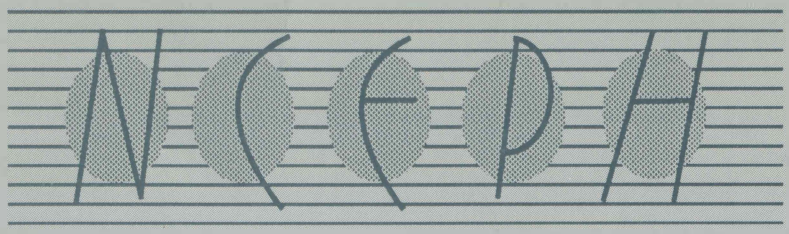

Blood donation and Human Immunodeficiency Virus infection: Do new and regular donors present different risks?

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1 Summary

This paper examines some problems inherent in assessing the risk of transmitting infection through blood transfusion. Blood from a recently infected donor may transmit infection which may not be detected at the time of transfusion. Inferences about the degree of risk must be made from the incidence and prevalence of infection in the community at large, and from the number of donated units of blood in which evidence of infection is found. We address the particular problem of comparing the relative risk in two donor populations, the repeat donors who give blood on several occasions, and the single donors who give blood only once.

2 Biological Background

Blood for transfusion in Australia is obtained by voluntary donation via the Red Cross Transfusion Service. It has long been appreciated that infections can be transmitted in transfused blood; hepatitis B (serum hepatitis) is a well known example [1]. The present epidemic involving the Human Immunodeficiency Virus-1 (HIV-1) highlights some problems typical of infection by a class of agents called retroviruses. A person infected with HIV-1 remains infected but clinically well for many years. An early response to infection is the production of antibodies to the infecting virus and these antibodies form the basis for a very specific test of infection. The test currently in wide use is for antibodies however, not for the virus, and will therefore return a negative result in the period between infection and the production of antibodies [2]. During this period, variously called the seronegative period or seronegative window, the infection in any blood donated will pass undetected. The seronegative period is of the order of weeks or months, and should not be confused with the time between infection and clinical illness which is measured in years or decades. There is not currently a test for the virus itself that can be usefully applied to the routine screening of blood for transfusion. The problem is shared by other retroviruses: HIV-2, HTLV-1, and HTLV-2 have been identified to date, but the list may grow.

The HIV epidemic in Australia is currently largely confined to people practising identified risk behaviours. Examples are receptive anal intercourse, the sharing of intravenous needles by injecting drug users and the use of prostitutes in areas where the HIV epidemic has already spread to the heterosexual population.

Potential blood donors are asked, and may be required by law, to refrain from donating blood if they practise risk behaviour. The voluntary exclusion of those placing themselves at risk has dramatically reduced the risk of transfusion-related HIV infection [3]. The number of infected units is now very small [12], and the number undetected is, presumably, even smaller. The risk might be further reduced, however, by recruiting donors from areas where the incidence of infection is small. It is the incidence, rather than the prevalence which is of importance because only those infected recently will be in the seronegative window period. Such a strategy might involve recruiting new donors in place of established regular donors. It has been common experience, however, that more seropositive units are obtained from new than from repeat donors [4] and this might superficially suggest that new donors represent a greater risk. A direct method of measuring risk from a

given population, or of comparing risks, is inappropriate for several reasons. We cannot wait to see how many recipients die of HIV infection because the median time between infection and death is about ten years. Present social values prevent us from testing recipients in order to detect HIV antibodies.

3 The Model Epidemic

We use a continuous model for the growth of an epidemic, in which the proportion of the adult population who have become infected by time t is $V(t)$. The epidemic began with $V(0) = 0$. We introduce the simplifications that an infected individual remains infected indefinitely, and that population growth is slow relative to the growth of the epidemic, so $V(t)$ is non-decreasing and the rate of change of $V(t)$ reflects the incidence of the disease. We ignore infected children because children do not donate blood, and infected children rarely survive childhood. We denote by $L(u)$ the distribution of the seronegative window[1] between the time of infection and the time the antibody test becomes positive. The probability, $T(t)$, that an individual selected at random is infected and has seroconverted by time t is therefore described by the convolution

$$T(t) = \int_{u=0}^{t} V'(u)L(t-u)du. \tag{1}$$

Unless $V(t)$ and $L(u)$ are known, little can be said of $T(t)$. The risk to the community lies not in those who have seroconverted, for they will be detected by the laboratory test and may therefore be considered harmless. The risk lies in the potential donors who have become infected, but have not yet seroconverted, and whose donated blood will be transfused into others. The population at large, in whom the progress of the epidemic is described by $V(t)$ and $T(t)$ will not, in general, be representative of the population of potential blood donors from whom a majority of risk individuals have excluded themselves. If some small proportion, ξ, of 'at risk' individuals do not exclude themselves from the donor population, then the proportion of infected individuals within the donor population would be $\xi V(t)$. We assume that the distribution of the seronegative period is the same as for the population at large, so that the proportion seropositive could be calculated from the convolution above, and will be $\xi T(t)$. The data of Ward *et al.*[5]

[1] That is to say that $L(u)$ is the probability that a person infected at time t has seroconverted at time $(t+u)$.

suggests that ξ is of the order of 0.026. The probability that a randomly chosen donor will be infected but seronegative at time t will then be $\xi[V(t) - T(t)]$.

In practice, infected donors may be brought to the attention of the blood bank when they seroconvert and subsequently donate blood. The most recently donated blood is then effectively harmless, because it has been identified as infected and will not be used clinically, but the status of previous donations is then in question. The probability that the previous donation was infected depends on at least two unknown factors, $L(u)$ describing the seroconversion distribution, and $g(u)$ describing the probability density function of times between one donation and the next. Because some 'regular' donors actually donate very infrequently a previous donation may not have been tested; this was often the case for early reports following the introduction of testing. Given that a donation at time t is infected, the probability that a previously untested donation was infected is

$$P = \frac{1}{V(t)} \int_u V(t-u)g(u)du.$$

For HIV-1, the seronegative period is usually 4 to 8 weeks. The Australian Red Cross does not recommend donation more frequently than once every twelve weeks. Accordingly, if a regular donor is found to be seropositive, then although the penultimate donation is at risk, previous ones may be considered safe provided the penultimate donation was seronegative. On a time scale of the order of the eight week seronegative period, the growth of the epidemic can be taken to be linear and the proportion having seroconverted will lag the proportion infected by the expected value, η, of the seronegative period. Then from (1) we have approximately

$$T(t) \approx V(t) - V'(t)\eta.$$

The probability that a donor selected at random is infected but seronegative is then $\xi\eta V'(t)$. The probability that a donor selected at random is seropositive is $\xi T(t)$ and the ratio of seronegative infected to seropositive is $\eta V'(t)/T(t)$. Because the epidemic growth is linear on the short time-scale determined by the seronegative period we may substitute $V'(t) \approx T'(t)$ and so express the ratio in terms of the observable measurements $T(t)$ and $T'(t)$. These are essentially the prevalence and incidence of seropositivity (although these are conventionally expressed per 100,000 population.) Accordingly the ratio of infected seronegative to those who test seropositive is

$\eta I(t)/P(t)$ where $I(t)$ is the incidence and $P(t)$ the prevalence [2].

We note that this does not involve the function $g(u)$ describing the distribution of times between donations. Had we asked the related and commonly posed question as to the number of infected seronegative units donated by a donor subsequently found to have seroconverted, then the answer would have involved the unknown function $g(u)$, and the more frequent the donations the greater the expected number of infected units passing undetected. Equally, however, more frequent donation leads to an increase in the number of uninfected units, so the ratio of the two remains the same, and $g(u)$ does not enter into calculations involving that ratio unless $g(u)$ for infected individuals differs from $g(u)$ for uninfected individuals. We do not dismiss the possibility that populations having different levels of risk might have different functions $g(u)$, and the data of Ward *et al.* [5] suggests that this might be the case. Of seven donors who gave infected but seronegative blood, six had given in the previous six months, but none were long-standing repeat donors.

3.1 Repeat Tested Donors

We now consider the ratio of infected seronegative to infected seropositive units in those units taken from repeat, previously tested, blood donors. We begin with the population discussed earlier, in which the probability that an individual selected at random is infected is $V(t)$. For repeat donors, a record is kept of any previous seropositive test, and individuals found to be seropositive are not subsequently recalled to donate. The question then arises, *'What is the ratio of infected seronegative to seropositive in units derived from repeat tested donors?'* We assume throughout that the time between donations exceeds the seronegative period, so that all seronegative infected donors will have seroconverted by the time of the subsequent donation. As before, we assume that the progression of the epidemic can be adequately approximated linearly in the interval between any two consecutive donations. From the previous argument a proportion $\xi\eta V'(t)$ in the repeat donor population is infected but seronegative. In the interval μ between donations a proportion $\xi\mu V'(t)$ of the donor population will seroconvert. Because that proportion was previously seronegative, none have been 'screened out'; by assumption all seropositives are detected. Hence

[2] Care in matching units of measurement is necessary here. Incidence is usually expressed in new cases per 100,000 per year. Accordingly the expected seronegative period of about 8 weeks should be converted to 0.065 year.

$\xi\mu V'(t)$ represents the proportion of repeat donors found positive at time $(t+\mu)$. Also, by assumption this includes all of the $\xi\eta V'(t)$ seronegative infected donors at the previous donation. Hence, $\xi\eta V'(t)$ of the $\xi\mu V'(t)$ seropositive donors at time $(t+\mu)$ are expected to have been infected but seronegative at the previous donation, representing a proportion η/μ.

In any particular case of a seroconverting repeat donor, the probability of the previous donation having been infected is, of course, η/x where x is the interval since that donor's previous donation, providing that x is not so long as to invalidate the assumption of linearity with time of $V(t)$.

3.2 Repeat Vs Single Donors

In order to compare repeat and single donors we divide the total population into two subpopulations, at random, so that $V(t)$, $L(u)$ and consequently $T(t)$ are identical for both. The intention here is to construct two populations of identical risk, and to compare the frequency with which seropositive units will be found. In the following, where we are discussing the relative risk of two populations, we omit the common constant ξ for notational brevity. The reader may wish to think of it as incorporated in $V(t)$. One population, designated $\mathcal{S}$ will donate on a single occasion. The other, designated $\mathcal{R}$ will become repeat donors, the interval between donations for individuals in $\mathcal{R}$ being a random variable with density $g(u)$. A model in which members of $\mathcal{R}$ have different values of $g(u)$ will be considered in §4.3.

We model the donation of blood from repeat donors as follows. An individual is selected at random from $\mathcal{R}$ and the selection process is terminated if the selected individual has previously tested positive (i.e., is already known to be seropositive). Otherwise, a donation is made and is tested. If that test is negative then the blood is passed for transfusion.

For the donation of blood from single donors, $\mathcal{S}$, an individual is selected at random and a blood donation made and tested. If that test is negative then the blood is passed for transfusion.

The question, as usually posed, is *'What can be said about the relative safety of donations from $\mathcal{S}$ and from $\mathcal{R}$, given the observed frequency with which donated units are found to test positive for antibodies against HIV?'* An easier formulation of the problem is *'If donations from $\mathcal{S}$ and $\mathcal{R}$ were equally safe, what could be said of the relative frequency with which units donated would be found to be seropositive?'*

Accordingly we show, for the hypothetical situation constructed above, that calls to repeat and single donors are equally likely to give rise to a

seronegative donation, and are equally likely to give rise to an infected seronegative donation. This is in fact a direct consequence of our construction, in which we produced subpopulations $\mathcal{R}$ and $\mathcal{S}$ from the same parent population using the same value of the small constant ξ.

For calls to $\mathcal{R}$, those not giving rise to a unit of seronegative blood can be divided into two categories, those aborted because the selected donor was previously found to be seropositive, and those aborted because the previously seronegative donor has since seroconverted. The relative proportions of these two will depend on $g(u)$, which describes the frequency of donation; the more frequent the donation, the less probable a seroconversion since the previous donation. Whatever the relative proportion, however, the sum of the two probabilities is $T(t)$, because those previously detected are still seropositive. Accordingly, the proportion of calls to $\mathcal{R}$ giving rise to a donated seronegative unit (which may or may not be infected) is $(1 - T(t))$, regardless of $g(u)$, as for population $\mathcal{S}$. Indeed, $\mathcal{S}$ is no more than an extreme case of $\mathcal{R}$ in which $g(u)$ describes a very long time since the last donation.

Similarly, $\mathcal{R}$ and $\mathcal{S}$ present the same risk, $V(t) - T(t)$, of giving rise to a seronegative infected donation because an individual seronegative at time t is seronegative at all previous times, and could not have been detected as seropositive previously.

Accordingly, calls to $\mathcal{R}$ and $\mathcal{S}$ are equally likely to give rise to a seronegative unit of blood, are equally likely to have that seronegative unit actually infected, and must be regarded as equally safe.

An alternative and perhaps more intuitive argument is as follows. The only factor distinguishing $\mathcal{R}$ from $\mathcal{S}$ is the exclusion in $\mathcal{R}$ of many of the donors who have previously seroconverted. Those excluded individuals, precisely because they have seroconverted, do not represent a risk. Since the only difference involves the exclusion of individuals which pose no threat, $\mathcal{R}$ and $\mathcal{S}$ must present the same risk. We mention for completeness that both arguments assume that there are no clerical errors involved. Once a seropositive individual is identified there is zero probability of the donated unit being used for transfusion. The argument also assumes that seropositive individuals remain seropositive. Counterexamples are exceedingly rare, and will not invalidate our overall conclusions. This should not be taken as implying, however, that seropositive individuals should be encouraged to donate.

Despite the equality of the risk they pose, in terms of the supply of an infected but seronegative unit, populations $\mathcal{R}$ and $\mathcal{S}$ will present different probabilities for supplying a seropositive unit, which will be found much

more commonly in $\mathcal{S}$ than in $\mathcal{R}$. For $\mathcal{R}$ the event that a unit is seropositive is the event that the chosen donor is now seropositive, but was seronegative at the time of the last donation. This probability is

$$T(t) - \int_{u=0}^{\infty} T(t-u)g(u)du \approx \mu T'(t).$$

Thus the ratio of seropositives from $\mathcal{S}$ to seropositives from $\mathcal{R}$ is

$$\frac{T(t)}{\mu T'(t)} = \nu \frac{P(t)}{I(t)}, \tag{2}$$

where as before $I(t)$ and $P(t)$ are incidence and prevalence, ν is the expected number of donations per year, assuming the donation frequency for members of $\mathcal{R}$ is relatively homogeneous.

3.3 Adjustment for deaths etc.

The model, as constructed, assumes that infected individuals survive indefinitely. In reality, a proportion die and others are diagnosed as carrying HIV quite independently of any involvement with the transfusion service. To what extent might the ratio above be altered if we take this into account? Obviously dead members of a population cannot donate blood, and those who know themselves to be infected would be very unlikely to do so. In Australia, more than 2000 have died or progressed to 'AIDS', a terminal state of HIV infection, and a further indeterminate number, thought to be about 10,000 know themselves to be infected. The present size of the epidemic is unknown, but an estimate of 24,000 is reasonable, in which case about half know themselves to be infected and a tenth have already died. Because HIV-1 rarely kills acutely, a regular donor who is seronegitive at one donation will not die of AIDS before the next donation. The problem for single donors is more difficult. If all infected individuals were equally likely to seek HIV antibody testing, then the probability of a first-time donor being found seropositive when donating blood would be $\xi[T(t) - D(t)]$ where $D(t)$ is the proportion of the population being either dead or diagnosed with HIV. On the other hand, the small proportion ξ of the population who are at risk but who still donate are precisely those least likely to have acted responsibly in seeking independent tesing for HIV. In that case, the probability of a first-time donor being found seropositive is $\xi[T(t) - D(t)]$ where $D(t)$ is now only the proportion who have actually died or who have developed incapacitating AIDS. Then $D(t)$ is perhaps a twelfth[3] of $T(t)$ and there will

[3] 2000 dead in a total of 24000.

be little error introduced in ignoring $D(t)$.

3.4 Untested vs. tested repeat donors

A related issue is the relative risk presented by two subgroups of repeat donors, those who have, and those who have not, had a previously tested donation. We would argue that the only difference between these subgroups is the exclusion of seropositive donors who, because of their seropositivity, present no risk; these two subgroups therefore represent the same risk. Cumming *et al.* *[4]* in offering evidence to the contrary estimate that untested repeat female donors represent a 50% greater risk than tested female repeat donors, and that untested male repeat donors represent a 44% greater risk than tested male repeat donors. Their argument is a Bayesian one in which the probability that, among repeat donors, a donation from a previously untested donor is seropositive is calculated from the identity,

$$P[X|U] = \frac{P[X]P[U|X]}{P[U]},$$

where X is the event that a donation is seropositive, and U is the event that the repeat donor was previously untested. The equivalent calculation was made also for previously tested repeat donors, and both calculations were made separately for male and female donors. On the right hand side of the identity, however, the terms $P[X]$ and $P[U]$ were calculated from historical data on a time frame different from a more current estimate of the term $P[U|X]$. One explanation for the apparent benefit of previous testing may represent an artifact introduced by a variation of $P[U|X]$ over time. Other explanations may exist, and the observation deserves close attention.

3.5 Variable donation frequencies

In the real world the repeat donor population, $\mathcal{R}$, is not homogeneous. Some repeat donors give frequently, others rarely, so that the mean time between donations varies from donor to donor. Published data on the time since last donation for seroconverting donors allows some approximation to this average for those who seroconvert, but because blood collection strategies vary from country to country, no single published figure could be considered typical. Even for a well defined regular donor population there are two interpretations of the mean time between donations. One average is arrived at by random sampling from the population, weighting all individuals equally

no matter how rarely they donate. A different, and shorter, average time might be arrived at by sampling donors at the blood bank thereby weighting in favour of frequent donors.

If donation frequency, and probability of seroconverting in any year are independent, then the average frequency of donation for seroconverting regular donors should be the same as the average frequency of donation for the regular donor population. We are not aware of any empirical studies relating to this point, although it is conceivable that the two might not be independent; injecting drug users who donate may do so frequently to monitor seropositivity status[4]. Even if seroconversion and frequency of donation are independent, the frequency of donation for seroconverting regular donors will be less than the average frequency obtained by recording the donation frequency of consecutive donors at the blood bank.

To allow for different donation frequency within the regular donor population the mean donation frequency of interest is the population-based mean, not the donated-unit-based mean. If we denote by $\overline{\nu}$ this mean frequency of donation, then equation (2) giving the expected ratio of the proportion of single donor units found to be seropositive, to the proportion of repeat donor units found to be seropositive becomes

$$\frac{\overline{\nu}P(t)}{I(t)} \tag{3}$$

where as before P and I are prevalence and incidence respectively.

4 Application

4.1 Data from U.K.

An examination of data from the United Kingdom [6] for the second half of 1987 gives an average time between donations for seroconverting regular donors of four to six months, so we estimate $\overline{\nu} = 2.4$. The ratio of incidence to prevalence may be estimated from the Day report [7] in which the projections for HIV-1 prevalence at the end of 1988 and end of 1990 are 14,000 and 15,500 respectively on the assumption of a constant incidence after the end of 1987. On that basis the prevalence and incidence at the end of 1987 had been estimated at 12,300 and 750 respectively, giving a ratio of 16.4 in

[4] In countries where donors are paid, there may be an incentive for injecting drug users to donate blood. Blood donation in Australia is unpaid.

1987. Then from 3 we have an expected ratio for the prevalence of seropositive units from first time and repeat tested donors of 39.4. That is, if the donor populations present the same risk, there should be 39.4 times more seropositive units per million from first-time donors as from repeat tested donors. The actual figures are 8 seropositives from 200,000 new donors and 4 from 1,100,000 repeat tested donors, a ratio of only 11.

4.2 Data from Australia

Various statistical approaches for the estimation of incidence and prevalence of HIV seropositivity are outlined in Solomon *et al.*[8, 9]. Because of the uncertainty surrounding estimates both of incidence and prevalence, we use a range of estimates. The Institute of Actuaries of Australia [9] uses a model based on the assumption that 2% of males aged over 15 years are in a risk category, and that transfer from the risk category to HIV infected is a Poisson process with intensity 0.7 for ages 25 to 35, reducing to zero at age 15 and 70. Alternative predictions using the observed incidence of AIDS, the end stage of HIV infection, to infer the rate of infection with the virus are based on back projection methods. Depending of the assumptions made about the functional form for the incidence of HIV infection and of the progression to AIDS, estimates of the prevalence and incidence of HIV vary. Table 1 summarizes the incidence and prevalence estimates for the actuarial model, and for two estimates based on back projection [9, 10]. The average ratio of prevalence to incidence in these estimates is 6.2. Regular donors are encouraged to donate four times a year, but the average number of donations actually collected is substantially less than this. If $\overline{\nu} = 2.4$ from U.K. [6] is typical, the expected ratio of seropositve units from first-time to regular donors should be about fifteen to one. Of 26 seropositive donors to 31 Dec. 1988 reported by Castelino and Whyte [11] at the fourth Australian National Conference on AIDS, there was no significant difference in detected seropositivity rates between first-time and multiple donors.

5 Conclusions

We conclude from the preceeding, and particularly from (3), that an assessment of the relative safety of blood from first-time and from regular donors depends on several factors. The average time between donations for regular donors, and the frequency with which seropositive units are donated by the two populations can presumably be obtained by examining the past records

of transfusion services. The ratio of prevalence to incidence of HIV infection cannot be obtained with certainty, however, and considerable doubt must surround its estimation. This is particularly true of back-projection methods of estimation which give essentially no information about incidence in the most recent year or two. Accordingly, the often-asserted premise that regular donors represent a lesser risk may lack a firm statistical basis.

Cumming *et al.* [4] assert that new donors present two to three times the risk of giving an HIV-infected unit, and they conclude, in part, that more frequent donations from established donors should be encouraged. More frequent donation does not, by itself, reduce risk, however, and unless it can be established that new donors present a greater risk, there is no basis for minimizing the size of the donor pool.

Prior to the screening of donors, the exclusion of known seropositive individuals from the regular donor pool would not have confounded the issue. In a study of 200,000 sera from donors in late 1984 and early 1985, Kleinman *et al* [13] found only a 30% to 50% increase in observed seropositives relative to expected amongst first-time donors, and noted that this is compatible with some individuals having donated blood in order to learn their HIV status at a time when testing was otherwise difficult to obtain. At most, the bias observed by Kleinman *et al.* is much less than that calculated by Cumming *et al.* The resolution of these inconsistencies may depend, in part, on knowledge of the changing nature of the epidemic.

The voluntary exclusion of those at risk cannot extend to an increasing proportion of those unknowingly at risk; the female partners of many bisexual males being perhaps the most obvious group. Paradoxically, if voluntary exclusion were totally successful, and that should be our aim, then there would be few males, and many more females, unknowingly in a risk category and likely to donate blood. It would then be safer to recruit from males than from females. The subgroups representing the safe donors in the past are not necessarily those who will be the safe donors of the future.

As different countries experience HIV epidemics amongst different risk groups, and as each region develops different strategies to discourage those individuals perceived to be a risk, so the optimal recruiting strategy will vary from one transfusion service to another. Historical precedent based on overseas or interstate experience will become an increasingly unreliable basis on which to devise donor recruitment campaigns. Local experience based on local incidence, prevalence, frequency of donation and observed seropositivity rates will be, at least in part, the appropriate guide.

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Table 1: Estimated Incidence and Prevalence of HIV in Australia

Method	Year	Incidence	Prevalence	ratio P/I
Actuarial	1986 - 87	4000	10,700	2.68
	1987 - 88	4500	15,200	3.38
	1988 - 89	4500	19,700	4.38
	1989 - 90	4900	24,600	5.02
Back Proj.	1986 - 87	2400	10,300	4.29
Solomon	1987 - 88	2100	12,400	5.90
et al.	1988 - 89	1700	14,100	8.29
	1989 - 90	1400	15,500	11.07
Back Proj.	1986 - 87	2280	13,530	5.93
Becker	1987 - 88	2280	15,810	6.93
et al.	1988 - 89	2280	18,090	7.93
	1989 - 90	2280	20,370	8.93

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