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April 18th 1988

Dear Dr Pickles

I enclose a revised version of the paper we prepared estimating the rates of missed HIV positive blood donations in the UK in 1986 and 1987. The copy I sent you on Friday required slight modification, and I would be grateful if you would ignore it!

Yours sincerely

GRO-C

Janet Mortimer

Dr Greenberg (copy each)
Dr Moore
Mr Lister

— You will be interested to see these calculations.

GRO-C: Dr. Pickles

19 APR 1988
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An Estimate of Rates of False Negative Results in Blood Donation Screening for HIV infection in the United Kingdom in 1986 and 1987 and the implications of these for the recipients of blood and blood products.

Summary

Using the formula of Ward et al the estimated number of HIV infectious donations accepted for transfusion in the UK in the two years from January 1986 to December 1987 is 11. Several of the assumptions on which the calculation depend are questionable, and it seems likely that this is an over-estimate. However, it is known that one such donation was accepted and resulted in the infection of two recipients, and it is probable that other so far undetected transfusion associated transmissions also took place during this time.

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False negative results in blood donation screening, which may lead to transfusion associated HIV infection, can arise from two causes. One is donation in the "window phase" before an infected donor has developed antibody. The other is the failure of the screening test to detect an infectious antibody positive donation.

Ward et al (1) calculate that in the United States the rate of HIV transmission by HIV-seronegative blood is 26 per million transfusions. Their estimate is based on the following assumptions:-

(i) that repeat donors who are found to be antibody positive have become infectious since the previous donation.

(ii) that antibody is not detectable for an average of 8 weeks after infection;

(iii) that all antibody positive donations are infectious;

(iv) that all HIV-infected new donors are antibody positive;

(v) that the donation frequency of HIV positive donors is the same as that of all donors;

(vi) that screening tests for anti HIV have a sensitivity of 99%.

Under assumptions (i) and (ii) the probability of accepting an HIV positive donation from a repeat donor is the sum of the probability that the donor is in the first 8 weeks of infection ("window phase") and the probability that the donor has antibody for HIV but is found falsely negative by the screening test. For new donors, under assumption (iv), only the second probability applies. Ward et al therefore apparently use the following calculation for their estimate of the number of infectious donations remaining after anti-HIV screening

$(\{N(r)*X(r)/N(r)*P(w)\} + \{N(r)*X(r)/N(r)*[1 - P(w)]*[1 - S]\})$ [repeat donors]

plus $(N(n) * X(n)/N(n) * [1 - S])$ [new donors]

where N(r) = number of donations from repeat donors,
X(r) = number of repeat donors found positive,
P(w) = the probability that the donor is in the "window phase",
S = sensitivity,
N(n) = number of donations from new donors and
X(n) = number of new donors found positive.

This simplifies to :-

$\{X(r) * P(w)\} + \{X(r) * [1 - P(w)] * [1 - S]\}$ [repeat donors]

plus $X(n) * [1 - S]$. [new donors]

In 1986 36 repeat and 18 new donors, and in 1987 12 repeat and 12 new donors were found positive in the UK. In our recent national survey of donor records the mean interval between donations in the UK was 40 weeks. Replacing the assumption of 99% sensivity with a perhaps more realistic 98% (i.e. assuming that 1/50 anti HIV positive donors would be missed) the number of infectious donations not identified by anti HIV testing were, according to Ward's estimation:-

for 1986 $36 * 8/40 + 36 * 32/40 * 1/50 + 18 * 1/50 = 8.2$

i.e. 3.7 per million whole blood donations

for 1987 $12 * 8/40 + 12 * 32/40 * 1/50 + 12 * 1/50 = 2.8$

i.e. 1.2 per million whole blood donations

There are several factors which bring the accuracy of these figures into

question, some of which would tend to reduce and others to increase the estimates relative to the true value.

Two factors which will tend to make the estimates too low are: firstly, that the rates of positivity used ignore those HIV positive donations missed because of the window phase and false negative antibody results; secondly, that the assumption that all HIV positive new donors will have antibody is unjustified: until a new donor makes a second seronegative donation we cannot be certain that the first was not made while in the window phase.

Other factors will tend to inflate the estimates. One is that although it is hard to establish the average interval between the onset of infectiousness and the appearance of antibody, it is probably less than the eight weeks assumed here. Furthermore the calculation was based on the average interval between donations for the panel as a whole (40 weeks); the mean for the 17 repeat donors found positive for whom the interval was known was more than three times as long. Another factor is the assumption that all positive repeat donors identified have been infected in the interval between donations. This is only justified when such a donor has been tested before. In the UK "look-back" has established that in at least 5 cases the donor was already infected at the time of a previous donation made before the introduction of screening. As these assumptions affect the dominant term in the calculation, they may be responsible for making the resulting estimates unrealistically high.

Unfortunately it is impossible to assess accurately the size of the often opposing effects that these various factors would exert on the estimates given above. It is likely that the true figures would be lower, but it is informative, despite their shortcomings, to adopt the estimates and to assume that there were 8 missed positive donations in the UK in 1986 and 3 in 1987. The number of significant HIV infections that would result from 11 missed positive donations depends on two things: the number of transfused units resulting and the number of recipients of these who were still alive a year

after transfusion. Unfortunately there are no national estimates for either of these values, but in a small survey at a single transfusion centre it was found that each donation resulted in an average of 1.6 transfused units, and that the recipients of no more than 60% of the units transfused were still alive a year later. These figures may not be representative of the UK Transfusion Service as a whole, but if they are, 11 HIV positive donations would be expected to give rise to 18 infectious transfusions, 11 of them to recipients still alive one year later.

The plasma from more than half the repeat donations taken each year is pooled and used to produce factor VIII concentrate, so it must be anticipated that the plasma from more than half the missed infectious donations will be used in this way. This means that if, in 1986-7, eleven infectious donations were missed, perhaps 7 or 8 of the 300 or so pools (Dr J Smith, personal communication) made from donations taken during these years would have been contaminated by HIV. The fact that despite screening occasional plasma pools may be contaminated justifies the heat treatment of coagulation factor concentrates to make them safe. However, the incidence of pool contamination is probably so low that evidence from serological investigation of recipients which shows HIV transmission has not occurred does not by itself demonstrate that heat treatment alone is providing a safe product.

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Reference : Ward, JW et al. Transmission of Human Immunodeficiency Virus by blood transfusions screened as negative for HIV antibody. New England Journal of Medicine. 1988 Vol 318 No 8 473-477.