Risk reduction: how to reconcile with epidemiology?

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Summary

Throughout Europe the prevalence and incidence of the various agents that are potentially transmissible by blood transfusion can vary from country to country, and there may be significant differences even within a single country. Before one can decide on the value and appropriateness of extra testing for a given marker, the following information needs to be obtained, checked for accuracy, collated nationally, and compared throughout Europe:

1. Prevalence of *confirmed* positivity rates for the markers of transfusion-transmissible infections (TTIs).
2. Carefully evaluated rates of seroconversion to provide data on incidence of these infections in blood donors.
3. Mean inter-donation intervals for regular blood donors.
4. Proportion of new and repeat donors (using agreed definitions within Europe).
5. Calculations of residual risk of the various infections per donation due to ''window-period' infectivity can then be made.
6. Investigation of reported cases of transfusion-associated infections, and collation of the data.

Surveillance of TTIs in blood donors

A centralised national scheme for the reporting and collation of data on blood donors found to be infected with transfusion-transmissible agents is the first prerequisite for the assessment of microbial risk from blood transfusion. All repeatably reactive donations should be confirmed by appropriate reference testing and only confirmed positive results should be reported to the national register. Data should be subdivided into confirmed positive rates for new donors and for repeat donors. The latter will presumably have been previously negative for a given marker and, if previously tested by an assay of the same sensitivity as when confirmed positive, the result will represent seroconversion subsequent to the previous donation. If the average inter-donation interval for repeat donors is known, estimates of incidence rates can be obtained. When incidence is multiplied by the window-period for a given infection, the residual risk per donation for that agent entering the blood supply can be computed.

When assessing seroconversion it is important to check the following (1a, 1b).

- the donor is indeed a repeat donor, and has previously been tested by an assay of equal sensitivity.
- the reactivities have been confirmed by Reference testing.

Ideally, a stored sample of the previous donation should be tested with reference assays (which may include PCR if appropriate) in parallel with the current sample. To this end, a programme for maintenance of a frozen archive of all blood donation samples (e.g. for 3 years storage) is of obvious value. Seroconversion rates for HCV in England have recently been analysed in detail on the above basis (2).

For new donors positive reactions may reflect prevalent or incident infection, but

seroconversion on the basis of a single sample is not generally determinable. An exception may be for HBV infection if carefully defined algorithms for anti-HBc IgM determination together with liver function testing and donor follow-up are in place. Usually, however, incidence of infection in new donors is estimated by surveying incidence in repeat donors and multiplying this parameter by a factor based on the ration of confirmed positivity rates in new and repeat donors. To this end, cumulative national surveillance of infection rates in blood rates is of great value, as exemplified from English data (courtesy of Kate Soldan) shown in figure 1 (a-b).

Ideally, surveillance following strictly defined rules for case ascertainment should be analysed for the whole of Europe. The European Plasma Fractionation Association (EPFA) currently obtains and collates such data under their own initiative and have recently prompted discussion about standardisation of definitions.

Calculation of residual risk

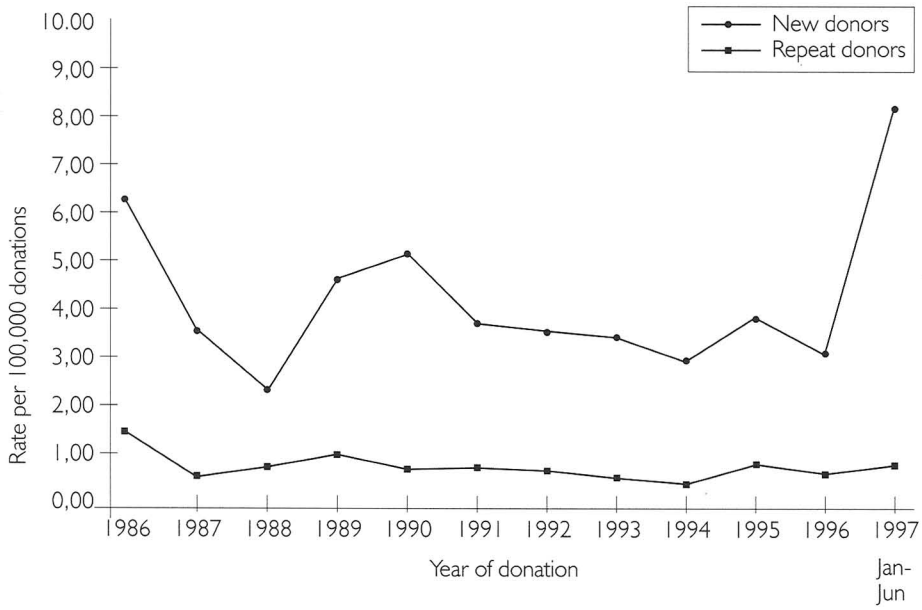
Several countries are now producing estimates of the residual risk from transfusion. An example of such an analysis from England is shown in table 1. For simplicity, the confidence intervals for the calculated risks are not shown, but they are generally relatively wide. In the figure, the risk from seroconverting donors is shown for HIV and HCV. In addition, risks due to false-negativity of assays (taking a probably conservative estimate of 98% sensitivity) and of risks due to process error are tabulated. An error rate of 0.5% has been used for the calculation, and again this is likely to be an overestimate in England as testing is fully automated, assays used employ sample and reagent colour monitors, and information transfer is fully computerised. Total residual risk is tabulated for repeat donors, and by extrapolation from seroprevalence data, for new donors. The situation for HBV is still under analysis. The risk from HBV seroconverting donors is similar to that for HCV. However, there is an additional element of risk from donors who may be at the žtail-end' of carriage (3) with subliminal levels of HbsAg but with persistent high titres of anti-HBc (due to chronic exposure to virus). In an analysis over several years at North London (unpublished data), only ¼ of investigated post-transfusion hepatitis B cases were due to seronegative donors in the window period. In the remaining ¾ of cases a donor with anti-HBc in the absence of HbsAg could be circumstantially implicated. At North London, at least, the residual risk from post-transfusion HBV is likely to be within the range of 1 in 50,000 to 1 in 200,000 $\pm$ appropriate confidence limits.

The English figures for risk can be compared with calculations from the USA (see table 2, courtesy of Dr. M. Contreras).

Direct surveillance of post-transfusion infections

Central reporting, investigation and collation of transfusion-associated infections form the basis of the French žHaemovigilance' programme and the UK Serious Hazards of Transfusion (SHOT) scheme (4). These schemes provide direct evidence of the level of residual symptomatic (in most cases) risk of microbial infection from transfusion. Taken together with the calculated theoretical residual risks, a picture of the relevance of different microbial agents in an individual country, or in different countries, can be developed. If the prevalences and incidences of an agent (or agents) is considered to be comparatively high, specific additional testing interventions can be contemplated.

Figure 1 **a) HIV infected blood donations: UK**



Note: The higher rate of HIV in donations from new donors during Jan - Jun 1997 ic being investigated further.

b) HIV infected blood donations: England and Wales

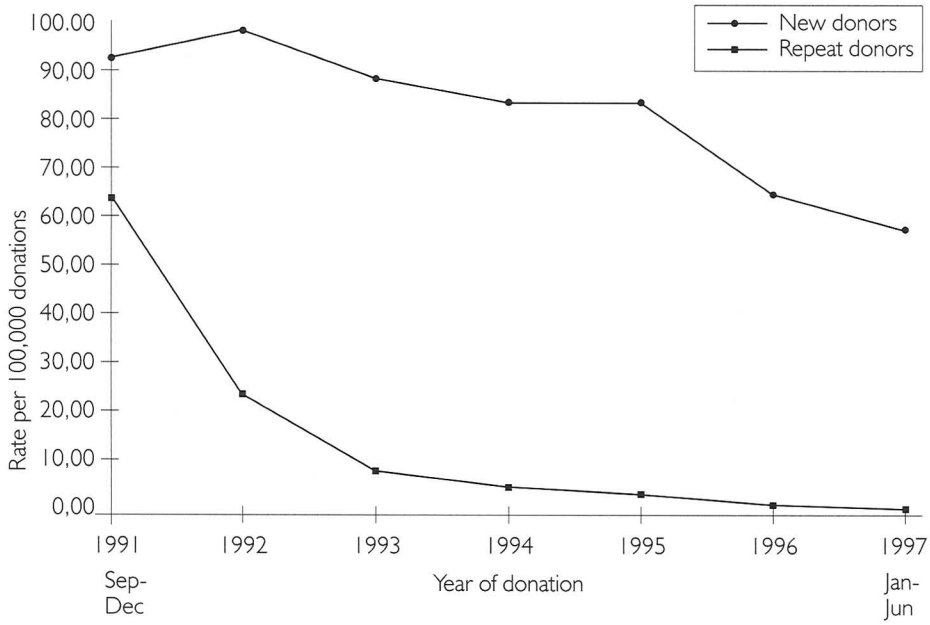


Table I.: Risk of infectius donation per 100,000 donations (England)

	HIV	HCV	HBV
from serocon. donors	0.015	0.059	?tailend
due to test intensitivity	0.015	0.322	carriers
due to process error	0.004	0.079	
Totals	0.034 (1 in 3×10^6)	0.460 (1 in 2×10^5)	
new donors	0.319 (1 in 6×10^5)	2.347 (1 in 4×10^4)	
repeat donors	0.019 (1 in 5×10^6)	0.204 (1 in 5×10^5)	

Soldan & Barbara, unpublished data

Table II.: Estimated current risk of TTIS (Usa/Uk)
Approximate estimated risk (per unit transfused)

Infection	USA	UK
Hepatitis B	1 in 66,000 1 in 200,000	1 in 50,000
Hepatitis C	1 in 121,000	1 in 200,000
HIV-1	1 in 563,000 1 in 825,000	1 in 2,500,000
Bacterial contamination		
• platelets	1 in 2,400 1 in 15,000	unknown
• red cells	1 in 1,000,000	unknown

Courtesy (M. Contreras)

Comparative microbial risks and additional testing

HBV

In Spain, the percentage of HbsAg positive donations varies from 0.008 to 0.13% at different blood centres (table 3, courtesy of Dr. M. Carasa). The former rate is of the same order of magnitude as in the UK donor population overall. The 16-fold difference of HbsAg rate might stimulate consideration of additional safety measures to reduce residual risk, especially if post-transfusion infection surveillance reveals an increased risk in areas of increased HbsAg positivity rates in blood donors. Such measures may include the use of additional anti-HBc screening to offset risk from 'tall-end' carriers (3). Only high-titre anti-HBc results are indicative of donor infectivity and donors with concomitant anti-HBs (e.g. greater than 100 miμ/ml) would be immune and suitable as donors (5) if complying w3ith other donor qualifications. An assay to detect anti-HBc as sole HBV marker and high titre anti-HBs simultaneously is currently under investigation (6). Such an assay may be of unique value in a Mediterranean context, where the prevalence of 'tall-end' carriers may be significant.

HIV

In the USA, despite the initial recommendations of the US Blood Product Advisory Committee (subsequently overturned by the Food and Drug Agency). HIV p24 antigen testing was introduced as an additional assay to reduce the risk of window

period transmissions. The projected rates of confirmed HIV-Ag positive, anti-HIV negative blood donors have turned out to be tenfold higher than the actual numbers detected. Only in areas of high acquisition rates of new infection, such as Thailand, is the introduction of HIV-antigen testing arguably cost effective.

Table III.: Blood donations infectious markers results Spain 1996
HbsAg

BTS	Tested Units	Reactive U	Confirmed U	Percentage	Seroconvers.
1	235,017	317	136	0.0578	9
2	34,309	59	17	0.0495	0
3	35,304	38	8	0.0226	3
4	30,566	11	11	0.0359	0
5	45,086	117	56	0.1242	-
6	22,728	15	4	0.0175	0
7	48,861	114	57	0.1166	5
8	78,128	106	30	0.0383	1
9	215,565	309	210	0.0974	9
10	29,526	88	39	0.1320	-
11	93,228	97	72	0.0772	2
12	194,246	409	206	0.1060	36
13	37,260	82	38	0.1019	-
14	25,353	43	2	0.0078	0
15	93,317	62	15	0.0160	0
16	10,837	5	5	0.0461	1
17	137,879	149	123	0.0892	0
	1,367,210	2,015	1,029	0.0752	66

Courtesy M. Carasa

Emerging agents

Human Herpes-Virus 8 (HHV8)

HHV8 is the eighth human herpes virus to be described. It is white-cell associated and is the causative agent of Kaposi's sarcoma (7). So far it is only a theoretical risk to the safety of the blood supply but in countries such as Italy where relatively high rates of seropositivity (with wide ranges in rates across the country) have been reported (8), from 7.3% in North/Central areas to 24.6% in Southern parts, the possibility of (?selective) anti-HHV8 screening could be considered.

Variant creutzfeldt - jakob disease (vCJD)

In the UK, where 23 cases of VCJD have been reported (4 of which were in individuals who had previously donated blood), a variety of measures have been put in place or will be considered following a formal Deaprtment of Health risk assessment (9). Obviously, the impact of differential epidemiology of potentially transfusion-transmissible agents is considerable.

Conclusion

Any analysis of residual risk from existing or emerging agents of potential significance to transfusion safety has got to be based on detailed and extensive surveillance and epidemiological parameters. Only when carefully defined and painstakingly monitored data are available for analysis can sensible and cost-effective decisions be made for additional interventions such as extra serological tests. PCR (on single or pooled donations) and leucodepletion be contemplated.

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