on reasonable assumptions.

Prevalence and incidence rate (IR) have commonly been used to measure TTI risks in the blood supply. Prevalence measures the percentage of donations that test positive on a screening and confirmatory test (including old and new infections), whereas incidence measures the rate at which new infections develop in a population at risk. Since donations that have positive screening tests are discarded, the greatest threat to the safety of the blood supply is the donation of blood in the infectious window period (WP), the time between infection and detectability by screening tests. Additional sources of transfusion risk attributable to variant viral strains, immunosilent carriers, and testing error[2-7] are thought to only minimally contribute to overall risk, especially when dual testing systems exist (i.e., serology and NAT).

RESIDUAL RISK ESTIMATION: THE IR/WP MODEL

The IR/WP model was developed in parallel by investigators from the National Heart, Lung, and Blood Institute-sponsored Retrovirus Epidemiology Donor Study (REDS),[8,9] the CDC,[10] and the American National Red Cross[10] and has been used in the US to estimate the probability of a WP donation for each viral TTI since the early 1990s. The model estimates the probability of having a potentially infectious donation being released in the blood supply, or residual risk, by multiplying the IR by the number of days during which an infection may be present but not detectable by current screening assays (i.e., the length of the WP). This modeling approach can be implemented without the need to fund special research projects and can be used to generate risk estimates for multiple agents using the same data set. Although the approach requires the presence of an appropriate infrastructure to compile and analyze blood donor data from a proportion of the donor population in any given country, this model has now been applied successfully worldwide to provide country-specific viral TTI estimates, as exemplified by several reports[11-14] in this issue of *Transfusion*.

The residual risk estimates obtained for Australia[15] and countries represented in this issue of *Transfusion,*[11-14] albeit showing some variation, are uniformly low and suggest that the donor selection process (self-selection, behavioral screening, and test screening) adopted by these countries is very effective (Tables 1-3). More importantly, these reports clearly demonstrate that HIV and HCV residual risk estimates are or will be further reduced to extremely low levels after mini-pool NAT implementation. For HIV, the estimated probability of having a potentially infectious donation being released in the blood supply varied from about 1 in 450,000 (Italy) to 1 in 3 million (Australia) donations before NAT, whereas residual risk estimates after NAT varied between 1 in 900,000 (Italy) and 1 in 5 million (Australia) (Table 1). Even more marked was the reduction for HCV, with risk estimates decreasing from about 1 in 120,000 (Australia) to 1 in 800,000 (France) donations before NAT (EIA 3.0) to approximately 1 in 1 million (Australia, Italy) to 1 in 10 million (France) after NAT (Table 2). Although HBV risk estimates need to be evaluated with some caution (see below), data from these reports suggest that of the major viral TTIs evaluated, HBV remains most likely to be transmissible by transfusion, with residual risk estimates of 1 in 75,000 (Spain) to 1 in 520,000 (Australia) donations (Table 3). Mini-pool HBV NAT testing only reduces the WP by about 10 days[20] because the ramp-up viremia

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TABLE 1. HIV risks in RPT donors and NAT yield by country

Country	Period of observation	Allogeneic collections: Donations ×10⁶/year (n)	Allogeneic collections: Study coverage (%)	IR/10⁵ person years (95% CI)	WP (days): Sero	WP (days): NAT	Residual risk/10⁶ RPT donations: Serology estimate	Residual risk/10⁶ RPT donations: Serology/NAT estimate	NAT yield/10⁶ donations: Predicted RPT*/all†	NAT yield/10⁶ donations: Observed
Australia[15]	7/00-6/01	1.0	100	0.6 (0.1-2.0)	22	11	0.3	0.2	0.2*/0.2†	0.0‡ p§ = 1.00
Europe EPFA[16,‖]/ Central[17]	1/97-NA	NA	NA	0.7 (0.5-1.1)	22	11	0.4	0.2	0.2*/0.3†	0.6‡ p§ = 0.50
France[12]	1/98-12/00	3.0	60	1.2 (0.7-2.0)	22	11	0.7	0.4	0.4*/0.4†	0.6‡ p§ = 1.00
Italy[13]	1/96-12/00	2.4	20	3.8 (2.8-5.0)	22	11	2.3	1.1	1.1*	
Spain[11]	1/97-12/99	1.4	71	3.2 (2.2-4.5)	22	11	1.9	1.0	1.0*	
US	1/91-12/93[8]	13.2[18]	8	3.4 (2.2-4.8)	22	11	2.0	1.0	1.0*	
	1/96-12/00¶	13.2[18]	8	1.6 (1.0-2.3)	22	11	1.0	0.5	0.5*	
	1/00-12/01[14]	13.2[18]	50	1.6 (1.2-2.0)	16**	11	0.7	0.5	0.2*	0.2†† p§ = 1.00

* Predicted yield for RPT donations obtained by multiplying RPT IRs (5th column) by the detectable RNA+ window (11 days).
† Predicted yield for all donations obtained by multiplying the estimated IR in all donors by the detectable RNA+ window (11 days); we assumed that 10 percent (Australia) or 20 percent (EPFA and France) of donations were FT.
‡ Observed yield per 10^6 donations (FT and RPT). There was one HIV yield case per 1.8 10^6 donations in France (written communication, Josiane Pillonel, June 2002).
§ Two-tailed two-sample exact Poisson test comparing predicted and observed yield donations.
‖ Representation from Denmark, England and Wales, Finland, Germany, and Switzerland. IR for EPFA estimated from the residual risk obtained by the Müller-Breitkreutz mathematical model and used as an estimate for Germany and Austria to allow for comparison of predicted versus observed NAT yield in Central Europe.
¶ REDS data.
** Accounts for HIV-1 p24Ag testing.
††Observed yield per 10^6 RPT donations.

TABLE 2. HCV risks in RPT donors and NAT yield by country

Country	Period of observation	Allogeneic collections: Donations ×10⁶/year (n)	Allogeneic collections: Study coverage (%)	IR/10⁵ person years (95% CI)	WP (days): Sero	WP (days): NAT	Residual risk/10⁶ RPT donations: Serology estimate	Residual risk/10⁶ RPT donations: Serology/NAT estimate	NAT yield/10⁶ donations: Predicted RPT*/all†	NAT yield/10⁶ donations: Observed
Australia[15]	7/00-6/01	1.0	100	4.7 (2.7-7.5)	66	7‡	8.5	0.9	7.6*/8.4†	1.0§ p‖ = 0.02
Europe Central[17]	1/97-NA	NA	NA	2.3 (0.3-4.7)[19,¶]	66	7‡	4.2	0.4	3.8*/4.5†	1.7§ p‖ = 0.13
EPFA[16**]	1/97-12/97	NA	NA	0.9 (0.7-1.2)	66	7‡	1.6	0.2	1.4*	
France[12]	1/98-12/00	3.0	60	0.6 (0.3-1.3)	66	7	1.2	0.1	1.0*/1.2†	0.6§ p‖ = 0.76
Italy[13]	1/96-12/00	2.4	20	4.1 (3.0-5.3)	70	12	7.9	1.3	6.6*	
Spain[11]	1/97-12/99	1.4	71	3.7 (2.6-5.1)	66	7‡	6.7	0.7	6.0*	
US	1/91-12/93[8]	13.2[18]	8	4.3 (2.4-6.9)	82	10‡	9.7	1.2	NA	
	1/96-12/00††	13.2[18]	8	2.9 (2.1-3.9)	70	8	5.6	0.6	4.9*	
	1/00-12/01[14]	13.2[18]	50	1.9 (1.5-2.4)	70	10	3.6	0.5	3.1*	2.6‡‡ p‖ = 0.43

* Predicted yield for RPT donations obtained by multiplying RPT IR (5th column) by the detectable RNA+ window (58-62 days).
† Predicted yield for all donations was calculated by multiplying the IR in all donors by the detectable RNA+ window (58-62 days); 10 percent (Australia) or 20 percent (Central Europe and France) of donations were assumed to be FT.
‡ The current HCV mini-pool NAT WP was assumed to be between 7 and 12 days, based upon the best current estimates for sensitivity of mini-pool HCV NAT. Any estimate in the original publication longer than 12 days was changed to reflect this assumption.
§ Observed yield/10^6 donations (FT, RPT). There was one HCV yield case/1.8 10^6 donations in France (written communication, Josiane Pillonel, June 2002).
‖ Two-tailed two-sample exact Poisson test comparing predicted and observed yield donations.
¶ IR based on 1994-95 second and third generation anti-HCV EIA data for Germany and was used as an estimate of the IR in Germany and Austria to allow for comparison of predicted versus observed NAT yield in Central Europe. We assumed that the WP for the HCV serology assay used in Central Europe[17] in 1997 onward was 66 days.
** Representation from Denmark, England and Wales, Finland, Germany, and Switzerland. IR estimated from the residual risk obtained by the Müller-Breitkreutz mathematical model.
††REDS data.
‡‡Observed yield/10^6 RPT donations.

TABLE 3. HBV risk and predicted NAT yield in RPT donors by country

Country	Period of observation	Allogeneic collections: Donations $\times 10^6$/year (n)	Allogeneic collections: Study coverage (%)	IR/10^5 person years (95% CI)	WP (days): Sero	WP (days): NAT	Residual risk/10^6 RPT donations: Serology estimate	Residual risk/10^6 RPT donations: Serology/NAT estimate	NAT yield/10^6 RPT donations: Predicted
Australia[15]	7/00-6/01	1.0	100	1.6 (0.3-4.6)	45	34	1.9	1.5	0.5
Europe									
France[12]	1/98-12/00	3.0	60	1.4 (0.9-2.2)	56	46	2.1	1.8	0.4
Spain[11]	1/97-12/99	1.4	71	8.4 (5.2-12.6)	59	34	13.5	7.8	5.7
US	1/91-12/93[8]	13.2[18]	8	9.8 (6.7-13.4)	59	34	15.8	9.1	6.7
	1/96-12/00†	13.2[18]	8	6.0 (4.0-8.7)	59	49	9.7	8.1	1.6
	1/00-12/01[14]	13.2[18]	50	3.0 (2.3-3.9)	59	49	4.9	4.0	0.8

* HBV IRs in RPT donors (adjusted from HBsAg) are presented.
† Data from REDS.

phase for HBV is characterized by a much slower doubling time (2.6 days) than for HIV (20.5 hours)[21] or HCV (14.9 hours).[22] The difficulty in decreasing HBV risks also stems from the fact that no risk factor can be identified in 30 to 40 percent of HBV cases[23] and the consequent inability to develop donor-screening criteria that are sensitive enough to effectively screen out HBV-infected donors and specific enough to avoid unnecessary deferral of healthy donors. Widespread implementation of HBV immunization programs should, in the future, help reduce risks of HBV transfusion transmission by decreasing the number of infectious donors and susceptible transfusion recipients.

ASSUMPTIONS OF THE IR/WP MODEL

To better interpret the data at hand and be able to compare IRs (and consequently residual risk estimates) obtained by various countries, the reader should become familiar with the IR/WP model's basic assumptions, key components, and major nuances in method. The basic assumptions of the model are that 1) WP donations represent the most dominant source of risk; 2) overall IR in repeat (RPT) donors is constant throughout the period of the study; 3) a recently infected donor is as likely to donate in the early interval after infection as he or she is to donate subsequently; and 4) if no further adjustment is made, first-time (FT) donors have the same IR as RPT donors. The first assumption appears to be robust for HIV and HCV with WP risk probably accounting for 90 percent or more of the total risk and other sources of risk (viral variants, chronic seronegative carriers, and testing error) for 10 percent or less.[7] This is also the case for HBV in countries performing anti-HBc screening, whereas HbsAg, anti-HBc-reactive chronic carriers likely contribute a level of risk equal or greater to WP risk in the absence of anti-HBc screening.[24,25] We have no reason to doubt the validity of the second assumption if the period of the study is short (or, for longer periods, if there does not appear to be changes in rates through time that can result from changes in the epidemiology of the agent in the population or revision of screening criteria).

The third assumption may be more problematic because more recent studies have noted that the seroconversion interval may be longer than expected for HIV[26] or HCV incident cases.[15,16] This would imply that some donors delay their return around the time of infection and suggests that the model (which assumes a steady-state rate of donation) may tend to overestimate the yield of tests that detect infection earlier (i.e., NAT or HIV p24Ag). Consistent with this concern, the IR/WP model predicted that eight HCV NAT-only donations would be detected in Australia (of 0.97 million donations screened) compared with the one observed ($p = 0.02$, Table 2), and Seed et al.[15] reported that the duration of the seroconversion interval for HCV seroconverters was much longer than for the other viruses. Similarly, an apparent difference in observed versus expected HCV yield was noted for Central Europe, although these results were not significant ($p = 0.13$) and need to be viewed with caution because regional incidence data (Germany, 1994-95)[19] may not accurately estimate NAT yield data that would be obtained throughout Central Europe after 1996. There was no significant difference in predicted versus observed HCV yield data in France or in the US. This is compatible with the finding of no delay in return for HCV seroconverters in the US.[26] Further, no significant differences were found in any study between observed (0.0-0.6/10^6 donations) and predicted (0.2-0.4/10^6 donations) yields for HIV (Table 1). (Although NAT yield data are now becoming available for several other countries,[27] we were not able to evaluate whether observed and expected yields differed for countries for which we could not find published IR data.) Thus, the IR/WP model seems to predict reasonably well the yield of new assays unless donors significantly delay their return around the time of infection and seroconversion.

Finally, the recent development of a sensitive/less-sensitive HIV-1 assay[28] and evaluation of NAT-yield

data[14] now permit assessment of IRs in FT donors. Janssen et al.[28] reported a 2.4-fold higher IR in FT donors (7.18/100,000 person-years) than in RPT donors (2.95/100,000 person-years) using the sensitive/less-sensitive HIV-testing strategy. Using NAT-yield data, Dodd et al.[14] confirm this 2-fold differential in IRs between FT and RPT donors for HIV (2.1×) and extend this finding to HCV (2.4×). It is therefore now possible to estimate IRs in all donation if the relative proportion of FT and RPT donors is known. Most developed countries report that their donation base consists of about 20 percent FT and 80 percent RPT donors, which implies that the overall donor IR can be approximated by multiplying the IR obtained in RPT donors by 1.2 ([0.2 × 2 × IR in RPT donors] + [0.8 × IR in RPT donors]).

ESTIMATING THE IR

The IR/WP model can only be applied if two key statistics, the IR and the WP, are known with accuracy. Let us first turn to IR estimation because this statistic armed with a 95 percent CI allows for comparison of risks between countries that rely on similar testing systems and, therefore, similar WPs (95% CI around residual risks are usually unavailable because data is often too limited to allow calculation of variability around the WP estimate). IRs are derived by dividing the numbers of known confirmed incident cases (detected by serologic or NAT screening) by the number of person-years or the sum of the periods during which donors are at risk (i.e., are not infected yet). This derivation is confined to RPT donors because this population is followed for a certain period, allowing us to evaluate how many donors are incident cases (i.e., first test negative on all assays and then test positive for a particular marker on a subsequent donation). The minimum statistics required for IR calculations are the number of incident cases (the numerator), the total number of RPT donations, and the mean interdonation interval length (multiplication of the last two entities provides the number of person-years or denominator). Alternatively, if donation histories are available for all RPT donors, we can derive person-years by summing up the length of all interdonation intervals. Because a number of adjustments can be made to both the number of incident cases and to the number of person-years, the reader should assess the following factors to determine if studies are directly comparable:

1. Was there an adjustment for false-positive confirmatory tests? Some studies (e.g., Alvarez et al.,[11] REDS), upon further review of their laboratory results, have excluded false-positive donations, thereby providing a more accurate count of true sero- or NAT-incident cases.
2. Was the full length of the seroconversion intervals included in the person-years calculation or just a portion (often half) to try to adjust for when the infection probably occurred during the interval? In our experience, this adjustment does not have any demonstrable impact on the magnitude of the IR estimate.
3. Was there an adjustment for nontransfused seronegative and seroconversion units? Studies (e.g., Pillonel et al.,[12] Velati et al.,[13] REDS) may choose to exclude interdonation intervals that start with a donation that would not have been transfused because it was reactive for another marker or, when applicable, because the donor used the Confidential Unit Exclusion process. This may lead to a slight decrease in the number of incident cases and person-years.
4. Were all interdonation intervals that start with a donation tested by serology alone and end by a donation tested by both serology and NAT (or p24Ag for HIV) lengthened by the reduction in the WP? The IRs may be overestimated if this adjustment is not made, although this adjustment will only have a significant impact when the reduction in WP is substantial. In Tables 1 through 3, this adjustment was only applied to REDS IRs calculated for the period 1996-2000 because the US implemented NAT for HIV and HCV in 1999.
5. Was the measured HBsAg IR taken as the HBV incidence, or was an adjustment factor calculated to account for the transient nature of HBs-antigenemia? All IRs reported in Table 3 refer to HBV, with most having been adjusted from HBsAg using the method developed by Korelitz et al.[29] More recently, REDS investigators have used a different mathematical derivation to estimate HBV incidence[30,31] that results in similar, albeit slightly higher, estimates.

With these caveats in mind, we can first note that the IRs in RPT donors are small (Tables 1-3). When compared with rates in US blood donors, rates in the US general population are about 9 times higher for HIV (15.0 vs. 1.6), 7 times higher for HCV (13.4 vs. 1.9), and nearly 40 times higher for HBV (114.4 vs. 3.0).[32] Second, some variation exists between countries. Southern Europe (Italy, Spain) had higher HIV IRs than other European countries, the US, or Australia (Table 1). IRs for HCV were highest in Australia (in marked contrast to HIV), followed by Southern Europe (Italy, Spain) and the US (Table 2). Lowest HCV estimates were obtained for the European Plasma Fractionation Association (EPFA)-European countries and France (Table 2). For HBV, rates appeared similar in Australia and France, intermediate in the US, and highest in Southern Europe (Table 3). In the US, the HBV rate obtained at REDS centers was higher than reported by Dodd et al.[14] and probably reflects REDS geographic representation. There appears to have been a decrease in IRs in RPT donors over the last decade in some countries, as noted by Pillonel et al.[12] in France (all markers) and by

Dodd et al.[14] (HBV only) in the US. REDS has also noted that IRs for HIV and HBV have decreased in the US between the early and the late 1990s.

ESTIMATING THE INFECTIOUS WP

The second key statistic needed to estimate residual risk is the length of the WP for each test. WP estimates for HCV and HBV used in the model are generally based upon analyses of data on the time of exposure by transfusion to the development of a positive test. In contrast, the WP estimate for HIV is a theoretical number derived from mathematical modeling of TTIs occurring from HIV-seronegative units donated by persons who subsequently seroconverted.[1,7] WP estimates for HIV and HCV have been relatively well characterized;[7] however, the WP for HBV is more uncertain because the mean of 59 days is based upon a series of only seven evaluative transfusion-transmitted cases.[33] Although the model uses these WP estimates, what we are really interested in is the period during which a donation is infectious; this infectivity period may or may not be the same as the length of the WP commonly used to estimate residual risks (Tables 1-3). For example, it is unclear whether a donation given in the early stages after exposure (i.e., during the so-called eclipse [RNA–] pre-ramp-up viremia [intermittent RNA+] and very early ramp-up viremia [low viral load] phases) contains enough virus to be infectious.[7] In particular, the significance and infectivity of the low-level intermittent blips of RNA or DNA recently detected in plasma donor seroconversion panels in the pre-ramp-up viremia phase are uncertain and have not been included in the model for residual risk.[22,34] Further studies including additional animal transmission model systems,[35] donor lookback studies as described by Roth et al.[17,25] (where prior units from sero- or NAT-positive RPT donors are traced and recipients of these units tested), and recipient traceback studies[36] (investigation by recall or testing of stored donation specimens of donors whose blood products were transfused to recipients who subsequently acquired an infection after transfusion) are clearly needed to answer these questions and permit better estimation of risks. For example, Weusten et al.[37] used minimum chimpanzee infectious doses data to statistically predict human infectivity, relative to viral load and NAT assay performance, in a recently published mathematical modeling of WP risk. Although this is a clear conceptual advance and seems like a reasonable approach, the animal infectivity data employed in the model were limited, and it is unclear whether the animal data is directly transferable to humans. Further work in this area is called for.

TTIs: PREDICTED VERSUS OBSERVED

It is difficult to assess whether the residual risk estimates that have been reported here are overestimated as a result of this uncertainty in WP estimates. In the US, the model would predict that about 7 potentially infectious HIV and HCV donations and 65 potentially infectious HBV donations may be released yearly (of approx. 13.2 million donations in the US per year[18]). Even these rates seem high relative to the paucity of TTI reports. Indeed, only a handful of HIV[38] and HCV[39] transmissions have been documented since NAT-screening was introduced in the late 1990s. For HBV, reports of post-transfusion infections are rare, with the exception of in regions endemic for HBV infection (e.g., Japan).[36] However, the rarity of confirmed transfusion cases should not be interpreted to discount these risk projections for the following reasons: 1) some available allogeneic units are not transfused (7.5% in the US);[18] 2) most countries do not have mandatory surveillance of recipients for TTI, and clinical case reporting would depend upon accurate diagnosis, which may be difficult if symptoms never develop or occur after many years, by which time the association with the original transfusion is difficult to substantiate (e.g., HBV is asymptomatic in 50-70% of adults and spontaneously resolves with no long-term consequences in the majority of cases);[40,41] 3) 24 to 34 percent of RBC recipients may not survive more than 1 year after their transfusion, and 36 to 49 percent may not survive more than 40 months after transfusion, thereby preventing diagnosis of transfusion transmission if it occurred;[42] 4) some recipients may already carry the infection (recent REDS data indicate that 0.25, 1.75, and 8.5% of recipients are positive for HIV, HCV, and anti-HBc, respectively, before surgery and transfusion); and 5) some recipients may not be susceptible to acquiring the infection if, for example, they have been immunized for HBV.

ESTIMATING RESIDUAL RISKS IN RESOURCE-RESTRICTED COUNTRIES

The estimated residual risks of viral TTIs, although probably conservative in magnitude, are now very low in developed countries. Further incremental reduction in major viral risk (e.g., from implementation of individual donation NAT or pathogen reduction) is predicted to achieve exceedingly small safety benefits at high cost.[7,43,44] These countries can now afford to turn their attention to reducing other risks of transfusion, such as those caused by bacterial contamination or transfusion errors. However, this is not the situation in most developing countries faced with high TTI prevalence and IRs, and lacking the resources or the infrastructure to implement appropriate serologic screening, let alone NAT screening. The WHO estimates that at least 13 million of the 75 million units collected in the world each year are not completely tested using basic serologic assays, including up to 45 percent of blood donations in developing countries.[45,46] Even when testing is performed, the

sensitivity of assays may be poor and inadvertent release of test-positive units may occur.[46,47] Measuring risks of TTIs in these settings also becomes extremely difficult. As discussed, application of the IR/WP model requires collection of accurate information on the number of incident cases, RPT donations, and average interdonation interval for RPT donors (or seroconversion interval length for all incident cases).[16] This level of testing and data management may not be achievable in some developing countries. It may actually be easier for some countries to test a sample of HIV+ donations by the sensitive/less-sensitive HIV-1 assay or to perform mini-pool NAT for HCV to estimate risks in their donor population than to record donation histories or FT and RPT status. Hence, alternative approaches to modeling risk need to be developed to assist developing countries in monitoring the safety of their blood supply.

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