The epidemiology of infections in blood donors and assessment of the risk of transfusion transmitted infections

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Abstract

Surveillance of infections in blood donors and blood recipients can be useful for both transfusion medicine and public health. This thesis describes how an enhanced surveillance system for transfusion-transmissible infections has been established in England and Wales.

Data from the surveillance system (1995 to 1999) have been used to monitor test performance and to describe the epidemiology of HBV, HCV and HIV in blood donors. The prevalence and incidence of HBV, HCV and HIV infections in blood donors have been monitored and were generally stable, and low compared to other countries and to other groups in the UK. HCV prevalence decreased throughout the 1990s. The exposure histories reported by infected donors indicate that donor selection largely succeeds in excluding high-risk groups, but also identify some failures in communication of, or compliance with, exclusion criteria.

Diagnosed, reported, post-transfusion infections were rare and after investigation only 20% (21) were shown to have been transmitted by transfusion. The majority (52%) of reported transfusion-transmitted infections, and resulting deaths (3 of 4) were due to bacteria. The number of undiagnosed infections is not known but was estimated for HIV, HBV and HCV by calculations of the probability of infectious donations entering the blood supply due to true or false negatively to tests performed on donations prior to release. Various methods and assumptions have been used to investigate the robustness of these estimates and to develop an appropriate method for ongoing use in England and Wales.

An enhanced surveillance system for transfusion-transmissible infections, that works in collaboration with national surveillance of infectious diseases and of non-infectious complications of transfusion, has been shown – despite some limitations - to provide data and analyses that have aided transfusion medicine and public health in England and Wales. This surveillance continues to develop and improve and further related work is planned.

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Preface

This thesis has been written by Kate Soldan. Where the published work of others is used, or referred to, this is referenced. The work described in this thesis was predominantly designed and conducted by Kate Soldan. The contribution of others to the work described is acknowledged below.

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1.1 Transfusion transmissible infections

Transfusion of blood collected from one individual into another carries with it the possibility of transmitting blood-borne infectious agents. This is particularly important as patients receiving blood transfusions are often immunosuppressed or otherwise relatively vulnerable to infection. Transmission of syphilis (*Treponema pallidum*) was recognised in the early days of transfusion when blood was transferred directly from donor to recipient. Testing donations for treponemal antibodies and storage of blood between collection and transfusion has overcome this problem. Since then, three viral infections - HBV, HCV, and HIV - have been the predominant transfusion-transmitted agents to cause disease and to prompt changes in transfusion practice. Selective exclusion of individuals from giving blood based on increased risk associated with these blood-borne infections, and the testing of blood donations for serological markers of these infections have greatly reduced the risk of infectious donations entering the blood supply. Nevertheless, some risk will always remain because donor selection and serological testing of donations cannot identify and exclude every infectious donation.

At certain stages in their natural history many viral, bacterial, and protozoal infections can be blood-borne and may be transmitted by transfusion. Fortunately for transfusion medicine, many blood-borne organisms cause symptoms during the period of blood-borne infectivity that render their victims too unwell, or obviously unfit, to donate blood. Other agents are only present in the blood transiently and some agents do not survive the conditions of blood storage outside the human body.

Variations in the length of time for which agents are present in the blood, and viable in stored blood, determine, to a large extent, variations in the risk of infectious donations being collected. Infections of most concern are those that have long periods of infectivity in the absence of any clinical signs or symptoms of infection and are stable in stored blood (for example, HBV, HIV and HCV). The length of time between infection and the development of detectable serological markers (the window period) also varies between agents (for

example, 22 days for anti-HIV (Busch MP, 1995) and 66 days for anti-HCV (Barrera JM, 1995) using current assays). During the very start of this period – often referred to as the "eclipse" –infectious agent (nucleic acid) is absent from the blood or only found in very small numbers and blood is unlikely to be infectious if transfused. The infectious window period is therefore shorter than the total window period. The shorter the infectious window period, relative to the total asymptomatic sero-positive infective period, the better is the detection of infectious donations by serological testing.

For infections with transient blood-borne infectivity (for example, HAV and parvovirus B19), the risk of infectious donations being collected depends upon the incidence of the infection in the donor population and the length of the infectious period.

This general pattern of markers of infection can not be assumed for all infectious agents, as has been recently found for the infectious agents that cause spongiform encephalopathies (e.g. BSE, CJD). These agents do not conform in a number of ways, for example they do not contain nucleic acids.

Viral infections

Donor selection and donation testing prevent HBV, HCV and HIV infectious donations from entering the blood supply. However, these interventions are not 100% effective and transmissions of HBV (Elghouzzi M-H, 1995), HCV (Kitchen AD, 1996; Vrielink H, 1995) and HIV (Conley LJ, 1992; Mak RP, 1993; Crawford RJ, 1987; CDR Weekly, 1997) by blood that tested negative for markers of infection have been documented in the UK and elsewhere. The expected risk of infectious donations entering the blood supply has also been estimated (Lackritz EM, 1995; Schreiber GB, 1996; Courouce AM, 1996). The potential of most other known blood borne viruses to be transmitted by transfusion and to cause morbidity or mortality in recipients is limited by relatively short periods of viraemia, and therefore low prevalence in donations, and by high immunity in recipients and low frequency of disease associated with infection. These factors, probably along with some transmissions resulting in mild, or non-specific symptomatology that is not precisely diagnosed, account for the rarity of clinically apparent HAV, parvo virus B19, CMV or EBV infection associated with transfusion. The case for

intervention against transfusion transmission of HTLVI & II infections has become more compelling as reports of disease associated with these viruses, and particularly of disease in transfusion recipients (who are often immunosuppressed), have increased. (HTLV I is the etiological agent of adult T-cell leukaemia/lymphoma and of tropical spastic paraparesis or human T-cell lymphotropic virus type I-associated myelopathy (Ferreira OC, 1997). HTLV II is thought to cause a neurological syndrome similar to HTLV-I associated myelopathy and there is some evidence suggesting HTLV II predisposes to skin and soft tissue bacterial infections in injecting drug users (Murphy EL, 1996).)

Box 1. Examples of viral infectious agents that have the potential for transmission by blood transfusion.
(Adapted from Barbara JAJ, 1994)

Hepatitis viruses

- Hepatitis A (HAV) - no carrier state (rarely transmitted)
- Hepatitis B (HBV) - carrier state
- Hepatitis D (HDV, or delta virus) - requires HBV
- Hepatitis C (HCV) - carrier state

Human retroviruses

- Human immunodeficiency viruses, HIV-1 & 2 - latent state
- Human T-cell leukaemia, HTLV-I & II - latent state

Herpes viruses

- Cytomegalovirus (CMV) - latent state
- Epstein-Barr virus (EBV) - latent state

Non-viral infections

Potentially, a large number and variety of non-viral agents may be transmitted by transfusion, both endogenous agents present in the donor at the time of donation and exogenous contamination occurring during collection and processing. The transmission of syphilis was a serious problem with early transfusions given directly from donor to patient. The storage of certain blood components (e.g. platelets) at 22°C rather than 4°C provides more favourable growth conditions for bacteria. Although rare, serious sequelae such as septicaemia and septic shock do occur (e.g. Boulton F, 1997) and approaches to identify and reduce the risks are under consideration.

Box 2. Examples of non-viral infectious agents that have the potential for transmission by blood transfusion.
(From Kitchen AD, 1994)

Bacteria

Endogenous bacteria

- Syphilis (*Treponema pallidum*)
- Lyme disease (*Borrelia burgdorferi*)
- Brucellosis (*Brucella melitensis*)
- *Yersinia entercolitica* (and others)

Exogenous bacteria

- Environmental species, for example *Staphylococcus epidermidis*, *Pseudomonas* spp. and *Serratia marcescens*

Rickettsiae

- Rocky mountain spotted fever (*Rickettsia rickettsii*)
- Q fever (*Coxiella burnettii*)

Parasites

- Malaria (*Plasmodium* spp.)
- Toxoplasmosis (*Toxoplasma gondii*)
- Trypanosomiasis (Chagas' disease and sleeping sickness)

Whether prion disease can be transmitted by transfusion is currently uncertain (Ricketts MN, 1997). Unknown infections and infections with increasing potential to cause harm to recipients due to the changing epidemiology of the infection, or changing vulnerability of blood recipients to disease, may pose the greatest risks of infection to recipients. Avoidance of unnecessary transfusion and vigilance of blood-borne infectious diseases in the general population and in blood recipients are therefore important general components of transfusion medicine. Vigilance of infectious diseases in blood recipients – particularly in multiply transfused patients - can also contribute to early public health knowledge of emerging infections and to their control.

Strategies to reduce risk

There are three main strategies for preventing infectious donations from entering the blood supply issued to hospitals. The first concerns the recruitment and selection of blood donors who do not have a known increased risk of infection. The second is the testing of donations for markers of infections. The third covers the control of cleanliness during component production.

Selection of blood donors

Donor recruitment and selection aims to select a group of individuals with a low risk of infection. To achieve this low risk both the prevalence of infection and the incidence of infection should be low. In practice incidence is often difficult to measure. The selection of a "low risk" group therefore often depends on identifying groups with low seroprevalence and without the characteristics or exposures associated with an increased risk of infection. There are some general guidelines for donor selection (which are well founded in experience). Voluntary donors are considered safer than paid donors, and repeat donors safer than new donors. However, selection of these individuals is not guaranteed to be effective - particularly for newly identified infections or for infections with changing epidemiology.

New knowledge about exposures of increased risk for blood-borne infections is regularly considered so that guidelines for pre-donation donor selection in the UK can be revised as necessary. Unapparent infections and non-recognition or denial of risk factors in donors prevents the exclusion of all infected donations by pre-donation selection criteria.

Donation testing

A pre-transfusion test for syphilis has been performed routinely on each blood donation since the beginning of the transfusion service in England and Wales in 1946. It has been known since 1941 that spirochaetes survive poorly at low temperatures (Turner TB, 1941) and the storage of blood at 4-6°C has largely eliminated syphilis transmission by transfusion. There is no mandatory requirement for testing in Europe and the need for testing is now a matter for debate. The most persuasive arguments for continuing have been the increasing use of products such as platelets that are stored at 22°C and the

expectation that testing for syphilis may exclude some individuals who may be at increased risk of other sexually transmitted infections, e.g. HIV and HBV.

Transfusion transmitted serum hepatitis has been recognised since the 1940s, and was particularly common in recipients of blood products when large pools were used as the starting material. With no test for the infection, the measures taken to limit transmission were restricting plasma pools to 10 donations and removing donors from the panel when a patient developed hepatitis following a transfusion of their blood. Identification of an antigen shown to be associated with hepatitis (called the Australia antigen) was followed by approval of donation testing in July 1971. By December 1972 all donations in the UK were being tested for hepatitis B surface antigen (Gunson HH, 1996).

Accounts of AIDS in recipients of blood and blood products began to be reported in the literature in the early 1980s (MMWR, 1982; Amman AJ, 1983). With no test available, in September 1983 information was distributed to all donors, and potential donors, asking persons not to give blood if they thought they had the disease or were at risk of acquiring it (i.e. homosexual men with many partners, injecting drug users and sexual contacts of people with AIDS). A test for anti-HIV has been used for all donations since 14th October 1985. The criteria for excluding individuals with an increased risk of infection have been revised as more has been learnt about the epidemiology of HIV infection in the UK. As argued by others (Hewitt PE, 1994), and as shown later in this thesis, donor selection remains important as a means of reducing the number of anti-HIV positive donations entering the testing process and of reducing the risk of donations collected following infection but before antibody can be detected (Hewitt PE, 1994).

Transfusion transmitted hepatitis continued, albeit at a much reduced frequency (Howell DR, 1995), after the introduction of donor screening for HBsAg. The majority of cases were due to an unknown agent, so called non-A, non-B hepatitis (NANBH). Some countries introduced surrogate tests for NANB hepatitis. These tests were assays for hepatitis B core antibody (anti-HBc) and tests for raised levels of liver enzymes (e.g. ALT).

In the late 1980s a virus, to be named HCV, was identified by cloning nucleic acid from plasma of a chimp with NANBH (Choo Q-L, 1989). A diagnostic assay was first produced in 1990. Specificity of the tests was

improved by early 1991 and testing of all blood donations commenced in the UK on 1st September 1991.

Over the years there has been a steady introduction of available measures to reduce risks that have been recognised. Table 1.1 shows the tests for markers of transfusion-transmissible infection that are currently performed on all blood donations in the UK. The introduction of each of these tests has led to a reduction in the number of transfusion-transmitted infections. During the first full year of anti-HIV (1986) and anti-HCV (1992) testing in England and Wales 38 and 807 positive donors were identified respectively - thus preventing the donations from these donors entering the blood supply. As time passes following the introduction of a marker test, and the population of repeat blood donors passes through the testing process, the overall rate of infectious donations identified decreases. The number of positive donations excluded from the blood supply in England and Wales by donation testing during 1997 is shown in Table 1.1. Many of these HBsAg, anti-HIV or anti-HCV positive donations are expected to infect recipients if transfused. As donations are now processed into several components, an infectious donation has the potential to expose several recipients to infection.

Table 1.1 Routine testing for markers of transfusion-transmissible infection in England & Wales and the effect of testing on the prevention of infections in blood transfusion recipients.

Assay	Date of introduction to routine donation testing	Number of positive donations excluded by testing during 1997	Reduction in transfusion-transmitted infections in England & Wales following introduction of routine test*
Treponemal antibodies	by 1950	100 (1 in 21,703 donations)	Uncertain: it is difficult to ascribe reduction in transfusion-transmitted syphilis to testing since storage at 4°C leads to inactivation of *T.pallidum*.
HBsAg	early 1970's	123 (1 in 21,710 donations)	There was a marked fall in post-transfusion acute HBV infections. E.g. North London blood centre recorded 30 reports of cases in 1970, 12 in 1972, 6 in 1974 and 3 in 1976 (Barbara JAJ, 1981).
Anti-HIV 1 Anti-HIV 1&2	October 1985 June 1990	29 (1 in 92,079 donations)	There have been 69 HIV infections diagnosed that were probably transmitted by transfusion in the UK prior to 10/85#, and 3 that were transfused between 10/85 and the end of 1997.
Anti-HCV	September 1991	236 (1 in 11,315 donations)	Transfusion prior to 9/91 has been associated with 128 (4.3%) of laboratory reports of HCV infection with risk factor information (1992-1996) (Ramsay ME, 1998). Between 1/10/95 and 30/9/99 2 cases of HCV transmission by transfusion post 9/91 have been reported+.

* Other factors, such as improved donor selection, will have contributed.

Source: PHLS AIDS Centre (data as of 1st September 1998).

+ Source: SHOT Report, 98-99.

Maximising the effectiveness of donation testing includes assuring good test performance. Strategies to achieve this include the evaluation of test kits, and test kit batches, for suitability and reliability in the blood centre setting, before their use by transfusion services. Monitoring performance once a test is in use is also important.

Testing blood donations improves the safety of the blood supply in two direct, and quantifiable, ways:

1. Infectious donations found to be positive for markers of infection at the time of donation are removed.
2. Infected donors are excluded from the donor population, and infected donations are therefore prevented from entering blood centres in the future. In practice this is only assured if infected donors do not conceal information about their previous donation, and the blood service's information system identifies them as infected donors if they attend to donate again. On rare occasions infected donors may re-attend for re-testing, either deliberately or in ignorance, and more than one infected donation from the same donor may enter the testing system.

Testing also improves the safety of the blood supply in three indirect ways – more difficult to quantify and to distinguish the effects of each from each other and from other causes:

1. Donors who are at increased risk of blood-borne infections are excluded from the donor population. As blood-borne infections often have common routes of transmission, donors with evidence of one infection may be at increased risk of having other blood-borne infections that are not detected by donation testing.
2. Also, some individuals who have been in contact with infected donors (e.g. sexual contacts) may be at increased risk of infection and infected donations may be prevented from entering blood centres if these individuals are instructed not to donate blood.
3. The diagnosis of infection in a donor, and the surveillance of infections and risk factors in donors can improve methods of donor selection, for example, the detection of HCV antibodies in blood donors revealed a large group of donors who had been exposed to blood-borne infections by injecting drugs (MacLennan S, 1994): donor selection has been revised in the light of this finding.

Additional serological tests are performed in some countries. Some aim to detect infections missed by current testing, for example, HIV p24 antigen and

anti-HBc. Others detect transfusion-transmissible infections that are currently not tested for in the UK, for example, anti-HTLV. Others detect surrogate markers of infection, for example, ALT for hepatitis viruses, low pH hemagglutination for parvovirus B19, alpha-neopterin for detecting inflammation. The countries in which additional tests have been adopted have tended to have higher frequency of infections, and therefore of risk of transmissible infection, than in England and Wales. However, this is not always the case. Factors such as the expected risk of disease occurring in recipients, the amount of public concern about blood safety and the infection in question, and the availability of resources have also played a part in determining the differences in blood testing strategies in different countries. The availability of tests for nucleic acids provides an opportunity to detect infections that cannot be detected by serological tests. Donations collected during the window period of early infection are the main candidates. Nucleic acid testing (NAT) should detect infectious donations from seronegative donors and from any seropositive donors that routine serological testing fails to detect. Nucleic acid tests for HCV RNA were introduced during 1999 in the UK (with increasing implementation as a pre-release test for fresh components over the following 2 years), with testing of mini-pools of (96) plasma samples followed by further testing of smaller pools and individual samples of positive mini-pools. Initially the primary motivation to introduce this testing was compliance with requirements for manufacture of pooled plasma products (Flanagan P, 1998) but implementation was not halted when the UK stopped using UK sourced plasma for product manufacture. The potential additional benefit for a blood service of such procedures for specific agents will depend on the epidemiology of the agent in their population (see Chapter 5).

Assessing the value of additional donation testing strategies must consider some or all of the following costs:

- The cost of test kits and reagents and related laboratory costs including staff time
- The costs of confirmatory testing on reactive donations
- The costs of notifying, counselling, and referring donors who are positive to new tests, or who have persistent false reactivity to the new tests used

- The costs of replacing donors excluded because of positivity (or false persistent reactivity) to the tests used
- The costs of any delay in the release of blood components while testing is performed
- The costs of added data management and added complexity to the blood release procedure
- The costs of look-backs - that is, of tracing and testing recipients who may have been exposed to infection by earlier donations from donors found to be positive.
- Costs of litigation due to transmissions
- Costs of lost confidence in transfusion (psychological costs) and in the political system responsible for transfusion.

Control of production and administration

Certain manufacturing processes and conditions can reduce the probability of transmitting an infection by blood transfusion. Strict control of cleanliness during component production limits the opportunities for bacterial contamination. Storage of whole blood and red cells at 4°C ± 2°C limits the growth of many bacteria that may be present in blood.

Developments to testing systems, and controls on those systems, that ensure the release only of components that are negative for markers of infection have been a crucial factor in the improvement of safety gained by donation testing. Automation of testing, along with inclusion of controlled steps in commercial tests, has enabled strict standardisation and close monitoring of the testing process. One example of an important addition to the testing processes is sample addition monitors that change colour (measurable on a spectrophotometer) when serum or plasma is added. Another is process control automation. Use of appropriate quality control samples, as well as the manufacturer's controls, and "go-no-go" samples, adds a further check on test performance. The computerisation of test results and of component release has helped to increase safety in the face of increasing numbers of donations and the increasing volume of data generated during the testing of each donation.

Practices beyond the transfusion centre also contribute to the prevention of transfusion-transmitted disease. Strategies to avoid transfusion as a treatment unless absolutely necessary, and to inactivate viruses by heat or solvent detergent treatments of products, prevent exposures. Strategies to provide prophylactic treatment to recipients can also play a useful role. For example, HBV immunisation is currently recommended for haemophiliacs, those receiving regular blood transfusions or blood products, or those carers responsible for the administration of such products (Salisbury & Begg, 1996).

Manufacturing processes that involve pooling donations or components, e.g. for treatment with solvent detergents, require careful consideration. Pooling (unless the infection is neutralised by antibodies also present in the pool) can lead to an infectious agent in one donation entering multiple products, and should be avoided for that reason. Pooling is particularly dangerous with regard to agents that are not excluded by current testing strategies, including agents that are as yet unknown.

Maintenance of cold storage until used at the bedside, and administration with sterile equipment is also important.

Consequences of transfusion-transmitted infections

Infected recipients do not necessarily develop disease, and estimating the effect of infections requires knowledge about the natural history of infections.

Transfusion-transmitted infections also bear a risk of onward transmission. The major risk factors for transmission of the persistent viral infections i.e. injecting drug use and sexual contact may be relatively rare amongst transfusion recipients because of their health and high average age. However, this is not always the case and other types of contact - especially those common in health care settings - pose a risk of secondary transmission.

1.2 Estimation of the risks of infectious donations entering the blood supply

Quantifying the risk of transfusion-transmission of infection can be attempted by several methods - each method having different limitations.

Existing surveillance systems monitor diagnosed transfusion-transmitted infections. Several factors common to transfusion-transmitted infections, and to

transfusion recipients, are likely to contribute to a lack of clinically apparent symptoms and therefore to under-diagnosis of infections. Other therapies may negate or modify symptoms. For example, many transfusion recipients are receiving antibiotic drugs and are therefore less likely to suffer observable consequences from bacterial infections. Transfusion recipients are sick or injured, and often elderly, and have high mortality from other causes. The recipients who receive relatively large numbers of transfusions, and are therefore at the highest risk of transfusion-transmitted infections, have the highest mortality rates. Long pre-symptomatic periods are common for persistent blood-borne virus infections and occurrence of disease is therefore far removed in the future. This period may be reduced when infected by a larger viral dose, at an older age, and in already ill or immunocompromised individuals, but this is not always known. Even so, transfusion in the past may be overlooked as a possible route of infection when diagnosis is delayed for a period.

For some infections (for example, HAV and B19), naturally acquired immunity may be quite high – especially in older age groups – meaning that transmission of infection may be considerably less frequent than infectious transfusions. Also, asymptomatic infection is more common amongst the younger age groups who have the lower levels of naturally acquired immunity; so infection transmissions may not result in any disease. Recognised and reported cases of transfusion-transmitted infections are likely to be those with the more apparent, and more severe, clinical consequences.

There are therefore many handicaps to the recognition of transfusion-transmitted infections and these lead to ascertainment biases and limitations in data based on reports of diagnoses. Actively following up transfused recipients and testing them for evidence of transfusion-transmitted infections can overcome these. In the UK, transfusion-transmission of infection with observed clinical consequences is rare - both in absolute terms and relative to incidents of infection transmission by other routes. The number of recipients that need to be followed up in order to obtain a precise estimate of transmission rates is therefore very large and such studies have become prohibitively expensive. Table 1.2 shows some examples, using the *rule of three* to estimate binomial confidence intervals, (Armitage, 1998) of the number of subjects needed in cohort studies to produce a 95% CI that excludes a given transmission rate in

studies that observe no cases (assuming no loss of power due to loss to follow-up or error in recipient tracing) i.e. the minimum size of cohorts needed to demonstrate that the true transmission rate is lower than the given rate.

Table 1.2. Sample size calculations for transmission studies.

Transmission rate (per number of units transfused)	Number needed in cohort for 95% CI on transmission rate of zero (i.e. when no transmissions observed) to exclude given rate.
1 in 10,000	30,000
1 in 100,000	300,000
1 in 3 million	9 million
1 in 10 million	30 million

A recent study of over 22,000 units issued in London and the South East found no transfusion-transmitted HIV, HBV, HCV or HTLV I&II infections (Regan FAM, 2000). Another approach is to estimate the number of infectious donations that current donation testing is not expected to detect. To attempt such estimation, information is needed about infection rates in the population donating blood, about the development and persistence of the markers that are tested for and about the tests, and testing system, used. The probability of a donation being collected during the window period when the tests used cannot detect evidence of infection depends upon the incidence of the infection and the length of the window period. The probability of symptoms that may prevent donation occurring during this period may also need to be considered. Incidence is usually calculated using observations of seroconversions in repeat donors or observations of acute infections in donors. The predictive value of a negative test result depends upon the prevalence of the marker and the sensitivity of the test. The probability of a marker positive donation being released into the blood supply due to a failure, or error, in the testing system also depends upon the prevalence of the marker and upon the probability of a failure or error.

Table 1.3 shows some key items of information required to calculate theoretical estimates of the risk of a donation infectious for a given organism entering the blood supply. The range of values in which each of the variables in Table 1.3 might lie depends on the sample used to estimate the variable, the biological variability involved, and the assumptions made in obtaining the working value.

Table 1.3 Key information for estimating the risk of donations infectious for known pathogens entering the blood supply despite donation testing.

Component of risk	Information needed and source of that information	
	Derived from donation testing	Other sources
i. Risk of seronegative infectious donation being collected during early infection	• Incidence of infection in donors	• Length of the infectious seronegative window period following infection
ii. Risk of seropositive donation entering the blood supply through test failure or process error	• Prevalence of marker used to indicate infectivity in donations	• Sensitivity of tests for the marker • Rate of errors that could lead to failure to identify or withdraw a positive donation
iii. Risk of seronegative infectious donation being collected from donors with established (not early) infection		• Frequency of seronegative, infectious individuals (other than those in the window period following infection) amongst blood donors

Table 1.4. Published risk estimation studies.

Country , Year of data/ estimates (Reference)	Estimated risk of infectious donations per million donations (range[1])	Window period (WP) risk estimated	Length of infectious window period used in days (Range)	False negative (FN) & error risk estimated	Test sensitivity (S) & error rate (ER) used	Estimate for new donor donation included
USA, 1986-87 (Ward, 1988)	HIV 26	Yes	56 (28-98)	Yes No	S: 99% -	Partially WP=No FN=Yes
USA, 1987 (Cumming, 1989)	HIV 6.5 (3.33-11.33)	Yes	56	No Yes	- ER: 0.1%	Yes
USA, 1987 (Brookmeyer, 1994)	HIV 4.64	Yes	56	No No	- -	Yes
UK, 1986-87 (Hickman, 1988)	HIV: 1986 3.2 HIV: 1987 1.1	Yes	56	Yes No	S: 98% -	Partially WP=No FN=Yes
Australia, 1985-90 (Dax, 1992)	HIV: 1.08	Yes	28-42	Yes No	S: 99.69%	Yes
USA, 1991-93 (Schreiber, 1996)	HIV: 2.03 (0.36-4.95) HTLV: 1.56 (0.50-3.90) HCV: 9.70 (3.47-36.11) HBsAg: 6.65 (2.87-13.43) HBV: 15.83 (6.82-31.97)	Yes	22 (6-38) 51 (36-72) 82 (54-192) 59 (37-87)	No No	- -	No
USA, 1992-93 (Lackritz, 1995)	HIV: 1.52-2.22	Yes	Average of 25	No Yes	- ER: 0.5%	Yes
France, 1992-94 (Courouce, 1996)	HIV: 1.75 (0.3-4.6) HTLV: 0.17 (0.0-1.6) HCV: 4.48 (1.7-10.0) HBsAg: 3.13 (0.9-11.2) HBV: 8.45 (2.8-25.2)	Yes	22 (6-38) 56 (24-128) 66 (38-94) 51 (36-72)	No No	- -	No
Germany & Austria, 1993 (Schwartz, 1995)	HIV (Austria): 1.9 (0.7-4.8) HIV (Germany): 1.1 (0.4-2.6)	Yes	22	Yes Yes	S: 99% ER: 0.1%	Yes
Austria & Germany, 1994-5 (Riggert, 1996)	HCV (Austria): 111 (61-161) HCV (Germany): 208 (25-756)	Yes	74	Yes Yes	S: 98% ER: 0.1%	Yes
Australia, 1994-95 (Whyte, 1997)	HIV: 0.79 (0.22-1.37) HCV: 4.27 (2.82-10.01) HBsAg: 2.71 (1.70-4.00) HBV: 6.45 (4.05-9.52)	Yes	22 (6-38) 82 (54-192) 59 (37-87)	No No	- -	No
South Africa (Sitas, 1994)	HIV: 22(11-39)	Yes	34-98	Yes Yes	S: 99.9% ER: 0.1%	Yes
Germany, 1996 (Gluck, 1998)	HIV: 0.53(0.21-1.39) HCV: 8.8(3.3-31) HBV: 4.3(1.6-7.5)	Yes	22 82 56	No No	- -	No
Germany, 1990-95 (Koerner, 1998)	HCV: 1995 5(0.7-10) repeat HCV: 1995 50(36-67) new	Yes	74	Yes Yes	S: 98% ER: 0.1%	
EPFA countries[2], 1997 (Muller-Breitkreutz, 1999)	HIV: 0.43(0.18-0.82) HCV: 1.61(0.93-2.29) HBV: 2.51(1.57-3.70)	Yes	HIV: 22(6-38) HCV: 66(38-94) HBV: 59(37-87)	No No	- -	No
Thailand, 1990-93 (Kitayaporn, 1996)	HIV: 1990 380 (210-650) HIV: 1991 190 (100-340) HIV: 1992 200 (110-360) HIV: 1993 190 (50-670)	Yes	45	No No	- -	No
N.Thailand, 1989-94 (Sawanpanyalert, 1996)	HIV: 1,290 (880-1900)	Yes	45	No No	- -	No
Ivory Coast, 1991 (Savarit, 1992)	HIV: 5,400-10,600	Yes	56	Yes No	S: 99.0% -	Yes
Central & South America, 1993-94 (Schmunis, 1998)	HIV/HBV/HCV or T.cruzi: Average = 3,226	Different approach: estimates based on prevalence of infections and % of donations tested.				

[1] Various methods.

[2] Not-for profit blood services in Denmark, England, France, Finland, Germany, Scotland, Switzerland (NB data and estimates for Australia and American Red Cross are also included in paper).

Published estimates of the risk of viral transmission by transfusion for different blood services and different periods of time have varied in their methods and scope. Differences in the risk of infectious donations between the early days of HIV testing and more recent years (due largely to the reduced window period of more recent tests) and between countries of high infection prevalence and incidence and countries of low infection prevalence and incidence show clearly in the risk estimates produced for different years and countries. However, variations in the methods used to calculate risk estimates mean that relatively small differences in the estimates produced by countries using similar testing systems and with similar epidemiology are more difficult to interpret.

Table 1.4 summarises some published studies that have provided theoretical estimates of the risk of transfusion-transmitted infections. All of these studies have included estimation of the risk of window period donations (i.e. i. in Table 1.3) associated with donations from repeat donors. Some studies have included estimation of the risk of false negative results and errors (i.e. ii. in Table 1.3). In all, the risk of persistent (or fluctuating) seronegativity during established infections (i.e. iii. in Table 1.3) in blood donors has not been included or has been assumed to be zero.

In the USA the fall in the estimated risk of issuing HIV infectious donations between 1987 and the early 1990s was largely due to a reduction in the length of the window period used in the risk calculations (from 56 days to 22 days). The markedly higher estimated risk of HIV infectious donations in the Thai study is largely the result of the higher incidence of HIV infection in Thailand than in Europe and North America, although the longer window period used in this study also contributed to this higher estimated risk. The published studies have varied in whether they have estimated the risk from all donations, or just from donations from repeat donors. New (i.e. first time) donors differ from repeat donors in ways that affect the risk of an infectious donation entering the blood supply. Probably most important is that new donors have not been previously tested by the blood service for markers of infections used to exclude individuals from the donor panel. So, donations from new donors have a higher prevalence of infectious markers. Incidence of infection can be derived from donation testing in two ways; by testing donations for markers indicative of an early

infection (e.g. IgM class of antibody to hepatitis B core antigen, p24 HIV antigen, nucleic acids, or testing for low titre anti-HIV with recently proposed de-tuned antibody assays), or by using seroconversions in repeat donors that mark infections that have arisen since a previous donation. The former approach was not used in any of the studies listed in Table 1.4. All except one used the latter approach. Brookmeyer et al did not use donation testing data at all but utilised back-calculated estimates of the infection curve in the United States. Unfortunately seroconversions can only be observed in repeat donors: additional information and assumptions have to be used to obtain an estimate of incidence in new donors. Cumming *et al* used the prevalence observed in donations and assumptions about the time donors had been at risk of HIV infection to estimate incidence rates in donors tested for the first time. Lackritz *et al* used the prevalence observed in donations from new and from repeat donors during the first year of testing and assumptions about how the difference between these prevalences represented differences in incidence. Dax *et al* used the prevalence observed in donations and assumptions about the time course of HIV infection and about the probability of donating throughout that time.

More recently the use of de-tuned HIV antibody tests has been used to detect recent infections and to derive incidence (Jansen RS, 1998 and McFarland W, 1999). This method applies a sensitive and a less-sensitive (de-tuned) assay to samples and classifies samples that are positive to the sensitive assay and negative to the less-sensitive assay as early infections.

There has been no standard approach to the calculation of ranges around point estimates. Some studies have repeated the calculations using the "best" and "worst" values of some or all variables (e.g. window period length) to give the best and worst estimates. Some studies have used 95% confidence intervals around observed rates to allow for sampling variability in the data used.

One group has produced two studies that both used data from two countries (Germany and Austria) to produce comparable estimates for two blood services (Schwartz 1995, Riggert 1996). Another produced comparable estimates for a larger collection of blood services - those blood services collaborating in the European Plasma Fractionation Association's viral marker

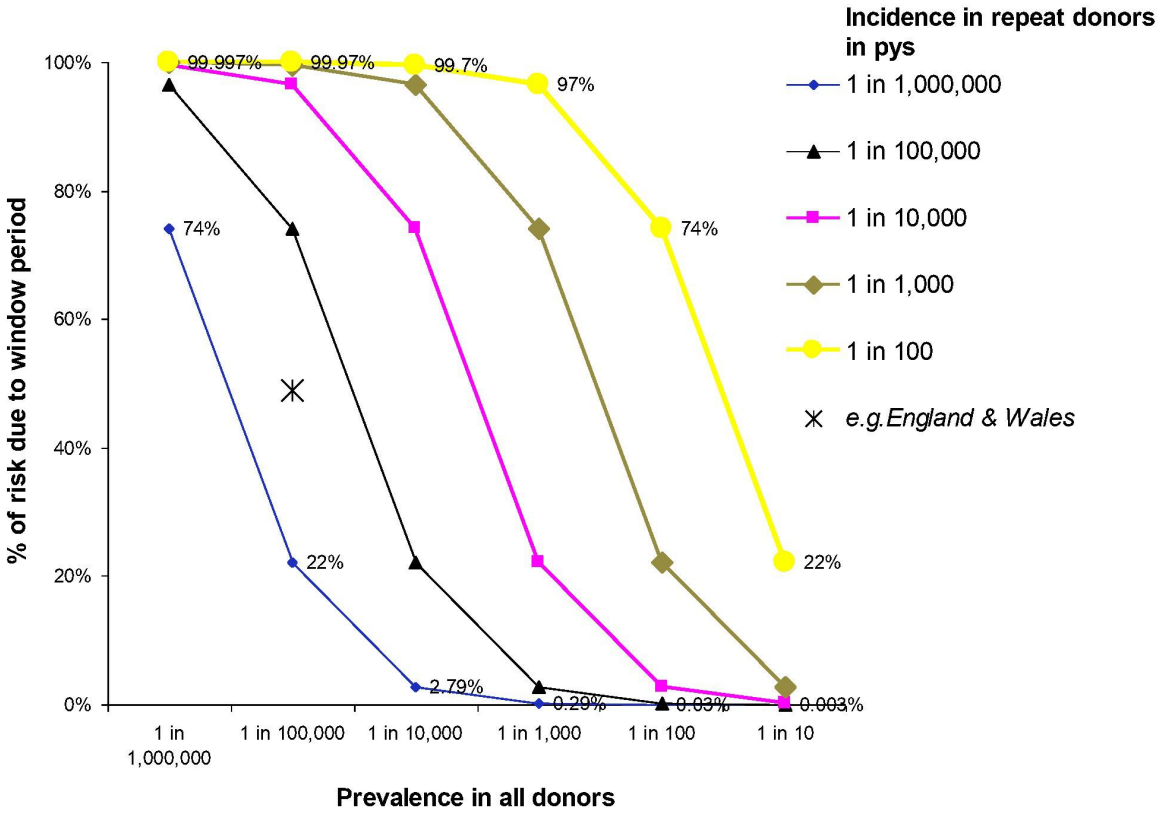
surveillance (Muller-Breitkruetz, 1999). The estimates for the 8 European collaborating blood services ranged from 0.05 infectious donations per million to 1.4 per million for HIV 1+2, from 0.43 to 4.97 per million for HCV and from 0.9 to 4.6 per million for HBV. As the same methods were used to generate the risk estimate for each blood service in this study, the differences in the risk estimates for the different blood services are - assuming the data submitted by each blood service were comparable - due only to statistical variability in the data used and to true differences in the risks dependent on the different epidemiology in the donors to the organisations.

Perhaps the most notable, and compelling, observation from reviewing these estimates is the disparity between the level of viral risk experienced in the less developed countries (e.g. Thailand, Ivory Coast) and that experienced in more developed countries (e.g. those in Western Europe and North America).

Studies frequently state that the risk of a donation being collected during the window period is the largest remaining risk of infection transmission (for infections that donations are tested for). This is often actually an assumption rather than a demonstrated fact. The relative importance of each component of the risk of accepting infectious donations varies between blood services depending on the specifications of donation testing, the proportion of donations collected from new donors and the rates of incidence and prevalence in the donating population. Figure 1.1 shows how the percentage of the total risk estimate due to the window period of early infection can vary with different prevalence and incidence. Many studies omit separate calculations for donations from new donors. However, donations from new donors consistently have higher prevalence and there are good reasons to expect they will also have higher incidence. The greater the proportion of donations collected from new donors the larger the contribution to the overall risk is that associated with donations from new donors (the Thai study reports that 76% of all donations were collected from new donors); and the greater the prevalence of infection the more important the risk of false negative tests and errors in the exclusion of seropositive donations. According to an analysis of data for England (Soldan K, Barbara J *et al* Unpublished work), 1993-1995, less than 10% of the total estimated risk of an HCV infectious donation entering the blood supply in England would be due to window period donations from repeat donors (if

window period for anti-HCV is 66 days (54-192), test sensitivity for anti-HCV is 98%, error rate is 0.5%). Studies that omit some components of risk or only consider donations from repeat donors would usually (to an extent dependent on their epidemiology and selection and testing practices) underestimate the risk of an infected donation entering the blood supply.

Figure 1.1 Variation in components of risk with varying prevalence and incidence



For an infection with a 22 day window period, using tests with 99.5% sensitivity and an error rate of 0.5%, e.g. HIV, and 11% donations from new donors.

In most risk estimation studies estimates of incidence based on seroconversions have been a key element. The use of seroconversions to estimate incidence involves an assumption that donors are not more likely to self-defer, either temporarily or permanently, after they have seroconverted and that the probability of an individual donating blood does not vary over the course

of antibody development after infection. There are some observations, such as longer than average inter-donation intervals in donors who have seroconverted for antibodies to HCV (Soldan K, 1998), and fewer than expected HIV p24 antigen positive, HIV antibody negative donations in the USA (Scheiber G, 1997), that suggest that donors are more likely to self-defer during the window phase. This may be due to a perception of recent risk, symptomatic primary infection, or perhaps just a disrupted life less conducive with donation around the time of their exposure to infection.

HBsAg negativity during established HBV infection can occur in healthy adults at the tail end of HBV carriage. Transmission from such donors has been observed (Soldan K, 1999) and this risk should be included in estimates of total risk where blood services use HBsAg alone as a marker of HBV infective donations.

Several other scenarios that could lead to infectious donations entering the blood supply are seldom considered in risk estimates. The sensitivity of assays is typically estimated using a panel of samples considered representative of the population positive for the marker concerned. The potential of newly recognised subtypes and variants of viral infections to escape detection by assays is not addressed by most risk estimation studies. Since HIV antibody testing began, there has been an emphasis on improving the sensitivity of tests with regard to early seroconversions concentrating on the HIV sub-type that has been most common in Europe and the USA, sub-type B. Other subtypes of HIV-1 infection have become more globally distributed, and the importance of ensuring assays have high sensitivity to a comprehensive range of HIV sub-types, should not be overlooked (Gurtler L, 1998). Mutant HBV infections, not detected by HBsAg tests, have also been shown to pose a risk (Jongerius JM, 1998).

Data that could verify or refute the results of risk estimation studies are rare. The introduction of nucleic acid technology (NAT) for testing donations should detect infectious donations missed by current serological tests and therefore provide some data to compare with the estimates. However, if the estimates from Europe and the USA are close to, or higher than, the true risk,

several years of data collection from NAT testing will be needed to test the accuracy of the estimates.

Use of risk estimate

The comparability of these estimates to other risks of morbidity is not straightforward. Infectious donations entering the blood supply do not directly translate to infected recipients and the actual risk of disease also depends upon the transmission rate, susceptibility of the recipient and the natural history of transfusion-transmitted infections in recipients. Information about natural history is often only available from case reports or from studies in other patient groups. The size of the infective dose, and the relatively poor health status of recipients, may make transmission, and rapid disease progression, more likely. On the other hand, some infectious agents may lose viability during their storage between collection and transfusion.

The communication and use of risk estimates is often difficult (Calman KC, 1997). Misunderstanding of these risk estimates, or ignorance of their limitations can lead to a false sense of confidence, or a false sense of alarm, in the safety of transfusion.

Only those components of risk that are known about are estimated and the accuracy of the estimates is only as good as the accuracy of the information used to derive them. While these estimates of the risk of infectious donations being accepted and entering the blood supply can be of value, they can give the misleading impression that the true and total infectious risk of transfusion is known. They should not be allowed to detract attention and resources away from un-estimated risks. The true infectious risks of blood transfusion involve both infections already known to be blood-borne (such as HBV, HIV and HCV), and those that have not yet been identified. The latter category may have considerable impact on blood services, for example the current concern and activity due to possibility of transmission of vCJD by transfusion (Barbara JAJ, 1998), and represents a potential hazard of transfusion that has been repeatedly realised as blood-borne infections have been recognised. These as yet unidentified risks justify the use of generic measures to limit the exposure of recipients such as restricting donation pooling, the use of viral inactivation and

the avoidance of unnecessary transfusion therapy irrespective of how low the estimated risks for HBV, HCV and HIV become.

1.3 Epidemiology of infections in blood donors and recipients: implications for public health

The testing of blood donations for markers of infectious disease has not only reduced the rate of transfusion transmitted infections, but has also provided opportunities for the relatively early treatment of the infections detected in "healthy" individuals (Seymour CA, 1994) and for the prevention of further transmission by other routes. Regional or national collation of the results of testing blood donations has contributed to knowledge about the frequency of infections in the population (McGarrigle C, 1997; MacLennan S, 1994). Comparisons of different geographical areas or different time periods can reflect differences in the frequency of infection in the population from which the donors come, or differences in the donor recruitment and selection, or donation testing, procedures. Despite the biases introduced by donor recruitment and selection, international comparisons (WHO, 1996; Naplas B, 1996) have typically provided rankings of infection rates that have concurred with information about infection rates in the population from other sources. The follow up of infected donors has also provided useful information about unrecognised, or unapparent routes of infection (Power JP, 1995; Hewitt PE, 1994). The collation of the probable routes of HIV infection of blood donors has contributed to the relatively scarce information about the extent of HIV transmission by sex between men and women in the UK (Gunson HH, 1991). The identification of newly acquired infections in repeat donors (i.e. the observation of seroconversions between donations) has been of particular interest as it has provided the opportunity to study the serology and infectivity of recent infections (Petersen LR, 1994), and to observe the complete natural history of infections that are typically only detected when clinical symptoms appear many years after infection. Information about seroconverting donors has also been used to identify and describe current, rather than past, probable routes of infection transmission (Soldan K, 1998).

In addition to the opportunistic use of data derived from donation testing and the follow up of donors found to be infected, the donor population has also

been used as a study base for special studies of the epidemiology and natural history of infections. The selection and recruitment of suitable controls for case-control studies is relatively easy and this study design has been used most recently to investigate risk factors for HCV infection (Goodrick MJ, 1994; Neal KR, 1994).

When considering the infectivity of blood from donors, and the natural history of infections transmitted by transfusion, knowledge obtained from observing infections transmitted by other routes may not be reliable. In particular, the progression of disease due to some viral infections may be affected by the infective dose. An infected blood component typically exposes a recipient to a far higher viral dose than other routes of transmission. Never-the-less, recipients exposed to infected blood have often been used for studying the natural history of blood-borne infections, particularly of the development of markers of infection and of symptoms in the early stages of infection, and of the onset of disease associated with chronic viral infections.

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Introduction

2.1 A brief history of blood transfusion

Records of transfusion of blood to human beings date back to one by Samuel Pepys over 300 years ago when Arthur Coga received a few ounces of sheep's blood before an audience with the Royal Society. James Blundell pioneered human transfusions during the 19th century, but it was the combination of the discovery of ABO blood groups by Landsteiner in 1900 and the impetus of the injuries of the two World wars and the Spanish Civil War that resulted in blood transfusion becoming an established medical therapy. History records the activities of several individuals as key to the development of blood transfusion therapy and of blood donors' organisations. Geoffrey Keyes became aware of the life-saving properties of blood transfusion whilst working as a medical officer during the First World War. He observed transfusion saving the lives of those who were in shock through loss of blood, and extending the possibilities of surgery. Returning to hospital work in London, Keyes was amazed at the lack of importance ascribed to transfusion and became an active promoter of transfusion among his colleagues. Resistance to consider the use of transfusion arose from the expense and awkwardness of direct transfusion as practised at that time. When his efforts to set up a donor panel at St Bartholomews were blocked he complained that "This prevailing uncertainty as to how or where to obtain a blood donor often results in the postponement of the decision to transfuse until the patient has passed from the category of hopeful to hopeless" (said by Keyes, 1924). Meanwhile however, a layman was independently solving this problem. In 1921 a meeting of the Camberwell Division of the Red Cross was interrupted by a request for volunteers to give blood at nearby King's College Hospital. Percy Lane Oliver (1878-1944) was one of the members who went along to the hospital. Oliver's blood was not compatible with that of the patient but he was deeply impressed by the beneficial effect of the donation obtained from his fellow member - who rejoined them none the worse for her donation. So much so that he set about changing

the situation he saw of patients who had neither relatives nor friends willing and able to donate blood being disadvantaged. Oliver put his public spirit and organisational skills to establishing a panel of volunteer donors to which hospitals had access strictly through his office. He arranged for hospitals that wished to use the service to blood group potential donors and he insisted on certain conditions and standards for the treatment of the donors at hospitals. His attention to the concerns and experience of the donors - whilst an annoyance to the hospitals - was crucial to maintaining the donor panel. For example, Oliver insisted on the use of sharp needles and the protection of donors from witnessing particularly distressing sights during the donating procedure (a common reason for donor resignation).

The Spanish Civil War provided impetus for, and experience in banking blood. Storage techniques had been proposed in the UK but had not been favoured over the use of fresh blood. After initial resistance it was again the imminence of war, in 1939, that prompted plans for four blood-storage depots in London funded by the Cabinet. The Medical Research Council (MRC) administered the depots on behalf of the Ministry of Health along with the Emergency Medical Service. The hospital based (Red Cross) panels became less in demand as the use of blood from the depots became standard. The Red Cross remained involved, along with other charities, in the organisation of panels and care of donors. In 1940 the need for depots outside London led to a scheme to establish a regional transfusion service. Depots bled in excess of local needs in order to produce plasma. The service expanded and the processes developed and became more sophisticated throughout the war.

As the end of the Second World War approached it was recognised that although the depots were set up to meet the needs of air-raid casualties, the bulk of their work had actually been in connection with the civilian sick and it would now be impossible to return to hospital based donor services. The MRC, whilst maintaining a research interest, withdrew from taking on routine supply and organisation. In 1945 the Treasury accepted the solution that the Ministry of Health (MoH) should provide the National Blood Transfusion Service by continuing with the existing structure of 12 regional centres situated at Newcastle, Leeds, Sheffield, Cambridge, Oxford, Bristol, Cardiff, Birmingham,

Liverpool and Manchester, and two centres, in Luton and Sutton, serving London and the South East. On 26 September 1946, the MoH took over full responsibility for transfusion services including training of staff and research into transfusion-related problems. The organisation of the service over the next 53 years has involved shifts of managerial responsibility (to regional health authorities and back to a centrally managed service), and changes in geographical location of blood centres (fully described by Gunson and Dodsworth, 1996). It has maintained a voluntary donor panel. Understanding of the clinical action of the components of blood and the separation of donations into those components has greatly increased the expertise involved in both the processing of blood donations and in the prescription of transfusions.

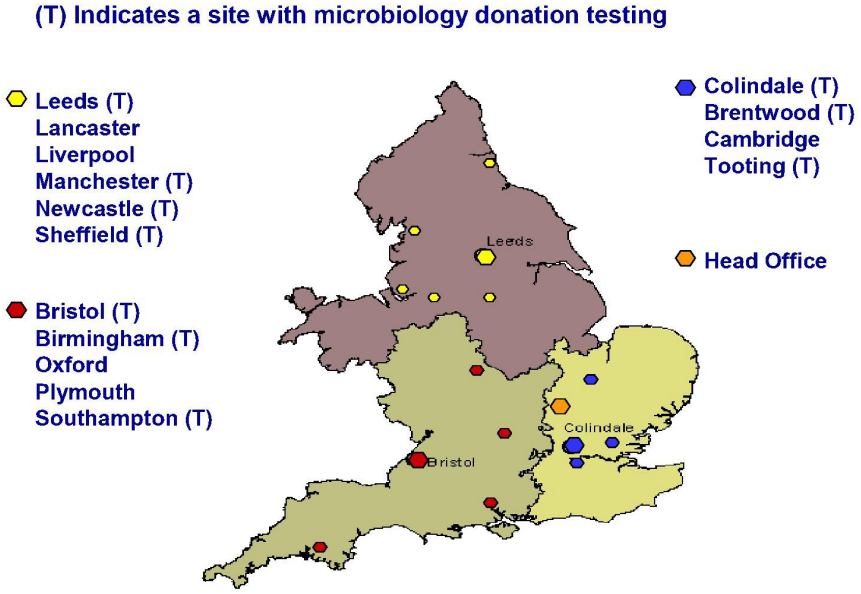
During the last 30 years, the transmission of infections by blood transfusion has had a great impact on the practice of transfusion medicine. One major consequence of the increased awareness of transfusion transmissible infections has been the development of microbiology and virology within the blood services to detect markers of infectious disease in donations. There has been an active relationship between transfusion microbiology and infectious disease epidemiology as knowledge gained by each has proved valuable to the other. The testing conducted on blood donations, and the observation of infections in recipients (when testing does not exclude infectious donations from the blood supply), has provided valuable sources of epidemiological information.

2.2 Current provision of blood transfusions in England and Wales

In 1993, the Department of Health in England established the National Blood Authority (NBA) as a Special Health Authority. Since that time it has taken on the responsibility for the management of the Bioproducts Laboratory, the International Blood Group Reference Laboratory and for the national co-ordination of the Regional Transfusion Centres (now called blood centres) - a task previously performed, to a lesser extent, by the now dissolved Central Blood Laboratories Authority and National Directorate of the National Blood Transfusion Service.

In July 1996, there were thirteen regional blood centres collecting, testing and storing blood in England, plus an Army blood supply depot. In July 1999, after reorganisation of the service, there were ten testing centres (see Figure 2.1). The Army Blood Supply Depot ceased collecting and testing blood from donors in July 1996. Blood centres remain in Cambridge (East Anglia), Liverpool (Mersey & North Wales) and Oxford but they no longer have full testing and processing capacity.

Figure 2.1 The Blood Centres of England



The Welsh Blood Transfusion Service (WBTS) is the responsibility of the Welsh Assembly and has one blood centre in Cardiff. The WBTS supplies plasma to BPL (when BPL are accepting UK sourced plasma) and functions similarly to the NBA on most operational matters. Donors in North Wales are recruited and managed by the blood centre at Liverpool (donations are tested by Manchester centre).

The English and Welsh blood transfusion services collect approximately 2.5 million donations each year. Donors can donate more than once each year and it can be estimated that 1.8 million donors are tested each year.

One component of the NBA's national co-ordination is donation testing and the collation of data arising from donation testing and from the investigation of post-transfusion infections.

The methods and processes of the blood transfusion services in the United Kingdom (England, Wales, Scotland and Northern Ireland) are standardised by the "Guidelines for the Blood Transfusion Service", more commonly known as "The Red Book" which is regularly revised by the Red Book Committee and its various specialist sub-groups.

Donor selection

Blood donations are collected from a selected sub-group of the population. Selection is both incidental and deliberate.

Blood donation is an "opt in" activity that requires individuals to receive, understand, and respond to information about the need for blood donations and how they can become blood donors.

Individuals who are healthy and aged between 17 and 60 years of age are targeted for recruitment to the donor panel. The age limits were revised in May 1998 when the lower age was reduced from 18 to 17 years - adding up to 600,000 potential new donors. The upper age for regular donors was increased at the same time from 65 to 70. The upper age limit for new donors remained at 60 years. Further selection criteria applied prior to blood donation try to ensure that individuals who may suffer any harm from donating blood, and individuals whose blood may cause harm to recipients are not accepted as blood donors. These criteria are collated in an appendix to the UKBTS/NIBSC Guidelines for the Blood Transfusion Service as an A-Z of Guidelines for the Medical Assessment of Donors (as a controlled document).

Many of these selection criteria aim to lower the frequency of infectious diseases in the population who are accepted to donate blood. Individuals with any clinical signs or symptoms of a recent, or chronic, infection are not accepted. Individuals who have any behavioural, or lifestyle, characteristics that are associated with an increased risk of blood-borne infections are also not accepted.

Guidelines for donor selection also include some procedural instructions that may affect the effectiveness of the criteria themselves. All donors are asked to confirm that they have consented to their donations being tested for the presence of infections that might be passed on to patients, and told that

they will be informed of the result. It is also emphasised to the donor that ill health within 14 days post-donation may indicate their donation would be unsuitable for use. In these circumstances they must inform the blood centre. Donation venues must have the following literature available:

1) Declaration to be signed by donors including the wording "I understand that I must read the literature explaining about HIV infection and AIDS. I agree that my blood donation can be tested for HIV (the virus associated with AIDS) and other infections that may be passed on by my blood. If my donation gives a positive result for any of these tests, I will be contacted for further tests and appropriate advice. I will inform the blood centre of ill health within 14 days post-donation as this may indicate that my donation would be unsuitable for use."

2) "Safety of Blood" leaflets. The most important exclusion criteria with respect to keeping the blood supply free from blood-borne infections are summarised on a leaflet. (Appendix 1).

3) Posters. Displaying information in 2).

Since 1999, every new donor has an individual interview that asks directly about their health, and their risks for infectious diseases including travel abroad, and a check that the donor has understood the Safety of Blood leaflet.

European legislation requires all blood donors to give informed consent to the procedure at each session. Since November 1998, a 'tick-box' health check questionnaire has been printed on the back of the session slips (Appendix 2). All new donors and those who have not given blood for some time have a one to one interview with the session nurse or doctor, and all known donors complete the medical questionnaire while they are awaiting or when they register to donate at a session. This gives donors who are in high risk categories for infections the information and opportunity needed to exclude themselves before donating; it also gives the blood service documented evidence of donors' answers to the health questions.

The signature of the person completing the medical assessment must be recorded.

In addition to the routine medical assessment, apheresis donors have a full blood count and their serum albumin and total serum protein levels measured at the initial visit and then at least every 6th visit or annually, whichever is the shorter interval. A medical officer in the light of these results then assesses the donor's fitness for apheresis. Volunteers with a platelet count below 150 x 10^9/l should not undergo platelet apheresis.

Bacterial contamination can be introduced into the blood donation during the collection process. This risk can be reduced by techniques for cleansing the site on the donor's arm from which the donation is taken. The cleansing technique of all staff that carries out donation procedures is checked once a month (with swabs taken for bacteriology), to assess the effectiveness of arm cleansing in practice.

Component production and issue

Most blood collected from donors is processed into blood components and blood products. Blood components, such as red cell and platelet concentrates, fresh frozen plasma (FFP) and cryoprecipitate, are prepared from a single donation of blood by simple separation methods such as centrifugation and transfused without further processing. Complex processes, using the plasma from many donors as the starting material, are used to prepare blood products such as coagulation factor concentrates, albumin and immunoglobulin solutions. This thesis is primarily concerned with blood components, and only concerns blood products to the extent that issues concerning donors overlap and because these two parallel uses of blood donations influence each other. Since May 1998 no UK-sourced plasma has been used for blood product manufacture in the UK. After a thorough cleansing and re-fitting scheme, plasma sourced from countries with no reported vCJD cases (the US) entered the product manufacture at the Bio Product Laboratory (BPL) in England and products derived from US plasma have been on release since November 1998. The epidemiology of infections in UK blood donors is therefore not relevant to blood products produced in the UK since 1998.

In most circumstances it is preferable to transfuse only the blood component or product required by the patient rather than using whole blood.

This so-called 'component therapy' is the most effective way of using donor blood which is a scarce resource, and also reduces the risk of complications from transfusion of unnecessary components of the blood.

The average volume of whole blood collected is 450ml, taken into 63ml of anticoagulant. Up to three donations can be collected from a single donor during a year. Blood stored at 4°C has a 'shelf-life' of 5 weeks when at least 70% of the transfused red cells should survive normally. Alternatively, donors can give up to 15 litres of plasma per year by plasma apheresis: each donation providing 500-600ml of plasma. Platelets and leucocytes can also be collected by cytapheresis up to 24 times per year.

The processing of blood into components of varying constituents and varying therapeutic properties is an increasingly detailed subject. Only some aspects of component therapy are relevant to this thesis. Storage conditions of different components affect the risk of bacterial multiplication and the viability of some other agents. Red cells and whole blood are stored between 2 and 6°C for up to 35 days. Platelet concentrates (from the pooling of platelets 'recovered' from (usually four) whole blood donors and from apheresis from single donors) are stored at 20-24°C on a special agitator rack for up to 5 days. Fresh frozen plasma and cryoprecipitate is stored at -30° C for up to one year (and used within 4 hours of thawing). The cellular content of components affects the transmission of cell associated infectious agents. CMV, HTLV I&II, and parvo B19 are associated with leucocytes and transmission of these viruses is less likely from acellular, or leucocyte depleted components

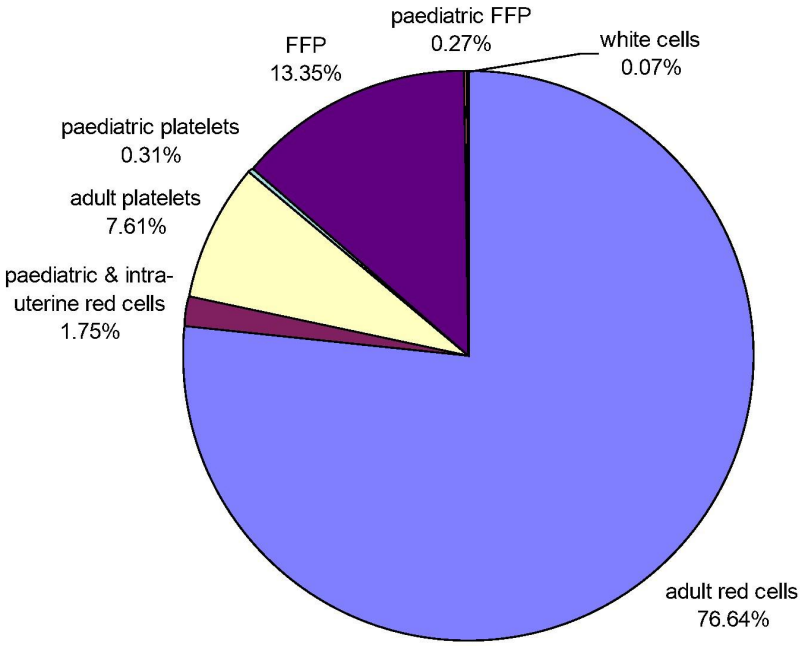
Donors who provide plasma and/or platelets and leucocytes by apheresis differ in their donation frequency and selection. Apheresis donors are selected from whole blood donors and have therefore already been through the donor selection and testing process at least once. The logistics of making apheresis donations requires the donor to commit more time to donating as well as to attend more frequently. Apheresis donation may therefore be inconvenient for individuals with a relatively busy job or life. While the additional donor selection probably acts to reduce the risk of blood borne infections the frequent donation pattern of apheresis donors means that should a donor acquire a new infection it is more likely that one or more donations will be collected during the infectious period.

Certain components, for example platelets, are often prescribed for conditions associated with immunosuppression. Immunosuppression may make a recipient less likely to mount a detectable immune response, and more vulnerable to disease, if transfused with an infectious component.

Since a recommendation in July 1998 an additional stage of component production that may affect infection transmission has been introduced in the UK - routine leucodepletion. Prior to this recommendation 9% of red cell units and 23% of platelet components underwent leucodepletion of some kind. This action followed reports from the Government's Spongiform Encephalopathy Advisory Committee (SEAC), that there was a theoretical risk of the transmission by leucocytes of the infectious agent in variant Creutzfeldt-Jakob disease (vCJD). Monitoring of leucodepletion uses the guidelines produced by the Biomedical excellence and safety in transfusion group of the International Society of Blood Transfusion (ISBT) - with initial validation of the process followed by statistical process monitoring using a sample of components. Monitoring requires a standard of the reduction of the leucocyte count to less then $5x10^6$ leucocytes per unit transfused in at least 99% of components filtered with at least 95% confidence. By February 1999 all platelet products were being leucodepleted and progress towards supplying leucodepleted red cell components was ongoing. The process of leucodepletion may affect the transmission of infectious agents other than vCJD. Some cell-associated viruses may be removed from components during leucodepletion. The effect of leucodepletion on bacterial contamination is uncertain: depending on the pre-filtration storage time and conditions, any bacteria contained in a blood donation may be ingested by leucocytes and so removed by leucodepletion or may remain free and unaffected by the phagocytic action of leucocytes.

During 1999, the English blood service provided over 2,893,627 components to 329 hospitals. These included 2,212,385 units of adult red cells, 50,383 units of paediatric red cells for newborn babies, 190 units of red cells for 'intra-uterine' transfusion, 219,556 adult doses of platelets, 8,887 units of paediatric platelets, 385,425 units of fresh frozen plasma, and 1,882 units of white cells (Figure 2.2) (NBA, 1999).

Figure 2.2 Components issued in England, 1999



Blood centres of England and Wales

The location of blood centres in England and Wales is shown in Figure 2.1. Donors registered with each centre live in the surrounding area, although donors may give blood elsewhere, for example, when on holiday. The donor's post-codes, and the site of the donation session (e.g. village hall, workplace, university campus) are linked to each donation record. Centres tend to predominantly supply their local hospitals, although blood components may be moved around the country to supply fluctuating demands.

Donors are recruited by advertisements in the press, on radio (usually designed and organised at local level), and occasionally by television advert campaigns (organised centrally). Existing donors are invited to encourage family and friends to consider becoming donors.

2.3 Surveillance of infectious diseases in England and Wales

The Public Health Laboratory Service (PHLS) Communicable Disease Surveillance Centre (CDSC) was established in 1977 to undertake national surveillance of communicable disease and to provide epidemiological assistance and co-ordination in the investigation and control of infection in England and Wales.

Data are collected at CDSC about the testing performed, and infections diagnosed, at Public Health Laboratories around England and Wales. Forty-nine public health and two-hundred and fifty National Health Service laboratories report a minimum dataset (age, sex of patient, method of identification, date of onset, first specimen, details of laboratory) on all clinically significant infections diagnosed at these laboratories.

Data are also collated from other sources including statutory notifications of infectious diseases, antenatal testing, seroprevalence surveys and vaccine administrators. Other datasets that are used for investigating particular aspects of some infectious diseases include death registrations, hospital episodes and sentinel General Practitioner reporting.

Surveillance of viral hepatitis

Acute HBV infections confirmed by laboratories in England and Wales are reported to the PHLS CDSC. Laboratory confirmation of acute HBV infection includes a positive result of a test for HBV anti-core IgM (anti-HBc IgM), or a positive result of a test for HBV surface antigen (HBsAg) together with symptoms compatible with acute HBV and, if available, a negative result of a test for IgM antibodies to hepatitis A virus (HAV). Additional cases ascertained by contact tracing or other investigations, for example, during outbreaks or lookback at previous donations of a donor found to have HBV infection, are included in the surveillance if they have evidence of recent infection (anti-HBc IgM positive or seroconversion to anti-HBc IgG) even in the absence of clinical illness. Children infected by perinatal transmission and identified during the follow up of known high-risk mothers are also included. Surveillance reports include clinical and demographic details and information about risk exposure(s) in the previous 6 months. These details are based on information passed to laboratory staff by the clinician requesting the test and supplied with the results (Balogun MA, 1999). An audit of reporting has estimated 82% of laboratory confirmed acute HBV infections are reported (Ramsay M, 1998). Acute HBV infection may be asymptomatic or cause non-specific symptoms; about one-third of infections in adults are expected to be symptomatic and this surveillance cannot ascertain all acute HBV infections. Acute infection surveillance has been shown to give reasonable estimates of the incidence of symptomatic infection (Polakof S, 1984), and as the proportion of asymptomatic infections in adults is expected to be fairly constant over time surveillance of acute symptomatic cases can also be used to monitor trends in the incidence of acute HBV.

The PHLS CDSC has carried out surveillance of HCV in England and Wales since 1990. The aim of this surveillance is to monitor trends in incidence and prevalence, to determine the major risk factors associated with infection in England and Wales and to inform health care planning, prevention and control strategies (Ramsay ME, 1998). Surveillance information is derived from reports of confirmed HCV infections from laboratories in England and Wales. The low

proportion of acute HCV infections that are symptomatic (Locarnini S, 1996), the long but variable interval between acquisition and chronic disease (Alter H, 1996) and the lack of serological markers of acute infection (Clemens JM, 1992; Zaaijer HL, 1993) mean that these reports cannot be used to estimate current or past HCV incidence. Risk factor information is routinely reported from laboratories as part of the surveillance but the quality of this information is variable and the distribution of reported risk factors reflects the prevalence of testing in different risk groups. Some reporting laboratories have participated in enhanced surveillance involving the collection of more detailed clinical and epidemiological information about individuals with prevalent HCV infections and submission of serum for genotyping. Ad hoc surveys of testing and seroprevalence surveys have been used to further enhance the routine surveillance. Seroprevalence studies have involved archive samples from unlinked anonymous surveys of GUM clinic attenders, antenatal women and adults attending hospitals.

Further information about the epidemiology and natural history of viral hepatitis infections is obtained by surveillance of chronic liver disease due to viral hepatitis, notifications of acute clinical hepatitis, reports of deaths from viral hepatitis, hospital admission for viral hepatitis, surveillance of paediatric HCV, surveillance of occupational exposure to sources positive for blood borne viruses, surveillance of infections in prisons and a register of HCV infections with a known date of acquisition that can be followed-up for clinical outcomes.

Surveillance of HIV infection

Reports of newly identified HIV antibody positive individuals and AIDS cases are sent by microbiologists and clinicians to the PHLS CDSC AIDS & STD Centre. Reports include clinical and demographic details and information about risk exposure(s). Whenever possible enough information is gathered from the initial report or through subsequent follow-up to allow consistent allocation of individuals to defined risk categories. Where there has been exposure to HIV infection by more than one route, allocation to the most probable route for purposes of summary statistics is based on a hierarchy of

risk associated with different possible routes of infection. All reports indicating heterosexual exposure to HIV infection, but with insufficient information for further sub-classification by risk and country of exposure, and all cases reported as having acquired infection through heterosexual exposure in the UK with no evidence of "high risk" partners, are systematically followed up to clarify their exposure category (Evans BG, 1992).

Many HIV infections amongst groups of the population remain undiagnosed and therefore undetectable though surveillance systems based on routine laboratory and clinical diagnosis. To provide a more complete and accurate picture of the epidemiology of HIV infection in the community data from the HIV and AIDS reporting surveillance are augmented by several other sources of data. These include an annual survey of people currently receiving care for their HIV infection (Survey of Prevalent HIV infections Diagnosed - SOPHID (Molesworth AM, 1998)), behavioural surveys (Johnson AM, 1994), reports from genitourinary medicine clinics (Hughes G, 1998), mortality reports (Nylen G, 1999) and the surveys in the Unlinked Anonymous HIV Seroprevalence Monitoring Programme (DOH, 1999).

Surveillance of other infections

Reports of other confirmed infections - besides viral hepatitis and HIV infection - that can be transmitted by transfusion are also received at CDSC. Many of these come either on paper or electronically into the main database of laboratory reports - LABBASE. For example, CMV and parvo B19 infections are monitored. Microbiologists report a minimum dataset on all clinically significant infections based on information provided by the clinician requesting the test and receiving the result. The data reported includes age, sex of patient, method of identification, date of onset of illness, date of first specimen and details of reporting laboratory. Some risk factor information is reported for certain infections, but is very variable in quality.

Data collected by, or via, the NBA and the PHLS CDSC are the basis for the studies of the epidemiology of infection in blood donors and the assessment of the risk of transfusion transmitted infection included in this thesis.

2.4 Background to this study

Rational

The study of the distribution and determinants of infections in the donors of blood donations that are tested for markers of infectious diseases can inform transfusion practices and contribute to knowledge about infection in the general population.

Blood donation testing detects infections that are typically persistent but asymptomatic. As donors are selected to be individuals with no recognised increased risk of infection, unusual routes of infection transmission may be detected in this group. The serial testing of repeat donors enables the detection of incident infections. Some demographic information is available for the total population of donors tested and non-infected donors are available to provide more detailed comparative "control" information if needed.

Careful pre-donation selection of blood donors who are believed to be at low risk of blood borne infections, and the introduction of routine testing of all blood donations for markers of T. pallidum (1950), hepatitis B surface antigen (HBsAg) (1970), antibodies to the human immunodeficiency virus (anti-HIV) (1985, anti-HIV2 1990) and antibodies to hepatitis C virus (anti-HCV) (1991), has greatly decreased the risk of transfusion transmissible infections. However, the demand for transfusions is increasing and the infectious hazards of transfusing blood components continue to cause concern. As transfusion transmitted infections have become more rare the efficiency of prospective studies to determine actual transmission rates has been reduced and alternative methods of estimating transmission rates based on observed incidents in recipients and on infection rates in donors have become more important.

Additional interventions against transfusion-transmitted infections are available, for example, testing donations for HBV core antibody, HIV p24 antigen and human T cell leukaemia virus type I (HTLV-I) and use of virus-

inactivation procedures on components and the use of alternative therapies. Predicting the benefits of these proposed interventions, and evaluating their effect once introduced, requires accurate information about the risks and consequences of transfusion transmitted infections.

In order to assess the risks and consequences of transfusion-transmitted infections the characteristics of blood-borne infections, of donations, and of blood recipients need to be considered. Over the years, knowledge about new agents and about potential failures in the strategies to exclude known agents has increased. Consequently the range of possible strategies to exclude infections from the blood supply has also increased and debate about the risks of infection transmission by blood transfusion has become more complex.

Appreciation of the value of surveillance of infections in blood donors and recipients, along with falling infection rates, led to a proposal to establish enhanced surveillance of transfusion-transmissible infections. This was facilitated by changes in the blood service to make it more of a National organisation with standardised methods and services.

The study population

All blood centres in the British Isles and Republic of Ireland (except the five blood centres of the Scottish Blood Transfusion Service), opted to collaborate in an infection surveillance system, jointly run by the NBA and the PHLS-CDSC, by providing data about testing performed and about infections detected.

Clinicians and laboratories in England and Wales report blood borne infections - including those in blood transfusion recipients - to the PHLS-CDSC.

Aims

The overall aim of this work is to monitor and study the epidemiology of transfusion transmissible infections in England and Wales and to develop and apply methods for estimating the risk of infection transmission by transfusion in order to inform and evaluate donor selection and donation testing strategies,

and to contribute to knowledge of the epidemiology of blood-borne infections in England and Wales.

The following specific aims are addressed: -

1 Establish enhanced surveillance of transfusion transmissible infections

1.1 To develop methodologies for the national surveillance of infections in blood donors and of suspected and confirmed cases of transfusion transmitted infections in recipients of blood and non-fractionated blood components in England and Wales. This surveillance system will provide data that will be used for the following aims.

2 Descriptive epidemiology of infections in blood donors

2.1 To describe and monitor the prevalence and incidence of infections with HBV, HCV and HIV in blood donors and examine these data for evidence of temporal trends in the total sample and in sub-samples of donations from new donors, repeat donors and donors of specific sex and age groups.

2.2 To analyse the demographic characteristics (age, sex, ethnicity, region of donation) of blood donors infected with HBV, HCV and HIV.

2.3 To describe the probable routes of infection for HBV, HCV and HIV infected blood donors.

3 Descriptive epidemiology of post-transfusion infections in blood recipients

3.1 To describe the characteristics, frequency and outcome of post-transfusion infections diagnosed in blood recipients.

3.2 To identify any preventable factors contributing to the transmission of infections from donors to recipients in diagnosed post-transfusion infections.

4 To conduct related epidemiological studies using data from the surveillance system.

5 Calculation of estimates of the risk of transfusion transmitted infections

5.1 To use data from the surveillance system, together with data and assumptions from other sources to estimate the risk of transmission of HBV, HCV and HIV infection by transfusion.

5.2 To conduct sensitivity analyses of the data and parameters in the assumptions used to estimate risks.

5.3 To compare the estimated expected rate of transfusion transmitted infections with observed rates of transfusion-transmitted infections detected by the surveillance system.

Aims 1 to 3 are addressed in Chapter 3. Aims 4 and 5 are addressed in Chapters 4 and 5 respectively.

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3.1 Methods

3.1.1 Review of information available at blood centres

During the first half of 1995, each blood centre in England (14 centres) and Wales (1 centre) was visited (see Chapter 2: Blood centres of England and Wales). The methods of managing infected donors and post-transfusion infection cases, and the information about infections in donors and recipients that was available at blood centres were surveyed. This information was collected by the researcher (KS) during visits to each centre. Key members of staff including medical staff and laboratory staff were interviewed using a semi-structured questionnaire to ensure the same issues were covered at each centre.

Donation testing

The microbiology departments of the 15 blood centres were visited. Microbiology departments at blood centres used various automated and semi-automated systems for screening donations for markers of infection. Typically, microbiology departments had their own computerised systems for managing donation testing. These systems had often been locally developed, and had different specifications in different blood centres. Microbiology systems linked into the blood centres' mainframe computers to draw on information about donations for testing and to input information about donations to be withdrawn, and about donations to be released for issue. Microbiology computer systems did not routinely hold information about the sex, age or the donation status of donors: staff had access to the mainframe computer to obtain such details for donors who were found to be repeatedly reactive. Donations found to be repeatedly reactive by manufacturer's criteria were withdrawn and a sample referred for confirmatory testing according to algorithms agreed locally with the confirmatory laboratory.

Management of reactive donations varied between blood centres in the following ways: -

- Management of donors who were persistently repeatedly reactive to a test and had been repeatedly shown by confirmatory testing to be negative for the infection varied between centres, and within centres for different infections: in some cases, after two, or three, repeatedly reactive donations with negative confirmatory tests, donors were deferred from donation until such time as the test kit in use was changed, in other cases donors were repeatedly bled and their reactivity and confirmatory test results monitored, and in other cases, donations from donors who had been shown to be reactive to a specific test kit, but repeatedly negative to confirmatory tests, were tested by alternative test kits and, if negative to the alternative test kit, these donations were released into the blood supply.
- Repeat testing, and referral for confirmatory testing, of donations which were not reactive by manufacturer's criteria but which had abnormal results when compared to the bulk of non-reactive donations (i.e. donations with results in the "grey zone") was standard at some blood centres, discretionary at others, and not done at others.
- Blood centres microbiology departments used various methods for managing information about donors whose donations had been repeatedly reactive to a screening test, including card indexes, log books and computer databases.
- Archive samples from positive donations were kept in various volumes (0.25, 0.5ml) for varying lengths of time (mostly 2 years).

Infected donors

Microbiology departments informed blood centre medical staff of donors with confirmed markers of infection. Medical staff responsible for the care of infected donors at the 15 blood centres were visited. Management of infected donors varied in the following ways: -

- Donors were informed of their positive test results by letter, by blood centre staff during a personal appointment (or occasionally a telephone conversation), or by their general practitioner (GP) depending on blood centre practice, the marker of infection and the geographical distance

and travel restraints of the donor. (If seen again by the NBS, a blood sample was usually taken to re-confirm the infection.)

- If seen by blood centre staff, each blood centre performed discussion of histories of exposure to blood borne infection, and recording of this information, differently.
- If referred to GPs for follow up, some blood centres sought to obtain exposure history information (for some, or all infections) from the GP and some requested no further information after referral to GPs.
- Some blood centres periodically requested further information from the clinical centres managing their donors' long term care, and a few offered donors further testing over a number of years, and so obtained information about donors' disease progression.
- The infection status of each donor, including infected donors, was stored on blood centre mainframe donor computers (including range of 4 branded systems and several in-house systems). Further information about infected donors was kept in paper files and sometimes also on computer databases.
- Blood centres did not consistently report donors with HBsAg to the PHLS-CDSC national surveillance. Reporting to PHLS CDSC and to local public health systems (Consultants in Communicable Disease Control (CsCDC)) was – at least in some cases – performed by the laboratory that performed the confirmatory testing; however it was uncertain how systematic and complete this reporting was.

Post-transfusion infections

Verbal or written reports about 15 blood centres' PTI investigation practices were obtained. News of cases of PTI reached the blood centres by various routes (e.g. hospital doctors, GPs, recipients, news reports, other blood centres). Information was usually directed to medical staff, but was occasionally received by Quality Assurance departments or microbiology laboratories and passed on to medical staff for management and investigation if necessary. Practices for investigating PTIs varied. One third (five) of blood centres did not have a standard operating procedure (SOP) for investigating

PTIs in place. The practices detailed within SOPs and described by centres with no SOP in place varied in the following respects: -

- Criteria for initiating an investigation
- Information given to implicated donors and policies on recalling, or awaiting the next visit, of implicated donors
- The size of archived donation samples available and the use of these samples in testing implicated donors
- The extent of look-back at previous donations from an implicated donor

and

- The dissemination of findings (one centre reported its post-transfusion hepatitis infections to PHLS-CDSC national hepatitis surveillance, others left reporting to PHLS CDSC to reference laboratories (usually PHLs) performing the testing of samples. Again, the extent and nature of local communication about these infections with CsCDC was not clear or systematic.).

The following estimates and conclusions were made from the information obtained from blood centres about PTI investigations conducted between 1991 and early 1995:-

- approximately 50 investigations had been conducted each year
- three-quarters of these had involved HBV or HCV infections
- 1 in 5 of the post-transfusion hepatitis investigations had concluded that a transfusion was the probable source of the recipient's infection.
- Nearly half of the post-transfusion hepatitis investigations had been in the South and North West Thames Regions. How much this predominance was directly due to higher rates of post-transfusion hepatitis, and how much due to more frequent communication between hospitals and the blood centres about such cases was not clear.
- Other PTI cases investigated included infections with HAV, HIV, CMV, bacteria and parasites.
- While individual cases were well documented at most blood centres, potentially useful information about these PTIs had not been consistently reported to any national surveillance centre.

3.1.2 Review of current surveillance systems and data

Three surveillance systems for infections in blood donors were in place in 1994.

The surveillance system for HIV antibody testing of blood donations had been initiated when HIV antibody testing began in October 1985. All UK blood centres sent a monthly report form to a central collating centre (1985-1994 Manchester Blood Centre and from 1994 onwards The National Blood Authority). The form requested details about i) the test kits used during the previous month, ii) the total number of donations tested and the number of donations from new donors tested, iii) the number of donations (total and from new donors) which were initially reactive to the HIV antibody test, iv) the number of donations (total and from new donors) which were repeatedly reactive to the HIV antibody test, v) the number of donations (total and from new donors) which were referred for confirmatory testing and vi) the sex, vii) date of birth, viii) number of previous donations and ix) the probable route of infection, if known, for each confirmed HIV infection detected. The form also asked for the results of testing of quality control specimens distributed by the Public Health Laboratory Service (PHLS).

In principle blood centres should also have been reporting all HIV positive donors to CDSC and their details entered into the national database of first confirmed HIV-1 antibody positive tests. In practice HIV positive donors were so rare that in most centres such reporting to CDSC had not become routine and reporting was not assumed to be complete. Each year, therefore, the NBS surveillance centre sent CDSC a list of the HIV positive donors identified so that centres could be prompted to complete reports for individuals not already reported to CDSC. Exposure history information was reported by blood centres to the NBS surveillance as free-text and was often unknown at the time of the surveillance report of the HIV infection: the probable route of infection was therefore often (90% of reports in 1994) not known by the NBS surveillance system.

A similar UK wide surveillance system for HCV antibody testing of blood donations had been initiated in September 1992 - one year after HCV antibody testing began in September 1991. Two forms were used for reporting HCV antibody testing information each month. One form requested numbers of donations tested, initially reactive, repeatedly reactive and sent for supplementary testing with a break down for donations from new donors and donations from previously reactive donors. A second form requested the RIBA and PCR results for donations receiving supplementary testing with a breakdown for donations from males and from females, and from new donors and from previously reactive donors. To allow time for supplementary testing to be completed, the second form was typically sent to the collation centre one month in arrears of the first form. No information about age or probable route of infection had been collected.

The data from both these NBS surveillance systems were collated and stored in DATAEASE databases. A set of standard summary tables was issued each month to the reporting centres and to others with an interest in donation testing.

The completing of the surveillance forms was discussed in detail with the Head of Microbiology or the other staff member(s) designated to complete these forms at each blood centre. A number of variations in blood centre practices, in interpretation of the surveillance forms and in preparation of data for these forms were resulting in non-standardised information being collated by the surveillance centre.

For example, the eligibility of donations from previously reactive donors to be included in the monthly surveillance data about HIV and HCV testing had been understood differently by different centres, despite an attempt to separate these donations on the HCV antibody testing surveillance forms. Variation in the rates of reactivity to tests, as observed in the surveillance data, were therefore partially due to variation in the practices for managing, and for reporting, previously reactive donors.

In 1987 North London Blood Centre established a register of HBsAg positive donors (Howell D, 1991; Howell D, 1993). Centres were asked to make an initial report of all HBsAg positive donors previously identified, as far back as records would allow. Since that date, some centres had reported HBsAg positive donors as they were identified, and all centres had been asked annually to report each (unreported) HBsAg positive donor identified during the past year. Some data about donations dating back to 1972 were collected. The registry report requested donor identifiers, sex, date of birth, ethnicity or country of birth, history of any relevant exposures or symptoms and history of previous donation. For some years no reports had been received from some centres and some centres had not responded to each end of year check for cases not reported during the year. Absence of any reports from some centres, and quite marked fluctuations in the numbers of cases reported each year from other centres suggested underreporting to varying, unknown extents.

No national collation of the results of testing donations for Treponemal antibodies had occurred.

3.1.3 Establishing NBA/PHLS-CDSC joint surveillance system

i) Organisation and collaboration

A Steering Group was convened to advise and oversee the development of the surveillance system and of related studies of transfusion transmissible infections. Table 3.1 shows the members of this group and the time committed by each to the project. The group met at ad hoc times through out the study period.

Table 3.1 NBA/PHLS-CDSC steering group members

Steering group member	Time commitment to project
Scientist, PHLS-CDSC Immunisation Division	Full-time
Consultant Microbiologist, PHLS-CDSC Immunisation Division	Project supervisor: Involvement in ongoing work. (until October 1996)
Consultant Epidemiologist, PHLS-CDSC	Steering group meetings (chair) &

Immunisation Division	advice as requested up till October 1996. From October 1996 - Project supervisor.
Head of Microbiology, NBS-North London Centre, & Consultant in Microbiology to the NBA	Co-supervisor: Involvement in ongoing work.
Principal Scientist, PHLS-CDSC AIDS Centre	Periodic collaboration on HIV surveillance data. Steering group meetings & advice as requested.
National Quality Assurance Manager, NBA	Steering group meetings & advice as requested.
Director, Sexually transmitted and blood-borne virus laboratory	Steering group meetings & advice as requested.
Deputy Director, PHLS-Laboratory of Hospital Infection	Steering group meetings & advice as requested.

A group of blood centre and hospital specialists was convened during 1995 to develop a surveillance system for all serious hazards of transfusion (SHOT). The surveillance of PTIs developed in collaboration with this group so that it functioned in parallel with a system for surveillance of non-infectious complications of transfusion. (The scientist (KS) sat on the SHOT working group and the Consultant Epidemiologist (MR) sat on the SHOT Steering Group.) In order to improve the ascertainment and reporting of cases, the SHOT group took a number of steps to increase the awareness of the hazards (both infectious and non-infectious) of transfusion and to publicise the surveillance systems when the non-infectious complication reporting system was launched in November 1996. These included an editorial in the British Medical Journal, notices in various other journals and mailings to all hospital haematologists.

ii) Objectives and requirements

The objectives of the surveillance of infection in blood donors were: -

- To measure and monitor the initial and repeat reactivity rates to all test kit batches in use for testing blood donations at blood centres

- To measure and monitor the prevalence of markers for blood borne infections in first time (tested) blood donors
- To measure and monitor the incidence of markers for blood borne infections in repeat (tested) donors
- To describe the demographic (age, sex, ethnicity and geographical region) characteristics, clinical signs and histories of exposure to blood borne infections of infected blood donors

The requirements of the surveillance of infection in blood donors were: -

- A standardised surveillance system, covering all mandatory testing of blood donations, and all infected donors.
- Clear definitions of the information requested on surveillance forms.
- A format of data that would allow transfer of data electronically from blood centres to the collation centre when the IT system allowed.
- Staff at each centre trained to report, and responsible for co-ordinating reporting and for distributing results from the surveillance system within centres as appropriate

The objectives of the surveillance of infection in blood recipients were: -

- To monitor the number of post-transfusion infections which blood centres are informed about, and the probable source of these infections
- To collate and describe the failures of current blood centre practices to exclude HBV, HCV and HIV infections from the blood supply
- To collate and describe reasons for the occurrence of bacterial, parasitic and other viral (for which donations are not tested) infections in the blood supply
- To collate and describe the characteristics of transfusion transmitted infections in blood recipients

The requirements of the surveillance of infection in blood recipients were: -

- A standardised surveillance system, covering all post-transfusion infections in blood recipients about which blood centres are informed
- Clear definitions of the information requested on surveillance forms.

- Routine receipt of reports of suspected transfusion transmitted infections which are reported to PHLS-CDSC national infection surveillance systems
- Staff at each centre trained to report, and responsible for co-ordinating reporting and for distributing results from the surveillance system within their centres as appropriate

iii) Surveillance of infections: the system/general approach

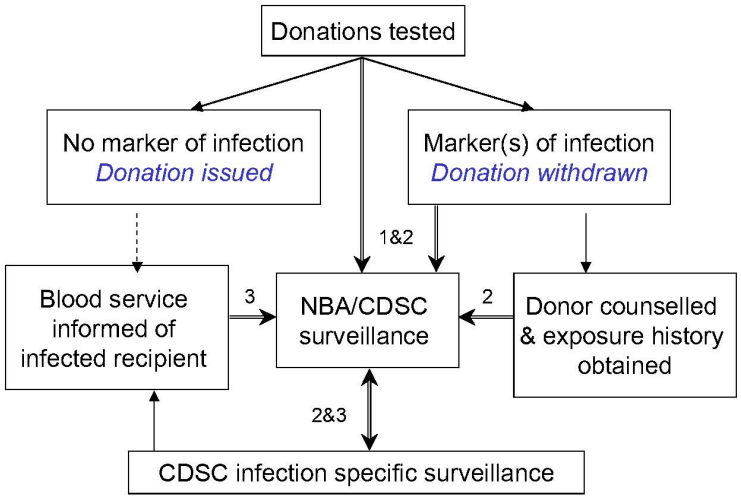
In order to meet the objectives listed above, and with consideration of the availability of information at blood centres, a new surveillance system was developed.

The surveillance system was divided into three, linked systems- each collecting a different section of data: -

1. Data about donations tested, initial and repeat reactivity to test kit batches and confirmed markers of infection detected. (Donation testing surveillance - DTS)
2. Data about donors with a confirmed marker(s) of infection. (Infected donor surveillance - IDS)
3. Data about infections in transfusion recipients about which blood centres are informed, and investigations conducted into implicated donations. (Post-transfusion infection surveillance - PTIS)

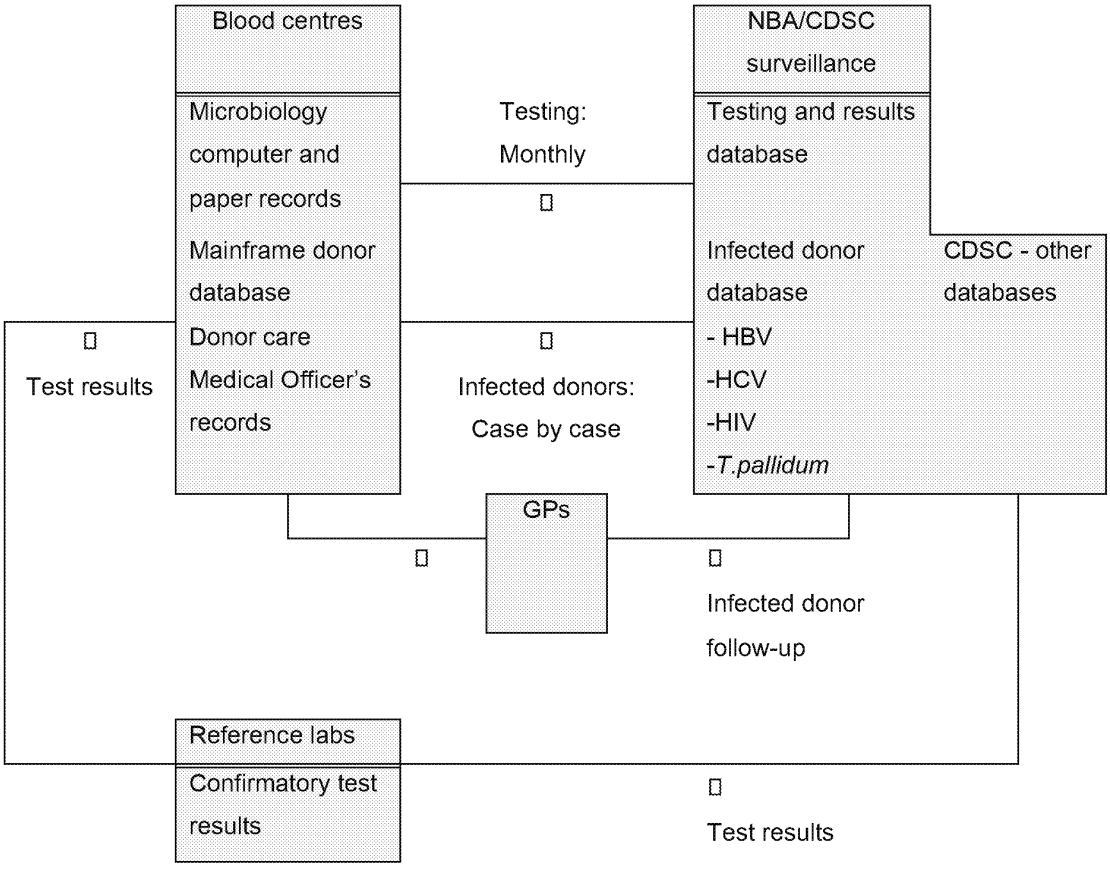
Figure 3.1 shows an overview of the NBA/PHLS-CDSC surveillance system. Figure 3.2 outlines the communications involved in generating the surveillance data relating to infections in blood donors.

Figure 3.1 NBA/PHLS-CDSC surveillance of transfusion transmissible infections



1. = Donation testing surveillance
2. = Infected donor surveillance
3. = Post-transfusion infection surveillance

Figure 3.2 Communication of information and surveillance reports



A set of surveillance forms was developed for each of the three surveillance systems. The format of these forms was determined by the data requirements and by the need for different pieces of information to be obtained from different staff within a blood centre, and at different times.

All the surveillance forms were printed on no-carbon-required double, or triple, A4 and A3 paper so a copy of each form sent to the surveillance centre could be kept at the blood centre. All surveillance forms were sent, in confidence, to the Medical Director of the National Blood Authority.

The three infection surveillance systems (DTS, IDS and PTIS) were introduced to blood centres in England, Wales, Northern Ireland, the Republic of Ireland, the Channel Islands and the Isle of Man on 1st October 1995. The Scottish Blood Transfusion Service (SNBTS) established a similar system for surveillance of donation testing in April 1995, and provided collated data, in a

format comparable to the NBA/PHLS-CDSC surveillance data, to the surveillance centre monthly. (The Serious Hazards of Transfusion (SHOT) surveillance system was introduced to UK hospitals on 1st November 1996.) Each system is described in detail below.

iv) Donation testing surveillance

Standardised information was required about the following parameters for each of the infections with mandatory marker testing: -

- Test kit batch specific numbers of donations tested.
- Test kit batch specific numbers of donations initially reactive.
- Test kit batch specific numbers of donations repeatedly reactive.
- Test kit batch specific numbers of donations sent for confirmatory testing.
- Test kit batch specific numbers of donations shown by confirmatory testing to be positive, negative and undetermined for markers of each mandatory tested infection.
- Donor type (i.e. first-time, "new" donor, or repeat "old" donor) specific numbers of donations tested.
- Donor type specific numbers of donations repeatedly reactive.
- Donor type specific numbers of donations sent for confirmatory testing.
- Donor type specific numbers of donations shown by confirmatory testing to be positive, negative and undetermined for markers of each infection for which testing is universal.

The donation testing surveillance monthly form pack (Appendix 3) consisted of six forms.

The first form (DTS Section 1) recorded the number of donations tested during the calendar month. The minimum requirement was the number of donations from new donors and the number of donations from repeat donors. Information about the number of donations tested by sex and by age group (<25 years, 25-34 years, 35-44 years and 45 years and over) was requested, but not

required. The form asked for counts of donations from new donors to exclude, if possible, the following categories of donors:

i. Potential donors who attend a session, but do not provide a specimen for microbiological testing.

ii. Donors who have donated to other transfusion centres in the UK.

iii. Repeat donors who attend a session un-called/without their donor certificate.

iv. Lapsed donors i.e. donors who have not donated for a certain number of years or more (e.g. usually 2 or 5 - specified on the form).

However, as blood centre computer systems could not always promise to exclude such donors from the new donation count, the form also recorded whether each of the four categories may have been included in the reported data, so that a correction could be applied to the data if necessary.

The second form (DTS Section 2) recorded the number of initially reactive donations during the calendar month. One line of data was required for each test kit batch used during the month: test kit name, batch number, number of donations tested by the batch and the number of donations which were initially reactive to the batch.

The other four forms in this monthly pack (DTS Section 3 a, b, c, &d) recorded information (test kit batch, donation number, donation date, donation type, initial and repeat test results, and whether sent for confirmatory testing) about each donation tested (with a donation date within the calendar month) and found to be repeatedly reactive to the test used. In addition, the same information was recorded about all other donations sent for further testing in order to confirm a suspected infection. A separate form was used for each marker of infection (HBsAg, anti-HCV, anti-HIV and *T.pallidum* antibodies). The confirmatory laboratory conclusions were also recorded on these forms.

Screening results were defined as:

Initially reactive (IR) - a donation found to be reactive at or above the manufacturer's defined cut-off in the first test using whichever validated screening assay is used for donation release. These donations (unless

within 6 months from a previously repeatedly reactive, confirmed negative, donor being monitored) were withheld for repeat testing with the screening assay.

Repeatedly reactive (RR) - a donation found to be consistently (at least in duplicate) reactive at or above the manufacturer's defined cut-off in whichever validated screening assay is used for donation release. These donations (unless within 6 months from a previously repeatedly reactive, confirmed negative, donor being monitored) are sent to a reference laboratory for investigation.

Donation types for DTS Section 3 forms were defined as:

New - donations from donors who, according to blood centre records and donor self-report, have never been tested by a blood centre for this marker of infection i.e. from donors for whom available NBS records and self-reported information from the donor do not specify any donation to a UK blood centre before, and from donors who have not donated since the introduction of testing for the marker for which their test results are reported. This latter type of new donor in DTS Section 3 would be classified as a repeat donor in DTS Section 1. For such donations, blood centres were asked to label the record as ONT (old, not tested) on the DTS Section 3.

Previously reactive (PR) - donations from donors whose blood is not permitted to enter the blood supply because of one, or more, repeatedly reactive donation(s) within the last six months, or at the last, or last-but-one donation (i.e. so-called flagged donors or X-filed donors). In practice this may include donations from donors who were previously reactive to the current test or to another test for the marker used in the past.

Not previously reactive (NPR) - repeat donors whose blood is eligible (pending donation testing) for the blood supply. These donations are from donors, who have been tested for the infection marker before, but have either

never been repeatedly reactive, or who have not been repeatedly reactive at the last, and last-but-one donation or during the last six months.

Confirmatory laboratory conclusions for DTS Section 3 were defined as:

Positive - found by the confirmatory laboratories tests and interpretation to be positive for the marker of infection.

Negative - found by the confirmatory laboratories tests and interpretation to be negative for the marker of infection.

Undetermined - found by the confirmatory laboratories tests and interpretation to be neither positive nor negative for the marker of infection, but concluded to be of undetermined marker status at this time.

Blood centres were asked to exclude the following samples from the reported data on each form:

i. Samples taken to re-confirm an infection in a donor i.e. "diagnostic" samples.

ii. Non-blood donor samples, e.g. antenatal samples, organ/tissue bank samples.

iii. Autologous donations i.e. donations collected from an individual for transfusion to the same individual at a later date.

and to also exclude from the Section 3 forms,

iv. Donation samples referred for antibody quantification for immunoglobulin preparation.

Donation testing surveillance forms were sent to the surveillance centre as soon after the end of each calendar month as possible, and by the 15th of the following month at the latest; complete confirmatory laboratory conclusions were not always available. Second copies of the DTS Section 3 forms, with completed confirmatory laboratory conclusions, were sent with the following months data if updated information was then available. If no report had been

received by the surveillance centre for the last month, or if any confirmatory laboratory conclusions remained outstanding for the last but one month, the blood centre was contacted by the surveillance centre and asked for the missing data.

Data were generally summarised and analysed as frequency of reactivity and positive donations per 100 and per 100,000 donations tested respectively.

During 1999, two routine analyses of the monthly donation testing data were developed -

Analysis of Monthly donation testing data

The aim of this analysis was to identify overall repeatedly reactive rates and infected donor rates for the most recent month that were outside the 95% prediction intervals based on the previous 36 months observed data (i.e. to alert to major changes in repeat reactivity and infection rates in blood donations collected by all reporting centres, possibly indicating a change in testing performance, donor selection or national infection rates in the donor population).

Programmes were written in GLIM (by Nick Andrews) to model the observed data (numbers tested, found repeatedly reactive and found confirmed positive) for the previous 36 months in order to predict an expected range, at a set level of confidence, for rates during the current month. Each month the data files were up-dated and the analyses re-run. The model gave out-lying observations during the thirty-six month period a lower weighting in the prediction of expected rates so that previous unusual observations did not make the model insensitive to changes in the observed data that might be of importance. The output gave the raw data for the month, the observed rates, the expected rates, the low and high limits of the ranges of expected rates (at a set confidence level) and a score of how much each observed rate differed from the expected rate. This score, called the exceedance score, reached 1 when the observed rate was equal to the high limit of the expected rate and -1 when the observed rate was equal to the low limit of the expected rate. Exceedance

scores of less then -1 or greater than 1 where therefore flagged as "unusual" observations.

$$\text{Exceedance score} = \frac{\text{(observed rate - expected rate)}}{\text{(high limit of expected rate - expected rate)}}.$$

The model was run twice each month - once at the 95% confidence level and once at the 80% confidence level.

Analysis of centre distribution of infected donors

The aim of this analysis was to identify centre specific proportions of all infections, during the current year, that were outside the 95% probable range of expected values based on the previous 3 years' data (i.e. to alert to a relative change in infection rates at any one centre, possibly indicating a localised increase (or decrease) in infections in the donor population). The smaller testing centres were excluded: data from 14 centres in British Isles entered this analysis each month.

Chi-squared analyses were performed by EXCEL to compare the distribution of infections between centres during the most recent six months with the distribution of infections between centres during the previous twelve months. Each month the "data" spreadsheet was refreshed with an update from the donation testing database and the outputs on the "results" spreadsheet were automatically re-calculated.

Chi-squared values indicating an observed rate for any centre outside the 95% confidence interval on the rate observed during the previous 3 years were flagged as "unusual" observations. Unusual observations were summarised each month in a table showing the number of consecutive months for which this result had been flagged as unusual.

v) Infected donor surveillance

The infected donor surveillance form pack (Appendix 4) consisted of two forms.

The first form (IDS Section 1) recorded demographic (sex, date of birth, post-code) and previous donation details (when, where and test results for the most recent previous donation) about the donor of each donation with a

confirmed marker of infection (HBsAg, anti-HCV, anti-HIV or *Treponemal* antibodies) and the details of all confirmatory tests performed on the donation. This form was designed for completion from blood centre records when the confirmatory laboratory conclusion was received.

In order to match the infected donor surveillance reports to donation testing surveillance reports of donations with confirmed markers of infection, the donation number was required on both the DTS and the IDS surveillance forms. In order to identify each infected donor, and to match infected donor surveillance reports to surveillance reports from other sources to the PHLS-CDSC, the soundex code of each donor's surname, and their first initial and date of birth were also required on the IDS forms. (Soundex codes are not unique for a single surname. Mainly because soundex codes ignore vowels, all soundex codes can relate to several names, for example, H300 is the code for Hutt, Heite, Hyde and Hoade, among many possibilities. However, if the soundex code is used in combination with the first initial, date of birth and sex, matching reports, and duplicate reports, can be identified and reports for an individual can be updated if additional information becomes available.) The extent of erroneous matching due to identical soundex and date of birth for different individuals has not been estimated. The probability of an infected donor record with identical soundex and date of birth and within the same region and the same period of diagnosis as another infection record is expected to be very small and erroneous matching is unlikely to cause error in the information collected. Instructions for the manual coding of surnames into soundex codes and a programme for the computer generation of soundex codes were sent to blood centres when the revised surveillance system was introduced.

The second form (IDS Section 2) recorded the donor details that only became available when a blood centre clinician, or other carer, subsequently communicated with the donor about the infection that had been detected. These details were: the donor's history of exposure to blood borne infections, the ethnic group of the donor (ethnic group is sometimes available from blood centre records, and reported on IDS Section 1), the donor's country of birth and whether the donor had any clinical signs of the infection. Ethnic group

information was requested to be based on donor self-report i.e. asked as "To which ethnic group does the donor consider himself/herself to belong?" The first version of this form also recorded how this information was obtained: from personal interview, from blood centre records, or from some other source e.g. GP or clinician to whom donor referred for further care.

If a IDS Section 1 was not received at the surveillance centre for a donation reported as positive by the DTS Section 3, a reminder was sent to the blood centre, initially during the quarter following the donation date and again each quarter as necessary (changing to by six-month periods from Jan 1997). Besides increasing reporting, this also functioned as a check that all positive donations reported to the donation testing surveillance were unique positive blood donors (i.e. resulted in detection of duplicate test reports for the same individual, or reports of samples other than blood donations). If an IDS Section 2 was not received, a periodic reminder was also sent, until the surveillance centre was informed that follow up of this donor had been closed without IDS Section 2 information being made available.

Follow-up of selected Infected Donor reports was conducted during the study period for various purposes e.g. to identify seroconverters, to investigate sources of infection that were unusual or possibly of public health interest e.g. infections reported to have been acquired in hospitals or in schools.

vi) Post-transfusion infection surveillance

The post transfusion infection surveillance pack (Appendix 5) initially consisted of three forms.

These forms were for reporting to the surveillance centre all infections (including HAV, HBV, HCV, HIV, bacterial and parasitic infections) in transfusion recipients about which blood centres were informed, and to subsequently report a summary of any investigations of the implicated components.

Information about the recipient, the recipient's infection and the transfusion(s) implicated as the possible source of infection formed the basis of the initial report. Subsequently, after appropriate investigations had been

completed, details about the findings of the investigation were reported on the other two forms.

The first form (PTIS Section 1) recorded each post-transfusion infection which blood centres were informed about. A post-transfusion infection (PTI) was defined by the following criteria:

- The receipt of transfusion had been confirmed.

and

- Infection in the recipient had been confirmed (by detection of antibody, antigen, RNA/DNA, or culture of an organism).

and

- There was no evidence that the recipient was infected prior to the transfusion.

or,

- The receipt of transfusion had been confirmed.

and

- The recipient had had a diagnosis of acute clinical hepatitis of no known cause (i.e. including no evidence of acute HAV, HBV, HCV, EBV, or CMV infection in post-transfusion samples to date).

This second definition was necessary to include cases of post-transfusion hepatitis of unknown type, and cases of post-transfusion HCV where serological markers of infection were not yet detectable.

One category of post-transfusion infections was exempt from reporting. The exception was for HCV or HIV infected recipients whose implicated transfusion(s) were not tested for anti-HCV or anti-HIV (i.e. transfusion under investigation occurred prior to the introduction of testing). These cases were exempt from reporting as they were frequent, often inconclusively investigated, and not informative about current blood safety.

If other possible sources of infection were known for a post-transfusion infection, an initial report was still requested.

This form recorded details about the recipient (soundex code, first initial, sex, date of birth, significant test results on pre- and post-transfusion samples, infection, date of onset of symptoms, date of diagnosis and history of other risk factors for infection) and about the transfusion (reason for transfusion, place of transfusion, date, type and number of components transfused). PTIS Section 1 also recorded whether, based on available information about the recipient and the implicated donations, an investigation of the implicated donations had been initiated.

The second (PTIS Section 2), and third (PTIS Section 3), forms recorded the outcome of any investigation of implicated components. PTIS Section 2 recorded the testing performed on samples from the implicated donations and donors. PTSI Section 3 recorded the conclusions of the PTI-case investigation. If one or more component(s) implicated in the PTI case had been produced by blood centre(s) other than the one which was informed of the PTI, copies of PTIS Sections 2 and 3 could be sent to the relevant blood centre(s) for completion and return to the case-initiating blood centre.

A probably transfusion-transmitted infection (TTI) was defined by the following general criteria: -

For viral infections: -

- Re-testing of the archived sample of an implicated donation found the donation to have markers of infectivity.

or

- Testing of subsequent samples obtained from the donor of an implicated donation found the donor to have markers of infection consistent with the donor having been infectious at the time of the implicated donation.

For bacteraemias: -

- Testing of the implicated donation found evidence of an organism also found in the recipient, or, in the absence of an organism identified in the recipient, of an organism expected to cause the symptoms observed in the recipient.

and

- No evidence that contamination of the implicated donation occurred after the transfusion was stopped.

Specific criteria applicable to the majority of cases are shown in table 3.2.

Table 3.2 Specific criteria for classification of post-transfusion infections as transfusion- transmitted infections.

Infection	*Donation archive*		*Donor*		*Recipient*[1]
HBV	HBsAg positive *or* HBV PCR positive	&	No tests performed after implicated donation, *or* Evidence of HBV infection at some time after implicated donation	&	Evidence of HBV infection (of same sub-type if known)
or,	No testing *or* Negative for all serology tests for HBV (with or without DNA)	&	Markers of acute HBV infection found <6 months after implicated donation, *or* Symptoms of acute hepatitis during 6 months after implicated donation and markers of HBV infection found subsequently, *or* Markers of resolved infection or HBV carriage found >6 months after implicated donation (without known date of infection after the implicated donation).	&	Evidence of HBV infection (of same sub-type if known)
or,	HBsAg negative, anti-HBc positive, anti-HBs negative/wk	&	No tests performed after implicated donation, *or* Same as archive, with or without a history of hepatitis.	&	Evidence of HBV infection (of same sub-type if known)
Infection	***Donation archive***		***Donor***		***Recipient***
HCV	Anti-HCV positive *or* HCV antigen positive *or* HCV PCR positive	&	No tests performed after implicated donation, *or* Evidence of HCV infection at some time after implicated donation.	&	Evidence of HCV infection (of same sub-type if known)
or,	No testing *or* Negative for all tests for HCV	&	Markers of HCV infection found after implicated donation (without known date of infection after the implicated donation) *or* Symptoms of acute hepatitis during 3 months after implicated donation and markers of HCV infection found subsequently.	&	Evidence of HCV infection (of same sub-type if known)
Infection	***Donation archive***		***Donor***		***Recipient***
HIV	Anti-HIV positive *or* HIV p24 Ag positive *or* HIV PCR positive	&	No tests performed after implicated donation, *or* Evidence of HIV infection at some time after implicated donation.	&	Evidence of HIV infection (of same sub-type if known)
or,	No testing *or* Negative for all tests for HIV	&	Markers of HIV infection found after implicated donation (without known date of infection after the implicated donation), *or* Symptoms of seroconversion illness during 3 months after implicated donation and markers of HIV infection found subsequently.	&	Evidence of HIV infection (of same sub-type if known)
Infection	***Donation archive /component***[2]		***Donor***		***Recipient***
Bacteria	Markers of specific bacterial infection *or* Cultures specific	&	No tests performed after implicated donation, *or* Evidence of specific blood borne bacteria, or of specific bacteria colonising venepuncture site, at some time after implicated donation.	&	Evidence of specific bacterial infection of same species and type as far as known, *or* Symptoms typical of specific bacterial

	bacteria				infection.
or,	No testing *or* Negative for all tests for bacteria	&	Evidence of specific blood borne bacteria, or of specific bacteria colonising venepuncture site, at or after time of implicated donation. or Symptoms of specific bacterial illness during month before or after implicated donation and any permanent markers of specific bacterial infection found subsequently.	&	Evidence of specific bacterial infection of same species and type as far as known, *and* no other identified source of infection.
Infection	***Donation archive/ component***		***Donor***		***Recipient***
HAV	No testing *or* anti-HAV positive	&	Acute HAV infection diagnosed during post-transfusion period	&	anti-HAV positive
or,	as above	&	anti-HAV positive	&	Acute HAV infection post-transfusion
Malaria	No testing *or* positive for plasmodium or malarial antibodies	&	Positive for malarial antibodies	&	Malaria diagnosed within x weeks of transfusion.

1. All without other proven source of infection, and without evidence of infection prior to transfusion, and with disease (or markers of infection) within limits of possible incubation periods.

2. If index component used then absence of evidence of contamination having occurred after the transfusion is also required.

All cases meeting these criteria, and any cases that were undetermined by these criteria, were reviewed by the consultant in microbiology for the National Blood Authority (Dr John Barbara) who used his own expertise, and consulted with other specialists, to confirm the classification or to determine whether "infectivity", "evidence of an organism" and "no evidence of contamination" were observed in undetermined cases.

Lists of post-transfusion infection reports received were sent six monthly to the reporters. These individuals were asked to check that all infections about which their blood centre had been informed were included on the list, and if not, to report them without further delay.

Additional information about certain cases that were of interest for a specific purpose, or specific period of time e.g. quality assurance data relating

to leucodepletion of components shown to have transmitted bacterial or cell associated infections, was collected from reporters as required

vii) Piloting, and revisions, of the surveillance systems

Pilot

Donation testing surveillance

The provisional surveillance forms were reviewed by the Steering group, the NBS Batch pre-acceptance group (BPAT) and by the microbiology departments at all blood centres, and the forms were revised in the light of the comments received.

The donation testing surveillance system was piloted in five blood centres for the month of August 1995. The five blood centres chosen for the pilot (Brentwood, North London, Leeds, Southampton and Bristol) represented the three geographical and organisational zones of the NBS and also represented the major computer systems in use in blood centres. Minor revisions to the formatting of the forms were made following this pilot month in order to aid completion of the information requested.

Infected donor surveillance and post transfusion infection surveillance

The provisional surveillance forms were reviewed by the Steering group, and by the medical consultants at all blood centres. Completion of the donor surveillance forms from information stored in HCV infected donor files at North London blood centre, and of the post-transfusion infection surveillance forms from information stored in PTI case files at South Thames blood centre was trialed. The forms were revised in the light of the comments received and the experience of their trial use. The forms were introduced for use at blood centres from 1st October for an initial pilot period of six months. Use of the forms continued after the pilot six months without revision.

Revisions

Revisions to Donation testing surveillance during the study period

Electronic reporting

During 1999 and early 2000, reporting on paper forms posted to the surveillance centre was replaced at all English and Welsh centres with

electronic reporting using Microsoft ACCESS and electronic mail. A standard database was designed to receive and manage data at centres and to export data each month to the surveillance centre. Data-entry screens mimicked the paper forms, and reports printed paper copies of the data (again formatted like the paper forms) to be in paper files if necessary. This standard database was customised for each reporting centre to fit their style of data collection (e.g. for daily data-entry or batch data-entry once or twice a month) and to perform local functions (e.g. lists of positive donations for medical follow-up, repeat reactivity rates by week for local test monitoring) in addition to the reporting function. Each centre's database contained all the data reported to date by that centre only. A second much smaller, "transfer" database was also installed at each centre. The data in this database was overwritten by an automatic data export process each month, and this transfer database was copied each month by electronic mail (email) to the NBA. Staff were trained to use the database, run the export and email the transfer database. Any problems or queries after instillation and training were dealt with by telephone by the surveillance co-ordinator who also held a copy of the design of each customised database.

Electronic reporting greatly reduced manual transcription of numbers and test results and reduced data-entry workload - both at the centres where data-entry shortcuts and bar-code readers speeded data-entry, and at the NBA where the bulk of the data was imported directly. The advantages of electronic reporting were greatest for the centres testing largest numbers of donations. The smaller participating centres of the Eire, Northern Ireland, the Channel Isles, and the Isle of Man continued using the paper reporting system.

One revision to the donation testing dataset was introduced into the electronic reporting system. During 1998, nucleic acid testing (NAT) for HCV RNA by PCR was introduced into the testing performed by the blood service. From 1st September 1999, frozen components were released as confirmed HCV RNA negative by pooled PCR testing. At the end of 1999, it was agreed that the donation testing surveillance system should monitor the NAT result for all anti-HCV positive donations.

NAT results

Nucleic acid testing (NAT) results for anti-HCV positive donations were added to the data reported each month at the beginning of 2000. These test results were initially collected retrospectively back to 1st September 1999, to cover the period for which all FFP had been issued as NAT negative. Subsequently data were collected back to 1st April 1999, when NAT testing moved from anonymous pilot testing to testing that resolved results to identified donations. The donation testing databases were modified so that the entry of the result of HCV PCR testing was requested on entry of an anti-HCV positive donation.

Revisions to Infected donor and post-transfusion infection surveillance during the study period

During 1999, following a meeting of all reporters to discuss the surveillance and the use of the data generated by the surveillance systems, the infected donor surveillance forms and the post-transfusion infection surveillance forms were revised (Appendices 6 & 7).

The revisions to the infected donor surveillance forms were: i) prompting for reporting the results of pooled and singleton PCR testing for HCV, ii) a question asking for information about exposures to be summarised as either a.) Donor has no identified risk despite satisfactory follow-up information available, b.) Risk for the donor not identified, possibly because of incomplete follow-up information, or c.) One or more probable risk factor identified, with the details of each risk factor only completed for those in group c), iii) revision of the risk factor grid to separate donors exposures from donor's heterosexual partner's exposures, and iv) a question asking (of group c.) donors) why the donor did not disclose the existing risk factor at the time of donating blood, instead of the question asking for the method by which the information on the report had been obtained.

The revisions to the post-transfusion infection surveillance forms were i) provision to specify that the report referred to a post-transfusion reaction suspected to be due to bacteria (rather than a confirmed bacteraemia), ii) alternative versions of the section 2 and 3 forms specific for post-transfusion bacteraemias and post-transfusion reactions suspected to be due to bacteria. These alternative forms (PTI(bac)) included questions on the age of the

component, the method of platelet collection, the method of any leucodepletion performed on the component and allowed more space for free text to describe the source of the samples available for culture and the investigations conducted on these samples.

viii) Co-ordination with laboratory reports to PHLS-CDSC

Co-ordination of reports to other specific infection surveillance systems

Blood centres were advised that with the introduction of the NBA/PHLS-CDSC surveillance system they were no longer requested to complete separate HIV antibody positive report forms, or HBsAg positive report forms, for the PHLS-CDSC. From the 1st October 1995 these reports for the PHLS-CDSC infection specific surveillance systems were generated from the NBS/PHLS-CDSC system using the information reported on the IDS and the PTIS forms.

The PHLS-CDSC HIV/AIDS surveillance centre sometimes receives further information about an HIV infected blood donor when the individual attends for care at another centre (usually a genitourinary medicine clinic), or when the individual is diagnosed with AIDS, or dies. This information is provided in confidence by voluntary reporters. The PHLS-CDSC HIV/AIDS centre also conducts follow up of individuals, including blood donors, who have no identified risk for HIV infection, or report only heterosexual contact in the UK with partners who have no known high-risk exposure. The PHLS-CDSC HIV/AIDS centre therefore may hold information about blood donors that is not known to the blood centres were the donors were tested. Periodically (quarterly from October 1995-December 1996 and six-monthly from January 1997), the NBA/PHLS-CDSC surveillance system cross checked reported information for HIV positive donors with the PHLS-CDSC HIV/AIDS centre, and the most up to date information was obtained. Information obtained from PHLS-CDSC HIV/AIDS centre was held separately to information reported by blood centres and was not communicated to blood centres except without any means of donor identification in summary tables.

The PHLS-CDSC HIV/AIDS centre informed the NBA/PHLS-CDSC surveillance system of any newly reported HIV positive individuals with transfusion in the UK reported as the suspected route of infection.

The PHLS-CDSC Hepatitis section informed the NBA/PHLS-CDSC surveillance system of any individuals reported with acute HBV infection with transfusion in the UK as a suspected route of infection, and of any anti-HCV positive report with transfusion in the UK since September 1991 (i.e. the start of anti-HCV testing of all blood donations) as the most probable route of infection.

In 1995, when many individuals who received transfusions prior to the introduction of anti-HCV testing of blood donations were requesting anti-HCV testing to investigate their infection status, the PHLS-CDSC Hepatitis section conducted a survey of the numbers of anti-HCV tests performed at PHLs and the reasons for testing and test results. Reports of infected recipients with a history of transfusion in England prior to testing were passed to the National Blood Service. These infections, probably acquired from untested anti-HCV positive transfusions, were excluded from the surveillance of post-transfusion infections and have been collated elsewhere (National Lookback Collaborators, 2001).

PHLS colleagues working on surveillance of specific organisms that may be transfusion transmissible were made aware of the NBA/PHLS-CDSC transfusion transmissible infection surveillance project and asked to pass on any relevant infection reports.

Interrogation of LABBASE

Public Health Service laboratories (PHLs), National Health Service laboratories and some private laboratories routinely report all detected infections to PHLS-CDSC Lab-Base.

Transfusion was not, during this time, included as a coded feature for any infections reported by laboratories to PHLS-CDSC Lab-Base. Infections that were, or might have been, associated with transfusion could therefore be identified only by searching a free-text field ("comments") for any mention of transfusion. Due to variation in both the completeness of infection reporting and the amount of information included on reports from different laboratories, analysis of clinical or epidemiological data provided with routine reports to CDSC Lab-base must be considered with caution.

Two investigations of reports to Lab-Base were conducted. Firstly, in July 1995, two selections were made from reports received by CDSC between the beginning of 1994 and week 27 of 1995. The first selection was of reports of bacteraemias with comments mentioning transfusion. Examination of the comments showed that for 40% (19) of these selected reports, there was no indication of infection associated with blood transfusion. For 3 isolates from 2 patients, comments indicated that the bacteraemia was definitely associated with transfusion. Both these cases had been investigated by the NBS. The remaining 29 isolates were concluded to represent possible cases of transfusion associated bacteraemia. The second selection was of a subset of organisms reported to Lab-Base. Organisms that were likely to be isolated from blood cultures relatively infrequently (<500 reports per year) and which might be transfusion transmissible were selected. 83 selected organisms (including *Yersinia enterocolitica* (23), *Pseudomonas fluorescens* (53), *Pseudomonas putida* (18), *Pseudomonas cepacia* (43), *Serratia marcescens* (269) and *Serratia liquifaciens* (96)) yielded 2,966 reports. Review of the contents of the free text fields suggested that, when the underlying clinical condition reported was one for which transfusion would almost certainly have been required, a history of transfusion had rarely been reported.

This pilot examination of Lab-Base led to a request for history of transfusion (yes/no) to be included as a standard prompted feature for selected organisms in future developments of the Lab-Base system so that selection of infections which may be associated with transfusion may be performed more accurately. Subsequent changes to the Lab Base system and methods of reporting have decreased the free text information reported and further use of this system has not been developed.

A second attempt to interrogate Lab-Base for information about transfusion-transmitted infections was made in 2000 when information was needed about CMV transmission by transfusion - particularly to neonates. All laboratory reports of CMV infection to CDSC (LABBASE) were queried for relevant information. As for bacterial infections, information about recent transfusion is not routinely requested for CMV infection reports: a free text field is available for reporters to note comments of possible relevance.

Of 2,925 CMV infections reported to LABBASE from 1/1/97 to date, 101 (3.5%) were in patients known to be less than 3 weeks of age. Fifty of these babies had comments associated with their CMV report - no comments mentioned transfusion. Of all 2,925 reports, 1,269 had comments and 5 of these mentioned transfusion:-

1. (Wk: 9717) 3-5 month old male baby, comment: preterm/jaundice/blood transfusion (N.B. Not the same case as the one reported to a blood centre during 1997.).

2. (Wk: 9836) 29 yr old female transplant recipient, comment: blood transfusion

3. (Wk: 9832) 54 yr old male, comment: H/O transfusion

4. (Wk: 9701) 57 yr old female, comment: thought to be from blood transfusion in Egypt

5. (Wk: 9813) 73 yr old male, comment: post transfusion

The three LABBASE reports during 1998 (9836, 9832, 9813) that mention transfusion were, according to information from blood centres, not reported to the blood services for investigation. This may be due to identification of another source of infection or under-reporting to the blood service.

Lab reports of infections in babies had comments more frequently than reports of infections in older aged patients.

No evidence was found of transfusion associated CMV cases during 1998/99. Four of 2,925 (0.14%) laboratory reports of CMV infection (1997 to date) mentioned a history of transfusion not known to have been abroad, but these do not seem to have been investigated by blood services.

As blood centres may not be informed of suspected post-transfusion CMV infections, and laboratory reports to CDSC do not routinely contain information about whether or not the patient has had a recent transfusion, the available data could not demonstrate there had been no such cases. Further follow up of selected LABBASE reports may be worthwhile if further work on this issue is required. As transfusion associated CMV cases in babies are of most importance, and reports for this group were also more detailed, a routine search of LABBASE for CMV cases in babies that mention transfusion in the comments, with follow up of any cases via the reporter, was considered, but has not been carried out.

ix) Routine reports of collated data from the surveillance centre

Donation testing surveillance data were collated monthly and a tabular report of the reactivity rates for the past month, and the confirmed infection rates for the last-but-one month, was sent to all blood centres and other interested centres by the 25th of the next month. The output from the monthly analysis of donation testing data where circulated to key staff overseeing donation testing and quality assurance. (Appendix 6 contains the report for September 1999 with centre and manufacturer names removed.)

Up until December 1996, data from the infected donor surveillance and post-transfusion infection surveillance systems were collated by calendar quarter and a tabular and graphical report (NBA/PHLS CDSC Infection Surveillance report) was sent to all blood centres and other interested centres at the end of the following calendar quarter. From January 1997, the frequency of infection surveillance reports was changed to be six monthly (Appendix 7 contains Report 10, with data to end June 1999).

The content and analyses included in these routine reports is described below.

3.2 Results

Donation testing

Between 1/10/95 and 30/09/99, 11,442,706 blood donations were tested by the blood services of England, Wales, Northern Ireland, the Channel Isles and Isle of Man and the Republic of Ireland and the results of testing these donations for HBsAg, anti-HCV, anti-HIV and Treponemal antibodies were reported to the surveillance system.

Appendix 6 shows the monthly report for September 1999. This report presents data on donations tested during September 1999, and cumulatively since October 1995. Tables 2a, 2b and 1c from the October 1999 report are also included in appendix 6: these tables show the confirmed positives during September 1999 and cumulatively from October 1995 to September 1999.

(Note: Manufacturers' and products' names and centre names have been blanked-out of the tables included in this thesis, as some of these data are confidential.)

Table 3.3 and Figure 3.3 summaries the specificity of the assays used over this period - according to the data reported.

Table 3.3 Summary reactivity to screening tests for HBsAg, anti-HCV, anti-HIV and T.pallidum antibodies: batches in use September 1999
All donations reported to NBA/PHLS CDSC Donation testing surveillance, 01/10/95 to 30/09/99 (4 years)

Test Kit (3 with highest usage, and others)	***Number tested***	***Number repeatedly reactive***	%	***Number confirmed positive***	***Falsely repeatedly reactive***
HBsAg					
Test 1 (i.e. most used)	518,381	439	0.085%	11	0.083%
Test 2	262,443	30	0.011%	10	0.008%
Test 3	130,996	205	0.156%	4	0.153%
Others	29,218	19	0.065%	0	0.065%
All test kits	941,038	693	0.074%	25	0.071%
Anti-HCV					
Test 1	259,004	235	0.091%	15	0.085%
Test 2	151,846	55	0.036%	4	0.034%
Test 3	66,602	39	0.059%	10	0.044%
Others	22,629	18	0.080%	0	0.080%
All test kits	500,081	347	0.069%	29	0.064%
Anti-HIV					
Test 1	344,895	168	0.049%	2	0.048%
Test 2	251,820	203	0.081%	4	0.079%
Test 3	144,762	68	0.047%	1	0.046%
Others	8,564	5	0.058%	0	0.058%
All test kits	750,041	444	0.059%	7	0.058%
T.pallidum					
Test 1	547,887	154	0.028%	12	0.026%
Test 2	68,502	33	0.048%	1	0.047%
Test 3	52,521	15	0.029%	1	0.027%
Others	43,706	53	0.121%	0	0.121%
All test kits	712,616	255	0.036%	14	0.034%
All test kits, all markers					0.227%
Test 1, all markers	58%				0.242%

Figure 3.3 False reactivity: most commonly used kits, others, and all tests

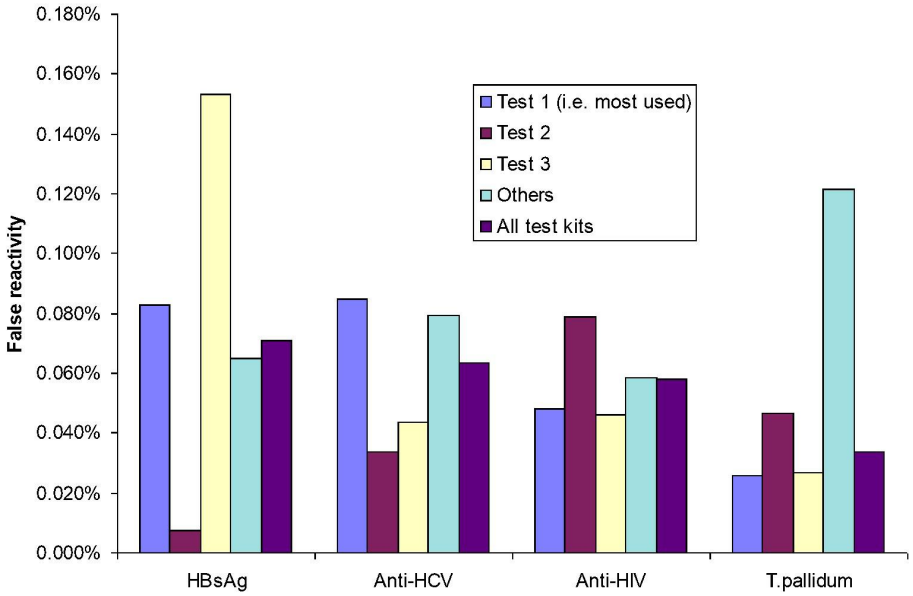


Figure 3.4 show the rates of repeat-reactivity and of confirmed markers of infection over the four-year period 01/01/96 to 30/09/99, for donations from new donors, donations from repeat donors and for all donations.

Figure 3.4 Frequency per 10,000 donations of reactivity and confirmed positivity for HBsAg, anti-HCV, anti-HIV and Treponemal antibodies for donations from new donors, donations from repeat donors and all donations, 1996-1999.

(See graphs on next twelve pages.)

Since September 1999 a statistical analysis has been run each month, using the reported data, to identify any unusual data that may indicate an important change in test performance, or in donor infection rates.

Analysis of Monthly donation testing data

During the first 12 months (September 1999 to August 2000), out of 288 observed repeatedly reactive rates and infected donor monthly rates this analysis identified (at the 5% significance level) 22 that were outside the 95% prediction intervals based on the previous 36 months observed data i.e. with an exceedance score greater or less than 1. These unexpected observed rates are shown in Table 3.4, with the exceedance score for the observed rate and the number of donations repeatedly reactive, or positive, that generated the observed rate.

Table 3.4 Unexpected repeatedly reactive (RR) rates and confirmed infection rates (at 5% significance level) observed in donation testing data for July 1999 - June 2000.

Month	Unexpected RR rate	Donor type	Exceedance score	Number RR
0100	HBsAg	New	1.40	55
0100	T.pall.	New	1.62	30
0200	anti-HCV	New	1.26	84
0200	anti-HIV	Repeat	-1.51	180
0200	anti-HIV	ALL	-1.26	230
0200	T.pall.	New	2.12	33
0200	T.pall.	ALL	1.08	190
0300	T.pall.	New	3.68	61
0500	T.pall.	New	1.83	42
0500	T.pall.	Repeat	1.43	246
0500	T.pall.	ALL	1.44	288
0899	T.pall.	ALL	-1.01	107
0999	T.pall.	Repeat	-1.08	80
0999	T.pall.	ALL	-1.02	98
1199	HBsAg	New	1.36	50
1299	HBsAg	New	-1.21	22
1299	anti-HCV	New	-1.19	61
1299	T.pall.	New	-1.21	13
	18			

Unexpected infection rate	Donor type	Exceedance score	Number infected
HBsAg	Repeat	1.40	3
anti-HCV	Repeat	-1.24	1
anti-HIV	New	1.02	2
anti-HCV	ALL	1.12	24
4			

The majority (82%) of unexpected observations were repeatedly reactive rates: 61% of these (11) concerned repeat reactivity to test for Treponemal

antibodies. The repeatedly reactive rate for Treponemal antibodies in new donors was high for 4 months, and low for 1 month during this year. 44% of unexpected repeatedly reactive rates were unexpectedly low. Only 4 unexpected infection rates were observed at the 5% significance level, one was an unexpectedly low rate. Only one of the unexpectedly high infection rates was based on more than 5 infections. None of the unexpectedly high infection rates persisted for more than one month.

Analysis of monthly centre distribution of infected donors

One hundred and forty-one of 1,344 (10%) observed centre and donor type specific infection rates (i.e. proportion of donations tested found to be positive) during the first year (July 1999 to June 2000) were flagged as falling outside the probable range at the 5% significance level based on the previous 3 years' data. There was an average of twelve flagged centre and donor type specific infection rates per month (range 7 to 17 flagged values). An average of 6.8 flags each month (range 1 to 13) referred to rates based on more than two infections.

The average number of flags per month (and range) with various restrictions in place are shown in Table 3.5.

Table 3.5 Number (range) of flagged results per month meeting criteria, N = number of positive donations generating the rate, X^2 = value of chi-squared for the observed rate.

Possible criteria for further attention	***HBsAg***	***Anti-HCV***	***Anti-HIV***	***T.pall.***
All flagged rates	2.3 (0-3)	2.3 (1-4)	1.5 (0-3)	5.7 (0-11)
Flagged: N > 1	2.0 (1-3)	2.0 (1-3)	0.8 (0-2)	5.4 (0-10)
Flagged: N > 2	0.9 (0-1)	1.8 (0-3)	0	4.1 (0-9)
Flagged: N > 5	0.3 (0-1)	1.3 (0-3)	0	0.8 (0-4)
Flagged: $X^2 > 5$	2.3 (1-3)	2.3 (1-4)	1.5 (0-3)	5.7 (0-11)
Flagged: $X^2 > 10$	0.9 (0-2)	1.2 (0-2)	0	4.4 (0-8)
Flagged: N > 1 and $X^2 > 5$	2.0 (1-3)	2 (1-3)	0.8 (0-2)	5.4 (0-10)
Flagged: N > 3 and $X^2 > 10$	-	-	-	1.4 (0-5)

85 flags passed criteria of N >1 and X2 > 5 for HBsAg, anti-HCV and anti-HIV and N > 3 and X2 > 10 for T.pallidum: 9 of these flags appeared for one month only: the remainder appeared for at least 2 consecutive months. Twenty-five (29%) were on new donor infection rates and 60 (71%) were on repeat donor infection rates.

Infected donors

During the period of study, a total of 1,829 donations (16.83 per 100,000 donations) collected by the English and Welsh Blood services had markers of infectious HBV, HCV or HIV infection. Of these infected donations, 903 (49%) had anti-HCV, 463 (25%) had HBsAg, 94 (5%) had anti-HIV and 369 (20%) had Treponemal antibodies. New donors contributed 12% of all blood donations, but 70% of infected donations. Table 3.6 summarises the rate of infectious marker detection in donations from new donors, donations from repeat donors and in all donations, collected by the English and Welsh Blood Service during the period 01/10/95 to 30/09/99. The completeness of reporting to the infected donors surveillance was monitored by matching of reports for infected donors to confirmed positive donations reported to the donation testing surveillance. The completeness of reporting patient details, and of reporting follow-up clinical and risk factor details, is shown in Table 3.6 and Figure 3.5.

The distribution of infections by age group and by sex of donors is shown in Tables 3.7 and 3.8 and Figures 3.6 and 3.7 for newly tested donors and previously tested donors respectively.

Table 3.6 Infections detected in blood donors and the completeness of reporting: Donations collected in England and Wales from 01/10/1995 to 30/09/1999

Surveillance reports[1]	Infections in blood donors *Total*[4] 01/10/1995-30/09/1999 HBV (HBsAg)	HCV (anti-HCV)	HIV (anti-HIV)	*T.pallidum* (*Treponemal* antibodies)
a. Donations with confirmed marker of infection	463	903	94	369
- per 100,000 donations tested	4.26	8.31	0.86	3.39
- 1 in x donations	23,477	12,037	115,635	29,457
donations from new donors (1,207,079)	391	656	56	177
- per 100,000 donations tested	32.39	54.35	4.64	14.66
- 1 in x donations	3,087	1,840	21,555	6,820
donations from repeat donors[2] (9,662,571)	72	247	38	191
- per 100,000 donations tested	0.75	2.56	0.39	1.98
- 1 in x donations	134,202	39,120	254,278	50,589
b. Infected donors reported	463	873	94	358
- % of infections reported[3]	100%	97%	100%	97%
c. Exposure histories reported	358	702	78	252
- % of infections with exposure history reported[3]	77%	78%	83%	68%

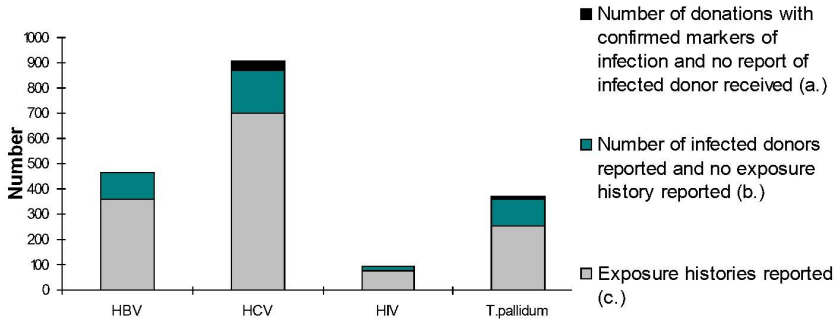
Source: a. Donation Testing Surveillance monthly reports, b. Infected Donor Surveillance Section 1 reports, c. Infected Donor Surveillance Section 2 reports.

[2] May include repeat donors newly tested for markers of infection.

[3] i.e. percentage of a.

[4] 9 donors had markers of more than 1 infection: 5 donors had HBsAg(carriage) and HCV, 1 donor had HBsAg(carriage) and HIV and 3 donors had HCV and Treponemal antibodies.

Figure 3.5. Infections detected in blood donors and completeness of reporting: Donations collected from 01/10/1995 to 30/09/1999



Descriptive epidemiology of infected donors

Table 3.7 Age and sex of infected blood donors: newly tested donors. Donations collected from 01/10/1995 to 30/09/1999

Reported infections	<25 years			25-29 years			30-34 years			35-39 years			40-44 years			45 years and over			Total			
	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	NK	Total
HBV(HBsAg)	56	45	101	41	15	56	37	11	48	41	19	60	34	14	48	49	36	85	258	140	3	401
HCV	36	21	57	44	19	63	102	61	163	128	59	187	100	72	172	80	44	124	490	276	2	768
HIV	6	6	12	10	7	17	10	4	14	4	3	7	2	0	2	1	2	3	33	22	0	55
T.pallidum	3	3	6	5	7	12	15	12	27	17	11	28	14	10	24	45	35	80	99	78	1	178
Total	101	75	176	100	48	148	164	88	252	190	92	282	150	96	246	175	117	292	880	516	6	1402

Donations tested[2] (thousands)	<25 years			25-34 years			35-44 years			45 years and over			Total		
	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total
By centres with known age & sex breakdown[3]	9.7	14.3	24.0	11.6	13.2	24.8	7.6	8.7	16.3	5.7	6.3	12.0	34.6	42.5	77.1
- % by age & sex	13%	19%	31%	15%	17%	32%	10%	11%	21%	7%	8%	16%	45%	55%	100%
All centres-*estimates*[4]	*151.5*	*224.1*	*375.6*	*181.2*	*206.9*	*388.1*	*119.5*	*136.5*	*255.9*	*89.0*	*98.4*	*187.4*	*541.2*	*665.9*	1207.1

Rate per 100,000 donations[5]	<25 years			25-34 years			35-44 years			45 years and over			Total		
	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total
HBV (HBsAg)	37.0	20.1	26.9	43.0	12.6	26.8	62.8	24.2	42.2	55.0	36.6	45.4	47.7	21.0	33.2
HCV	24.6	9.7	15.7	83.3	40.0	60.2	197.4	99.3	145.1	92.9	46.3	68.4	93.7	42.9	65.8
HIV	4.0	2.7	3.2	11.0	5.3	8.0	5.0	2.2	3.5	1.1	2.0	1.6	6.1	3.3	4.6
T.pallidum	2.0	1.4	1.6	11.4	9.5	10.4	26.7	15.9	20.9	52.1	36.7	44.0	18.9	12.1	15.2

[1] Infected donors include those who have never attended a reporting blood centre previously (i.e. "new" donors) and donors who have not been tested for the marker previously.

[2] The number of donations tested is the number of donations from "new" donors.

[3] Brentwood, Bristol, Dublin, Leeds and Manchester (some months).

[4] Estimates calculated by multiplying the total donations tested by the proportion found in each age and sex group at the four blood centres where age and sex breakdown was known.

[5] Adjusted for underreporting by multiplying the denominator estimate for each age and sex group by the proportion of all detected infections reported (cf table 1).

Table 3.8 Age and sex of infected blood donors: previously tested donors. Donations collected from 01/10/1995 to 30/09/1999

Reported infections	<25 years			25-29 years			30-34 years			35-39 years			40-44 years			45 years and over			Total			
	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	NK	Total
HBV(HBsAg)	3	2	5	1	3	4	8	0	8	5	3	8	5	5	10	18	7	25	40	20	1	61
HCV	12	4	16	9	1	10	7	5	12	11	7	18	9	8	17	18	14	32	66	39	0	105
HIV	3	3	6	5	4	9	7	1	8	3	1	4	4	3	7	4	1	5	26	13	0	39
T.pallidum	2	1	3	4	3	7	7	7	14	6	6	12	18	10	28	74	39	113	111	66	3	180
Total	20	10	30	19	11	30	29	13	42	25	17	42	36	26	62	114	61	175	243	138	4	385

Donations tested[2] (thousands)	<25 years			25-34 years			35-44 years			45 years and over			Total		
	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total
By centres with known age & sex breakdown[3]	18.3	27.8	46.2	65.1	63.2	128.4	86.6	76.6	163.1	122.9	97.9	220.8	292.9	265.6	558.5
- % by age & sex	3%	5%	8%	12%	11%	23%	16%	14%	29%	22%	18%	40%	52%	48%	100%
All centres-*estimates*[4]	*317.1*	*481.4*	*798.5*	*1127.1*	*1094.2*	*2221.3*	*1497.8*	*1324.6*	*2822.4*	*2125.8*	*1694.6*	*3820.4*	*5067.8*	*4594.8*	9662.6

Rate per 100,000 donations[5]	<25 years			25-34 years			35-44 years			45 years and over			Total		
	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total
HBV (HBsAg)	0.9	0.4	0.6	0.8	0.3	0.5	0.7	0.6	0.6	0.8	0.4	0.7	0.8	0.4	0.6
HCV	3.9	0.9	2.1	1.5	0.6	1.0	1.4	1.2	1.3	0.9	0.9	0.9	1.3	0.9	1.1
HIV	0.9	0.6	0.8	1.1	0.5	0.8	0.5	0.3	0.4	0.2	0.1	0.1	0.5	0.3	0.4
T.pallidum	0.7	0.2	0.4	1.0	0.9	1.0	1.7	1.2	1.5	3.6	2.4	3.0	2.3	1.5	1.9

[1] Infected donors include only those "repeat" donors who have had a previous donation tested for the marker (but were not necessarily previously negative).

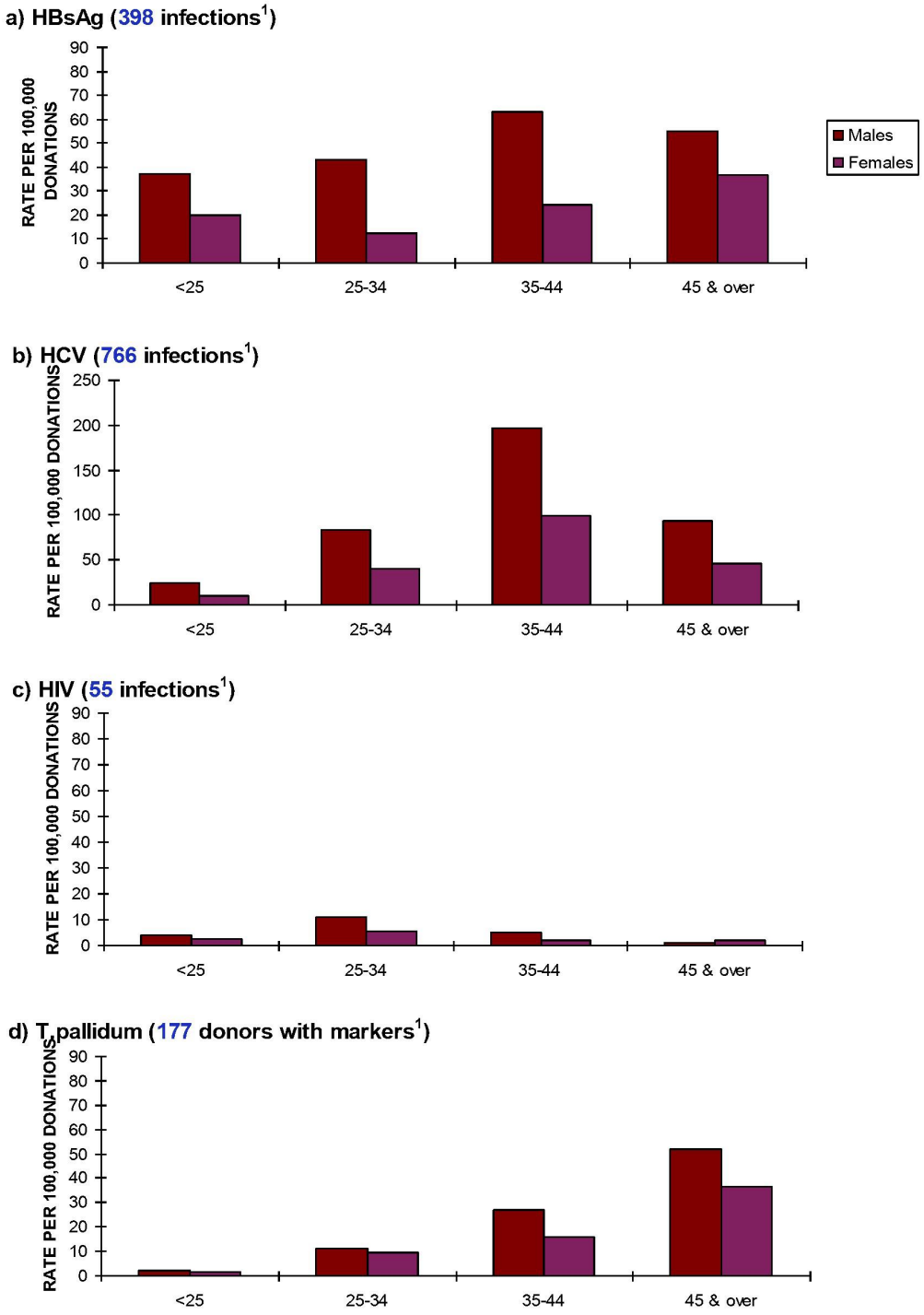
[2] The number of donations tested in the number of donations from "repeat" donors. Note - this will exceed the number of donors tested.

[3] Brentwood, Bristol, Dublin, Leeds and Manchester (some months).

[4] Estimates calculated by multiplying the total donations tested by the proportion found in each age and sex group at the four blood centres where age and sex breakdown was known.

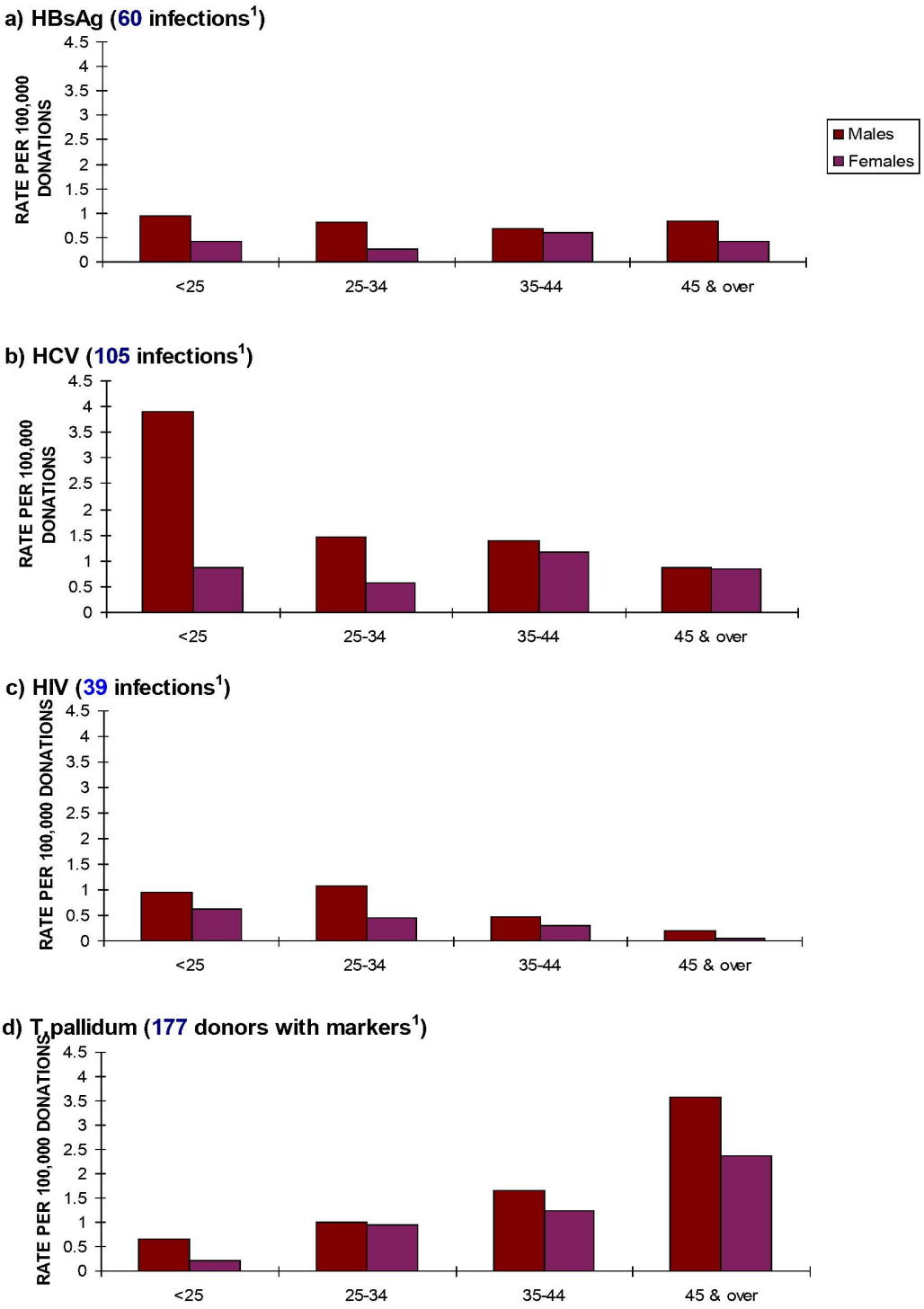
[5] Adjusted for underreporting by multiplying the denominator estimate for each age and sex group by the proportion of all detected infections reported (cf table 1).

Figure 3.6 Age and sex of infected blood donors: newly tested donors. Donations collected from 01/10/1995 to 30/09/1999.



[1] Rates adjusted for underreporting by multiplying the denominator estimate for each age and sex group by the proportion of all detected infections reported, e.g frequency of anti-HCV in males under 25 = (number anti-HCV positive males < 25 yrs /(number of donations, males < 25 yrs x 0.97[from table 3.6])).

Figure 3.7 Age and sex of infected blood donors: previously tested donors. Donations collected from 01/10/1995 to 30/09/1999.



[1] Rates adjusted for underreporting by multiplying the denominator estimate for each age and sex group by the proportion of all detected infections reported.

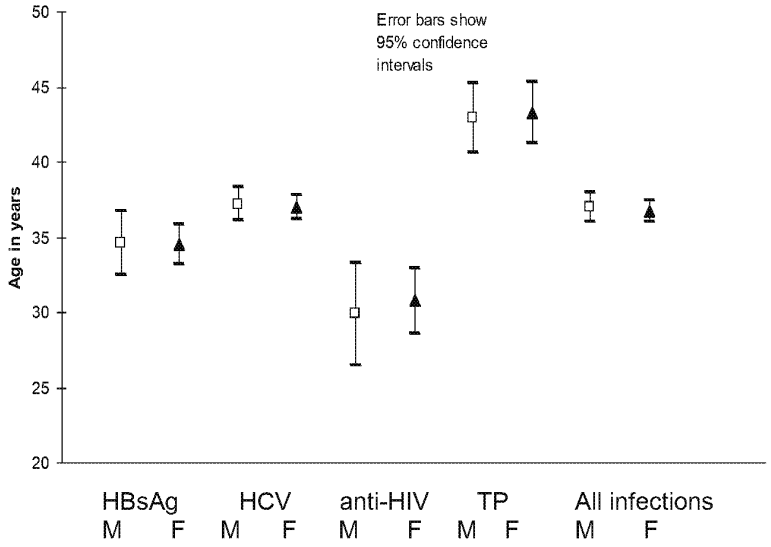
HBsAg and anti-HCV were 2.3 times and 2.2 times respectively more common in newly tested male donors than newly tested female donors. (chi-squared test $p<0.001$ for both markers). The mean age of newly tested donors who had HBsAg was 34.5 years (95% confidence interval 33.4 to 35.6), for anti-HCV it was 37.1 years (95% confidence interval 36.4-37.7), and for anti-HIV it was 30.4 years (95% confidence interval 28.6-32.3). (Table 3.9 and Figure 3.8)

The probable routes of infection for donors found to be positive for HBsAg, ant-HCV and anti-HIV are shown in Tables 3.11, 3.12 and 3.13 and Figure 3.10, 3.11 and 3.12 respectively.

Table 3.9 Mean age (and 95% confidence intervals) of newly tested infected donors by infection marker and sex: Donations collected 01/10/1995 to 30/09/1999.

	HBsAg	anti-HCV	anti-HIV	Treponemal antibodies	Any of these markers
Females	34.6 (32.5-36.7)	37.2 (36.1-38.3)	29.9 (26.5-33.3)	42.9 (40.6-45.2)	37 (36.0-38.0)
Males	34.5 (33.2-35.8)	37.0 (36.2-37.8)	30.8 (28.6-32.9)	43.3 (41.2-45.3)	36.7 (36.0-37.4)
Total	34.5 (33.4-35.6)	37.1 (36.4-37.7)	30.4 (28.6-32.3)	43.1 (41.6-44.6)	36.8 (36.2-37.3)

Figure 3.8 Mean age (and 95% confidence intervals) of newly tested infected donors by infection marker and sex: Donations collected 01/10/1995 to 30/01999.



The ethnic group of all donors was not available. The ethnic group of infected donors is shown in Table 3.10 and Figure 3.9.

Table 3.10 Ethnic group of infected blood donors. Donations collected from 01/10/1995 to 30/09/1999.

Ethnic group	HBV (HBsAg)		HCV		HIV		T. pallidum (Treponemal antibodies)	
	No.	%	No.	%	No.	%	No.	%
Infections reported	463	100%	873	100%	94	100%	358	100%
White	188	41%	671	77%	66	70%	169	47%
Black-Caribbean	12	3%	7	1%	8	9%	26	7%
Black-African	40	9%	4	0.5%	5	5%	14	4%
Black-Other	0	0%	0	0%	0	0%	3	1%
Indian/Pakistani/Bangladeshi	38	8%	15	2%	0	0%	10	3%
Chinese	34	7%	3	0.3%	0	0%	1	0.3%
Other Asian	40	9%	6	1%	0	0%	3	1%
Mixed and other	2	0.4%	2	0.2%	0	0%	0	0%
Not available	109	24%	165	19%	15	16%	132	37%

Figure 3.9 Ethnic group of infected blood donors. Donations collected from 01/10/1995 to 30/09/1999.

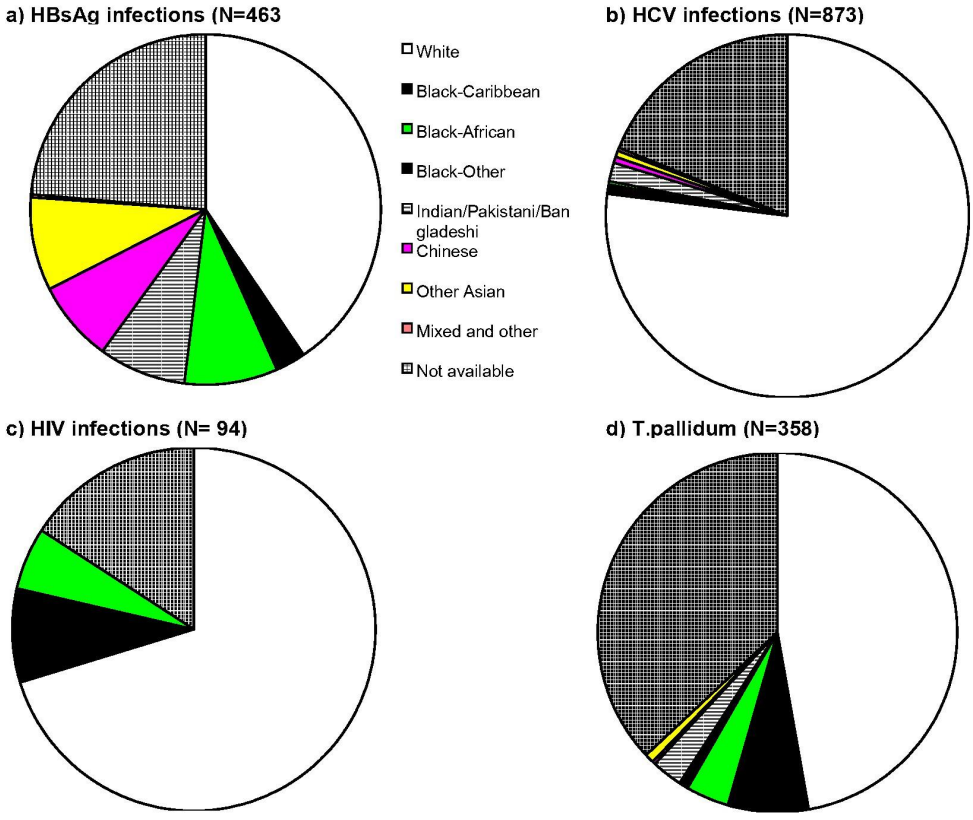


Table 3.11 Exposure categories of HBsAg positive blood donors. Donations collected from 01/10/1995 to 30/09/1999.

HBsAg positive blood donors

How infection was probably acquired	Newly tested donors[1]	Previously tested donors	All donors HBsAg positive	%
Injecting drug use	4	1	5	1%
Sexual intercourse				
between men	3	0	3	1%
between men and women				
exposure to "high risk" partner(s)[2]	*4*	*1*	*5*	*1%*
exposure abroad[3]	*12*	*5*	*17*	*5%*
exposure in the UK[4]	*8*	*1*	*9*	*3%*
incomplete information	*9*	*3*	*12*	*3%*
Blood factor treatment	0	0	0	0%
Blood/tissue transfer	11	1	12	3%
Mother to infant	54	2	56	16%
Blood contact - documented	4	3	7	2%
Blood contact - possible	39	7	46	13%
Family/household contact	10	1	11	3%
No identified exposure	153	22	175	49%
Total	311	47 [5]	358	100%

[1] Newly tested by the blood transfusion services included in this surveillance: may have had donations tested in other countries.

[2] Partner(s) exposed through sexual intercourse with men, IDU, blood factor treatment or blood/tissue transfer.

[3] Individuals from abroad, and individuals from the UK who have lived or visited abroad, for whom there is no evidence of "high risk" partner(s).

[4] No known "high risk" partner(s).

[5] Of these previously tested donors 28 report a previous negative result, 11 report an HBsAg positive previous donation (10 previously confirmed positive, 1 found to be positive on re-testing of archive) and for 8 the previous test results are not reported.

Figure 3.10 Exposure categories of HBsAg positive blood donors. Donation collected from 01/10/1995 to 30/09/1999.

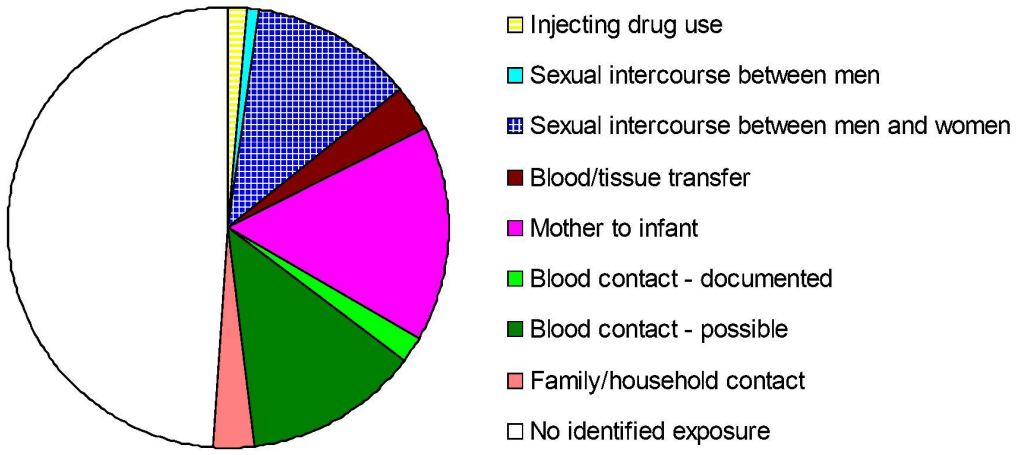


Table 3.12 Exposure categories of anti-HCV positive blood donors. Donations collected from 01/10/1995 to 30/09/1999.

How infection was probably acquired	Newly tested donors[1]	Previously tested donors	All donors HCV positive	%
Injecting drug use	209	9	218	31%
Sexual intercourse				
between men	0	1	1	0%
between men and women				
exposure to "high risk" partner(s)[2]	*49*	*3*	*52*	*7%*
exposure abroad[3]	*6*	*0*	*6*	*1%*
exposure in the UK[4]	*2*	*1*	*3*	*0%*
incomplete information	*1*	*1*	*2*	*0%*
Blood factor treatment	1	0	1	0%
Blood/tissue transfer	95	11	106	15%
Blood contact - documented	13	1	14	2%
Blood contact - possible[5]	120	17	137	20%
Family/household contact	2	1	3	0%
No identified exposure	132	27	159	23%
Total	630	72 [6]	702	100%

[1] Newly tested by the blood transfusion services included in this surveillance: may have had donations tested in other countries.

[2] Partner(s) exposed through IDU, blood factor treatment or blood/tissue transfer (pre Sept 91).

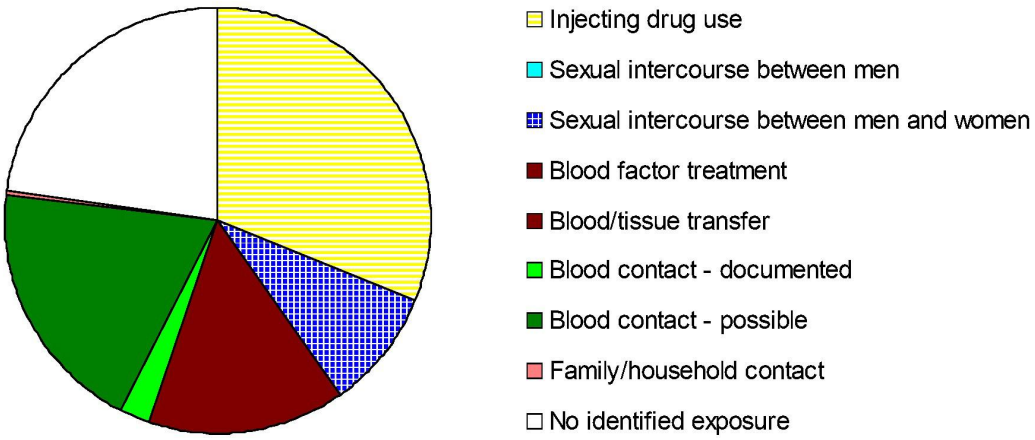
[3] Individuals from abroad, and individuals from the UK who have lived or visited abroad, for whom there is no evidence of "high risk" partner(s).

[4] No known "high risk" partner(s).

[5] Includes tattoos, acupuncture, possible occupational exposure to blood.

[6] Of these previously tested donors 35 report previous negative donations, 16 report previous reactivity not confirmed positive, 10 report previous positivity (8 previously confirmed positive, 2 found to be positive on re-testing of archive) and for 11 the results of the previous donation are not reported.

Figure 3.11 Exposure categories of anti-HCV positive blood donors.



Donations collected from 01/10/1995 to 30/09/1999.

Table 3.13 Exposure categories of anti-HIV positive blood donors. Donations collected from 01/10/1995 to 30/09/1999.

How infection was probably acquired	Newly tested donors[1]	Previously tested donors	All donors HIV positive	%
Injecting drug use	1	0	1	1%
Sexual intercourse				
between men	13	16	29	31%
between men and women				
exposure to "high risk" partner(s)[2]	6	1	7	7%
exposure abroad[3]	8	7	15	16%
exposure in the UK[4]	11	11	22	23%
incomplete information	5	1	6	6%
Blood factor treatment	0	0	0	0%
Blood/tissue transfer	0	0	0	0%
Other	0	0	0	0%
No identified exposure[5]	11	3	14	15%
Total	55	39 [6]	94	100%

[1] Newly tested by the blood transfusion services included in this surveillance: may have had donation tested in other countries.

[2] Partner(s) exposed through sexual intercourse between men, IDU, blood factor treatment or blood/tissue transfer.

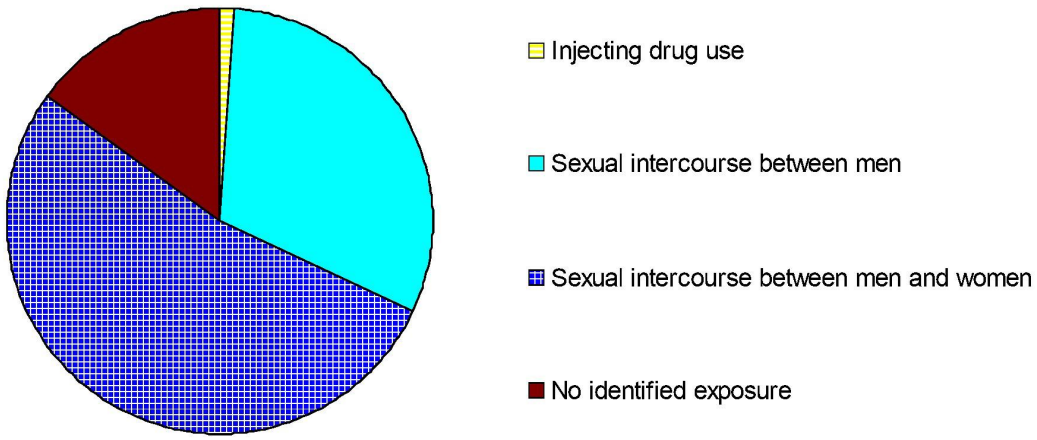
[3] Individuals from abroad, and individuals from the UK who have lived or visited abroad, for whom there is no evidence of "high risk" partner(s).

[4] No known "high risk" partner(s).

[5] Investigation continuing.

[6] All 39 positive previously tested donors had a previous anti-HIV tested donation in the UK recorded: all are reported to have been anti-HIV negative.

Figure 3.12 Exposure categories of anti-HIV positive blood donors. Donations collected from 01/10/1995 to 30/09/1999.



Exposure history information was reported for 67% of donors with confirmed reactivity for Treponemal antibodies: 27% of Treponemal antibody positive donors with exposure history information available had a history of Syphilis reported and 5% had a history of Yaws.

The second version of the infected donor surveillance form asked for reasons for non-disclosure prior to donation of probable routes of infection. 60 of 129 exposure histories reported on these new forms (to 30/06/1999) included a response to this question. The reasons donor selection criteria did not exclude these donors are shown in Table 3.14; amongst the remaining 59, only 2 reported an identified probable route of infection. For 30 of the 60, the probable route of infection was not a reason for pre-donation exclusion. For 11, the probable route of infection occurred outside the period of time for which the donor selection criteria apply. For 19 (13 HCV, 3 HIV and 3 TP) a risk factor was disclosed during post-diagnoses counselling that should have resulted in exclusion from donation: the reported reasons these risk factors were not disclosed prior to donation are shown in Table 3.15.

Table 3.14 Classification of applicability of donor selection criteria to infected donors with reasons why probable route of infection was not disclosed prior to donation reported (up to 30/06/1999).

	HBV	%	HCV	%	HIV	T. pallidum	***Total***	***%***
No exclusion criteria applied	14	93%	14	38%	1	1	***30***	***50%***
Exclusion criteria expired	1	7%	10	27%	0	0	***11***	***18%***
Exclusion criteria did apply	0	0%	13	35%	3	3	***19***	***32%***
Total	***15***	***100%***	***37***	***100%***	***4***	***4***	***60***	***100%***

Table 3.15 Reasons for non-disclosure prior to donation of risk factors for which exclusion criteria applied.

How infection was probably acquired	Infection	Reason stated for non-disclosure prior to donation
Injecting drug use	HCV	Single IDU only, therefore did not think it applied.
	"	Thought blood would be tested. Needed to know blood group for work.
	"	Told S.O. past history of hepatitis but informed by a hospital last year that no longer has it. Did not tick IDU because linked it with the hepatitis which had discussed with the S.O.
	"	Was only trying to help, and thought all was tested anyway.
	"	Did not think it relevant - a long time ago and did not share needles/syringes, although did share other injecting equipment[1]
	"	Did not think it was relevant as it was along time ago.
	"	Thought it was too long ago to matter.
	"	Knows others in the same situation who are long-term donors.
	"	Did not fully understand the safety of blood leaflet.
	"	Asked for advice prior to session, and was assured that if had been cleared of hepatitis B and it was more than 12 months ago, it was OK.
	"	Didn't adequately read safety of blood leaflet. Also tries to forget one episode of IDU.
Sexual intercourse between men	HIV	Says that discussed with GP who told him it was OK to donate, and thinks "Blood Service has a prejudice against gays"[2]
	"	Did not see risk as had not had anal sex, and rated oral sex as messing around only.
	"	Regular donor - hard to self-exclude now.[3]
	T.pallidum	Assumed infection fully eradicated therefore OK.[4]
Sexual intercourse between men and Women	HCV	Thought was in the clear as partner said had never shared a needle - only spoons (heroin addict) and was tested and negative in the past.
	"	Did not understand that spouse's history excluded donor, as spouse in no longer using drugs.
	T.pallidum	Has had blood tests before but no positive results.
	"	Not aware of risk.

Notes: 1,2,3&4 were repeat donors. 1= not previously tested. 2,3 = previously negative. 4 = previously reactive.

Transfusion-transmitted infections

Infectious complications following transfusion differ from non-infectious complications in several ways that may affect the ascertainment and investigation of incidents. The onset of symptoms related to a transfusion-transmitted viral infection may occur from several weeks to years after the date of the transfusion. Reports of infections transmitted by transfusion in any particular year, or period of years, can therefore accrue over the subsequent year(s). The number of cases ascertained by the end of any period is therefore expected to be an incomplete picture of the infections transmitted during that period. Acute infections, such as bacteraemias, that tend to be clinically apparent and diagnosed within days after receipt of the infectious transfusion, may be relatively complete but chronic viral infections will be underrepresented.

In addition, the occurrence of disease, or the observation of serological markers of infection, in individuals who have donated blood can lead to the ascertainment of transfusion-transmitted infections by tracing and testing of recipients exposed to components collected from donors during potentially infectious periods. Recipients may be asymptomatic at this time and only identified by this investigation.

Post-transfusion infections (PTI) may be due to an infected (or contaminated) transfusion or infection may have been acquired from another source. Investigation of markers of infection in an implicated donation, or in subsequent samples from the donors of implicated donations, can confirm transfusion as the probable cause of infection, or identify the need to investigate other possible sources. The blood service must therefore be informed about implicated transfusions so that investigations can be conducted to confirm or refute the suspicion that the implicated transfusion(s) may have been infectious. This is essential to prevent further transmission(s) by other components and/or by chronically infected donors, and to reveal any systematic errors or deficiencies in the blood service testing. Such investigations may involve microbiological testing of many donors and may take several months to complete.

One category of post-transfusion infections is not included in these data. In January 1999, a meeting of reporters agreed that HCV and HIV infections diagnosed in recipients who had received transfusions in the UK that were not tested for anti-HCV (i.e. pre September 1991) or anti-HIV (i.e. pre October 1985) respectively should be excluded from reporting. The blood service is rarely able to conduct follow-up investigation of donors implicated in these cases and these cases do not contribute to knowledge of the current infection transmission risks of blood transfusions. Numbers and details of such infections were therefore not included in data for the surveillance system after January 1999, and 4 previous reports have been excluded retrospectively.

Data received by 31/12/99 about incidents of transfusion-transmitted infections initially reported by blood centres during the four years from 1/10/95 to 30/9/99 are included in this thesis.

Unless the investigation was closed due to the identification of a probable source of infection other than transfusion, investigations that were closed without being able to conclusively investigate the source of the post-transfusion infections were classified as post-transfusion infections with inconclusive investigation. Table PTI 1 and Figure PTI 1 show the number of reports by their status by report year.

Table PTI 1 Status of post-transfusion infections reported 01/10/1995 to 30/09/1999 by report year.

Report year	Outcome of donor investigation/comment				
	Probable transfusion transmitted infection	Investigation concluded not transfusion-transmitted	Inconclusive investigation	Full investigation pending	*Total* [1]
1. 01/10/95-30/09/96	3	8	1	0	*12*
2. 01/10/96-30/09/97	8	12	4	3	*27*
3. 01/10/97-30/09/98	3	20	8	2	*33*
4. 01/10/98-30/09/99	7	17	3	8	*35*
Total	*21 (19%)*	*58 (54%)*	*16 (15%)*	*13 (12%)*	*108*

[1] An additional 23 post-tranfusion reactions suspected to be due to bacteria were reported.

Figure TTI 1. Post-transfusion infection (PTI) reports by report year.

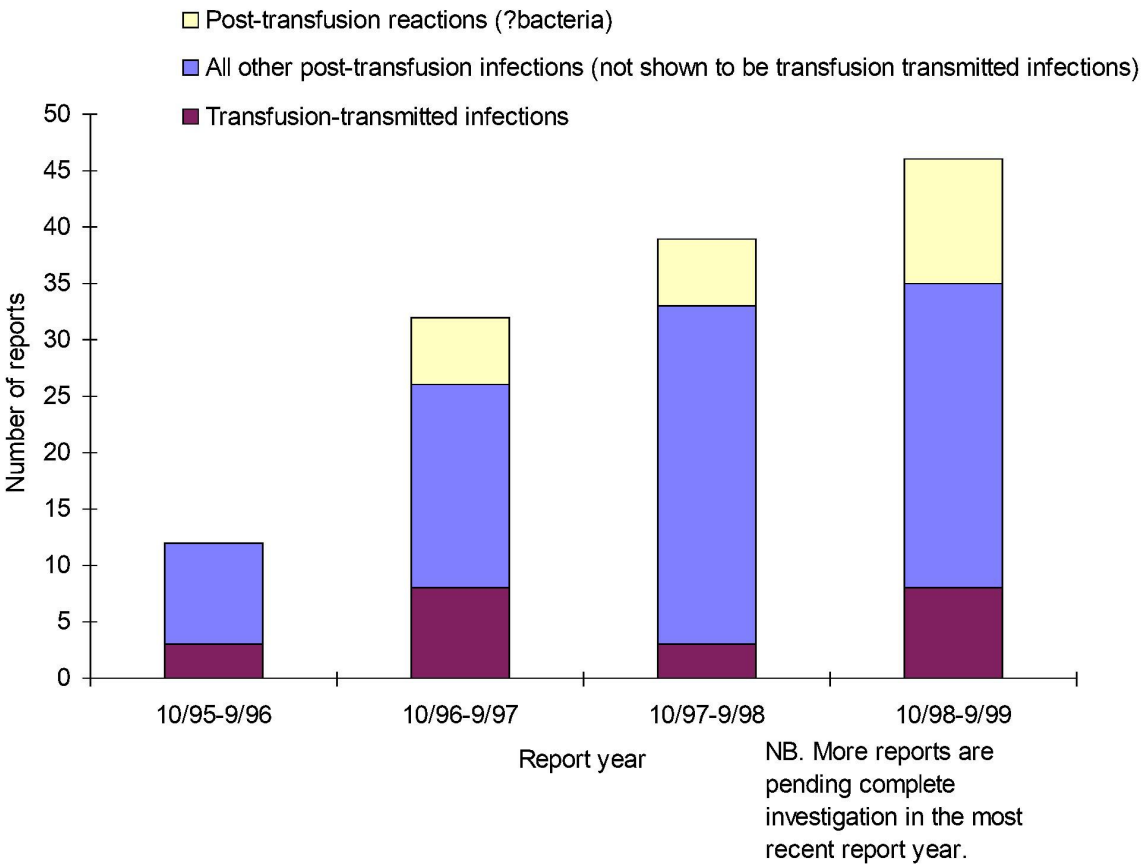


Table PTI 2 shows the number of reports by their status and by infection. Figure PTI 2 shows the status of reports up to the end of September 1999 at 31/12/99.

Table PTI 2 Status of post-transfusion infections reported 01/10/1995 to 30/09/1999 by infection.

Infection	Outcome of donor investigation/comment				
	Probable transfusion transmitted infection	Investigation concluded not transfusion-transmitted	Inconclusive investigation	Full investigation pending	*Total* [1]
HAV	1	1	-	-	*2*
HBV[2]	5	26	3	6	*40*
HCV[2]	2	25	7	6	*40*
HIV[3]	1	3	1	-	*5*
Bacteria	11	3	5	1	*20*
Malaria	1	-	-	-	*1*
Total	*21 (19%)*	*58 (54%)*	*16 (15%)*	*13 (12%)*	*108*[2]

[1] An additional 23 post-transfusion reactions suspected to be due to bacteria were reported.

[2] Including one dual HBV and HCV post-transfusion infection concluded not transfusion transmitted.

[3] One additional investigation failed to confirm or refute transfusion transmission of HIV infection during the early 1990s. As the patient had received multiple transfusions, and had no other risk factors for infection, transfusion with HIV infectious blood was concluded to be the probable, although unproven, source of infection.

Figure PTI 2 Post-transfusion infections reported 01/10/1995 to 30/09/1999.

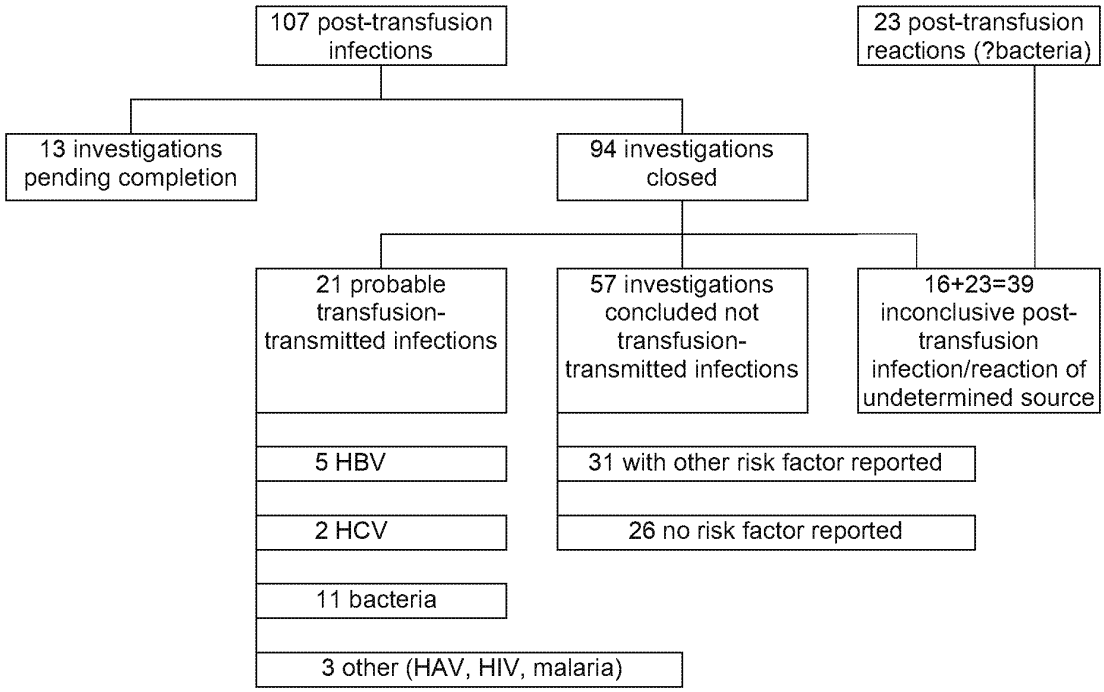


Table PTI 3 shows the cumulative number of transfusion-transmitted infections reported by the end of September 1999 by infection and year of transfusion.

Table PTI 3 Cumulative total transfusion-transmitted infections: reported between 1/10/95-30/9/99 by date of transfusion.

The number of incidents is shown with the total number of identified infected recipients in brackets.

Year of transfusion	pre-1995	1995	1996	1997	1998	1999 (to end Sept)	Total	Deaths
Infection								
HAV	-	-	1(1)	-	-	-	1(1)	
HBV	1(1)[b]	1(1)	1(1)	1(1)	1(1)-		5(5)	
HCV	-	-	1(1)	1(1)	-		2(2)	
HIV[c]	-	-	1(3)	-	-	-	1(3)	
Bacteria	-	1(1)	1(1)	3(3)	3(3)[ax2]	3(3)[a]	11(11)	3
Malaria	-	-	-	1(1)[a]	-	-	1(1)	1
Total	1(1)[b]	2(2)	5(7)	6(6)[a]	4(4)[ax2]	3(3)[a]	21(23)	4

Notes: [a] Infection was implicated in the death of a recipient.

[b] One household member who was caring for the recipient has been diagnosed with acute HBV.

[c] One additional investigation, initially reported during 97-98 and concluded during 98-99, failed to confirm or refute transfusion transmission of HIV infection during the early 1990s. As the patient had received multiple transfusions, and had no other risk factors for infection, transfusion with HIV infectious blood was concluded to be the probable, although unproven, source of infection.

During the first four years of reporting (i.e. 01/10/95 to 30/09/99) to the surveillance system for post-transfusion infections, 107 post-transfusion infections were reported (including 1 dual infection). Twenty-one were classified, after investigation, as transfusion transmitted infections (see Table PTI 3). Sixteen (15%) post-transfusion infections were classified as post-transfusion infections of undetermined source due to incomplete investigation of the transfusion(s) implicated as the source of the infection. For 58 (54%) post-

transfusion infection reports, investigation into the case was completed and no evidence was found to implicate transfusion as the source of infection. At least one other risk factor for infection other than transfusion was identified for 31 (53%) of these infections.

During the years 1996-1999 an additional 23 reports were received about post-transfusion reactions that were suspected to be due to bacteria but for which no evidence of bacterial infection (or endotoxin) that could have caused the reaction was sought and found in the recipient or implicated component (i.e. did not satisfy the criteria for a post-transfusion infection as stated above, but may have been reactions of bacterial origin). These reports started during the second report year when a parallel system for reporting non-infectious hazards of transfusion was established and hospitals were encouraged to report all post-transfusion complications. A new category was added to the report form for these cases as they were clinically important post-transfusion complications. The absence of confirmation of infection in the recipient was likely - at least in some cases - to be due to absence of the appropriate sample for testing, rather than absence of any infection. The cause and source of these cases cannot be resolved as certainly as the other cases, and they are presented separately throughout.

Reports were received from 15 of the 21 blood centres (between 1-16 cases each) participating in the surveillance system. The six centres that did not report any cases included 3 small centres that tested less than five thousand donations per year. These six centres collect approximately 5.4% of the donations tested by blood centres participating in the surveillance system. Seven hospital clinicians reported more than one infection: 23 hospitals transfused more than one of the investigated recipients (20 x 2 reports, 2 x 3 reports, 1 x 4 reports).

Post-transfusion reactions:

None of the 23 post-transfusion reactions suspected to be due to bacteria were clearly shown to be due to transfusion-transmitted bacteria. Six of these recipients died: for one the transfusion reaction was implicated in the death of the recipient. Brief details of these cases are shown in table PTI 4.

Table PTI 4 Cases of post-transfusion reactions suspected to be due to bacteria.

Report year	PTR organism	PTR symptoms	PTR organism in unit	PTR organism in recipient	PTR other source
2		Febrile, back pain	No	No	
2		Unspecified reaction	No	No	
2	Staph. warneri	Pyrexia, breathless, hypertension	Yes (contamination?)	No	
2		Febrile, hypertension	No	No	
2	Pseudomonas aeruginosa	Cardiovascular collapse, respiratory arrest	Yes (contamination?)	No	
2		Hypertension	No	No	
3	Pseudomonas vesicularis	Febrile	Yes (contamination?)	No	
3		Hypotension, trachycardia	No	No	
3	Mixed	Hypotension, breathless, died(cardiac arrest)	Yes (contamination?)	No	
3	Serratia liquifacians	Febrile, rigors	Yes	No	
3	E.coli	Hypotension, faint, cyanosis	Yes	No	
3	Staph. epidermidis	Unspecified reaction	Yes (contamination?)	No	
4		Allergic reaction, wheezing, hypoxia, uticarial rash	No	No	?HLA
4		Rigors, (died-aortic aneurysm)	No	No	
4		Died(cardiac arrest)	No	No	
4		Unspecified reaction	No	No	
4		Febrile, rash	No	No	
4		Unspecified reaction, died(other causes)	No	No	
4		Hypertension, pulmonary oedema	No	No	
4		Hypotension, rash, pulmonary oedema	No	No	?Trali
4		Unspecified reaction	No	No	
4		Septicaemia reaction	No	No	
4		Unspecified reaction, died(other causes)	No	No	

Details of transfusion transmitted infections

A. Infections for which donation testing is mandatory

Hepatitis B virus

Five transfusion transmitted HBV infections were reported.

HBV1. One recipient (29 year old female) had clinical acute HBV infection four months after transfusion of 2 red cell units. One donor was found to have a history of HBV infection 5 years prior to the implicated donation and to be anti-HBc positive and anti-HBs negative (HBV DNA negative). An HBV infectious, HBsAg negative, donation collected from a donor during the tail end of carriage of HBV infection was concluded to be the probable source of the recipient's HBV infection.

HBV2. One recipient (26 year old male) had acute clinical HBV infection five months after transfusion of a red cell unit (one of 14 red cell units given over a year) that was found, by testing of the archived sample of the donation to be anti-HBc negative but HBV DNA positive. At the time of the investigation, the donor recalled having viral symptoms and abdominal pains 5 months post-donation and was found to be anti-HBs positive. The probable source of the recipient's HBV infection was concluded to be an HBV infectious though HBsAg negative and anti-HBc negative donation collected from a repeat donor during early acute infection.

HBV3. One recipient (67 year old female) had acute HBV infection five months after transfusion of three red cell units. One of the donors was found to have markers of resolved HBV infection eleven months after donating the implicated donation. An HBV infectious, HBsAg negative, donation collected from a donor during acute (asymptomatic) infection was concluded to be the probable source of the recipients HBV infection.

HBV4. One recipient (59 year old male) was found to be an HBsAg and HBeAg positive HBV carrier 6 years after transfusion with 8 red cell units. One of the donors was found to have markers of resolved HBV infection and it was also discovered that this donor had developed acute HBV (confirmed by the local laboratory) 3 months after donating the implicated donation. No archived sample of the donation was available for further testing. The probable source of the recipient's HBV infection was concluded to be an HBV infectious but HBsAg negative donation collected from a new donor during acute infection. Secondary transmission seems to have occurred as a household member who was caring for the infected recipient was diagnosed with acute HBV at the same time as the recipient's diagnosis.

HBV5. One recipient (73 year old female) was found to have markers of acute HBV infection four months after transfusion of a red cell unit (one of three units received during a month) collected from a donor who developed acute HBV infection between one and two months after donating blood. The recipient was traced after the donor's General Practitioner informed the blood service of the donor's infection status. The archive of the implicated donation was confirmed to be HBsAg negative on re-testing but was found to be HBV DNA positive by nested PCR. (DNA was not detectable by PCR on a 1 in 96 dilution.) The recipient died three months after her HBV diagnosis from the

underlying reason for transfusion: HBV infection was not implicated in the recipient's death. The probable source of the recipient's HBV infection was concluded to be an HBV infectious, though HBsAg negative, donation collected from a repeat donor during early acute infection. The blood donor did not report any risk factor for HBV infection that is currently included as criteria for the exclusion of individuals from donating blood.

Both of the donations implicated in cases HBV3 and HBV4 above were collected from donors who subsequently disclosed risk factors for HBV infection that should, according to donor selection criteria in place at the time, have been recognised as making them ineligible for blood donation. Further investigation is needed to identify the reasons why these donors were not recognised as ineligible for donation.

Hepatitis C virus

Two transfusion transmitted HCV infections were reported.

HCV1. One recipient (79 year old female) was traced and tested for HCV infection, seven months after transfusion with a single red cell unit, when a repeat donor was shown to have seroconverted for anti-HCV between donations. The pre-seroconversion donation was subsequently shown by testing of the archived sample to be HCV RNA positive. An HCV infectious, anti-HCV negative, donation collected from a repeat donor during acute (asymptomatic) infection was concluded to be the probable source of HCV infection for the recipient.

HCV2. A repeat donor was found to be anti-HCV positive and HCV RNA positive. The archived sample of the previous (first) donation from this donor was re-tested and was also anti-HCV and HCV RNA positive. The recipient (a 64 year old male) of this red cell unit was traced and tested fourteen months after transfusion and was found to be anti-HCV positive and HCV RNA positive. Investigation by the blood service found an error had occurred during the re-testing of the donation that was initially reactive to the anti-HCV test. The duplicate repeat tests were read as negative because the samples were unintentionally dispensed into blank wells that are used to fill out part plates so they can be handled by automated machinery. It had been common practice to blank these out with a black marker pen so that in the event they were accidentally used for samples they would return a fail-safe positive reaction.

However new machinery had been introduced which read these as negative. Once the problem was identified corrective and preventative action was put in place to ensure that a different mechanism is used to ensure that blank wells will, if accidentally used, return a positive result and "fail safe". The probable source of the recipient's HCV infection was concluded to be an HCV infectious, anti-HCV positive, donation from a new donor. The donation was not excluded from the blood supply because of a laboratory error during the testing process.

The donations implicated in cases HCV1 and HCV2 were collected from donors who did not report any risk factor for HCV infection that are currently included as criteria for the exclusion of individuals from donating blood.

HIV

One transfusion transmitted HIV infection was reported.

HIV1. A recipient (47 year old female) was tested for HIV infection when she developed signs of HIV infection, after transfusion therapy involving over 100 units of red cells and platelets over a seven-month period. The archived sample of one donation (giving rise to a platelet unit transfused to the patient), from a repeat donor who had not been shown to be anti-HIV negative on a subsequent donation, was found to be HIV DNA positive. The donor was subsequently found to be anti-HIV positive. An HIV infectious, anti-HIV negative, donation collected from a repeat donor during acute (asymptomatic) infection was concluded to be the probable source of the recipients HIV infection[1]. The recipients of the red cells and the fresh frozen plasma produced from the infectious donation were subsequently shown to have also been infected with HIV by transfusion (one recipient had died of non-HIV-related causes).

The donation implicated in case HIV1 was collected from a donor who subsequently disclosed risk factors for HIV infection that, according to donor selection criteria in place at the time, made the donor ineligible to donate blood.

B. Infections for which donation testing is not mandatory

Bacteria

Eleven transfusion-transmitted bacteraemias were reported.

BAC1. One recipient (male, age not reported) suffered septic shock after transfusion with 2 platelet units. The same serotype of group B streptococcus was isolated from the patient, the implicated unit and from a throat swab from the donor.

BAC2. One recipient (21 year old female) developed rigors, nausea, and peripheral vasoconstriction soon after transfusion with a pooled platelet unit began. *B. cereus* serovar H18 was isolated from the platelet pool and from the arm of one of the donors who contributed to the pool.

BAC3. One recipient (21 year old female) entered endotoxic shock after transfusion with a red cell unit. The red cell unit was subsequently found to be haemolysed and was shown to contain *Serratia liqufaciens*. No evidence of infection was found in the donor by arm swabbing and by testing blood for antibodies. The source of the contamination was not identified.

BAC4. One recipient (4 year old male) suffered a bacteraemia after transfusion with a platelet unit. *Escherichia coli* was cultured from the pack and from the patient. No damage to the pack or source of the contamination was identified.

BAC5. One recipient (61 year old female) suffered a bacteraemia after transfusion with a (leucodepleted) pooled platelet unit. The pack and an arm swab from one of the four donors were both shown to contain *Bacillus cereus*, serotype H29.

BAC6. One recipient (32 year old female) developed a bacteraemia after transfusion with red cells and platelets and died two days after the transfusion. *Staphylococcus aureus* was isolated from the recipient and from skin and nasal swabs from one of the implicated donors.

BAC7. One recipient (27 year old male) developed bacteraemia after transfusion with two leucodepleted, 4-day-old apheresis platelet units from the same donor. The recipient recovered and was asymptomatic one week after the transfusion. *Staphylococcus epidermidis* was isolated from the platelet packs and from the recipient (and these two isolates had identical banding patterns). *Staph. epidermidis* (with a different DNA fingerprint) was subsequently cultured from swabs of the donor's arms. *Staph. epidermidis* was not grown from swabs taken after standard skin preparation. No failure in the donor arm cleansing procedure at the time of donating the implicated donation had been noted. The probable source of the recipient's bacteraemia was

concluded to be transfusion with platelets contaminated with skin flora from the donor's arm.

BAC8. One recipient (52 year old male) suffered a severe febrile reaction during transfusion of a leucodepleted, 3 day old apheresis platelet unit, and died later the same afternoon. On inspection the next day the remainder of the platelet pack had some signs of bacterial contamination (unusual orange colouration and small specks visible when held up to the light). *Escherichia coli* was cultured from the recipient's blood and from the platelet pack (and these two isolates had identical biochemical profiles). No leaks or defects were identified in the platelet pack. An interview with the donor confirmed absence of symptoms of infection at and around the time of donation and swabs of the donor's arm skin were negative on culture. The probable source of the recipient's reaction, and cause of death, was concluded to be transfusion with platelets contaminated with *E.coli*. No source of the contamination was identified.

BAC9. One recipient (78 year old female) suffered symptoms including feeling hot, sweaty and dyspnoeic during transfusion of a pooled, leucodepleted, 4-day-old platelet unit. The recipient subsequently recovered and was completely asymptomatic two weeks after the transfusion. Blood cultures were not taken from the recipient. *Staphylococcus epidermidis* was cultured from the platelet pack and from the red cell unit made from the same donation. An interview with the donor confirmed absence of symptoms of infection at and around the time of donation and swabs from the skin of the donor's arm were negative on culture. The probable source of the recipient's transient reaction was concluded to be transfusion with platelets contaminated with *Staph. epidermidis*. No source of the contamination was identified.

BAC10. One recipient (63 year old female) developed urticaria, rigors and pyrexia during transfusion of a pooled, leucodepleted, 4-day-old platelet unit. The recipient was pyrexial for three days after transfusion and was treated with broad-spectrum antibiotics. *Bacillus cereus* was cultured from the recipient's blood and from the platelet pack (and these two isolates were both of type 29). *B cereus* (type 29) was also cultured from swabs from the skin of the donor's arm (both pre- and post- arm cleansing). The probable source of the recipient's reaction was concluded to be transfusion with platelets contaminated with *B. cereus* from the donor's arm.

BAC11. One recipient (58 year old female) suffered a respiratory and cardiac arrest during transfusion of a second unit of red cells (33 day old, not leucodepleted) and died the same day. *Yersinia entercolitica* (serotype 09, biotype 3) was isolated from the patient's blood, the implicated red cell pack, and the archive of the implicated donation and a fresh sample of blood taken from the donor 5 months after the donation. On follow-up the donor reported a history of diarrhoea a few weeks prior to the donation. The probable source of the recipient's reaction, and cause of death, was concluded to be transfusion with red cells contaminated with *Yersinia entercolitica* from the donor's blood.

The four cases BAC7-10 were associated with leucocyte-depleted platelets since all platelets issued in the UK were leucocyte depleted. The numbers of cases before and after universal leucodepletion were too small to detect any effect of leucodepletion on bacterial contamination of components.

Other

HAV1. One transfusion transmitted HAV infection was reported. The recipient was traced and tested for HAV infection, one month after transfusion with three red cell units, after a donor reported HAV infection that developed ten days after donation. An HAV infectious donation collected from a donor during acute (asymptomatic) infection was concluded to be the probable source of HAV infection for one recipient[2]. The recipient of the platelets from the implicated donation was found to be non-immune and not infected.

MALARIA1. One transfusion transmitted malaria (*Plasmodium falciparum*) infection was reported. The recipient developed cerebral malaria two weeks after transfusion with two red cell units and died within two weeks of diagnosis. One new donor was found to have malarial antibodies when a subsequent sample was tested.

Morbidity and mortality of recipients with transfusion transmitted infections

The majority of recipients with transfusion transmitted infections suffered serious morbidity as a result of their infection. Table PTI 5 shows the breakdown of cases by morbidity and by infection. Major morbidity was defined as acute symptomatic confirmed infection or persistent viral infection. Minor

morbidity was defined as asymptomatic resolving viral infection. As such "minor" infections would only be diagnosed incidentally, it is not that surprising no reports - predominately originating because of clinical disease - fall into this category.

Table PTI 5 Morbidity by infection for transfusion-transmitted infections, 1995-1999.

	TTIs								All PTIs	
	HAV	HBV	HCV	HIV	Bacteria	Malaria	Total	Mean age(SD) [range]	N	Mean age(SD) [range]
Death attributed to infection	0	0	0	0	3	1	4	55(19) [32-78]	10	57(27) [0-85]
Death due to underlying condition	0	1	0	0	1	0	2	[20, 72]	4	51(25) [20-72]
Major morbidity due to infection	1	4	2	1	7	0	15	50(24) [4-80]	81	47(22) [0-84]
Minor morbidity due to infection	0	0	0	0	0	0	0	-	0	-
Patient outcome not known	0	0	0	0	0	0	0	-	12	53(19) [4-75]
Total	1	5	2	1	11	1	21	51(23) [4-80]	107	49(22) [0-85]
Mean age(SD) [range]	80	51(22) [26-72]	[61, 79]	46	42(24) [4-77]	78				

The average age of these recipients was 51 years (St dev of mean: 23, 95% confidence interval: 41-61, median: 58, range 4-80 years) and was similar to the age of all recipients reported with post-transfusion infections (mean: 49, St dev of mean: 22, 95% confidence interval: 45-53, median: 50, range 0 to 85 years).

Details of post-transfusion infections not found to be transfusion transmitted infections

Sixteen (15%) post-transfusion infections (5 Bacteraemia, 3 HBV infection, 7 HCV infections and 1 HIV infection) were classified as post-transfusion infections of undetermined source due to incomplete investigation of the transfusion(s) implicated as the source of infection. For 58 (54%) post-

transfusion infection reports (26 HBV infections, 25 HCV infections, 3 bacterias, 3 HIV infections and 1 HAV infection), investigation was completed and no evidence was found to implicate transfusion as the source of infection. A probable source of infection other than transfusion was identified for 31 of these infections.

Reporting delay

For the 11 transfusion-transmitted bacterial infections, symptoms occurred on the same day as the transfusion. Blood centres were informed of the bacteraemias suspected to be associated with transfusion on the same day (n = 7), the next day (n = 2), 2 days (n = 1) and 7 days (n = 1) after transfusion. The median interval between the initial information being reported to the blood centre and the completion of the initial surveillance report form by the blood centre was 32 days (mean 57, St dev 65, range 3-228).

Four of the transfusion-transmitted viral infections (1 HAV, 1 HBV and 2 HCV) were diagnosed with sub-clinical infections (45 days, 130 days, 224 and 440 days after transfusion respectively) during the follow up of suspected infectious donations. The other five transfusion-transmitted HBV infections and the malaria transmission were diagnosed with infection 86, 98, 141, 455, 2303 (HBV) and 42 (malaria) days after transfusion. The median interval between the initial information being reported to the blood centre and the completion of the initial surveillance report by the blood centre form was 64 days (mean 73, St dev 45, range 16-127). Some of this period of time – at least in some cases – was whilst confirmation of the recipient's infection details was awaited.

Underreporting

The cases ascertained by this surveillance system were diagnosed, suspected to be attributable to transfusion, communicated to the blood service, and reported by a blood centre to the surveillance centre. At any one of these steps, other post-transfusion infections may have been missed and the extent of underreporting of post-transfusion infections is therefore unknown. The proportion of post-transfusion infections that are reported each year may vary as other factors such as testing performed on transfusion recipients, awareness

of transfusion as a possible source of infection, reporting of information to blood centres and reporting of information from blood centres to the surveillance centre vary.

3.3 Discussion

Donation testing

A system for collecting standardised data about routine donation testing for four serological markers of infection has been established. Data about reactivity rates and infection rates are available. The identity of every positive donation is collected to enable matching with infected donor reports and monitoring of infected donor reporting rates.

Testing specificity

The specificity of donation testing was high - less than 0.3% (1 in 333) of donations were referred for confirmatory testing due to false reactivity to the full suite of screening tests. There was an increase in repeat reactivity to HBsAg tests amongst repeat donors that was associated with a poorly performing batch of test kits from a single manufacturer.

Removing tests performed on donors who were being monitored because of past reactivity to tests from the data removed the dependence of repeat reactivity rates in repeat donor donations on variations in the policy on bleeding these donors.

Some misclassification of donor type is expected to occur in the donation testing data. Some misclassifications are identified when infected donor reports are matched to donation testing data and contain information that allows re-classification of donor type. However, as the small changes in the numbers of donations tested in each donor category have little effect on rates, this misclassification is not expected to cause any important errors in the data.

Infection rates in blood donations

The overall rates of infected donations in England and Wales were low and rates were much lower in donations from repeat donors than in new donors.

Most donations of blood (89%) came from repeat donors. HIV antibodies were detected in 0.86 per 100,000 donations tested in England and Wales. Comparative data from other European countries shows rates per 100,000 donations of 2.41 in France (1995), 1.49 in Germany (1993), and 0.28 in Finland (1995) (WHO, 1996). HCV antibodies were detected in 0.05% of donations from new donors in England and Wales, compared with 0.28% in France (1994), 0.16% in Germany (1995), 0.05% in Finland (1995) and 0.04% in Denmark (1995) (Naplas, 1996). Difference in the recruitment and selection of donors, as well as differences in the prevalence and incidence of infections in the general population, affect the rates of infection in donations of blood. The tests that are used also affect these rates: for example, in the UK, blood donations are tested for HBsAg whereas in Denmark and France, blood donations are tested for HBsAg and antibody to hepatitis B core antigen.

There was a significant trend (at 5% significance level) to increasing anti-HCV prevalence in donations from new donors at the very end of the study period, and a significant decrease in anti-HIV prevalence in donations from new donors (Figure 3.4). However, although a trend was identifiable (at the 95% confidence level) neither of these trends were strong. Annual data for HCV prevalence in new donors from 1995 to 2000 show a significant ($p<0.01$) downward trend.

Monthly analysis of donation testing data

Monitoring of donation testing data and of all observed centre and donor type specific infection rates identified by analyses as outside the probable range (at the 5% significance level) based on the previous 3 years' data allows deviations in the data to be noticed. Many of the unusual results identified by the monthly analyses were relatively minor fluctuations that required no follow-up. Deviations that meet certain criteria can be highlighted for further attention. The first year of analyses has allowed criteria for further attention to be set at a workable level.

None of the unusual results identified during this first year of running these analyses, have identified a problem with donation testing or been connected with an outbreak in the general population. Two documented outbreaks of syphilis infection occurred in England during this time period (CDR,1998; CDR,

1999). Both these outbreaks predominately affected individuals in high-risk groups: none of the individuals linked to these outbreaks were identified though blood donation testing. The performance of the analyses in the event of an outbreak that does involve blood donors was not observed (upto August 2000).

The analyses supplement the usual vigilance of unusual infections. The analyses would not identify outbreaks that do not result in significant changes in rates of infection. The occurrence of a single acute HBV infection in a blood donor would be unlikely to significantly change the rate of HBsAg positivity in blood donations but can warrant an outbreak investigation - for example if the individual who is infected has an identified risk that may have also affected other individuals (e.g. a recent invasive medical procedure), or if others are likely to have been exposed to the infected individual (e.g. a health care worker performing exposure prone procedures). These analyses would be unlikely to identify small but important changes in the number, or proportion, of infections that were acquired recently or between donations i.e. acute infections and seroconversions.

These routine analyses have the potential to identify changes in test performance and changes in the frequency of infected blood donors that may be important. Further investigation of changes in test performance may lead to identifying bad test batches or operational problems. Further investigation of changes in infection frequency may lead to identifying an outbreak of infection or a failure in donor selection at a local or national level.

Criteria for defining results that warrant further attention may be changed in the light of further experience.

These analyses continue to be run each month. Reporters and other relevant staff within the blood service and the Public Health Laboratory Service will be informed of any results that meet the criteria for further attention.

Infected donors

A system for collecting standardised data about blood donors found to have HBV, HCV, HIV or Treponemal infections on donations testing has been established. Data about demographic characteristics, previous donations, and risk factors for infection are available. Anonymous identifiers enable matching

with other sources of data about these infections, such as laboratory reports, and AIDS case reports to PHLS CDSC.

Anti-HCV was the most prevalent marker of infection in blood donors in England and Wales (1995-1999), followed by HBsAg, treponemal antibodies and, least frequently, anti-HIV (Table 3.6).

There was a decrease in the prevalence of anti-HCV in donations from new donors, and in donations from repeat donors during the years 1995-1999. Almost two-thirds of anti-HCV positive donations from repeat donors during this period of time (starting four years after the introduction of anti-HCV testing) were from donors who were being tested for anti-HCV by the blood service for the first time (compare numbers of "new" and "repeat" positives in Tables 3.6 with "newly tested" and "previously tested" respectively in Table 3.12). The decline in the prevalence amongst donations from repeat donors is largely due to the removal of these positive individuals from the donor panel. The decrease in prevalence amongst donations from new donors may be due to a decreasing prevalence in the population or due to improved donor selection. The process of donor selection has been changed and expanded during this period (see Chapter 2) – and this was in fact partly motivated by the finding at the start of anti-HCV testing of a large number of anti-HCV positive donors reporting a history of injecting drug use. It is therefore likely that improvements in donor selection are responsible for a decrease in anti-HCV prevalence in new donors. As documented in Chapter 4, the recent incidence of anti-HCV in repeat blood donors is extremely low. If incidence was greater in the past, there may also be a truly decreasing prevalence in the population of new donors – typically younger individuals than repeat donors – who present to give blood each year.

The biggest difference in the epidemiology of infection in blood donors and in the general population is the frequency of infection – shown by both the relatively low prevalence and relatively low incidence. For example the prevalence of anti-HIV infection in antenatal women outside London during 1999 was 0.02%, (UASSG, 2000), 4.7-fold that observed in new donors in England and Wales (i.e. including London). The prevalence of HBsAg in samples from hospital patients (15-44 years old, excluding those requesting HBV testing) collected in 1996 from 16 microbiology laboratories in England and Wales was 0.37% (Gay NJ, 1999), over 11-fold that observed in new donors.

Also, the characteristics of infected blood donors differ from the characteristics of many other groups of diagnosed individuals due to the pre-selection of individuals to give blood – particularly the selection of healthy individuals and the selection of individuals who are not at known high risk of infection. For example, the relatively low proportion of HIV infections acquired by injecting drug use (1% (n=1) compared to 9% (n=3,608) amongst all reported anti-HIV positive diagnoses reported to PHLS CDSC (up to June 2000) (CDR,2000). The distribution of probable routes of infection reported for infected donors differed quite markedly from that observed amongst all reports of newly diagnosed infections. The most common risk factors for HIV, HBV and HCV were present amongst infected donors, however they accounted for a much smaller proportions of infections than in other tested groups. For many of these risk factors (e.g. sex between men, injection drug use) donor selection aims to specifically exclude donors with these risk factors. The relative infrequency of these risk factors in infected donors suggests that this is successful, however, there may also be an information bias in the reported risk factors – with donors more likely to withhold information about exposure histories that should have excluded them from donating blood. Follow-up by the PHLS CDSC HIV/AIDS Centre did identify a probably route of infection that should have led to permanent exclusion from donating blood for 7.5% (N=7) of anti-HIV positive donors who did not report this route to the blood service.

The selection of low risk individuals to be blood donors, and the resulting distribution of probable routes of infection acquisition in blood donors biased towards low risk exposures and no known route of infection, can be useful for pubic health work. Low risks for infection, and unusual routes of infection, are relatively more likely to be observed amongst donors, who therefore can act as a sentinel group for infections in groups with exposures believed to be of low risk, for example sex between men and women in the UK with partners with no identified increased risk for HIV infection. Donors with no identified risk of infection, or with reported exposure histories that are of uncertain risk, for example sexual exposure as a reported source of HCV infection, may also be good subjects for studies to identify unrecognised risk factors and evaluate exposure histories of uncertain risk. For 46% of HBsAg positive donors (detected between 1/10/95 and 30/6/96) no exposure associated with an increased risk of HBV infection was identified. During the same time period,

there was no exposure associated with an increased risk of HCV infection identified for 14% of anti-HCV positive donors, and, for a further 28% of anti-HCV positive donors, a *possible* exposure, of unknown risk, was identified. These possible risk factors included sexual contact with a partner with no known HCV infection or known increased risk of HCV infection, possible contact with blood during acupuncture, body piercing, invasive medical/dental procedures, and possible occupational contact with blood: these are common exposures that may be coincidental with, rather than associated with, infection. Whether these possible exposures represent true risks for infection could be determined by analytical epidemiological studies, for example case-control studies, providing enough such cases (and suitable controls) are available for study.

Some strong features of the epidemiology of these blood-borne infections show clearly amongst blood donors despite the selection biases in this population. The predominance of individuals with non-white ethnicity amongst HBsAg positive individuals (Table 3.10) and the high proportion of HCV infections acquired by injecting drug use (Table 3.12) have been frequently observed in other groups and are well known features of the epidemiology of these viruses. The excess of males amongst all infections has also been observed in other surveys, for example amongst hospital patients the prevalence of HBsAg carriage was 0.63% in males, 0.15% in females (Gay NJ, 1999). Available denominator data show that approximately half of all donations (45% of donations from new donors and 52% of donations from repeat donors) are collected from male donors. Should this change, to collect a larger (or smaller) proportion of donations from male donors, we would expect to see an increase (or decrease) in the prevalence of infection in donations. The sex ratio amongst donors is clearly important when comparing the prevalence of infection found in different surveys. The higher prevalence of blood-borne infections observed in some other European blood services might be at least partially accounted for by a higher proportion of donations from male donors.

The age and sex distribution of HBsAg, anti-HCV, anti-HIV and Treponemal antibodies differ (Table 3.7 and Figure 3.6). HBsAg positives include donors with acute HBV infection and donors with chronic HBV (carriage), however as acute infection is relatively uncommon the pattern of this

age-distribution is predominantly that of HBV carriage. A study of the prevalence of anti-HBc (i.e. a marker of having been infected with HBV) amongst a large sample of donations collected at two blood centres in 1995 found anti-HBc prevalence increased steadily with increasing age, and again was significantly higher in males (Soldan K, 2000). If this peak is due to a cohort of donors infected with HCV in the past that are now passing through the donor population, and incidence of infection is now much lower, we would expect to see (all other things being constant) a continuing decrease in the prevalence of anti-HCV in donations from new donors.

HIV infected donors had both a lower peak age group, and a significantly lower average age (Table 3.9) than the donors with other infections. Donors found positive for treponemal antibodies were the oldest group of infected donors, and the only group to show a steady increase with increasing age across the whole age span. As the majority of these donors have persistent markers of past infection this pattern is to be expected as both the time at risk of exposure increases with age, and syphilis infection was more common in the past. As for HBV, there are some cases of acute syphilis amongst these data. Cases of recent infection are the most important for both the blood service and for providing public health information, but are relatively few in number compared to past infections and so not well described by the data presented here. Further work is needed to ensure that infected donor reports specify when the donor has acute syphilis, and to monitor this sub-group of donors separately so that any small but important changes in their frequency, or characteristics, are not overlooked.

Interpretation of the ethnic groups of infected donors is very limited by the lack of data about the denominators of donations tested from donors in each ethnic group. The proportion of donations collected from ethnic minorities is known to be relatively small compared to the proportion of the total population in these groups, but exact data were not available. In an attempt to obtain some information about the proportion of donors who are of Asian ethnicity, a computer programme (NAMPECHAN) that was developed by Bradford County Council to identify names of Indian sub-continent origin (and their religion and language) has been applied to a cohort of 40,000 new donors (work not included in this thesis). This was also applied to HBsAg positive donors and the results indicated the prevalence of HBsAg in donors with a South Asian name

was 7.5 times higher than in the rest of the donor population. This supports the picture of HBsAg association with non-white ethnicity seen in Figure 3.9 a) when compared to the other infections (i.e. in Figure 3.9 b), c) and d)). HIV infection and treponemal antibodies appear (in the absence of denominator information to confirm this) to have an association with black ethnic groups. The association of HIV infection in England and Wales with having lived in sub-Saharan Africa is well documented. Between 5 and 10% of donors with positivity for treponemal antibodies report a past history of Yaws, a tropical ulcerative disease caused by a treponemal infection, and probably responsible for at least some of the association of this test result with African ethnicity.

The data in Tables 3.14 and 3.15 show that most infectious donations are from individuals who do not report exposure histories that should have led to their exclusion from donating blood. The collection of infectious donations from donors with a risk factor that occurred over twelve months ago could be avoided by lifetime deferral of these donors from blood donation. However, as the risk factors in the "12-month exclusion" category tend to be relatively common in the potential donor population life-long deferral may mean the loss of an unacceptable number of donations – the vast majority of which are expected to be from un-infected donors. The collection of infectious donations from donors with risk factors that should have excluded them from donating blood indicates failures either in the communication, understanding, or compliance with, donor selection criteria. In some cases, the donor may be unaware of their risk at the time, for example if the donor was unaware of a sexual partner's infection or risk of infection. These donations are extremely difficult to prevent. In other cases, donors are both aware of their risk and of the selection criteria but do not comply with the blood service's request to not give blood. A small sample of reasons for this is given in Table 3.15 and collection of these data continues. As the blood service has to rely on donors to comply with selection criteria, this is a vulnerable point in the process of providing a safe blood supply and deserves ongoing monitoring. Donors' perception of the blood service, and their trust in its staff and systems may affect their compliance with donor selection as well as their response to donor recruitment. These data may be used to monitor the compliance of various risk groups with donor selection, and to identify risk groups who are not aware of, or not minded to comply with,

donor selection criteria so that communication can be targeted at the groups in which donor selection is most often failing.

Transfusion-transmitted infections

A system for collecting standardised data about all post-transfusion infections that blood centres are informed about has been established. Data about demographic characteristics, the transfusion episode, clinical consequences of infection and other risk factors for infection are available. Anonymous identifiers enable matching with other sources of data, (e.g. laboratory reports) about these infections.

Reports have been received from most centres. Many hospitals have not reported any cases, however reports have originated in hospitals all over the country and most reporting hospitals (and reporting hospital clinicians) have reported just one case. There were no large clusters of cases associated with any one reporting individual or hospital. This distribution of reports suggests that the mechanisms for hospitals to notify blood centres are in place all over the country, and that there are no serious biases in reporting.

Reported transfusion-transmitted infections are rare: only 21 confirmed cases were recognised during this 4-year period of reporting. Investigations of a further 87 cases of post-transfusion infection were reported. Half (54%) of the PTI reports have been shown not to be caused by transfusion. For 15% of the reports the investigation was inconclusive and for the remainder investigation continues. Exclusion of transfusion as the source of infection and dissemination of this information can have useful infection control implications as other sources of infection – perhaps assumed to be unlikely at first - may then be further investigated and, if identified, become the subject for infection prevention. This has been the case in some hospital-acquired hepatitis infections eventually associated with infected health care staff.

Twenty-three cases of post-transfusion reactions suspected (but not confirmed) to be due to bacteria were also reported. Conclusive investigation of a suspected bacteraemia in a transfusion recipient relies heavily on the collection and handling of relevant samples at the hospital where the transfusion was performed. This means that absence of evidence of an

infection (or toxin), in donations given to recipients who had post-transfusion reactions that were suspected (on clinical presentation) to be due to bacteria does not equate with evidence of absence of a transfusion-transmitted infection (or toxin).

The intervals between transfusion and diagnosis of transfusion-transmitted infections were long - many weeks, months or years. Infections transmitted by transfusion between 1/10/95 and 30/9/99 will continue to be ascertained by the surveillance system as diagnoses are made in the future.

The delay in reporting (1 to 2 months) suggests that the data are not timely enough to act as early warning of outbreaks of transfusion-transmitted infections e.g. as a result of a batch of contaminated blood packs. (Parallel reporting of incidents that indicate a break down in quality assurance acts as a mechanism to quickly detect such problems.)

Four transfusion-transmitted viral infections (1 HAV, 1 HBV and 2 HCV infections) were detected by follow-up of recipients after the detection of infections in blood donors. In one case of HAV the donor reported an HAV diagnosis shortly after donating blood. In two cases of HCV infection the donor's infection was diagnosed by the blood service by the testing of a subsequent donation. In one case of HBV the donor's GP informed the blood service of the donor's infection. None of these transfusion-transmitted infections had caused symptomatic, diagnosed disease in the recipients. Two of these transfusion-transmitted infections (1 HBV and 1 HCV) were due to a donation collected from a donor during the marker negative "window period" early in a recent infection. One (HCV) was due to a laboratory error resulting in a false negative test result. One (HAV) was due to an infection for which no routine microbiology testing is performed.

Eleven transfusion-transmitted bacterial infections were due to collection of a donation from a donor with an infection for which no routine microbiology testing is performed.

Four transfusion-transmitted infections reported during this period resulted in the death of the recipient (3 bacteria, 1 malaria).

Several reports have been received of components that were observed to have visual signs of bacterial contamination before use, were not transfused, were sent for bacteriological investigation and were found to contain bacteria expected to cause disease in a recipient if transfused. Inspection of

components (especially platelets) detected contamination and prevented morbidity in these incidents. Such inspection is encouraged. These reports indicate "near-miss" bacterial transmissions. The investigation of the source of the contamination in these cases can be as informative as the investigation of transmissions, and the possibility of requesting and collating some information about these cases in the future is being considered.

An unknown, but probably relatively large, proportion of transfusion transmitted infections are expected to be clinically unimportant, and undiagnosed - at least for many years and the extent of under-diagnoses of clinically important transfusion transmitted infection, and of underreporting of diagnosed infections to blood centres and to CDSC is not known.

Based on the cases reported the following recommendations have been made:-

- National collation of data arising from these cases needs to continue over several years before a picture of the extent and nature of the infectious complications of transfusion can emerge.

- Clinicians should report all post-transfusion infections diagnosed in their patients to the blood service (via their regional blood centre) for appropriate investigation. Blood centres should, in turn, complete an initial report form as soon as possible.

- The quality of investigation of transfusion reactions suspected to be due to bacteria is variable. Hospitals should consult guidelines and the blood service about the investigation of such cases, including the sampling and storage of implicated units. National guidelines (from the NBS) on the investigation of these cases are currently being revised following comments from users.

- Donors' clinicians (and donors themselves) can aid the detection of transfusion-transmitted infections, and hence their appropriate care, by communicating with the blood service about any relevant history of blood donation on diagnoses with blood borne infections.

3.4 Summary and Conclusions

Surveillance of infections in blood donors and in blood recipients has benefits for transfusion medicine and for general infectious disease control and epidemiology. The surveillance system established in England and Wales built on the existing systems in the National Blood Service for monitoring donation testing and on the existing systems in the PHLS for disease specific infection surveillance, to enhance the surveillance of transfusion transmissible infections. Data about donation testing, frequency of infections, characteristics of infected donors, frequency of recognised transfusion-transmitted infections and characteristics of transfusion-transmitted infections are collated, analysed and disseminated regularly.

These data have demonstrated that the prevalence and incidence of HBV, HCV and HIV in blood donors in England and Wales during 1996-1999 were low and fairly stable. Over the total time period (1995-1999) there were significant trends towards decreasing anti-HCV prevalence in donations from new donors, and decreasing anti-HIV prevalence in donations from new donors, however the strength of these trends was no greater than have been observed for other similar length periods that are not significant when longer time periods are analysed.

No outbreaks of infection or crises in test performance were detected by the surveillance over the period of time described here, but analyses were designed and implemented that have the potential to identify these through irregularities in donation testing results.

Detailed reports were received for 98% of infected donations detected in England and Wales. Risk factor information was available from the NBS for 76% of all infections, and was obtained via the PHLS CDSC for 65% (20/31) of the anti-HIV positive donors who did not provide information to the NBS. Collection of data about each infected donor allowed identification of donors who had seroconverted for HBsAg, anti-HCV or anti-HIV between donations and therefore enabled estimates of incidence to be made. Further work will investigate factors associated with seroconversion.

Information about the probable route of infection has been collected in a standard format for every reported infected donor and enabled comparison of the risk factors for the different infections.

Only 20% of post-transfusion infections were concluded after full appropriate investigations to be transfusion-transmitted infections. Just over half of the cases concluded to be caused by transfusion (11/21) were due to bacterial contamination of transfusions. HBV was the most common transfusion-transmitted viral infection reported. Transfusion-transmitted HBV, HCV and HIV infections occurred due to the following occurrences: donation in the early stages of infection (without the marker of infection used in testing), donation in the tail-end stage of carriage of HBV infection, false negative test results due to error in the laboratory. Two non-bacterial infections for which blood is not tested also occurred (HAV, malaria). The frequency of recognised, reported transfusion-transmitted infections was shown to be very low, and to be low relative to the number of reports of non-infectious complications of transfusion. However, the extent of underreporting of transfusion-transmitted infections is not known and may be greater for many infections than it is for non-infectious complications that are fast and acute in onset after transfusion.

The surveillance system for transfusion-transmissible infections in England and Wales is an ongoing, systematic, collation of data that are analysed and disseminated to those in charge of control and prevention of transfusion-transmitted infection, and infections in the general population. The data held in the surveillance databases provides a baseline for future monitoring of the epidemiology of transfusion-transmissible infections and holds potential for both descriptive and analytical epidemiological studies.

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4.1 Introduction

Studies that provide specific analyses and estimates have been conducted using data from the surveillance system, and additional information specially collected for the purpose of the further study. Two of these studies are described below. The first collected further information about donors who appeared – from the surveillance reports – to have seroconverted for anti-HCV and determined the incidence of HCV infection amongst repeat donors in England during 1993 to 1995. The second collected further information from blood centres about all acute HBV infection reported to PHLS between 1991 and 1997 as associated with transfusion and described the frequency of confirmed transfusion-transmitted cases and the reasons for HBV infectious blood entering the blood supply.

4.2 Survey of HCV seroconversions in blood donors: England, 1993-95.

Introduction

In September 1991, UK Blood Transfusion Services began routinely testing all blood donations for antibody to hepatitis C virus (anti-HCV). Since then, approximately 2 million healthy adults have been tested for anti-HCV annually by the English National Blood Service (NBS). National collation of test results, and of characteristics of anti-HCV positive donors, provides valuable information about the donor panel, and about a selected sample of the adult population of England.

The majority of acute HCV infections are asymptomatic, and most probably pass undetected. An anti-HCV positive donation, preceded by an anti-HCV negative donation, suggests recent infection. The testing of donations from repeat donors therefore provides a rare opportunity to identify incident HCV infections. Information about incident HCV infections is of interest to blood transfusion services and to public health workers as it relates to current, rather than past, HCV transmission. Pre-donation selection of blood donors aims to exclude donors who have recognised risks for contracting blood borne infections. Incident infections in blood donors usually indicate one of three scenarios: a failure in the definition or application of pre-donation selection criteria; an unrecognised exposure to blood borne infection, or infection through an exposure that is not included in pre-donation selection criteria because it is a frequent exposure of blood donors and thought to be associated with a relatively small risk of infection. There remains a small risk of transmission of HCV by transfusion due to anti-HCV negative, infectious donations and due to failures in the testing and exclusion of seropositive donations. The number of donors who seroconvert for anti-HCV between donations is one piece of information needed to estimate the risk of collecting a donation from a recently infected donor who has not yet developed detectable anti-HCV, and hence the risk of transmitting HCV infection by transfusion.

A survey of seroconversions for anti-HCV detected by English blood centres from September 1991 to December 1995 was conducted during 1994/95 and the results of this survey have been used, along with data from the infection surveillance system of the National Blood Authority and Public Health Laboratory Service Communicable Disease Surveillance Centre (NBA/PHLS CDSC), to estimate the rate of seroconversion for anti-HCV in repeat donors in England during 1993-1995.

Subjects and methods

Sample

Blood donations in England are obtained from voluntary unpaid donors. Pre-donation selection excludes individuals who are outside the age-range 18-65 years, have had known high risk exposures for contracting blood borne

infections, or have any medical condition which contraindicates either the loss of 450ml of blood, or the giving of their blood to patients. The number of repeat donors in 1994 constituted approximately 4% of the 18-65 year old population of England in the middle of 1994.

During the study period all donations were tested for anti-HCV using enzyme-linked immunosorbant assays (ELISAs). Initially-reactive donations were re-tested by ELISA. Donations that were reactive on repeat testing were not issued and supplementary tests (additional ELISAs and recombinant immunoblot assays (RIBAs), and, in some cases, polymerase chain reaction (PCR) for HCV DNA)) were performed to clarify the infection status of donors.

Donors with evidence of HCV infection were contacted by the blood centres and were offered additional testing and counselling by the blood centre followed by referral to a relevant medical specialist, or were referred to their general practitioner for further management (Ryan KE, 1994). Risk factors for HCV infection were discussed with donors during their follow up and any acknowledged by the donor were recorded.

Case definition

A standardised algorithm for confirmatory testing of blood donations was not used during the study period and variation in the tests used had to be accommodated. In order to include all true biological seroconversions but exclude any spurious "seroconversion" caused by changes in test format and performance over time, or due to false reactivity in the tests, a comprehensive case definition was developed and agreed. (Box 3)

Box. 3 Criteria for determining seroconversion for anti-HCV.

Pre-seroconversion donation		Post-seroconversion donation		
RIBA 3.0 non-reactive	and	RIBA 3.0 positive	}	
	or		}	not PCR negative
ELISA non-reactive & RIBA 2.0 non-reactive	and	ELISA (of same manufacturer and generation as pre-seroconversion test) positive & RIBA 2.0 positive	} and	**if** < 12 months after pre-seroconversion donation
	or		}	
ELISA 3.0 non-reactive	and	ELISA 3.0 positive & RIBA positive	}	

Methods

In July 1994 all English blood centres were asked to return information about the tests performed and results obtained on the first anti-HCV positive donation (i.e. post-seroconversion donation) and the last anti-HCV negative donation (i.e. pre-seroconversion donation) for each donor considered to have seroconverted for HCV between donations since anti-HCV testing began in 1991. Seroconversions identified after July 1994 were also reported and included in the survey. Information was also requested about possible exposures to HCV infection. In October 1995 the national system for the surveillance of donation testing was revised and seroconversions were then identified from routine surveillance reports.

Test results were examined to see if they met the case definition. If they did not, the reporting blood centre was contacted and asked for any additional test results or to perform additional tests on archived samples - most commonly they were asked to perform parallel RIBA tests on samples from pre- and post-seroconversion donations. Follow-up of missing returns, and requests for additional information continued during 1995.

During 1991 (September-December) and 1992 the majority of repeat donors tested for anti-HCV were being tested by the NBS for the first time. As a previous negative anti-HCV test is a pre-requisite for HCV seroconversion, rates for 1991 and 1992 were not calculated.

The rate of post-seroconversion donations in all donations from repeat donors was calculated by dividing the number of seroconversions by the

number of donations from repeat donors. The numbers of donations from repeat donors tested for anti-HCV during 1993, 1994 and 1995 was obtained from the national system for the surveillance of donation testing. The incidence of HCV seroconversion was calculated by dividing the number of seroconversions by the number of person years (PYs) at risk. The number of PYs was estimated by dividing the number of donations from repeat donors by the average annual number of donations per repeat donor. The average number of donations per repeat donor at one blood centre (that tests 5% of the repeat donor donations in England) was 1.71 over a one-year period, and 3.49 over a three-year period (1993-95). The average annual number of donations during the three-year period 1993-95 was therefore taken as 3.49/3 = 1.16: this is equivalent to an average interval between donations of 0.86 years.

Table 4.1 Seroconversions for anti-HCV amongst repeat donors in England 1993-1995.

	1993	1994	1995	1993-1995
Number of donations from donors who have seroconverted for HCV since a previous donation	5	3	6	14
Number of donations from repeat donors tested for HCV antibody	2,140,712	2,116,178	2,105,038	6,361,928
Frequency of donations from donors who have seroconverted for HCV since a previous donation	1 in 428,142	1 in 705,393	1 in 350,840	1 in 454,423
Rate of seroconversion per 100,000 PYs (95% confidence interval)	0.40 (0.17-0.96)	0.24 (0.08-0.75)	0.49 (0.22-1.08)	0.26 (0.15-0.43)

Results

Twenty-three reports of putative HCV seroconversion in repeat donors tested between September 1991 and the end of 1995 were received. The test results available for 7 of these did not satisfy the case definition. As centres were asked to report only those donors for whom full testing information was available, these 7 reports do not represent all the possible additional cases of

recent HCV infection in repeat donors where the data is insufficient to satisfy our case definition. Two of the donors that fulfilled the study case definition for anti-HCV seroconversion were diagnosed during 1991 or 1992 and 14 of the cases were diagnosed during the study years, 1993-1995 (Table 4.1). The difference in the rates for 1993, 1994 and 1995 was not significant (p=0.59). PCR tests results were available for 10 of these 14: 9 were PCR positive, and one donor, whose first seropositive donation was taken two years after the last seronegative donation, was PCR negative. Five blood centres reported no HCV seroconversions. Three centres reported more than one HCV seroconversion: one centre in the Thames regions' reported 4 cases and had the highest rate of seroconversion; two centres, outside the Thames regions, reported 2 cases each. There was no significant heterogeneity between the rates by centre (deviance = 15.9, 13 degrees of freedom, p=0.25).

The average interval between donation of the pre-seroconversion and post-seroconversion donation for the fourteen cases was 1.29 years (median 1.38 months, range 0.42-2.33 years). This interval was 1.5 times the average inter-donation interval (1993-95) for all repeat donors.

The reported probable exposures to infection of the seroconverters are shown in Table 4.2, along with their sex and average age (information about ethnic group was not gathered). The approximate average age of all repeat donors was 40 years.

Table 4.2 Acknowledged probable exposures in donors who had seroconverted for anti-HCV.

Probable exposures to HCV infection	Donor selection criteria (1995) instruct exclusion	Number (%)of seroconverting donors		
		Total	Males	Females
Injecting drug use	Yes	2 (14%)	2	
Sex between men and women		5 (36%)	1	4
- known HCV infected partner	Yes[1]	1	1	0
- IDU partner[2]	Yes	2	0	2
- partner with tattoos	No	1	0	1
- partner from high HCV prevalence country	No	1	0	1
Blood contact with person with risk factors	No	1 (7%)	1	0
None identified	No	4 (29%)	2	2
No information	-	2 (14%)	2	0
Total	5 (36%) Yes 9 (64%) No	14 (100%)	8	6
Mean age (years) (95% confidence interval)		30.5 (26.6-34.4)	31.4 (26.1-36.7)	29.3 (21.1-37.5)

[1] At the time of donation this selection criterion was not in use (Kitchen AD, 1996).

[2] For 1 the partner was tested for anti-HCV, and found to be positive, after the donor's diagnosis, for the other the anti-HCV status of the partner is not known.

Discussion

English blood centres identified 412 anti-HCV positive repeat donors during 1993-1995. Very few (14) of these can be shown to represent incident HCV infections. This survey provides an estimate of the minimum rate of HCV seroconversion in repeat donors in England during 1993-95. The case definition for HCV seroconversion used in this study was chosen to exclude spurious seroconversion due to changes in test format and performance. The sensitivity and specificity of ELISAs and RIBAs used for anti-HCV testing changed between 1991 and 1995 with the introduction of third generation tests during 1993. By the time of this survey many of the archived samples from the pre-seroconversion donations under investigation had been used for repeat and supplementary tests, or discarded, according to each blood centre's protocols: repeat and supplementary testing of pre-seroconversion donations was therefore limited. By requiring evidence of comparably confirmed negativity for

the last seronegative donation, some cases of true seroconversion may have been excluded. Previous reports of HCV seroconversions with less strictly applied case definitions (Shopnick RI, 1995) have been quite justifiably challenged (Kessler C, 1995) and we chose to identify clear-cut, rather than probable, cases. Also, the survey was conducted retrospectively, and relied on retrieval of blood centres' records of tests performed on donations up to four years previously. For these reasons, this study may underestimate the number of seroconverting donors, and therefore the rate of seroconversion among repeat donors in England. Donations from repeat donors who were being tested for anti-HCV by the NBS for the first time during 1993-95 could not be excluded from the denominators that we used. A study conducted on donations during 1993 by one blood centre found 1.8% of donations from repeat donors to be from donors not previously tested for anti-HCV by the blood centre (Atrah, 1996). This inaccuracy in our denominator is likely to result in a further, although very slight, depression of the seroconversion rates as estimated from these data.

One blood centre has published reports about 3 donors diagnosed during 1993 (Atrah HI, 1995), and a further 4 donors diagnosed during 1994 and 1995 (Atrah HI, 1996) who were thought to have seroconverted for HCV. The blood centre obtained denominators of previously negative donors tested for anti-HCV during 1993 and estimated the seroconversion rate during 1993 to be 2.78 per 100,000 (1 in 35,937) previously negative, repeat donors (Atrah HI, 1996): more than ten-fold the estimate from our national study. However, the case definition used by this centre may have been flawed (Allain J-P, 1997 and Hewitt PE, 1997); only one of the cases described satisfied the case definition that we used. We consider the estimate of the HCV seroconversion rate in repeat blood donors derived by this single centre to be erroneously high.

Pre-donation selection criteria aim to select a sample of the population who do not report a recognised risk for blood borne infections prior to donation (Guidelines for the Blood Transfusion Services in the United Kingdom Section 1.1.5 Medical Assessment of Donors, 1997). Since the early 1980's potential donors have been given explanatory literature and since 1999, direct questioning about risk factors has been introduced for all new donors, and for donors who have not attended for two years or more. One centre has

additionally used a donor-completed questionnaire. The procedure for eliciting information about exposures to risks for HCV infection from infected donors has varied though out the UK. A standard questionnaire for interviewing donors is soon to be introduced. Information obtained post-donation from infected donors may be affected by both interviewer-related, and donor-related, biases. The majority of HCV infected blood donors have reported a history of injecting drug use (MacLennan S, 1994, Crawford RJ, 1994, Goodrick MJ, 1994, Neal KR, 1994, Gesinde MO, 1992 and Atrah HI, 1994), typically many years prior to donating blood. Almost one third of the HCV seroconverters in this study had no risk for HCV infection identified by the blood service. Testing the sexual partners of seroconverting donors may help to establish the true extent of heterosexual transmission in the donor population. Uncommon routes of transmission, and possible exposures that are not thought to be associated with risk of HCV infection, should also be investigated.

Seroconversion for HCV amongst repeat blood donors in England is very rare. This implies that the incidence of HCV in the population represented by repeat blood donors is now very low, and/or that pre-donation selection criteria effectively exclude most repeat donors with current exposure to HCV. During 1993-95, 14 donations (less than 1 in 450,000 donations), were obtained from donors who had seroconverted for HCV since a previous antibody negative donation. During the same period, 15 donations were obtained from donors who had developed detectable anti-HIV since their previous donation. The number of repeat donors who become infected with HCV, or other blood borne infections, but do not return to donate after their seroconversion cannot be ascertained by donation testing. In the future, tests for nucleic acids may enable detection of antibody negative, infectious donations.

The HCV status of the recipients of the seronegative, pre-seroconversion donations was not determined in this survey. Blood centres conduct tracing recipients of potentially infectious donations and one of the 14 pre-seroconversion donations has been shown to have transmitted HCV infection (Kitchen AD, 1996).

Donations from new donors contributed 12% of the total number of donations collected in England in 1993-1995. Seroconversion rates in new donors cannot be directly measured and there are reasons to expect that recent

infections in new donors may be more frequent than in repeat donors; repeat donors have been subjected to the post-donation selection criteria of negativity for tests for HCV, HBV, HIV and *T.pallidum* infection markers, and new donors may be more likely to donate blood in order to obtain testing following an exposure to infection.

Surveillance of donation testing and of donors who seroconvert for HCV between donations continues to be an important component of monitoring the safety of the blood supply. Study of possible exposures to infection that are associated with seroconversion for HCV, and of the course of HCV infection in seroconverting blood donors, who have a relatively precisely known date of HCV infection, should further contribute to our understanding of the epidemiology and natural history of HCV infection.

4.3 Review of acute HBV infection laboratory reports: Reports of acute HBV infection associated with blood transfusion in England and Wales, 1991-1997.

Introduction

Blood donations in England and Wales are collected from healthy donors who do not acknowledge factors associated with an increased risk of blood borne infections. All donations issued for transfusion (since early 1970's) have been found negative for hepatitis B surface antigen (HBsAg) as a marker of transmissible hepatitis B virus (HBV). These measures have resulted in low rates of HBV transmission by transfusion, but have not eliminated all infectious donations from the blood supply. HBV infections in recipients are investigated by National Blood Services (NBS) to identify if they were transmitted by transfusion, and prevent other transmissions, or to identify the need to explore sources other than transfusion. An implicated donation is concluded as having been probably infectious for HBV if it was:- i) collected from an HBsAg negative donor for whom there is evidence of acute infection at that time, or ii) collected from an HBsAg negative donor for whom there is evidence of infectious HBV carriage (i.e. antibody to hepatitis B core antigen (anti-HBc) present but antibody to HBsAg not, or weakly, present (Ilzuka H, 1992)), or iii) HBsAg positive (as shown by review of test results or re-testing of archived serum) and

erroneously released into the blood supply. Mutant HBV infections, not detected by routine HBsAg tests, also pose a risk of infectious donations being transfused (Jongerius JM, 1998).

Laboratories in England and Wales to PHLS CDSC report acute HBV infections, and the probable route of infection, voluntarily.

Methods and results

Acute HBV reports to CDSC were reviewed and information was sought from the NBS about reports associated with transfusion between 1991 and 1997 (Table 4.3). Between 1991 and 1997 24 of 4,185 (0.6%) acute HBV reports were associated with transfusion in England and Wales. For 10 reports, investigation by the NBS was either not feasible (e.g. donation identifiers not available) or inconclusive (e.g. one of more donor not traced for re-testing), or NBS information was not available retrospectively. Fourteen probably infectious donations identified by the NBS fell into two categories: 3 (21%) were collected from HBsAg negative donors during acute HBV infection and 11 (79%) were collected from HBsAg negative donors during late HBV carriage. No reports of erroneous release of HBsAg positive blood were identified.

Table 4.3 Acute HBV reports associated with transfusion, England and Wales, 1991-1997.

Year	Total reports[1]	Transfusion in UK as the most probable route of infection	NBS identified HBsAg negative probably infectious donor with		NBS investigation outcome not available, or inconclusive
			acute HBV	HBV carriage	
1991	572	5	0	2	3
1992	531	3	1	1	1
1993	629	5	1	4	0
1994	631	3	0	2	1
1995	613	5	0	1	4
1996	581	2	1	1	0
1997	628	1	0	0	1
1991-1997	4,185[2]	24 (0.57%)	3	11	10

[1] Data at 31/3/98.

[2] For 21 (0.50%) of these reports (1991-1997) the most probable route of infection was transfusion abroad (not known to have been confirmed by

investigation of the implicated donations), and for 3 reports no information about the place of transfusion was provided.

Discussion and conclusions

The NBS of England and Wales issue over 2.5 million donations annually. The cases presented here underestimate the number of transfusion-transmitted HBV infections: HBV is often asymptomatic and not all acute HBV infections are diagnosed and reported to CDSC.

Surveillance of acute HBV infections shows that transfusion transmission of HBV in England and Wales does occur, but is rare. The contribution of this route of transmission to the total burden of acute symptomatic HBV is small and acute infections in donors cause the minority of transfusion-associated cases. A similar breakdown of causes of transfusion-transmitted HBV was observed by North London blood centre during 1985-1993 (John Barbara - personal communication).

Donor selection criteria aim to exclude individuals with recent risk factors for the acquisition of blood-borne infection. Persistent HBV infections often follow perinatal or childhood infection and therefore are less likely to be excluded by donor selection.

Testing donations for anti-HBc, as is routine in some other countries, would have detected most of the HBsAg negative infectious donations identified. Since anti-HBc testing would also detect non-infectious donations from donors with naturally acquired immunity to HBV: further tests would be needed to avoid unnecessary loss of donations.

The post-transfusion infection surveillance that is described in Chapter 4, and that forms the infectious part of the Serious Hazards of Transfusion (SHOT) scheme (Williamson LM, 1996), will continue to monitor post-transfusion HBV infections. Policies to vaccinate multiply transfused individuals (Salisburg & Begg, 1996) remain justified. Testing of donations for anti-HBc has been considered but not adopted to date in the UK. The findings of this survey suggest that this now warrants further consideration of the costs and benefits, as anti-HBc testing could prevent the majority of transmissions from donors at the HBsAg negative tail end of HBV carriage. One caveat to this is that HBsAg tests have improved in sensitivity during the last 5 years, and the HBsAg

negative period at the tail end of carriage may now be much shorter than in the earlier years included in this survey. Of the five reports of transfusion-transmitted HBV infection to the PTI surveillance (1995-1999, see Chapter 3), only one was concluded to be due to a donor in the tail end of carriage.

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CHAPTER 5. ESTIMATIONS OF THE RISK OF TRANSFUSION TRANSMITTED INFECTIONS 164

5.1 Introduction

Knowledge of the risks of transfusion transmitted viral infections is helpful in monitoring the safety of the blood supply and to evaluate the likely benefits of new strategies to improve transfusion safety. The current very low risk of transfusion-transmitted infections in the UK makes prospective study of transfusion recipients a prohibitively long and costly method to obtain accurate transmission rates (Table 1.2). Also, the results from direct observation are soon out of date as either the epidemiology of the infections considered, or transfusion service practices, change.

The advantages of estimating transmission risk using routinely available data and evidence-based assumptions include the speed and low cost, and the ease of revision in the light of new data or changing circumstances.

Generating estimates of the risk of transfusion-transmitted infections requires firstly identifying the circumstances that could allow an infectious donation to enter the blood supply, and secondly, assessing the likelihood of each, and then any, of the circumstances occurring.

In the UK, during the entire period of this study, all blood donations were tested for hepatitis B surface antigen (HBsAg), human immunodeficiency virus

antibody (anti-HIV) and hepatitis C antibody (anti-HCV) (and for Treponemal antibodies as a marker of syphilis infection). Donations with any of these markers detected by the testing performed were excluded from the blood supply. Even in the presence of such testing, several circumstances could lead to HBV, HCV or HIV infectious donations entering the blood supply:

1. *Sero-negative infectious donations.* A period of sero-negativity - the 'window period' - prior to detectable levels of antibody or antigen, follows infection with HBV, HIV or HCV. During acute, resolving, HBV infection there is a second HBsAg negative, infectious window, following the transient presence of detectable HBsAg in the blood. During the tail end of HBV carriage HBsAg may fall below detectable levels for a considerable period of time before HBV infectivity is lost (Hoofnagle, 1986). HBsAg testing cannot therefore be assumed to detect all established HBV infections and the risk of HBV infectious donations collected from sero-negative infectious donors during the tail end of HBV carriage should be included to give an overall risk estimate.

Although some patients have been described with HIV infection, and some with HCV infection, who have no antibodies to these infections, such cases are, so far, restricted to immunosuppressed individuals (e.g.Durand F, 2000). For this analysis, it has been assumed that HIV and HCV infections, once established in immunocompetent individuals, result in persistent antibody presence and therefore can always be detected by antibody testing, and that individuals who are known to be immunosuppressed, or have characteristics that suggest they are likely to be immunosuppressed, are excluded from donating blood.

2. *False negative test results.* Tests for HBsAg, anti-HIV and anti-HCV are never 100% sensitive and some positive samples will give false negative results. The high sensitivity of the tests chosen for blood donation testing, and the low prevalence of these markers in UK donations, result in a very high positive predictive value for a negative test result. As large numbers of donations are tested however, the low risk of a false negative should not be assumed to be negligible. The sensitivity of tests to infections in donors may alter if sub-types, or mutant strains, of infections that were not included during the tests' evaluations become more prevalent in the donor population. Sub-types and mutants do occur and can result in alarms about transfusion safety. The relative contribution of different test sensitivities to the overall risk of

infectious donations entering the blood supply is therefore of interest and should be monitored.

3. *Laboratory error.* Laboratory errors can result in a positive sample being credited with a negative result - either due to an error in sampling or conducting the test, or due to an error in recording test results. Controls on every part of the testing process and the information technology involved in recording results aim to prevent such errors occurring and going unnoticed. However, these may not always work, or may not prevent an unforeseen circumstance leading to the release of a positive donation, and the risk resulting from errors should be considered.

In this chapter, data from infection surveillance databases and from special surveys are used, along with estimates of the sensitivity and window periods of current tests, and the estimated rate of error in the testing process, to estimate the risk of HBV, HIV and HCV infectious blood donations entering the blood supply issued to hospitals from English blood centres between 1993 and 1998.

5.2 Methods

Study population

Information about all donations tested during six years, 1993 to 1998, at all blood centres in England (15 at the beginning of the period, reducing to 10 by the end of the period) was included in the study.

Donations were sub-classified into donations from new donors and donations from repeat donors. A repeat donor was a donor who had a recorded attendance as a donor previously. A new donor was a donor who had not attended previously according to that blood centre's current records, although, in some cases, such donors may have attended many years ago, or at another blood centre previously. A positive donation from a repeat donor did not always represent a seroconversion since the last attendance for three reasons. Firstly, not all repeat donors who have attended a donor session previously had given a donation (for example, if they failed haemoglobin tests) and been tested for all infections previously. Secondly, repeat donors who have had a marker of

infection detected by the blood service in the past, and been asked not to donate again, do occasionally re-donate (7% of positive donations from previously tested donors between 1/10/95 and 31/12/98 were from previously confirmed positive donors). Thirdly, as new tests are introduced into donation testing and the sensitivity of tests improve, donors who have not been tested previously or who were negative to previous test kits may be found to be positive (32% of positive donations from previously tested donors between 1/10/95 and 31/12/98 were from donors who had not been previously tested for the infection detected). Details about the testing of previous donations from positive donors were therefore sought so that they could be accurately classified as first-time tested donors and previously tested donors. Previously tested donors were sub-classified as donors who had seroconverted and donors who were, or may have been, seropositive at the time of the previous test and could not be shown to have seroconverted. It was not possible to similarly classify the total numbers of all donations tested from repeat donors into those from first time tested donors and those from previously tested donors. A portion of the denominator used in the incidence estimates may therefore not have been previously tested for anti-HCV and this may dilute the HCV incidence estimate a little. However a study at one blood centre of donations tested during 1993 found that only 1.8% of all donations from repeat donors had not been previously tested for HCV (Atrah, 1996): the effect on the results of such a small, and diminishing, amount of misclassification in the denominator is negligible and no adjustment to compensate for this was made.

Collection of data needed to estimate the risk of infectious donations entering the blood supply

Prevalence of HBsAg, anti-HCV and anti-HIV in new and repeat donors

The numbers of HBsAg, anti-HIV and anti-HCV seropositive donations from new and repeat donors and the numbers of donations tested from new and repeat donors during each year were obtained from surveillance databases and special surveys of HBsAg positive donations and anti-HCV positive donations and used to calculate the prevalence of each infection within donations from new and from repeat donors.

Incidence of HBsAg, anti-HCV and anti-HIV in new and repeat donors

Incidence rates in repeat donors were derived from observed seroconversions. Repeat donors who had seroconverted for anti-HIV were identified from surveillance reports to the NBS and to the Public Health Laboratory Communicable Disease Surveillance Centre (PHLS-CDSC) AIDS/HIV Centre. Repeat donors who had seroconverted for anti-HCV were identified by a retrospective survey of blood centre records (Soldan, 1998) prior to October 1995 and from the NBA/PHLS CDSC surveillance system from October 1995 to the end of 1998. The results of screening and confirmatory tests performed on the last negative, and the first positive, donation were reviewed for all cases of putative anti-HCV seroconversion. Cases with possible but not proven seroconversion, e.g. due to test batch variation, or unsupported interpretations of indeterminate test results were classified as probable false seroconversions, and were not included as seroconverters. The results of HBsAg tests on any previous donations from the donors of HBsAg positive donations were also collected either directly from blood centres or from reports to the infected donor surveillance and repeat donors who had seroconverted for HBsAg were identified. The criteria used to identify a seroconverter from their test results are shown in Table 5.1. A seroconverter was defined as a donor who had made a seropositive donation during the study period (1993-98) and had made a seronegative donation within the ten years prior to the positive donation. Some other similar studies conducted in other countries have classified as seroconverters only those donors whose positive donation and previous negative donation fell within the study period. This method of defining seroconverters within a study reduces the number of seroconverters, but, as the inter-donation interval for the excluded seroconverters is very long, the contribution these make to the risk of a window period donation may be negligible. To investigate the effect of only including seroconverters whose negative donation was within the study period, this approach was also tried and the resulting incidence rate estimates, and risk estimates, were compared. Incidence rates in repeat donors were calculated as the number of seroconverting donors divided by the total number of person years at risk. The number of person years at risk was calculated as the number

of donations made by repeat donors multiplied by an estimate of the average interval (in years) between donations from repeat donors (see below).

Table 5.1 Criteria for defining seroconverters from donation testing results.

Pre-seroconversion donation		Post-seroconversion donation		
HCV				
1. RIBA 3.0 non-reactive	and	RIBA 3.0 positive	} and	not PCR negative **if** < 12 months after pre-seroconversion donation
or				
2. ELISA non-reactive & RIBA 2.0 non-reactive	and	ELISA (of same manufacturer and generation as pre-seroconversion test) positive & RIBA 2.0 positive		
or				
3. ELISA 3.0 non-reactive	and	ELISA 3.0 positive & RIBA positive		
HBV				
1. Negative for HBsAg by EIA, or RIA	and	Positive for HBsAg by EIA or by RIA, confirmed by positivity for other HBV marker(s).	and	No evidence of false negative results pre-seroconversion
HIV				
1. Negative for anti-HIV by EIA	and	Positive for anti-HIV by EIA confirmed by alternative EIAs and positivity to Western Blot or PCR.		No evidence of false negative results pre-seroconversion

Incidence was estimated using seroconversions after a negative donation within the previous ten years and for the more recent three-year study period, after a negative donation within that three-year study period.

Because donors who seroconvert may have shorter or longer inter-donation intervals between their pre-seroconversion donation and their post-seroconversion donation than the majority of donors, the probability of a window period donation may actually be greater or less than the average probability that is calculated by the method described below (see “Probability of bleeding an infectious window period donation”, page 178). For example, if infected donors

had inter-donation intervals 3 times the length of ordinary inter-donation intervals, the chance of the final day of their inter-donation interval being during a randomly falling window period of X days during their inter-donation interval would be 1/3 the chance of the final day of a non-seroconverting donor's inter-donation interval being during a randomly falling period of X days during their inter-donation interval. The probability of a window period donation as calculated above was therefore multiplied by an adjustment factor S.

$$S = \frac{\text{inter-donation interval for non-seroconverting donors}}{\text{inter-donation interval for seroconverting donors}}$$

S was calculated for each infection using the mean inter-donation interval for non-seroconverting donors and the median inter-donation interval observed for seroconverters detected during the years 1996-98.

S_{HIV} = 315/514 = 0.61 (NB.mean interval for seroconverters =709, St dev =704)
S_{HCV} = 315/419 = 0.75 (NB.mean interval for seroconverters =577, St dev =407)

This adjustment was not applied to the calculations for HBV risk because, as explained on page 171, the inter-donation intervals of detected HBsAg seroconverters were biased towards shorter intervals due to the transient nature of HBsAg.

S_{HBsAg} (not used)= 315/154 = 2.05 (NB. mean interval for seroconverters = 175, St dev = 72)

If it is assumed that the detected HBsAg seroconverters are the lower ranking of all the (inferred) HBV incident donors with respect to inter-donation intervals, they occupy the bottom 37 % of inter-donation intervals. The mean inter-donation interval of the bottom ranking 37% of the anti-HIV and anti-HCV seroconverters (ranked by inter-donation interval) was 227 days. This artificially biased inter-donation interval for the HIV and HCV infected donors is much closer (1.3 times) to that observed for the biased sample of HBV infected donors, than the average for all HIV and HCV seroconverters (662 days - giving an interval 3.8 times the HBV sample). The assumption was therefore made that the total (63% unobserved) group of HBV infected repeat donors had a similar distribution of inter-donation intervals to HIV and HCV infected repeat

donors and that the value of S most appropriate for the HBV estimates was therefore calculated using the average for all anti-HIV and anti-HCV seroconverters.

S_{HBV} = 315/478 = 0.66 (NB. mean interval = 662, St dev = 613)

For the years for which seroconversions were identified from Infected Donor reports, and there was some underreporting, the numbers of seroconversions for each infection and for each year were adjusted for underreporting by multiplying the identified numbers by 1/the proportion of all infections in repeat donors that were reported during that year.

HBsAg adjustment

HBsAg is generally transient in individuals infected with HBV as adults and the HBsAg test will have reverted to being negative in many HBV infected donors by the time of their next donation. All the long term HBsAg testing of donations will identify carriers and only some of the donors with transient antigenaemia. The probability of detection of an incident infection by subsequent HBsAg testing therefore had to be calculated.

Other workers, including Korelitz et al (1997), have published estimates of HBV incidence using a method that takes transient antigenaemia into account by calculating the weighted probability that donation testing would detect seroconversion. Korelitz et al assumed that 70% of infected donors would have transient antigenaemia lasting an average of 63 days (the mid point of two published estimates, (Hoofnagle, 1978; Mimms, 1993)), that 25% of infected donors would have no antigenaemia and that 5% would have persistent antigenaemia.

In this study it was similarly assumed that 5% of donors would have persistent antigenaemia. For the remaining 95% of infections it was assumed that 85% would have typical transient antigenaemia lasting an average of 63 days and that 10% would have a heightened and more rapid clearance of antigen lasting just 30 days (Hoofnagle, 1986).

The chance that an incident HBV-infected donor would be detected by HBsAg testing was therefore:

Probability of detection as HBsAg seroconverter = (5%x1)+(85%xT_1)+(10%xT_2)

where,

T_1 = probability that a donor with typical transient antigenaemia is HBsAg positive at time of donation, and

T_2 = probability that a donor with rapid transient antigenaemia is HBsAg positive at time of donation

with,

$$T = \frac{\text{duration of antigenaemia}}{\text{Inter-donation interval}}$$

The average inter-donation interval for the 20 HBsAg seroconverting donors detected during 1996-1998 was 175 days (St dev 72). So,

T_1 = 63/175 = 0.36

T_2 = 30/175 = 0.17

and

Probability of detection as HBsAg seroconverter = (5% x 1) + (85% x 0.36) + (10% x 0.17)

= 0.373, or 37%

The observed HBsAg incidence rate was therefore multiplied by 1/0.373 = 2.68 to give an estimate of the total HBV incidence rate.

New donor risk factor estimation

The incidence of HIV and HCV in new donors cannot be measured directly from current routine test results (specialised testing such as anti-HCV avidity testing and de-tuned anti-HIV testing offer potential for direct identification of recent infections). An adjustment figure (Z) was calculated to represent the difference in incidence between new donors and old donors. This was applied to the incidence rates in repeat donors to produce an estimate of the incidence rates in new donors i.e. incidence in new donors = incidence in repeat donors x Z. Several methods were used to estimate Z.

New donor incidence multiplier method 1: The ratio of the frequency of acute HBV in donations from new donors to the frequency of acute HBV in donations from repeat donors was used to derive Z.

$$Z_1 = \frac{\text{Acute HBV donations per 100,000 donations from new donors}}{\text{Acute HBV donations per 100,000 donations from repeat donors}}$$

Using data from North London Blood Centre, 1993-1998 where 7 acute HBV donations were collected amongst 215,366 donations from new donors and 9 acute HBV donations were collected amongst 1,251,411 donations from repeat donors, Z was estimated as shown below.

$$Z_1 = \frac{7/2.15366}{9/12.51411} = \frac{3.25}{0.72} = 4.51$$

New donor incidence multiplier method 2: A method used in a study by Lackritz *et al* (1995) was used. This method is based on the understanding that at the start of testing, when no repeat donors have been excluded because of a positive test result, the seroprevalance of a persistent marker of infection is equivalent to the cumulative incidence of the infection. If the time at risk of infection has been the same for new donors and repeat donors, the ratio of the seroprevalence in new donors and repeat donors during the first period of testing can be used as an estimate of Z. The period of time used should not contain any repeat tests on the same individual. Lackritz *et al* took the first year of testing. As donors can donate up to 3 times each year (every 16 weeks), and some repeat donors do donate more than once a year, the ratio for each calendar quarter during the first 15 months of testing was calculated to check the period of testing used for calculating Z did not include any quarter that showed a ratio that may have been inflated by inclusion of negative repeat donors in the denominator for the repeat donor prevalence (see table 5.2). The prevalence of anti-HIV amongst new donors during the first year of testing (Oct-85-Sep-86) was 5.15 times that amongst repeat donors. During the first six months and second six months of testing the prevalence in new donors was 3.67 times that amongst repeat donors, and 6.08 times that amongst repeat donors respectively. The prevalence in new donors in 1997 was 6.73 times the prevalence in repeat donors, and has remained at around this level since (ratio for 1987 to 1997 = 8.43). Z_2 was therefore taken as the ratio for the first six months as by the second six month period the ratio had increased towards the ratio observed once repeat donors with prevalent infections had been excluded from the donor panel. It was assumed that when HIV testing was introduced all donors had been at risk of HIV infection for 6 years, since 1980.

$Z_{2(HIV)}$ = Anti-HIV prevalence in new donors during 1st 6 months of testing
Anti-HIV prevalence in repeat donors during 1st six months of testing

$$Z_{2(HIV)} = 3.67$$

Table 5.2 HIV prevalence during first 15 months of anti-HIV testing of blood donations.

Time period	Total tested donations	New donations	Donations from repeat donors	Total HIV positives	New donor HIV positives	Repeat donor HIV positives	Prevalence per 10,000 repeat donor donations	Prevalence per 10,000 new donor donations	Ratio of new donor to repeat donor prevalence
Q1 (Oct-Dec'85)	527969	63356	464613	8	3	5	0.11	0.47	4.40
Q2 (Jan-Mar'86)	565299	67836	497463	10	3	7	0.14	0.44	3.14
Q3 (Apr-Jun'86)	560966	73914	487052	12	6	6	0.12	0.81	6.59
Q4 (Jul-Sep'86)	558289	67856	490433	20	9	11	0.22	1.33	5.91
Q5 (Oct-Dec'86)	561962	77642	484320	27	11	16	0.33	1.42	4.29
Q1-Q2	1093268	131192	962076	18	6	12	0.12	0.46	3.67
Q3-Q4	1119255	141770	977485	32	15	17	0.17	1.06	6.08
Q1-Q4	2212523	272962	1939561	50	21	29	0.15	0.77	5.15
Q2-Q5 (86)	2246516	287248	1959268	69	29	40	0.20	1.01	4.95
Q1-Q5	2774485	350604	2423881	77	32	45	0.19	0.91	4.92
1987	2223713	287553	1936160	12	6	6	0.03	0.21	6.73
1987-1997	27022326	3380026	23642300	236	129	107	0.05	0.38	8.43

Data about anti-HCV positive donations per month were not available for the first year of anti-HCV testing (September 1991 to August 1992). The prevalence of anti-HCV amongst new donors during the first full year of testing (1992) was 4.05 times that amongst repeat donors. Adjusting this ratio by the increase observed in the anti-HIV data between the first six month's ratio and the first year's ratio resulted in an estimate of the ratio for the first six months for anti-HCV of 2.88 (=4.05 x (3.67/5.15)).

It was assumed that when HCV testing was introduced all donors had been at risk of HCV infection since the age of 15 years. Repeat donors have an average age of approximately 42 years and new donors have an average age of approximately 33 years. The new donor incidence multiplier for anti-HCV was therefore estimated as the estimated prevalence ratio for the first six months of 1992 multiplied by the difference in the time at risk for new donors and repeat donors.

$Z_{2(HCV)}$=(Prev new dons 1992)x(Ratio for HIV 1st 6mo)x(Repeat dons yrs at risk)
(Prev repeat dons 1992) (Ratio for HIV 1st 12 mo) (New dons yrs at risk)

$$Z_{2(HCV)} = 4.05 \times 0.71 \times 1.5 = 4.32$$

New donor incidence multiplier method 3: A third method was adapted from Cumming *et al*. Cumming *et al* estimated incidence by using the time at risk to convert prevalence rates (the results of cumulative incidence) to annual incidence rates. Half the total time since the beginning of HIV infection spread and the present time was used as a measure of time at risk for new (and previously untested) donors. Cummings *et al* (1989) proposed using half the total time in order to compensate for the increasing, and non-linear, risk of HIV infection over this time. We applied this method to 1993-1998 prevalence data for repeat donors and new donors in England, assuming HIV infection spread began in England in 1980, that new donors had been at risk of HCV infection since the age of 15, and that new donors had been at risk of HBV infection since birth. Z_3 was then estimated by dividing the annual incidence rate for new donors by the annual incidence rate for repeat donors. For HCV - an infection with a relatively high prevalence in repeat donors - the comparable "annual incidence" for repeat donors was the sum of the incidence calculated from seroconversions and annual incidence calculated from prevalence as for new donors.

$$Z_{3HIV} = \frac{\text{annual incidence new donors}}{\text{annual incidence repeat donors (as in Table 5.5)}} = 1.82$$

where,

$$\text{Annual incidence new donors} = \frac{\text{prevalence during 1993-1998}}{\text{average annual time at risk}}$$

$$= 0.69/100{,}000\text{pys}$$

with,

$$\text{Average annual time at risk} = \frac{\text{(Sum of (each year in study-1980)/6)}}{2}$$

$$= 7.8\text{yrs}$$

and

$$Z_{3HCV} = \frac{\text{annual incidence new donors}}{\text{annual incidence repeat donors}} = 7.68$$

where,

$$\text{Annual incidence new donors} = \frac{\text{prevalence during 1993-1998}}{\text{average annual time at risk}}$$

= 3.92/100,000pys

with,

Average annual time at risk = (average age – age first at risk)

= (33-15) = 18yrs

and ,

Incidence repeat donors =

$$\text{Incidence repeat donors} = \text{Incidence of seroconversion} + \frac{\text{prevalence during 1993-1998}}{\text{average annual time at risk}}$$

= 0.26 [from Table 5.5] + 0.25 = 0.51/100,000pys

and

$$Z_{3HBV} = \frac{\text{annual incidence new donors}}{\text{annual incidence repeat donors (as in Table 5.5)}}$$

= 2.70

where,

$$\text{Annual incidence new donors} = \frac{\text{prevalence during 1993-1998}}{\text{average annual time at risk}}$$

= 1.1/100,000pys

with,

Average annual time at risk = (average age – age first at risk)

= (33-0) = 33

New donor incidence multiplier method 4: A fourth method of estimating Z was adapted from Dax *et al* (1992). This method used prevalence data and probability of donating during the seronegative window period stage of infection (i.e the seronegative window period as a proportion of the total time course of infection for new donors, and the seronegative window period as a proportion of the inter-donation interval for repeat donors). Dax *et al* assumed that the number of first-time donors who donate whilst in the window period is the product of the proportion of the time course of infection during which the tested marker is not present and the prevalence of the marker in new donors, and that the number of repeat donors who donate whilst in the window period is the product of the proportion of the inter-donation interval during which the tested marker is not present and the prevalence of the marker in repeat tested donors. Z_4 was estimated as the ratio of these numbers. Again, because of the high

prevalence in repeat donors (due to accumulated past incidence), the comparable calculation for repeat donors included incidence derived from prevalence.

$$Z_4 = \frac{\text{window period donations new donors}}{\text{window period donations repeat donors}}$$

with, for HIV

Window period donations new donors = (22/(10 x 365)) x (89/1,662,238) = 0.032/100,000

WP donations repeat donors = (22/(45 x 7)) x (42/12,939,000)
= 0.023/100,000

Z_{4HIV} = 1.39

with, for HCV

WP donations new donors = (66/(25 x 365)) x (1,172/1,662,238)
= 0.51/100,000

WP donations repeat donors = ((66/(45 x 7)) x (29/12,939,000)) + ((66/(25 x 365)) x (570/12,938,971)) = 0.047 + 0.032 = 0.079/100,000

Z_{4HCV} = 6.46

with, for HBV

WP donations new donors = (110/(25 x 365)) x (607/1,662,238)
= 0.44/100,000

WP donations repeat donors = (110/(45 x 7)) x (46/12,939,000)
= 0.12/100,000

Z_{4HBV} = 3.67

Table 5.3 summarises the estimates of Z obtained from applying these methods to English data. The value of Z used for our "standard" estimates was the mean value for each infection.

Table 5.3 Values of new donor window period risk multiplier (Z)

	HBV	*HCV*	*HIV*
Method 1: Direct observation of acute infections	4.51	NA	NA
Method 2: Cumulative incidence at start of testing	NA	4.32	3.67
Method 3: Incidence from prevalence and time at risk.	2.70	7.68	1.82
Method 4: Prevalence and WP as proportion of total infection course	3.67	6.46	1.39
Mean (all available methods)	***3.63***	***6.15***	***2.29***

The overall incidence rate of an infection was calculated as the weighted average of the incidence rates in new and repeat donors.

Inter-donation intervals

The average inter-donation interval estimates was derived from data provided from one blood centre for the three-year period 1993-1995. 606,193 donations were collected from 173,777 repeat donors, giving 3.49 donations per donor over 3 years, or 3.39/3 = 1.16 donation per year. The average inter-donation interval was estimated as 365/1.16 = 314 days or 45 weeks (0.86 years).

The inter-donation interval for the seroconverters was calculated directly from the dates of the last negative and first positive donation.

Estimation of risk of infectious donations entering the blood supply

Probability of bleeding an infectious window period donation

The probability of a seronegative donation being made during the window period was calculated firstly (WP method 1) as equal to the incidence of infection in donors, multiplied by estimates of the infectious window periods during acute infection.

$$WP\ risk_1 = \text{incidence} \times \text{window period}$$

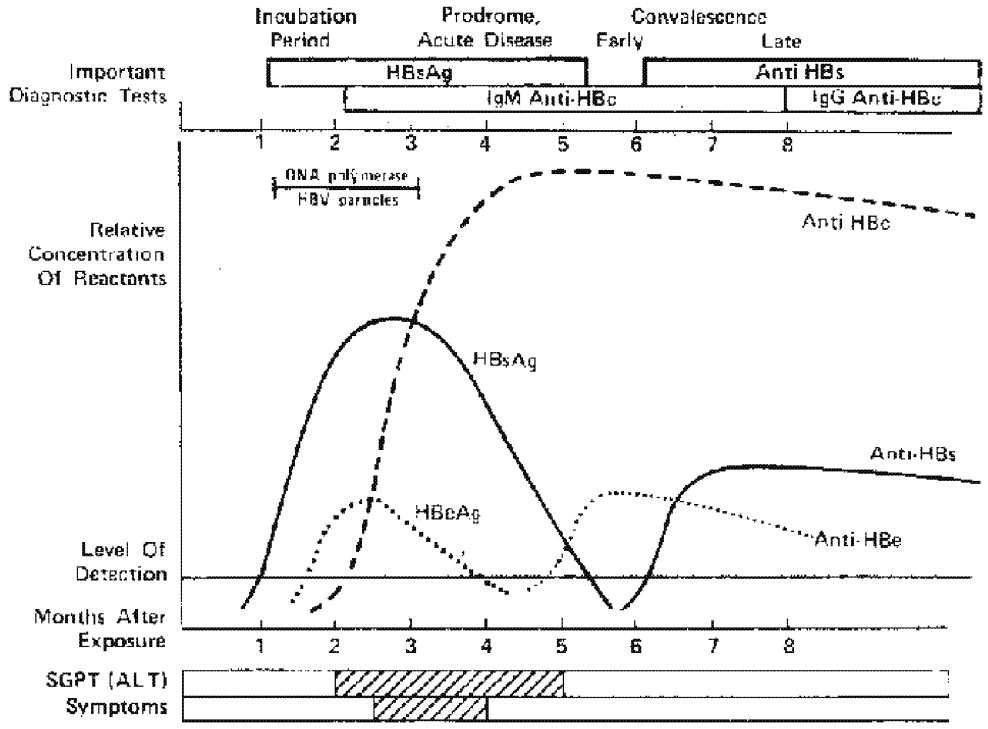
Tests used during the study period detect anti-HIV and anti-HCV 22 days (Busch, 1995) and 66 days (Barrera, 1995) after HIV and HCV infection respectively. The upper and lower values of these window periods were 6 days and 38 days for anti-HIV and 54 days and 192 days for anti-HCV.

The patterns of infectivity and serological markers for HBV are slightly more complex. Figure 5.1 shows the patterns of serological markers during acute, resolving infection. Three windows during which infectious blood could be collected were considered: the "early acute window" after exposure and prior to any serological markers, the "late acute window" of resolving infection when HBsAg is below detectable levels but anti-HBs is not present and some infectivity remains, and the "tail-end window" at the end of HBsAg carriage when HBsAg falls below detectable levels in advance of total loss of infectivity.

Current tests detect HBsAg a median of 59 days after HBV infection, with upper and lower values of 37 days and 87 days respectively (Mimms, 1993).

Figure 5.1 Serological and clinical patterns observed during acute HBV infection.

(From Manual of Clinical Microbiology, Lennete, Balows, Hausler and Shadomy)



The period between loss of HBsAg and loss of infectivity during resolving acute infections - the late acute window - was estimated to be another 30 days (range 10 to 50). The average effective total window period during acute infection was calculated as the early acute window for all infections plus the late-acute window for 95% of infections expected to resolve and therefore to pass through this late acute window.

Total HBV acute window = 59 + (0.95 x 30) = 87.5 days

With lower and upper values of 46.5 days (37 + (0.95 x 10) and 134.5 days ((87 + (0.95 x 50).

Donations bled immediately after a donor has been infected are unlikely to contain enough viruses to be infectious. This period immediately after infection when nucleic acids cannot be recovered from the blood is often called the "eclipse" period, and results in the infectious window period being shorter then the total window period from infection to positive serological markers. It is thought likely that this eclipse period is proportional in length to the total window period, however, for simplicity and in the absence of specific data a 7-day non-infectious period immediately after infection was taken for each virus. The antibody/antigen window period estimates, and the lower value for these estimates, were therefore decreased by seven days to give an infectious window period.

Upper and lower limits to the risk estimates were calculated using the extremities of the ranges of the incidence rate estimates, and of the ranges of the window periods. 95% credibility intervals for the risk estimates were calculated by simulation to reflect the sampling variability of the incidence and prevalence estimates and uncertainty about the infectious window period. This was done by using Poisson distributions with observed rates for the number of seroconversions and the prevalence numerators, and a triangular distribution for the infectious window period. The inter-donation interval, proportion of donations from new donors, time at risk adjustment factor and number of donors tested during the first year of testing were kept constant.

An alternative approach to estimating the risk of a window period (WP method 2) was also used. This approach did not work from incidence, but by

summing the probability of previous donations from seroconverting donors having been made during the window period.

$$\text{WP risk}_2 = \frac{\text{number of SC x (WP/median pre-SC donation interval)}}{\text{number of repeat donor donations}}$$

This method has been used by Gluck, 1998 and Muller-Breitzeutz, 2000. This method has the advantage of directly accommodating the effect of longer inter-donation intervals in donors who seroconvert than in other donors.

Probability of test failure or error

The risk of a seropositive donation not being identified by testing was equal to the probability of false negative test result estimated using the sensitivity of the test and the prevalence of the marker.

$$\text{FN risk} = \frac{\text{(prevalence)}}{\text{sensitivity}} \text{ x (1-sensitivity)}$$

Upper and lower limits on the risk were calculated using the upper and lower 95% confidence intervals for the prevalence rate. The sensitivity of anti-HCV tests was 99% (PHLS, 1995) and the sensitivity of anti-HIV tests was 99.5%. The sensitivity of HBsAg tests was assumed to be 1.

Process error was defined as any technical or human error in the testing, recording, or discarding of infectious donations. The error rate was estimated to be 0.5%, based on data from USA (Linden, 1994 a&b). No published rates of technical or human errors in the testing, recording, or discarding of donations in the UK were available. There is evidence that errors do still occur in England: one case of transfusion transmitted HCV by an anti-HCV positive donation released by an error in the testing process has been documented (see Chapter 3) and two incidents of HCV testing failures allowing donations from HCV infected donors to be released (neither resulting in infection of a recipient) have been reported. The risk of a Process Error involving an infectious donation was equal to the estimated probability of a Process Error (0.5%) multiplied by the probability of a donation being seropositive.

$$\text{PE risk} = \text{prevalence x error rate}$$

Probability of HBsAg negative donations during tail-end carriage

The frequency and duration of HBsAg negative, infectious, periods at the tail end of HBV carriage in blood donors was not known. The relative frequency of observed transfusion transmitted HBV by these two causes was used to scale-up the estimates of risk due to donations from acute donors to the overall risk due to donations from acute donors and donations from tail-end carriers. A review of all cases of reported acute HBV infection associated with transfusion in England and Wales between 1991 and 1997 (Soldan, 1999) found 11 of 14 (79%) cases were due to donations from donors with HBV carriage and 3 were due to donations from donors with acute HBV infection (none were due to errors) (see Chapter 4). A similar observation has been made by North London blood centre where 10 of 13 (77%) cases between 1985 and 1993 were due to donations from donor bled during the infectious, but HBsAg negative, period at the tail-end of HBsAg carriage (Barbara, personal communication). The risk of infectious donations from tail-end carriers was therefore estimated by multiplying the risk of window period donations by 11/3 = 3.67. The upper and lower limits for this estimate were calculated using the upper and lower limits of the window period risk and the upper and lower limits of the 95% confidence interval of the proportion of observed transmission due to carriers.

Sensitivity analysis

The effect of uncertainty in the data and assumptions used in the estimations was investigated by varying the parameters used and recording the absolute and percentage change in the resulting estimates. Two groups of variations were considered.

Firstly, variations were made in the parameters (usually derived from other data and assumptions) that were used for which there was little supporting evidence, and therefore may have been incorrect. Several parameters in this category were varied. The accuracy with which incidence can be derived from observations of reported seroconversions in repeat donors can be questioned (as discussed in chapter 4). In order for a new infection to be detected the donor has to donate once before infection and once after infection. Further more, the criteria used to define a seroconversion were designed to exclude the

relatively large numbers of "apparent" seroconversions, and the requirement for documented proof of a change from negative to positive, comparable, serology, may have excluded some true seroconversions as well as many "apparent" seroconversions. The number of seroconversions is therefore likely to be an underestimate of the true number of new infections in the person years observed. A 50% and a 100% increase in the numbers of new infections entering the incidence calculations was used in the sensitivity analyses to investigate the effect on the resulting risk estimates of a higher incidence rate. Another source of possible error in the incidence estimates was the derivation - rather than observation - of the person years at risk. The mean inter-donation interval was used, but the estimate of the mean may have been wrong, and the use of the mean rather than the median may also have resulted in error in the incidence rate denominator. A 20% increase and decrease in the person years at risk entered into the incidence calculations was used in the sensitivity analyses to investigate the effect on the resulting risk estimates of a varied true number of person years at risk. The new donor multiplier was a very uncertain parameter. The upper and lower estimates of the new donor multiplier obtained from the various methods described earlier was used in the sensitivity analyses to investigate the effect on the resulting risk estimates of the uncertainty in this parameter. The rate of errors in blood centres that would allow the release of positive donations is not well known. Errors are known to have occurred and the rate used in the best estimates was in line with published rates and observations within the blood service. However, this is contentious and the rate could be higher of lower. A 100% increase (i.e. 1 error every 100 donations tested) and decrease (i.e. no errors) in the error rate was used in the sensitivity analyses to investigate the effect on the resulting risk estimates of different error rates.

Secondly, variations were made in parameters that were relatively well known (usually observed), but that may change over time. Several parameters in this category were varied. The prevalence and incidence of infection markers in blood donations may change over time. During the period considered, the prevalence of anti-HCV in blood donations collected in England and Wales was declining (from 17.9 to 6.8 positives per 100,000), the prevalence of anti-HIV was not changing, but did fluctuate from year to year with minimum of 0.7 to a maximum of 1.1, and the prevalence of HBsAg was falling slightly from 5.0 to

4.5 positives per 100,000 donations. The overall incidence of each infection in repeat donors was not obviously changing over this period, but may change in the future depending on the epidemiology of these infections in the donor population and on donor recruitment and selection practices. A 50% rise and fall in prevalence (in all donations) and incidence (in repeat donors) of infection in blood donations was used in the sensitivity analyses to investigate the effect on the resulting risk estimates of changing frequency of infection in the donor population. Eleven percent of donations were collected from new donors over the period studied: this was consistent each year. The proportion of donations collected from new donors may change in the future as donor recruitment and selection practices change to meet the demands for blood. A 50% rise and fall in the proportion of donations collected from new donors (i.e. from 5.5% to 16.5) was used in the sensitivity analyses to investigate the effect on the resulting risk estimates of changing proportions of donations collected from new donors. Serological tests are, in general, expected to continue improving in sensitivity and in the detection of early window period infections. A 20% and 50% reduction in window period, and a 20% and 50% improvement in sensitivity were used in the sensitivity analyses to investigate the effect on the resulting risk estimates of improvements in test performance.

Estimates for the variations described above in each parameter, and for the range of all parameters in each category, and for all parameters in both categories together, were produced.

5.3 Results

Prevalence of infection

During the six-year period 1993-1998, English blood centres tested 14,601,238 donations: 12,939,000 (89%) of these donations were from repeat donors and 1,662,238 (11%) were from new donors. A total of 2,621 (0.02%) donations were found to have confirmed markers of HIV (145, 0.99 per 100,000), HCV (1,771, 12.1 per 100,000) or HBV (705, 4.83 per 100,000) infection.

Table 5.4 shows the prevalence rates of markers of HBV, HCV and HIV infection in blood donations in England, 1993-1998.

Table 5.4 Prevalence of HBsAg, anti-HCV and anti-HIV in blood donations in England 1993-98.

Donation type	*1993-1995*			*1996-1998*			*1993-1998*		
	Tested (1,000s)	*Pos*	*prev. per 100,000*	*Tested (1,000s)*	*Pos*	*prev. per 100,000*	*Tested (1,000s)*	*Pos*	*prev. per 100,000*
HBsAg									
From repeat donors	6,361.9	41	0.64	6,577.1	57	0.87	12,939.0	98	0.76
From new donors	870.2	322	37.00	792.0	285	35.98	1,662.2	607	36.52
All donations	7,232.1	363	5.02	7,369.1	342	4.64	14,601.2	705	4.83
Anti-HCV									
From repeat donors	6,361.9	414	6.51	6,577.1	185	2.81	12,939.0	599	4.63
From new donors	870.2	727	83.54	792.0	445	56.18	1,662.2	1,172	70.51
All donations	7,232.1	1,141	15.78	7,369.1	630	8.55	14,601.2	1,771	12.13
Anti-HIV									
From repeat donors	6,361.9	30	0.47	6,577.1	26	0.40	12,939.0	56	0.43
From new donors	870.2	49	5.63	792.0	40	5.05	1,662.2	89	5.35
All donations	7,232.1	79	1.09	7,369.1	66	0.90	14,601.2	145	0.99

Incidence of infection

Based on data from one blood centre about the number of donors tested during 1993-1995, the average inter-donation interval for repeat donors over that three-year period was estimated to be 45 weeks (average number of donations per year per repeat donor = 1.16).

The new donor incidence adjustments (Z) used were 3.63 for HBV, 6.15 for HCV and 2.29 for HIV.

Table 5.5 shows the incidence rates of seroconversion for HBsAg, anti-HCV and anti-HIV in repeat blood donors in England, 1993-1998.

Table 5.6 shows the estimated incidence in new donors, and the weighted incidence in all donors in England, for the 2 three year periods and the total study period 1993-1998.

Estimates of risk of donations from infected donors entering the blood supply

Tables 5.7a), b) and c) show estimates of the frequency of donation from a) new donors, b) repeat donors and c) all donors with HIV, HBV or HCV infections entering the blood supply for the periods 1993-95, 1996-98 and 1993-98.

Upper and lower limits of the ranges were calculated using the 95% confidence interval for the incidence rates, the range of the length of the window periods during acute infection, the upper and lower limits of the 95% confidence interval for the prevalence rates. Upper and lower limits of the range on the total (combined) risks were calculated using the upper and lower limits of the component risks.

Figure 5.2 shows the proportion of the total calculated risk that was due to each component of risk.

Table 5.5 Incidence of seroconversion for HBsAg, anti-HCV and anti-HIV in repeat donors in England, 1993-98.

	1993-1995			*1996-1998*			*1993-1998*		
	Person years	*No. of sero's*	*incidence per 100,000pys*	*Person years*	*No. of sero's*	*incidence per 100,000pys*	*Person years*	*No. of sero's*	*incidence per 100,000pys*
HBsAg	5,505,515	25	0.4628	5,691,697	20	0.3591	11,197,212	46	0.4101
Anti-HCV	5,505,515	14	0.2543	5,691,697	15	0.2691	11,197,212	29	0.2618
Anti-HIV	5,505,515	15	0.2725	5,691,697	27	0.4744	11,197,212	42	0.3751

Table 5.6 Estimated incidence in new donors, and weighted incidence in all donors.

	1993-1995		*1996-1998*		*1993-1998*	
	incidence in new donors	*incidence in all donors*	*incidence in new donors*	*incidence in all donors*	*incidence in new donors*	*incidence in all donors*
HBsAg	1.2407	1.6333	0.9627	1.2349	0.8590	1.4286
Anti-HCV	1.5639	0.4119	1.6550	0.4181	0.8590	0.4153
Anti-HIV	0.6239	0.3147	1.0863	0.5401	0.8590	0.4302

Table 5.7a) Estimates of the frequency of donations from NEW donors with HIV, HBV or HCV infections entering the blood supply (1993-1998).

	1993-1995	1996-1998	1993-1998
a) HBV			
Risk of donation from infected donor per 100,000 donations:			
- due to window periods of acute infection	0.655	0.508	0.581
95% credibility interval	0.413 - 1.050	0.300 - 0.836	0.421 - 0.892
- due to test error	0.000	0.000	0.000
- due to process error	0.185	0.180	0.183
Range	0.165 - 0.205	0.159 - 0.201	0.168 - 0.197
- total	0.840	0.688	0.763
Range	0.578 - 1.255	0.459 - 1.037	0.589 - 1.089
- estimated number of HBV infected donations	7	5	13
Range	5 - 11	4 - 8	10 - 18
b) HCV			
Risk of donation from infected donor per 100,000 donations:			
- due to window periods of acute infection	0.189	0.201	0.195
95% credibility interval	0.131 - 0.658	0.137 - 0.677	0.159 - 0.623
- due to test error	0.844	0.568	0.712
Range	0.783 - 0.905	0.515 - 0.620	0.672 - 0.753
- due to process error	0.418	0.281	0.353
Range	0.388 - 0.448	0.255 - 0.307	0.333 - 0.373
- total	1.451	1.049	1.260
Range	1.301 - 2.011	0.907 - 1.604	1.163 - 1.748
- estimated number of HCV infected donations	13	8	21
Range	11-18	7 - 13	19 - 29
c) HIV			
Risk of donation from infected donor per 100,000 donations:			
- due to window periods of acute infection	0.016	0.027	0.022
95% credibility interval	0.0073 - 0.0419	0.0141 - 0.0686	0.0117 - 0.0527
- due to test error	0.028	0.025	0.027
Range	0.020 - 0.036	0.018 - 0.033	0.021 - 0.033
- due to process error	0.028	0.025	0.027
Range	0.020 - 0.036	0.018 - 0.033	0.021 - 0.032
- total	0.072	0.078	0.075
Range	0.048 - 0.114	0.049 - 0.119	0.0542 - 0.118
- estimated number of HIV infected donations	1	1	1
Range	0.4 - 1.0	0.4 - 0.9	0.9 - 2.0

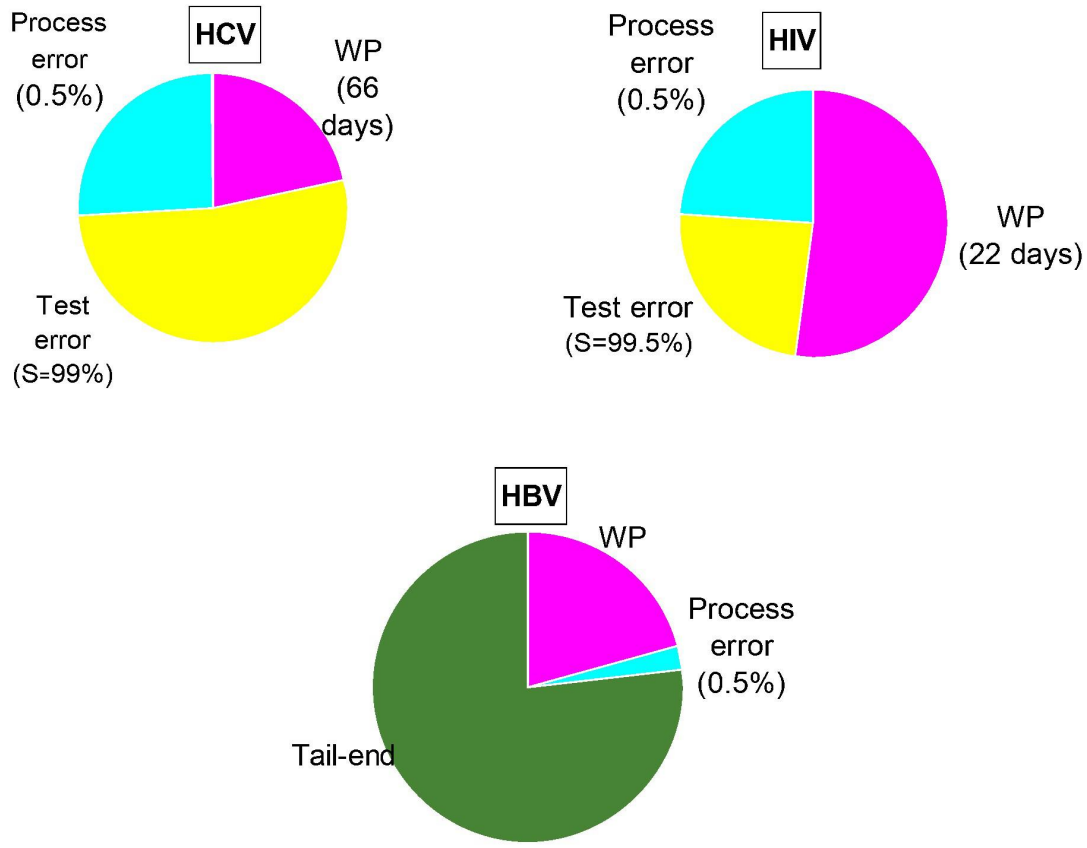
Table 5.7b) Estimates of the frequency of donations from REPEAT donors with HIV, HBV or HCV infections entering the blood supply (1993-1998).

	1993-1995	1996-1998	1993-1998
a) HBV			
Risk of donation from infected donor per 100,000 donations:			
- due to window periods of acute infection	0.180	0.140	0.160
95% credibility interval	0.114 - 0.289	0.083 - 0.230	0.116 - 0.246
- due to test error	0.000	0.000	0.000
- due to process error	0.003	0.004	0.004
range	0.002 - 0.004	0.003 - 0.006	0.003 - 0.005
- total	0.184	0.144	0.164
range	0.116 - 0.293	0.086 - 0.236	0.119 - 0.251
- estimated number of donations	12	9	21
range	7 - 19	6 - 15	15 - 32
b) HCV			
Risk of donation from infected donor per 100,000 donations:			
- due to window periods of acute infection	0.031	0.033	0.032
95% credibility interval	0.021 - 0.107	0.022 - 0.110	0.026 - 0.101
- due to test error	0.066	0.028	0.047
range	0.059 - 0.072	0.024 - 0.033	0.043 - 0.051
- due to process error	0.033	0.014	0.023
range	0.029 - 0.036	0.012 - 0.016	0.021 - 0.025
- total	0.129	0.075	0.102
range	0.110 - 0.215	0.058 - 0.159	0.090 - 0.177
- estimated number of donations	8	5	13
range	7 - 14	4 - 10	12 - 23
c) HIV			
Risk of donation from infected donor per 100,000 donations:			
- due to window periods of acute infection	0.007	0.012	0.009
95% credibility interval	0.0032 - 0.0183	0.0061 - 0.0299	0.0051 - 0.0230
- due to test error	0.002	0.002	0.002
range	0.0015 - 0.0032	0.0012 - 0.0028	0.0016 - 0.0028
- due to process error	0.002	0.002	0.002
range	0.0015 - 0.0032	0.0012 - 0.0028	0.0016 - 0.0028
- total	0.012	0.016	0.014
range	0.006 - 0.025	0.009 - 0.036	0.008 - 0.029
- estimated number of donations	1	1	2
range	0.4 - 1.6	0.6 - 2.3	1.1 - 3.7

Table 5.7c) Estimates of the frequency of donations from ALL donors with HIV, HBV or HCV infections entering the blood supply (1993-1998).

	1993-1995	1996-1998	1993-1998
a) HBV			
Risk of donation from infected donor per 100,000 donations:			
- due to window periods of acute infection	0.235	0.182	0.208
95% credibility interval	0.150 - 0.380	0.109 - 0.303	0.153 - 0.323
- due to test error	0.000	0.000	0.000
- due to process error	0.024	0.024	0.024
range	0.023 - 0.028	0.021 - 0.026	0.022 - 0.026
- due to tail end carriers	0.860	0.667	0.762
range	0.581 - 7.547	0.160 - 2.079	0.208 - 2.701
- total	1.118	0.874	0.994
range	0.753 - 7.954	0.290 - 2.408	0.383 - 3.050
- equivalent to 1 in x donations	89,424	114,480	100,616
range	12,572 - 132,801	41,534 - 345,161	32,784 - 260,960
- estimated number of donations	81	64	145
range	54 - 575	21 - 177	56 - 445
b) HCV			
Risk of donation from infected donor per 100,000 donations:			
- due to window periods of acute infection	0.049	0.052	0.050
95% credibility interval	0.034 - 0.173	0.036 - 0.178	0.042 - 0.164
- due to test error	0.154	0.090	0.123
range	0.151 - 0.169	0.080 - 0.093	0.117 - 0.128
- due to process error	0.076	0.044	0.061
range	0.075 - 0.084	0.039 - 0.046	0.058 - 0.064
- total	0.280	0.186	0.233
range	0.259 - 0.425	0.155 - 0.317	0.217 - 0.356
- equivalent to 1 in x donations	357,688	537,791	428,305
range	235,183-386,100	315,259-645,161	281,057-480,405
- estimated number of donations	20	14	34
range	19 - 31	11 - 23	32 - 52
c) HIV			
Risk of donation from infected donor per 100,000 donations:			
- due to window periods of acute infection	0.008	0.014	0.011
95% credibility interval	0.004 - 0.021	0.007 - 0.035	0.006 - 0.027
- due to test error	0.005	0.005	0.005
range	0.004 - 0.007	0.003 - 0.006	0.004 - 0.006
- due to process error	0.005	0.005	0.005
range	0.004 - 0.007	0.003 - 0.006	0.004 - 0.006
- total	0.018	0.023	0.021
range	0.012 - 0.035	0.014 - 0.046	0.014 - 0.038
- equivalent to 1 in x donations	5,422,019	4,365,928	4,823,425
range (millions)	2.90 - 8.13	2.18 - 7.19	2.62 - 6.99
- estimated number of donations	1	2	3
range	0.9 - 2.5	1.0 - 3.4	2.1 - 5.6

Figure 5.2 Components of the risk of donations from infected donors entering the blood supply.



The results of the alternative window period method (method 2) for the risk of window period donations from repeat donors, along with the comparable results from window period method 1 are shown in table 5.8. The results of the incidence method without adjustment (S), were - as expected - higher than the results of the alternative method. The amount by which they were higher reflected the extent to which the inter-donation intervals of seroconverters were greater than of other donors. After adjustment for this difference, the incidence method estimates were the same as the alternative method's results. It is worth noting that if the mean rather than the median inter-donation intervals for seroconverting donors were used to calculate the adjustment factor S, the results of the incidence method were lower (73%) than the results of the alternative method.

Table 5.8 Results of window period risk estimates method 2.

Window period risk in repeat donors per 100,000 donations	***1993-1995***	***1996-1998***	***1993-1998***	% of method 2
a) HBV				
Method 2	0.0674	0.0523	0.0597	
Method 1 - before adjustment (S)	0.1020	0.0791	0.0904	151%
Method 1 - after adjustment (S)	0.0673	0.0522	0.0596	100%
b) HCV				
Method 2	0.0310	0.0328	0.0319	
Method 1 - before adjustment (S)	0.0411	0.0435	0.0423	133%
Method 1 - after adjustment (S)	0.0308	0.0326	0.0317	99%
c) HIV				
Method 2	0.0069	0.0120	0.0095	
Method 1 - before adjustment (S)	0.0112	0.0195	0.0154	163%
Method 1 - after adjustment (S)	0.0068	0.0119	0.0094	99%

HBV risk due to tail-end of carriage

Based on the ratio of the causes of observed transfusion transmitted HBV infections (due to donations from acute donors and donations from tail-end carriers), the risk of donations from tail end carriers was estimated to be 0.76 per 100,000 donations (range with 95% confidence limits of proportion acute amongst observed, 0.21 to 2.7 per 100,000).

Sensitivity analysis

1. Weakly supported parameters

Identification of seroconverters for incidence estimates

If seroconverters were identified - as in some studies - as positive repeat donors with a previous negative donation during the study period rather than within the past 10 years (as above), the numbers of seroconverters and the length of the inter-donation intervals for seroconverters were reduced. Table 5.9 shows the number of seroconverters, the values for S (adjustment to allow for different inter-donation intervals for seroconverters) and the resulting window period risk estimates and overall risk estimates for the 1996-98 period with the seroconverters identified as positive repeat donors with a negative donation within the study period. For HCV the number of seroconverters was reduced and the median inter-donation interval (and therefore S) changed little: the risk

estimate therefore reduced. For HIV the number of seroconverters reduced by a greater amount and the inter-donation interval also decreased greatly (and S increased) so the resulting risk estimates were reduced more markedly. Estimates for HBV were not re-calculated in this way as detected seroconverters for HBsAg were of short inter-donation intervals (seroconverter detection only affected by 2%, by fall from 4 to 1 for the first year of the period) due to the transient nature of HBsAg and this revision was not applicable.

Table 5.9 Changed criteria (3 year period) for identifying seroconversions for incidence.

	a) HBV[1]		*b) HCV*		*c) HIV*	
		% of "best"		% of "best"		% of "best"
Number of seroconverters 1996-98	17	83%	9	59%	9	33%
Seroconversion inter-donation interval(days)	-	-	371	89%	168	33%
S (seroconverter IDI/average IDI)	-	-	0.78	104%	1.09	179%
Risk of infected donation per 100,000 donations:						
- due to window periods of acute infection	-	-	0.035	67%	0.008	57%
- total	-	-	0.169	91%	0.017	74%

The effect of changes in the numbers of seroconversions, and in other factors that effect incidence rates, was also shown by the sensitivity analyses.

Table 5.10 shows the effects of variations in the parameters used in the risk model for all donations, 1993-98. H = value giving higher risk estimate, L = value giving lower risk estimate.

Table 5.10 Sensitivity analyses results (excluding component of HBV risk due to tail-end carriers).

	HBV					HCV					HIV				
"Best" model:	0.21	0.02	0.23	100%	0.43M	0.05	0.18	0.23	100%	0.43M	0.011	0.010	0.021	100%	4.8
Changes to parameters relatively poorly known:															
	WP	*ER*	*TOT*	*% of "best"*	*1 in x*	*WP*	*ER*	*TOT*	*% of "best"*	*1 in x*	*WP*	*ER*	*TOT*	*% of "best"*	*1 in x*
New infections															
H: x1.5	0.31	0.02	0.34	145%	0.30M	0.08	0.18	0.26	111%	0.39M	0.016	0.010	0.026	126%	3.8M
HH: x2	0.42	0.02	0.44	190%	0.23M	0.10	0.18	0.28	122%	0.35M	0.022	0.010	0.032	152%	3.2M
Pys															
L: x1.2 (13,436,654)	0.17	0.02	0.20	85%	0.51M	0.04	0.18	0.23	96%	0.44M	0.009	0.010	0.019	91%	5.3M
H: x0.8 (8,957,770)	0.26	0.02	0.28	122%	0.35M	0.06	0.18	0.25	105%	0.41M	0.013	0.010	0.023	113%	4.3M
New donor multiplier															
H: upper value of range	0.22	0.02	0.25	107%	0.40M	0.06	0.18	0.24	102%	0.42M	0.012	0.010	0.022	107%	4.5M
L: lower value of range	0.19	0.02	0.22	93%	0.47M	0.04	0.18	0.23	97%	0.44M	0.010	0.010	0.020	95%	5.1M
Error rate															
H: 100% up (0.01)	0.21	0.05	0.26	110%	0.39M	0.05	0.24	0.29	126%	0.34M	0.011	0.015	0.026	124%	3.9M
L: 100% down (0)	0.21	0.00	0.21	90%	0.48M	0.05	0.12	0.17	74%	0.58M	0.011	0.005	0.016	76%	6.3M
All the above															
All HIGH values	0.56	0.05	0.61	262%	0.16M	0.14	0.24	0.38	164%	0.26M	0.031	0.015	0.046	220%	2.2M
All LOW values	0.16	0.00	0.16	69%	0.63M	0.04	0.12	0.16	68%	0.63M	0.008	0.005	0.013	64%	7.6M
Changes to parameters liable to change over time:															
Prevalence															
H: x1.5	0.21	0.04	0.24	105%	0.41M	0.05	0.27	0.33	139%	0.31M	0.011	0.015	0.026	124%	3.9M
L: x0.5	0.21	0.01	0.22	95%	0.45M	0.05	0.09	0.14	61%	0.70M	0.011	0.005	0.016	76%	6.3M
Incidence in RDs															
H: x1.5	0.31	0.02	0.34	145%	0.30M	0.08	0.18	0.26	111%	0.39M	0.016	0.010	0.026	126%	3.8M
L: x0.5	0.10	0.02	0.13	55%	0.78M	0.03	0.18	0.21	89%	0.48M	0.005	0.010	0.015	74%	6.5M
New donor proportion															
H: x1.5 (16.5%)	0.23	0.03	0.26	113%	0.38M	0.06	0.23	0.29	125%	0.34M	0.011	0.012	0.024	115%	4.2M
L: x0.5 (5.5%)	0.18	0.01	0.20	85%	0.51M	0.04	0.13	0.17	71%	0.60M	0.010	0.007	0.017	83%	5.8M
Test sensitivity															
L: 1-sensitivity halved	*NA: sensitivity 100% in "best"*					0.05	0.12	0.17	74%	0.58M	0.011	0.007	0.018	88%	5.5M
LL: sensitivity 100%						0.05	0.06	0.11	48%	0.90M	0.011	0.005	0.016	76%	6.4M
Window period for test															
20% down	0.18	0.02	0.20	87%	0.50M	0.04	0.18	0.22	96%	0.45M	0.009	0.010	0.019	90%	5.4M
50% down	0.13	0.02	0.16	67%	0.64M	0.03	0.18	0.21	89%	0.48M	0.005	0.010	0.015	74%	6.5M
All the above															
All HIGH values	0.34	0.05	0.39	170%	0.25M	0.09	0.35	0.44	188%	0.23M	0.017	0.019	0.036	173%	2.8M
All LOW values	0.06	0.01	0.06	28%	1.5 M	0.01	0.02	0.03	13%	3.2 M	0.003	0.002	0.004	21%	23.4M
All parameters (except "new infections")															
All HIGH values	0.47	0.10	0.57	247%	0.17M	0.13	0.47	0.59	254%	0.17M	0.025	0.028	0.054	258%	1.9M
All LOW values	0.05	0.00	0.05	20%	2.2 M	0.01	0.00	0.01	3%	12.8 M	0.002	0.000	0.002	10%	50.0M
Variation				12-fold					76-fold					27-fold	

HBV

The estimates for risk of HBV infected donations entering the blood supply were most affected by changes in the rate of incidence of HBV, or any parameters that affected the estimated incidence rate. Reasonable variation in the "uncertain" parameters resulted in highest and lowest risk models with total estimates that were 3.8-fold different, from 1 in 625,000 donations to 1 in 125,000 donations. Reasonable variation in the "changeable" parameters resulted in highest and lowest risk models with total estimates that were 6.1-fold different, from 1 in 1.5 million to 1 in 254,000 donations. When reasonable variations in all the parameters used in the sensitivity analyses were combined (excluding variation in "new infections" so as to not duplicate the effect of error in the incidence rate), the highest and lowest risk models gave total estimates that were 12-fold different, from 1 in 2.2 million to 1 in 0.17 million donations. These are the very outside expected limits of the risk estimates.

HCV

The estimates for risk of HCV infected donations entering the blood supply were most effected by changes in the prevalence of anti-HCV, and in parameters such as test sensitivity that were combined in the model to estimate the number of anti-HCV positive donations released due to test or process error. Reasonable variation in the "uncertain" parameters resulted in highest and lowest risk models with total estimates that were 2.4-fold different, from 1 in 629,000 donations to 1 in 261,000 donations. Reasonable variation in the "changeable" parameters resulted in highest and lowest risk models with total estimates that were 14-fold different, from 1 in 3.2 million to 1 in 228,000 donations. When reasonable variations in all the parameters used in the sensitivity analyses were combined (excluding variation in "new infections" so as to not duplicate the effect of error in the incidence rate), the highest and lowest risk models gave total estimates that were 76-fold different, from 1 in 12.8 million to 1 in 0.17 million donations. These are the very outside expected limits of the estimates.

HIV

The estimates for risk of HIV infected donations entering the blood supply were most affected by changes in the rate of incidence of HIV, or any parameters that affected the estimated incidence rate. Reasonable variation in the "uncertain" parameters resulted in highest and lowest case models with total estimates that were 3.5-fold different, from 1 in 7.6 million donations to 1 in 2.2 million donations. Reasonable variation in the "changeable" parameters resulted in highest and lowest case models with total estimates that were 8.4-fold different, from 1 in 2.8 million to 1 in 23 million donations. When reasonable variations in all the parameters used in the sensitivity analyses were combined (excluding variation in "new infections" so as to not duplicate the effect of error in the incidence rate), the highest and lowest case models gave total estimates that were 27-fold different, from 1 in 50 million to 1 in 1.9 million donations. These are the very outside expected limits of the estimates.

5.4 Discussion

Sensitivity analyses

Reasonable variation in "uncertain" parameters affected the estimates by 2 to 4 fold. This is not a significant amount of variation. However, variation in the "changeable" parameters resulted in a much greater range of estimates – with up to more than 70-fold variations. The particularly wide range of estimates produced for HCV resulted from the sensitivity of the HCV model to the prevalence of infection. It is not unrealistic to include a 50% reduction in anti-HCV prevalence, as the prevalence of anti-HCV did fall by over 50% during the period studied. These results suggest that lowering the prevalence of HCV in blood donations, or improving the detection of anti-HCV positives (by improved test sensitivity, reduction of lab error rate) is the most fruitful avenue for reducing the total risk of donations from HCV infected donors entering the blood supply. One qualifying point about this risk is that not all of these donations – and more so for HCV than for HBV and HIV – will be infectious. Seventy-five percent of anti-HCV positive donors are HCV RNA positive by PCR, and it is probable that only RNA positive donations will transmit infection to recipients. The HCV risk estimates could therefore by reasonably reduced by multiplying the "error" component by 0.75. This would give a "best" overall estimate of 0.19

per 100,000 (1 in 533,000) and a highest risk of 0.48 per 100,000 (1 in 210,000). (As the lowest risk model sets sensitivity to 1 and error to 0, no error component exists).

In contrast, for HBV and HIV the incidence of infection and parameters that affect the risk of window period donations had the greatest effect on the risk estimates. This suggests that for these infections – with very low prevalence already achieved in the donor population - the most fruitful avenues to reduce the risk further are strategies to reduce the number of seroconversion in donors, and reductions in the window period of tests.

The use of the incidence method without adjustment for longer periods between donations for seroconverters can result in considerable overestimation of the risk of window period donations. This may partially explain observations of lower risk than predicted - for example after the introduction of p24 ag testing in the US.

The prevalence and incidence rates of blood-borne viruses in English blood donors during 1993-1995 were very low. Seroconversion rates for HIV and HCV were less than one tenth the rates reported for 1991-1993 at five USA blood centres (Schreiber , 1996), and less than one sixth the rates reported for 1992-1994 in France (Courouce, 1996). Low prevalence of these infections in the UK, and current donor education and selection appears to be effective in securing relatively small numbers of seroprevalent donors and, as far as we can identify, seroconverting donors to the English National Blood Service. Current tests for anti-HIV, anti-HCV and HBsAg have high sensitivity and are performed by automated processes with stringent quality and process control procedures and computerised information transfer. Overall, therefore, the risk of infectious donations entering the blood supply is extremely small. Testing sero-negative donations, or components, for viral nucleic acids may have the potential to provide a direct measurement of infectious donations entering the blood supply *(see below).* Prospective assessment of recipients is one way to directly measure rates of viral transmission from blood components. However, as the low risks of infection transmission now make the required size of such studies to accurately estimate risk prohibitive, a theoretical approach has been taken to estimating the number of infectious donations that may enter the blood supply from English blood centres. There are several potential sources of error in the

data, and in the assumptions, used in this study. These errors may have led to over- or under-estimation of the true risk.

The estimates of risk associated with window period donations are highly dependent on accurate and complete identification of seroconversion in blood donors. The definition of a seroconversion in a repeat donor required detailed information about the first sero-positive donation and the last sero-negative donation. If this information was absent, a true seroconversion may have been excluded from this study. Our seroconversion rates, and therefore risks, may be underestimates. The sensitivity analysis showed that exclusion of "possible" seroconversions could - if all possible seroconversions were true seroconversions - have led to underestimation of the window period risk.

Blood components that are produced from repeat donor donations are associated with lower risks than similar components from new donors. The methods used to estimate the incidence of infections in new donors made various assumptions - for example, that the incidence rate of HIV and HCV was constant over different age groups, and that the ratio of incidence amongst new and repeat donors had been constant since 1986 for HIV and since 1992 for HCV. These assumptions are unlikely to be valid, and considerable uncertainty therefore surrounds the estimates of the risks of window period donations from new donors. The use of several different methods to generate an estimate of the new donor risk multiplier gives some security against the errors of any one method, but does not necessarily improve the accuracy of the resulting measure of increased risk. Although new donors contribute only 11% of all donations, they contribute a larger proportion to the total risk estimates. The sensitivity analysis showed that the use of different new donor incidence multipliers caused the window period risk estimates to vary by plus or minus approximately 15%.

The inter-donation interval between seroconversion is longer than the average inter-donation interval; the average inter-donation interval for the 13 HCV seroconversions detected during 1993-95 was 63 weeks. This will tend to lead to overestimation of window period risk by the incidence method unless an appropriate adjustment is made. The adjustment used produced the same window period risk estimates as an alternative method of estimating the window period risk. Studies that have used the incidence methods without similar adjustment, and have included seroconversion with inter-donation intervals that

differ from the rest of the donor population will have over, or under, estimated the risk. Even with this adjustment made, the estimates are still sensitive to the inter-donation interval.

The transient nature of HBsAg causes several complications to estimating the risk of window period donations from HBV infected donors. Other studies that have assumed that the observed inter-donation interval for donors who seroconvert for HBsAg is also characteristic of donors who acquire HBV infection but never donate during their HBsAg positive period of infection may have over estimated the risk of window period donations from donors with HBV infection.

Donors who donate during an infectious window period, but do not re-attend to give a post-seroconversion sero-positive donation may contribute infectious donations to the blood supply that would not have been included in these estimates. Indeed, there are plausible reasons why donors may be more likely to donate only, or for the last time, during an infectious window period. Despite alternative testing options and donor education, people who have a self-perceived exposure risk may attend donation sessions in order to obtain infection tests, and these donation attendances may occur in the sero-negative window period. Also, in the course of a donation attendance a donor may become aware that he/she is not eligible to donate due to a recent exposure risk. One English blood centre has a confidential donation exclusion option to allow donors to declare exposure risks in confidence and withdraw their donation from the blood supply without taking any non-routine action (Brennan, 1995). If this option is not utilised, and at sessions where it is not available, a donor with an exposure risk may find it easier to proceed with his/her current donation attendance and self-defer from further donation.

A process error rate of 0.5% was used. Donation testing and release is largely automated and computerised in English blood centres and the probability of an error may well be considerably lower than 0.5%. The error risk contributes 24%, 26% and 2% to the overall risk for HIV, HCV and HBV infectious donations respectively. Sensitivity of tests used during the study period was taken as 99% for HCV tests and 99.5% for anti-HIV tests. Test failure consequently accounted for 24% and 52% of the total HIV and HCV risks respectively.

Since the introduction of anti-HCV testing in 1992, the prevalence of anti-HCV in donations from repeat donors has declined steeply as seroprevalent donors have been removed from the donor panel. The majority of anti-HCV positive repeat donors detected during 1993-1995 were first-time tested donors. The prevalence of anti-HCV in donations from repeat donors is expected to continue to decline until all repeat donors have been tested for anti-HCV. The estimated risk due to sero-positive donations from repeat donors is therefore also expected to decrease. This was shown in the comparison between the first and second three-year period of study. While the risk of window period donations dependent on seroconversions remained constant, the risk of errors and test failures dependent on the prevalence of infection fell.

There is an additional theoretical risk of HIV and HCV infection, not included in our estimates, from sero-negative infectious donations from donors with no detectable antibody to these infections.

In contrast to HCV and HIV, the estimated risk for HBV infectious donations is relatively high when compared to published risks from the USA. This may be largely due to a difference in donation testing strategy. Testing for hepatitis B core antibody is routine in the USA, and some other European blood services. This additional test was introduced, before a specific test for HCV infection was available, as a surrogate marker for a risk of HCV infection. However, where implemented, it also served to remove the risk of HBV infectious donations entering the blood supply due to HBsAg sero-negative donations from donors with anti-HBc and evidence of HBV infectivity. The detection of tail-end carriers by HBsAg tests is expected to have improved in recent years as the sensitivity of HBsAg tests has increased; the ratio of observed tail end to acute transmitters that was used may therefore be out-of-date and resulting in overestimation of the risk of infectious, HBsAg negative donations from tail end carriers.

The additional safety that may be gained by strategic policy changes such as more stringent donor selection, donation testing or by performing viral inactivation procedures on tested components may be estimated by appropriate alteration to the data and assumptions used in the calculations described. The low level of the current risk estimates and the considerable uncertainty

surrounding them, implies that predicting the benefits of additional safety measures will be difficult to do with certainty, and that observing any future improvement in the viral safety of blood components from English blood centres will be even more difficult. Variations in estimates are easily obtained by changing methods and assumptions and the estimates are more sensitive to changes in some of these factors than to changes in observed prevalence and incidence rates.

Findings of different results from the different methods to estimate the new donor multiplier, and from different methods to estimate the window period risk using English data may not be experienced when these methods are applied to other data. In general, the methods used would be more robust in countries with higher prevalence and incidence. The estimates for England are relatively fragile and vulnerable to errors in assumptions and to errors in generalisations. It is now accepted that prospective studies cannot accurately measure the risk of transfusion-transmitted infection in the UK. It may also be the case that calculations described above also lack the precision to accurately detect the true risks in the UK - at least not with accuracy good enough to, for example, evaluate the relative expected benefit from two alternative approaches to improving blood safety.

Donations from new donors were associated with a higher risk of prevalent, and of incident, infection than donations from repeat donors. Donations from new donors constituted only 11% of tested blood donations during the study period, but made a significant contribution to the total risk. New donors accounted for 33%, 62% and 38% of the estimated number of donations entering the blood supply each year from donors with HIV, HCV and HBV infections. Studies that do not consider the risk from new donors are likely to underestimate the total risk.

Comparison with observed, reported transmissions

Several additional factors need to be considered in order to estimate the number of recipients infected as a result of these donations from infected donors. These factors include the infectivity of the donations, the number of components made from each donation, the percentage of untransfused components, the number of components to which each recipient is exposed, the

prevalence of immunity in recipients and the rate of infection from transfused components. Recognition of transfusion transmitted HIV, HCV and HBV is impaired because of the occurrence of sub-clinical infections, long lag periods between infection and disease onset and is also obscured by high mortality from other causes. Furthermore, transfusion may not be suspected as the cause of even clinically apparent post-transfusion infections, and suspected transfusion transmitted infections may not come to the attention of the blood transfusion service. Furthermore, donors are encouraged to notify the blood centre if they are ill in the weeks following donation. Reported symptoms of acute hepatitis or HIV seroconversion illness may therefore lead to withdrawal from the blood supply of infectious donations from seroconverting blood donors, and a consequent reduction in the risk to recipients. The effect of such prompted withdrawals of potentially infected components has not been quantified.

Since HIV antibody testing of blood donations began in the UK, one HIV infectious donation to the Scottish National Blood Service has been detected by the observation of seroconversion in a donor, with subsequent identification of infection in a recipient in the UK (Crawford, 1987) and one HIV infectious donation to the English National Blood Service has been detected by the observation of infection in a recipient and subsequent identification of a seroconversion in a donor (Martlew, 2000). Three cases of transfusion transmitted HCV infection by HCV antibody tested blood donations have been reported.

Table 5.11 shows the risk estimates alongside observed rates of clinically recognised cases and the results of a recent prospective study of the recipients or almost 22,000 blood components (Regan, 2000).

Table 5.11 Sources of quantitative data and estimates in the UK about how many transfusion-transmitted infections occur (or are reported)

Infection	Surveillance of apparent cases, 1995-1999 (see PTI surveillance - chapter 4 *)	Prospective study of transfusion recipients, approx. 22,000 donations (Regan, 2000) [95% CI]	Estimated infectious donations released into the blood supply per year, 1993-98 [ranges]
HAV	1 (Hewitt,1997)	NA	NA
HIV	1 (3 recipients infected)	0 [0 - 423]	0.5 [0.3 – 0.9]
HCV	2	0 [0 - 423]	6 [5 – 9]
HBV	5	0 [0 - 423]	24 [9 – 74]
HTLVI&II	0	0 [0 - 423]	NA
Bacteria	11	NA	NA

NA = Not available.

The estimates derived from calculations predict more transmission by transfusion than are clinically recognised. This discrepancy can be explained by poor ascertainment of cases for a number of reasons. It was estimated in 1987 by Mortimer et al, that 50% of blood components were transfused to patients who were dead within one year. High mortality in the post-transfusion period has been observed more recently in the cohort of patient traced in the course of the HCV Lookback programme (Robinson, 2001) in which - amongst those reported to have died - 47% died within one year of their transfusion. Patients who die shortly after their transfusion are unlikely to receive diagnoses of a transfusion-transmitted infection during this time. Severe disease - due to the underlying reason for transfusion, and, or, symptoms caused by treatments may obscure the clinical presentation of transfusion-transmitted infections and make their diagnosis - even if symptomatic - less likely. Many transfusion-transmitted infections are likely to be asymptomatic for many years. Some infections may occur in patients who have other more probable risk factors for infection and so transfusion is never investigated as the source.

Both of the HCV infections and one of the HBV infections that have been clinically recognised, and reported between October 1995 and September 1999 (see Chapter 4) were detected by the blood service identifying an infected

donor, not by diagnoses in the recipients, who until contacted and offered testing, were unaware of their infection.

The estimates suggested that 85% of donations entering the blood supply from donors with HBV, HCV or HIV infection were donations from donors with HBV. 63% (five of eight) of reported transfusion-transmitted HBV, HCV and HIV infections were HBV.

The estimates suggested that 6% of donations entering the blood supply from donors with HBV, HCV or HIV infection were due to process error: 1 of 8 (12.5%) reported transfusion-transmitted HBV, HCV and HIV infections were due to process error.

5.5 Post-script re recent developments in donation testing

Continuing concern about the safety of blood, and continuing advances in testing assays and technologies, has led to new, additional tests being proposed for all blood donations, and to one new assay – for HCV nucleic acid – being introduced in England and Wales. The methods of estimation described above have recently been used to predict the yield of nucleic acid testing for HCV and to evaluate the expected benefits of other new testing strategies. This post-script includes some of this work, and demonstrates the use of the risk estimation methods that have been described in this thesis to inform discussions about strategies for testing blood donations.

Combined HIV antibody and antigen tests

Combined tests for anti-HIV and HIV p24 antigen are now available and have been approved for use for donation testing in England. These tests have been shown to shorten the time from infection to test positivity by around 4 days. These tests will be expected to reduce the risk of window period donations from HIV infected donors by 27% (see sensitivity analysis above)

HCV NAT testing

Nucleic acid testing (NAT) of pools of 96 donation samples began in England in early 1999. The system used combines the Qiagen (Hilden, Germany) extraction system, using the Qiagen robotic processor (Bio Robot 9604, Qiagen), with the Roche Amplicor HCV version 2.0 assay using the automated COBAS system. Results of sensitivity testing using Roche Amplicor

2.0 assay, following the probit analysis approach recommended by the Paul Ehrlich Institute, identifies that when a pool of 96 donations is used, the 95% detection limit will be 2,000 IU/mL in the donation (Harrison, unpublished data). (NB. The relationship between Genome Equivalents (geq) and International Units (IUs) is approximately 1IU to 4 geq for the National Institute for Biological Standardisation and Control working standard.)

NAT of 2 million donations during 1999 yielded 1 anti-HCV negative, HCV NAT positive donation

NAT testing might be expected to detect a proportion of the risk estimated above due to the window period of early infection - by using NAT window rather than serology window i.e. only 20 rather than 59 days, 66% of HCV serology window period detected. NAT testing is also expected to detect the proportion of the false negative component of the risk estimates above that are viraemic as well as serologically positive. This can be estimated by multiplying the false negative risk estimate by the proportion of prevalent infections that are expected to be viraemic i.e. 75% for HCV, 100% for HIV. NAT would also detect any truly sero-negative, viraemic infections - assumed to be negligible in the estimates above.

The expected findings of NAT testing (plus truly sero-negative, viraemic infections) in England are shown in Table 5.12.

Table 5.12 Expectations for findings of HCV and HIV NAT.

Component of risk	Estimates 1996-98 **HIV** NATposWP 7d % viraemic: 100%	 **HCV** NATposWP: 39d % viraemic: 75%
i. window period risk	0.0079: 1 in 13M *(26% of total)*	0.0229: 1 in 4.4M *(19% of total)*
ii. false negative risk test failure process error	 0.0177: 1 in 5.6M 0.0043: 1 in 23M	 0.0671: 1 in 1.5M 0.0332: 1 in 3.0M
Total	0.0299: 1 in 3.3M	0.1232: 1 in 0.8M

The 90% confidence intervals on an observation of 1 in 2 million is 1 in 40 million to 1 in 0.4 million, i.e. the observed rate during 1999 was consistent (statistically, at the 10% significance level) with a true rate of 0.05 to 4.75 per 2 million. Table 5.13 shows the probabilities of observing 1 or fewer positives in a sample size of 2 million for different “true” rates.

Table 5.13 Poisson probabilities.

"True" rate	Sample tested	p of observing up to 1
1 per 0.5 million (i.e. 4 in 2 million)	2 million	p = 0.091
1.0 per million (i.e. 2 in 2 million)	2 million	p = 0.406
0.5 per million (i.e. 1 in 2 million)	2 million	p = 0.735

The estimates were therefore not significantly different from the observation during 1999. However, the observed rate would have had to be many times higher than expected for a difference to be apparent. Some possible reasons for estimates of HCV infectious donations being *overestimates* are shown in Table 5.14. The most likely reason for *underestimation* of risk by the method used was underestimation of HCV incidence in repeat donors based on seroconversions (i.e. if all seroconversions were not detected). Other possible reasons for underestimation of HCV risk include occurrence of anti-HCV negative, PCR positive donors during chronic infection, and the opposite of all the reasons shown in Table 5.14.

Table 5.14 Reasons why the assumptions/data used in estimates of the frequency of infectious donations entering blood supply in England could overestimate the observed frequency of NAT positive donations.

Reason	Evidence
• NAT negative "eclipse" period during anti-HCV negative window period, i.e. infectious window shorter.	• Some evidence of this from US studies.
• Test sensitivity better than 99% and error rates less than 0.5%.	• ? thought probable by test experts.
• Prevalence of anti-HCV in donations has fallen.	• Observed in UK - fall of 25% between 1993-95 and 1995-97.
• Seroconverting donors have a longer inter-donation interval (between sero-negative and sero-positive donation) than average donors do. The model may not fully adjust for this.	• Observed in UK data (1.4 times longer) and in EPFA survey data (personal communication Konstanze Muller-Breitkreutz).
• New donor risk multiplier overestimated.	• None available, however, evidence for estimated multiplier was weak.
• Some anti-HCV positive donations are not infectious i.e. are NAT negative.	• Only 75% of anti-HCV positive donors with PCR test results are PCR positive.
• Rate of seroconversion in donors has fallen.	• None.

NAT is expected to prevent (and measure) a proportion of estimated risk of donations from infected donors not detected by serology. This proportion is estimated as approximately 74% for HCV and 80% for HIV. The probability of the observed findings of HCV NAT (1 in 2 million), if estimates (revised, 1996-98) are correct, is 0.1 - 0.4. The observed findings suggest true risk may be lower than estimated - one possible reason for this - worth further investigation - is incorrect assumption about donation patterns following infections (this has been observed in other voluntary donor populations). Alternatively, the error and false negative component of the models could be too high.

In order to estimate the impact of a range of new tests/strategies on the release of infectious donations into the blood supply, these models were extended with some extra parameters regarding the performance of proposed additional tests, to estimate the infectious donations that could be prevented from entering the blood supply by the use of additional tests. The assumptions made (in addition to those described earlier in this chapter), and the results are given below.

For each yield the "best" estimates - generated from calculations using the "most likely" parameter values - and the results of "high" and "low" calculations (or models, or scenarios) giving the best and worst yields that can be expected, were calculated. For some parameters there was very little evidence for the correct values to use. This is partially reflected in the ranges of values used in the "high" and "low" models (or scenarios).

Different scales were needed on the graphs to express the risks and yields for each infection. To ease comparison of the yield estimates, all the yield graphs are plotted on the same scale in the final figure. This still leaves differences in the severity of the infections averted, and differences in the costs of the interventions for the reader - and for further work - to consider.

New models were constructed, using only the parameters shown below, for HTLV and bacteria. Ranges were also calculated using parameter values that applied for different donation (i.e. from new or repeat donors), or component (e.g. platelets, or red cells), types where applicable.

Although the aim of this work was the evaluation of testing strategies, donor selection is an important alternative strategy to reduce infectious risk, and

an indication of the effect it can have on the risks calculated was included as follows.

Infected donors who report (after donation and diagnosis of their infection) a history that should have led to exclusion from blood donations accounted for approximately 20% of all infected (HBsAg, anti-HCV or anti-HIV) donations collected during 1996-98. Table 5.15 below shows the potential reduction in prevalence and incidence of HBsAg, anti-HIV and anti-HCV that would be obtained if these donors were successfully excluded from donating blood.

Table 5.15 Reduction that could be achieved by excluding PRE-donation all donors who report (POST-donation) a history of sex between men or a history of injecting drug use, and all donors who have had a previous positive donation (based on infected donors reported in England and Wales, 1996-98).

	HBsAg	Anti-HCV	Anti-HIV
Reduction in prevalence	4%	27%	23%
Reduction in incidence	5%	7%	26%

This is an underestimate of the reduction in risk that could be achieved by better compliance with existing donor selection criteria because i) only the permanent exclusion criteria were considered, ii) there is likely to be some underreporting of these risk factors post-donation.

The risks of HBV, HCV and HIV infectious donations were re-calculated after reducing the prevalence and incidence data by these amounts – to show the minimum reduction in risk that could be achieved by improved donor selection. The point estimates of these risks ("Risk: with improved donor selection") are shown on the graphs.

Another alternative strategy – inactivation – has not been considered. This could be added to the models in the future, or considered as a potential strategy to prevent the remaining risk.

HIV

The following additional tests were considered: -

a) anti-HIV/HIV p24 antigen combined tests

b) HIV NAT for DNA on single samples

c) HIV NAT for RNA on pooled (48) samples

d) HIV NAT for RNA on single samples

The extra assumptions used (those with * are varied below) in the "best" model were: -

II. All false anti-HIV negative donations and antibody positive donations released in error are negative for HIV antigen, positive for HIV PCR (both RNA and DNA, in single and pooled samples).

III. * Combined anti-HIV/HIV Ag assays will detect new infections 4 days before current anti-HIV tests (3rd gen ELISAs) (i.e. giving total WP of 18 days, infectious WP of 11 days).

IV. * HIV NAT for DNA on single samples will detect new infections 6 days before.

V. current anti-HIV tests (i.e. giving total WP of 16 days, infectious WP of 9 days).

VI. * HIV NAT for RNA on pooled samples will detect new infections 10 days before current anti-HIV tests (i.e. giving total WP of 12 days, infectious WP of 5 days).

VII. * HIV NAT for RNA on single samples will detect new infections 12 days before current anti-HIV tests (i.e. giving total WP of 10 days, infectious WP of 3 days).

The "high" model estimated the highest yield consistent with the probable limits of the assumptions used, and the "low" model estimated the lowest yield consistent with the probable limits of the assumptions used. The assumptions used and varied are shown below.

Assumption	***High model***	***Best model***	***Low model***
Anti-HIV/HIV Ag benefit	5 days	4 days	3 days
HIV DNA single benefit	7 days	6 days	5 days
HIV RNA pooled benefit	12 days	10 days	8 days
HIV RNA single benefit	14 days	12 days	10 days
Prevalence anti-HIV	10% increase	Observed 1996-98	10% decrease
Incidence HIV	10% increase	Observed 1996-98	10% decrease
	High model #2		***Low model #2***
Donations tested	New donors	All/average	Repeat donors

HCV

The following additional tests were considered:-

a) HCV Ag tests (in addition to anti-HCV)

b) HCV NAT for RNA on pooled (48) samples

c) HCV NAT for RNA on single samples

The extra assumptions used (those with * are varied below) in the "best" model were: -

II. All false anti-HCV negative donations and antibody positive donations released in error are negative for HCV antigen, and 75% are positive for HCV PCR (both single and pooled samples).

III. * HCV Ag assays will detect new infections 53 days before current anti-HCV tests (3rd gen ELISAs) (i.e. giving total WP of 13 days, infectious WP of 6 days).

IV. * HCV NAT for RNA on pooled samples (48) will detect new infections 55 days before current anti-HCV tests (i.e. giving total WP of 11 days, infectious WP of 4 days).

V. * HCV NAT for RNA on single samples will detect new infections 57 days before current anti-HCV tests (i.e. giving total WP of 9 days, infectious WP of 2 days).

The "high" model estimated the highest yield consistent with the probable limits of the assumptions used, and the "low" model estimated the lowest yield consistent with the probable limits of the assumptions used. The assumptions varied are shown below.

Assumption	***High model***	***Best model***	***Low model***
HCV Ag benefit	58 days	53 days	48 days
HCV RNA pooled benefit	56 days	55 days	54 days
HCV RNA single benefit	58 days	57 days	56 days
Prevalence anti-HCV	10% increase	Observed 1996-98	10% decrease
Incidence HCV	10% increase	Observed 1996-98	10% decrease
	High model #2		***Low model #2***
Donations tested	New donors	All/average	Repeat donors

HBV

The following additional tests were considered:-

a) anti-HBV core tests

b) HBV NAT pooled (48) samples

c) HBV NAT on single samples

The extra assumptions used (those with * are varied below) in the "best" model were:

II. * All donations collected during the HBsAg negative, infectious, window of late acute infection are anti-HBV core positive.

III. All donations collected during the HBsAg negative, infectious, period at the tail-end of HBV carriage are anti-HBV core positive.

IV. All HBsAg positive donations released in error are anti-HBV core positive and are HBV NAT positive (both single and pooled samples).

V. * HBV NAT on pooled samples (48) will detect new infections 6 days before current HBsAg tests (i.e. giving total WP of 53 days, infectious WP of 47 days).

VI. * HBV NAT on single samples will detect new infections 15 days before current HBsAg tests (i.e. giving total WP of 44 days, infectious WP of 37 days).

VII. * The risk of infectious donations from tail-end carriers is in ratio to the risk from acute infections as observed amongst reported transfusion-transmitted HBV cases in England and Wales during 1991-97 when 11 of 14 cases were due to tail-end carriers. The detection of tail-end carriers by HBsAg tests is expected to have improved in recent years as the sensitivity of HBsAg tests has increased, this ratio may therefore be out of date – making the "low" model closer to today's reality.

The "high" model estimated the highest yield consistent with the probable limits of the assumptions used, and the "low" model estimated the lowest yield consistent with the probable limits of the assumptions used. The assumptions varied are shown below.

Assumption	*High model*	*Best model*	*Low model*
Late acute window period	50 days	30 days	10 days
HBV NAT pooled benefit	9 days	6 days	3 days
HBV NAT single benefit	18 days	15 days	12 days
Prevalence HBsAg	10% increase	Observed 1996-98	10% decrease
Incidence HBV	10% increase	Observed 1996-98	10% decrease
Tail-end:acute ratio	15:3	11:3	3:3
	High model #2		***Low model #2***
Donations tested	New donors	All/average	Repeat donors

Bacteria

A new model was constructed to estimate the number of contaminated donations expected to be detected/prevented by the following strategies if applied in England and Wales:

a) revised donor arm cleansing
b) diversion of first mls
c) testing of platelets

The assumptions used (those with * are varied below) in the "best" model were:

II. * 1 in 1700 red cell units and 1 in 200 platelet units are contaminated with bacteria
III. * Revised donor arm cleansing would prevent 50% of contaminations of all units.
IV. * Diversion would prevent 50% of contaminations of all units.
V. * Testing all platelets pre-release would prevent 80% of contaminated platelets.

The "high" model estimated the highest yield consistent with the probable limits of the assumptions used, and the "low" model estimated the lowest yield consistent with the probable limits of the assumptions used. The assumptions varied are shown below.

Assumption	***High model***	***Best model***	***Low model***
Contamination frequency in red cell units	10% increase	1 in 1,700	10% decrease
Contamination frequency in platelets	10% increase	1 in 200	10% decrease
Prevented by arm cleansing	65%	50%	35%
Prevented by cleansing and diversion	65%	50%	35%
Detection by testing	99%	80%	50%
	High model #2		***Low model #2***
Units	Platelets	All	Red cells

Please note: Not all contaminations are of equal importance/severity, but all are treated as equal in the model above. This model could be refined to consider endogenous bacteria and skin contaminants separately. As endogenous bacteria are more often associated with serious complications in recipients, and are not prevented by arm cleansing or diversion, this may clarify comparison of the yield of platelet testing vs cleansing and diversion.

HTLV

A new model was constructed to estimate the yield of the following strategies for testing for HTLV infection if applied in England and Wales:

a) anti-HTLV testing pooled samples

b) anti-HTLV testing single samples

The assumptions used (those with * are varied below) in the "best" model were:

-

II. * The prevalence of HLTV infection in blood donations is 2 per 50,000 donations.

III. * Leucodepletion reduces the prevalence of infectious donations by two-thirds.

IV. * The sensitivity of anti-HTLV tests is 98% in single samples, 92% in pooled samples (48).

The key assumptions and ranges are shown in the table.

Assumption	*High model*	*Best model*	*Low model*
HTLV prevalence in donors	1 in 20,000 (LSE)	1 in 50,000	1 in 100,000 (Scotland)
Reduction by leucodepletion	50%	67%	95%
Sensitivity of anti-HTLV tests I. single samples II. pooled samples	 99.5% 95%	 98% 92%	 95% 88%
Reduction in infectivity due to leucodepletion	50%	66%	95%

This simple model could be expanded to consider the incidence of HTLV infection in blood donors and then used to additionally estimate the yield of proposed applications of the test such as:-

I. Anti-HTLV testing all donors once only

II. Anti-HTLV testing all donors once, and then repeating testing at specified time intervals

RESULTS

The results are shown in the tables below – expressed first as number of donations tested to prevent one infectious donation, and then as the number of infections prevented per million donations tested.

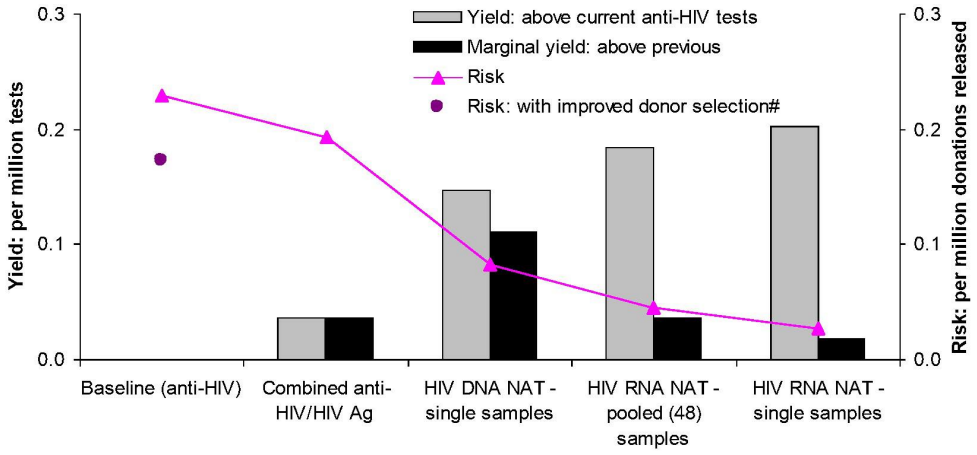
Table 5.16 Donations tested (millions) to prevent 1 HIV infectious donation.

Additional test added	*Yield: above current anti-HIV tests*	*Marginal yield: above previous*	*Leaving a risk of 1 in x million*
Combined anti-HIV/HIV Ag	27.5	27.5	5.2
Range: high & low yield assumptions	20.0 To 40.8	20.0 To 40.8	5.0 To 5.5
Range#2: new & repeat donors (best model assumptions)	13.8 To 31.6	13.8 To 31.6	1.4 To 7.9
HIV DNA NAT - single samples	6.8	9.0	12.2
Range: high & low yield assumptions	5.8 To 8.0	8.2 To 10.0	12.5 To 12.2
Range#2: new & repeat donors (best model assumptions)	1.6 To 11.5	1.8 To 18.0	6.1 To 14.0
HIV RNA NAT - pooled (48) samples	5.4	27.5	22.0
Range: high & low yield assumptions	4.5 To 6.7	20.0 To 40.8	33.4 To 17.5
Range#2: new & repeat donors (best model assumptions)	1.5 To 8.4	13.8 To 31.6	11.0 To 25.2
HIV RNA NAT - single samples	5.0	55.0	36.7
Range: high & low yield assumptions	4.1 To 6.1	50.0 To 61.1	100.1 To 24.5
Range#2: new & repeat donors (best model assumptions)	1.4 To 7.4	27.6 To 63.1	18.4 To 42.1

Table 5.17 HIV infectious donations prevented per million donations tested.

Additional test added	*Yield: above current anti-HIV tests*	*Marginal yield: above previous*	*Leaving a risk of x per million*
Combined anti-HIV/HIV Ag	0.04	0.04	0.19
Range: high & low yield assumptions	0.05 to 0.02	0.05 To 0.02	0.20 to 0.18
Range#2: new & repeat donors (best model assumptions)	0.07 to 0.03	0.07 To 0.03	0.71 to 0.13
HIV DNA NAT - single samples	0.15	0.11	0.08
Range: high & low yield assumptions	0.17 to 0.12	0.12 To 0.10	0.08 to 0.08
Range#2: new & repeat donors (best model assumptions)	0.62 to 0.09	0.54 To 0.06	0.16 to 0.07
HIV RNA NAT - pooled (48) samples	0.18	0.04	0.05
Range: high & low yield assumptions	0.22 to 0.15	0.05 To 0.02	0.03 to 0.06
Range#2: new & repeat donors (best model assumptions)	0.69 to 0.12	0.07 To 0.03	0.09 to 0.04
HIV RNA NAT - single samples	0.20	0.02	0.03
Range: high & low yield assumptions	0.24 to 0.17	0.02 To 0.02	0.01 to 0.04
Range#2: new & repeat donors (best model assumptions)	0.72 to 0.13	0.04 To 0.02	0.05 To 0.02

Figure 5.3 HIV – estimated yield (best model) infectious donations per million.



With all donors who report reasons for permenent deferral excluded.

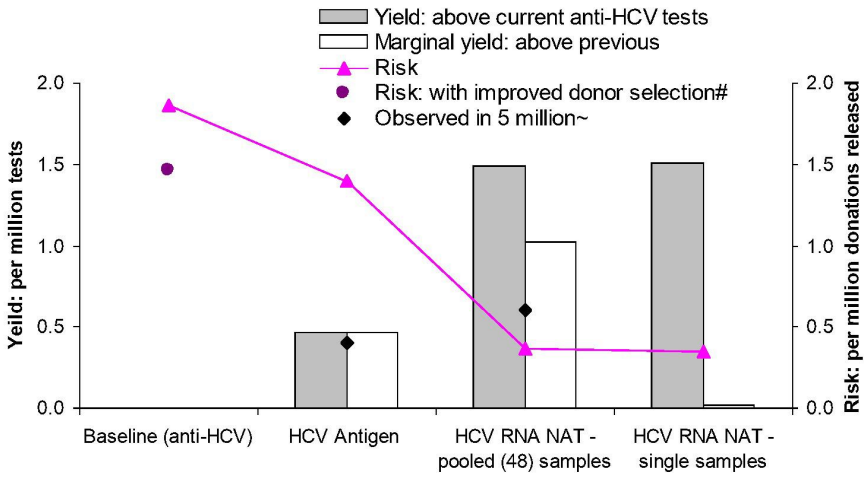
Table 5.18 Donations tested (millions) to prevent 1 HCV infectious donation.

Additional test added	*Yield: above current anti-HCV tests*	*Marginal yield: above previous*	*Leaving a risk of 1 in x million*
HCV Antigen	2.15	2.15	0.72
Range: high & low yield assumptions	1.79 to 2.64	1.79 to 2.64	0.67 to 0.77
Range#2: new & repeat donors (best model assumptions)	0.56 to 3.41	0.56 to 3.41	0.12 to 2.18
HCV RNA NAT - pooled (48) samples	0.67 [1]	0.97	2.71
Range: high & low yield assumptions	0.61 to 0.75	0.92 to 1.05	2.52 to 2.94
Range#2: new & repeat donors (best model assumptions)	0.12 to 1.61	0.16 to 3.03	0.45 to 7.83
HCV RNA NAT - single samples	0.66	57.04	2.85
Range: high & low yield assumptions	0.60 to 0.74	51.86 to 63.38	2.65 to 3.08
Range#2: new & repeat donors (best model assumptions)	0.12 to 1.58	14.71 to 90.48	0.46 to 8.57

Table 5.19 HCV infectious donations prevented per million donations tested.

Additional test added	*Yield: above current anti-HCV tests*	*Marginal yield: above previous*	*Leaving a risk of x per million*
HCV Antigen	0.46	0.46	1.39
Range: high & low yield assumptions	0.56 to 0.38	0.56 to 0.38	1.49 to 1.29
Range#2: new & repeat donors (best model assumptions)	1.80 to 0.29	1.80 to 0.29	8.69 to 0.46
HCV RNA NAT - pooled (48) samples	1.49	1.03	0.37
Range: high & low yield assumptions	1.65 to 1.33	1.09 to 0.95	0.40 to 0.34
Range#2: new & repeat donors (best model assumptions)	8.24 to 0.62	6.44 to 0.33	2.25 to 0.13
HCV RNA NAT - single samples	1.51	0.02	0.35
Range: high & low yield assumptions	1.67 to 1.35	0.02 to 0.02	0.38 to 0.32
Range#2: new & repeat donors (best model assumptions)	8.31 to 0.63	0.07 to 0.01	2.18 to 0.12

Figure 5.4 HCV – estimated yield (best model) infectious donations per million.



With all donors who report reasons for permenent deferral excluded.
~ Observed frequency of positive donations per million donations tested.

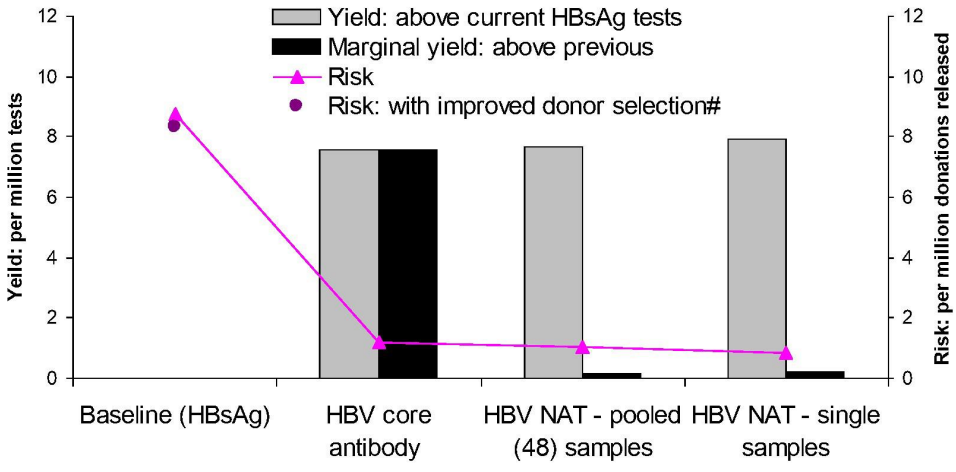
Table 5.20 Donations tested (millions) to prevent 1 HBV infectious donation.

Additional test added	*Yield: above current HBsAg tests*	*Marginal yield: above previous*	*Leaving a risk of 1 in x million*
HBV core antibody	0.13	0.13	0.85
Range: high & low yield assumptions	0.06 to 0.34	0.06 to 0.34	0.77 to 0.95
Range#2: new & repeat donors (best model assumptions)	0.04 to 0.18	0.04 to 0.18	0.30 to 1.11
HBV NAT - pooled (48) samples	0.13	7.37	0.96
Range: high & low yield assumptions	0.06 to 0.34	4.47 to 16.38	0.94 to 1.00
Range#2: new & repeat donors (best model assumptions)	0.04 to 0.17	2.64 to 9.58	0.34 to 1.25
HBV NAT - single samples	0.13	4.92	1.20
Range: high & low yield assumptions	0.06 to 0.33	4.47 to 24.58	1.18 to 1.05
Range#2: new & repeat donors (best model assumptions)	0.04 to 0.17	1.76 to 6.39	0.43 to 1.55

Table 5.21 HBV infectious donations prevented per million donations tested.

Additional test added	*Yield: above current HBsAg tests*	*Marginal yield: above previous*	*Leaving a risk of x per million*
HBV core antibody	7.56	7.56	1.18
Range: high & low yield assumptions	16.29 to 2.91	16.29 to 2.91	1.29 to 1.06
Range#2: new & repeat donors (best model assumptions)	22.24 to 5.67	22.24 to 5.67	3.28 to 0.90
HBV NAT - pooled (48) samples	7.70	0.14	1.04
Range: high & low yield assumptions	16.52 to 2.98	0.22 to 0.06	1.07 to 1.00
Range#2: new & repeat donors (best model assumptions)	22.62 to 5.78	0.38 to 0.10	2.90 to 0.80
HBV NAT - single samples	7.90	0.20	0.84
Range: high & low yield assumptions	16.74 to 3.02	0.22 to 0.04	0.85 to 0.96
Range#2: new & repeat donors (best model assumptions)	23.19 to 5.93	0.57 to 0.16	2.34 to 0.64

Figure 5.5 HBV – estimated yield (best model) infectious donations per million.



With all donors who report reasons for permenent deferral excluded.

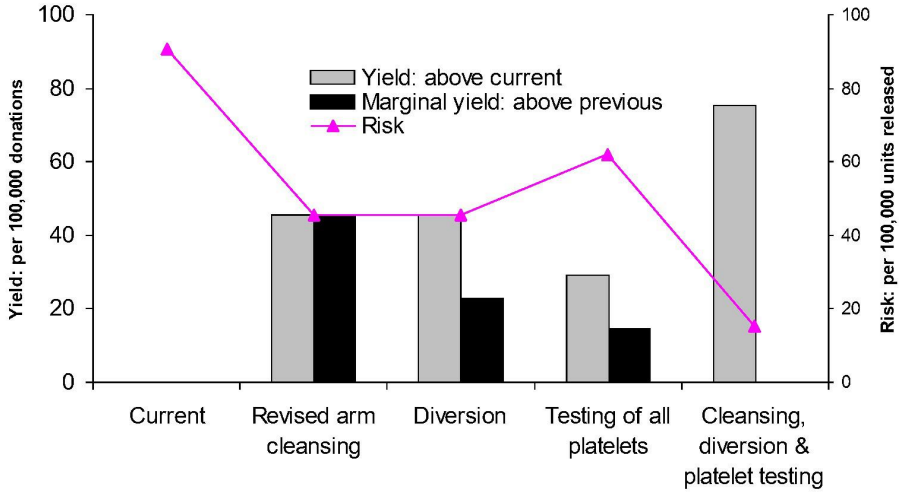
Table 5.22 Donations tested (100,000s) to prevent 1 bacterially contaminated unit.

Additional test added	*Yield: above current*	*Marginal yield: above previous*	*Leaving a risk of 1 in x 100,000s*
Revised arm cleansing	0.022	0.022	0.022
Range: high & low yield assumptions	0.015 to 0.035	0.015 to 0.035	0.029 to 0.019
Range#2: platelets & RBCs (best model)	0.004 to 0.034	0.004 to 0.034	0.004 to 0.034
Diversion	0.022	0.044	0.022
Range: high & low yield assumptions	0.015 to 0.035	0.082 to 0.029	0.029 to 0.019
Range#2: platelets & RBCs (best model)	0.004 to 0.034	0.008 to 0.068	0.004 to 0.034
Testing of all platelets	0.035	0.069	0.016
Range: high & low yield assumptions	0.031 to 0.038	0.090 to 0.059	0.015 to 0.018
Range#2: platelets & RBCs (best model)	0.003 to 0.000	0.005 to 0.000	0.010 to 0.017
Cleansing, diversion & platelet testing	0.013	-	0.065
Range: high & low yield assumptions	0.012 to 0.018	- -	0.059 to 0.036
Range#2: platelets & RBCs (best model)	0.002 to 0.023	- -	0.040 to 0.068

Table 5.23 Bacterially contaminated units prevented per million donations.

Additional test added	*Yield: above current*	*Marginal yield: above previous*	*Leaving a risk of x per 100,000*
Revised arm cleansing	45	45	45
Range: high & low yield assumptions	65 to 29	65 to 29	35 to 53
Range#2: platelets & RBCs (best model)	250 to 29	250 to 29	250 to 29
Diversion	45	23	45
Range: high & low yield assumptions	65 to 29	12 to 35	35 to 53
Range#2: platelets & RBCs (best model)	to	to	to
Testing of all platelets	29	14	62
Range: high & low yield assumptions	32 to 26	11 to 17	68 to 56
Range#2: platelets & RBCs (best model)	400 to 0	200 to 0	100 to 59
Cleansing, diversion & platelet testing	75	-	15
Range: high & low yield assumptions	83 to 54	- to -	17 to 28
Range#2: platelets & RBCs (best model)	475 to 44	- to -	25 to 15

Figure 5.6 Bacteria – estimated yield (best model) contaminated units per 100,000.



NB. The yeild shown here does not distinguish between contaminations from donors' venepuncture, and contaminations due to endogenous bacteria. Only platelet testing prevents the release of units contaminated with endogenous bacteria, or during processing.

Table 5.24 Donations tested (millions) to prevent 1 HTLV infectious donation.

Additional test added	*Yield: above current*	*Marginal yield: above previous*	*Leaving a risk of 1 in x million*
Anti-HTLV test donations in pools (48)	0.16	0.16	1.88
Range: high & low yield assumptions	0.18 to 0.15	0.18 to 0.15	0.80 to 16.67
Anti-HTLV test each donation	0.15	2.50	7.50
Range: high & low yield assumptions	0.15 to 0.15	0.89 to 28.57	0.80 to 16.67

Table 5.25 HTLV infectious donations prevented per million donations tested.

Additional test added	*Yield: above current*	*Marginal yield: above previous*	*Leaving a risk of x per million*
Anti-HTLV test donations in pools (48)	6.13	6.13	0.53
Range: high & low yield assumptions	5.42 to 6.61	5.42 to 6.61	1.25 to 0.06
Anti-HTLV test each donation	6.53	0.40	0.13
Range: high & low yield assumptions	6.54 to 6.64	1.13 to 0.04	1.25 to 0.06

Note: Preliminary work in Scotland suggests that the loss of sensitivity resulting from pooling can be reduced, without incurring specificity problems, by adjustment of the cut-off (to below manufactuerers criteria). If so, the yield for pools would approach that calculated for single samples.

Figure 5.7 HTLV – estimated yield (best model) infectious donations per million.

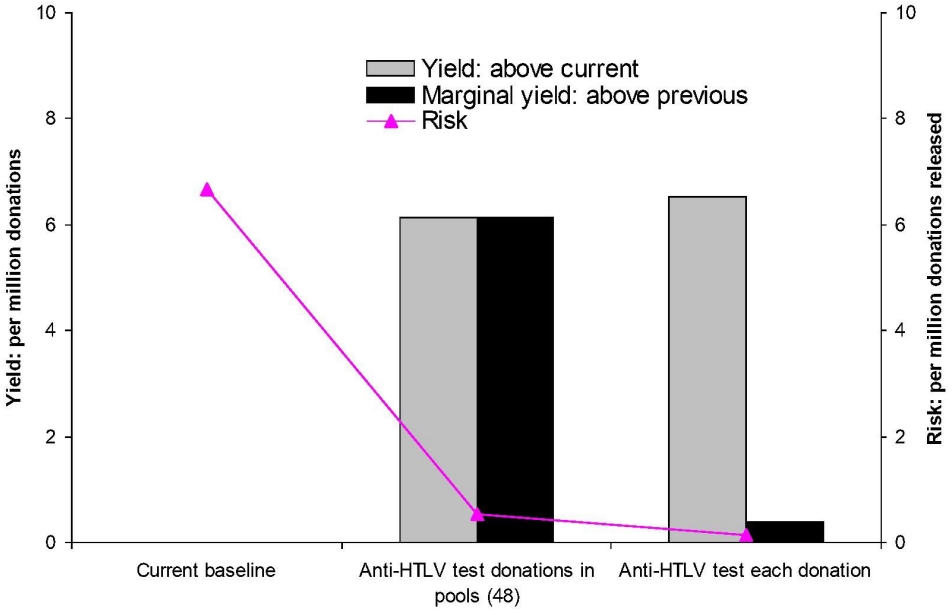
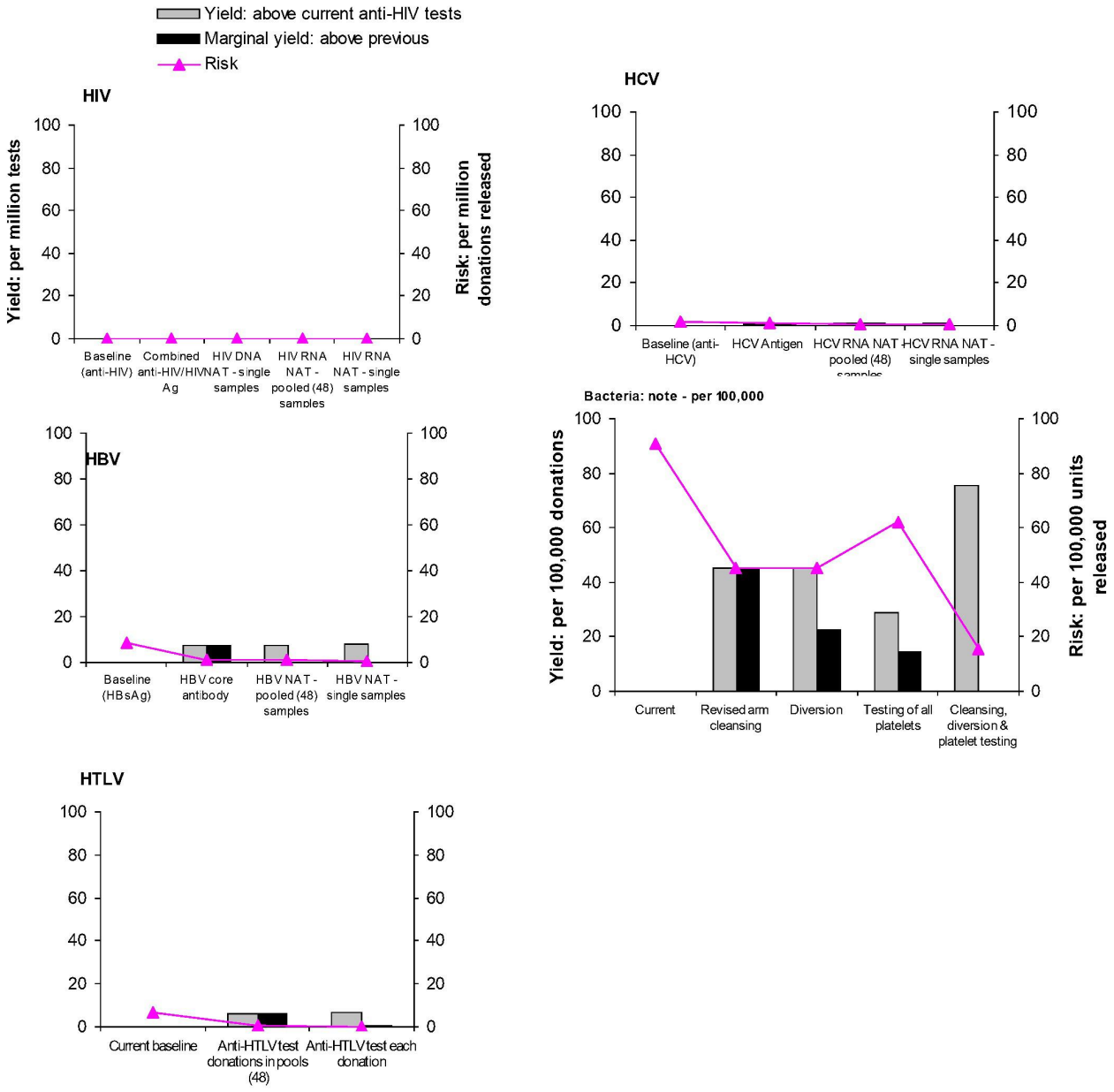


Figure 5.8 Re-production of graphs with same scale (except Bacteria)



From these estimates, is appears that strategies to prevent bacterial contamination, testing for anti-HBV and testing for anti-HTLV would have greater positive effects on the safety of the blood supply than expanding nucleic acid testing. Differences in the susceptibility to, and severity of the infections prevented, and differences in the costs of the interventions, have not been evaluated. These three strategies are however probably amongst the cheapest

considered. Bacteria have caused more reported transfusion-associated deaths in recipients than all other infectious risks in recent years (chapter 4).

Chapter 5 references

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Chapter 6. Discussion & Conclusion

Discussion

By way of summary and conclusion, I will review the TTI surveillance and related studies described in this thesis and discuss further work that could contribute to blood safety and public health knowledge.

Adequacy and limitations of the surveillance system established

The work described has established ongoing and systematic collection, analysis and interpretation of data relevant to blood safety and the epidemiology of HBV, HCV and HIV in blood donors. Timely data from this system are disseminated regularly to a wide range of colleagues and organisations responsible for the control and prevention of these infections. This work therefore meets the criteria for surveillance (e.g. Last JM, 1988).

Some aspects of this surveillance system are atypical. In particular, the aims of the post-transfusion infection surveillance require a high degree of completeness and accuracy in the data collected for each reported case, and do not include the detection of changes in trend or distribution. In these respects it is more akin to a collation of case histories than a classical surveillance system. The time lag between the occurrence of an incident and the availability of complete information reported to the post-transfusion infection surveillance system mean that this surveillance is not expected to prompt timely control measures for any individual case. The contribution to control measures is via provision of information for more general priority setting and the evaluation of practices. These features are characteristic of enhanced surveillance systems of rare conditions, where fewer, more accurate, data are needed. Also, the ongoing, standardised, nature of the data collection and the regular dissemination of data can be used to justify its description as surveillance.

The two most obvious limitations of the post-transfusion infection surveillance are the unknown extent of under-reporting, and the poor likelihood of detecting transfusion-transmitted infections that cause either delayed-onset conditions or conditions that are not yet associated with blood-borne infectious agents. The former is a common problem for infectious disease surveillance. As discussed in chapter 1, prospective studies to inform this are not currently feasible in England and Wales except to estimate a maximum transmission rate, and therefore a maximum underreporting rate. The most recent study found no HBV, HCV or HIV transmissions amongst 22,000 donations, giving an upper estimate of transmission of 1 in about 500 units transfused. Observed transfusion-transmitted infections are very rare. The discrepancy between expected infectious donations released and observed infections although large, is not more than can be explained by a combination of under-diagnosis and under-reporting. How this partitions between under-diagnoses and under-reporting is not known. One source of information about underreporting of post-transfusion infections has been the HCV lookback. In the course of tracing and testing recipients, several HCV infected recipients were identified who had had post-transfusion hepatitis that had never been reported to the blood service. This pre-dated the surveillance system described and may or may not be similar today. Increased awareness of post-transfusion infections due to both the HCV/lookback experience and to the publicity of the SHOT system mean, hopefully, this is less likely to still occur. The risk estimations described in this thesis are another avenue to estimate under-diagnosis and under-reporting.

Much of the published literature about the estimation of the remaining risk of HBV, HCV and HIV from transfusion does not consider three aspects of the risk of infectious donations entering the blood supply that this thesis show to be important. Firstly is the omission to consider donations from new donors. In England and Wales, and elsewhere, there is evidence that new donors have a higher risk of both prevalent and incident infections. Although new donors only contribute 12% of donations in England and Wales, their donations contribute between one-third and two-thirds of the risk of HBV, HCV or HIV infectious donations entering the blood supply. Secondly, many studies have not considered the risk of false negative donations entering the

blood supply due to test sensitivity less than 100% or due to errors. The risk of window period donations is likely to dominate in situations of relatively low prevalence and high incidence. However, in situations as described in England and Wales, a significant proportion of the risk may be due to false negative test results. Thirdly, the most commonly used method does not adjust the risk estimation if seroconverting donors tend to leave a longer, or shorter, interval between donations than non-seroconverting donors. Again, the data analyses in this thesis show that this will result in overestimation, or underestimation of the risk respectively.

Rapid data from Donation Testing Surveillance does not benefit from detailed data of confirmatory test results and standardised classification of test results that follows. This has meant that the infection status of some donations has been incorrectly classified in the rapidly disseminated donation testing data. While this is not likely to have caused any significant errors in the summary data that are monitored, it has meant some inconsistencies – all be them minor - between early and subsequent data. It is planned that this will be avoided in future by obtaining confirmatory test results directly, and more rapidly, from a single laboratory that conducts all the confirmatory testing.

The exposure history information reported to the Infected Donor surveillance may be incorrect, or biased, for several reasons. Firstly, the information is usually self-reported by the infected donors. These donors may forget to mention exposures that are relevant, even when asked, or may choose to with-hold relevant information if they prefer either the member of staff they talk to, or the blood service to not know. In particular, this might be expected if the donor has an exposure history that was specified by the blood service as a reason to not donate blood. For example, 7% of HIV infected donors (1995-1999) who were reported by the blood service as having no identified risk factor, or with heterosexual sex as their probable route of infection where found by further investigations conducted by CDSC to have probably acquired their infections from sex between men. Secondly, each member of staff who records this information on the infected donor report form may have tendencies towards identifying, or recording, some risk factors more than others.

The monitoring of transfusion itself (who, why, how often etc) – could be seen as a component of the surveillance of blood safety. This is not routinely done in the UK but the data such monitoring would provide is increasingly sought after and would inform the blood service about changes in transfusion practices and requirements for components.

Opportunities for associated work

During the period of study described, several related areas of work have developed in collaboration with, if not directly dependent on, the surveillance system. In 1997, a register of individuals with a known date of HCV infection was established to study the natural history of HCV (Harris HE, 2000). This register initially consisted of HCV infected patients identified to be recipients of blood from donors subsequently found to be HCV infected, and presumed HCV infectious at the time of their donation to the infected recipient. Donors who seroconvert for anti-HCV between donations (within 3 years) are now also invited to enter this register to extend its observations to "known" date infections acquired by other routes.

Tissue donations collected by the English NBS centres have been increasing in both importance and numbers. In 1999, four centres started participating in a pilot system for the surveillance of infections in tissue donors that was established to run in parallel, and collect comparable data, to the blood donor surveillance. This is due to be expanded and extended in 2001.

Blood centre microbiology departments are equipped and skilled for the efficient running of tests on large numbers of samples. Several centres in the English NBS have taken on the testing of antenatal samples. Surveillance of antenatal HBsAg and anti-HIV testing is being established. These data are of use to public health work concerned with the control of sexually and vertically transmitted infections. They can also be used to inform the blood service of the prevalence of infections in the populations from which donors are drawn, and hence inform donor selection, and the success of donor selection in obtaining donations with a lowered prevalence of infection when compared to antenatal women.

Further work

The surveillance of Donation Testing will be improved by direct capture of data from the confirmatory laboratory and by feedback from the detailed reports for infected donors into a version of the donation testing database. This would allow the exclusion of certain groups of positive donations that do not actually represent an infection (e.g. donations from donors with HBsAg positivity due to recent immunisation, positive donations later shown to be due to contamination of the sample) from the testing data and so be more correct for true infection rates. The DT database would remain the most accurate for test specificity data, and the timeliest for infection rate data.

The surveillance of Infected Donors will be improved by follow-up of possible seroconverters and possible acute HBV or syphilis infections to enable routine, accurate, identification of donors with recent infections.
A programme of risk factor research with tested methods for follow-up of risk factors in donors with no identified risk, and evaluation of the risk associated with possible exposures reported by cases, would be a worthwhile extension of the information available from the surveillance. A case-control study protocol has been developed to investigate risk factors for HCV and HBsAg infection in donors with no identified risks reported. One hundred cases and two controls for each case would be needed to be expected to detect, with 5% significance and 80% power, relative risks for HCV infection of around 3-4, and relative risks for HBV infection of around 2-3, for exposures common to between 10% and 70% of controls. The methods of this study are currently being piloted on cases of seroconversion for anti-HCV or HBsAg with no identified risk reported. These cases are perhaps the most informative as they provide information about current risk factors, and information about the risk factors for donors who are most likely to donate during the window period of early infection.

Possible methods for investigating risk factors for positivity to tests for pre-symptomatic vCJD are being considered, with the aim being to design a study to investigate risk factors for positivity to tests for vCJD and conduct appropriate preparatory work so that such a study can go ahead without delay once a test becomes available. No test is currently available for vCJD, and in

the absence of a test, and of precisely identified risk factors within the UK population, there is no way to differentiate individuals who are more likely to be incubating infection from those less likely to be incubating infection. As soon as a test is available that identifies infection, or is even a rough surrogate for infection, this will change. The blood service is likely to use any available tests to try to exclude possibly infectious donations from the blood supply. There will be urgent interest in the use of the test to identify individuals, and numbers of individuals, in the population that may be at risk of disease/infectivity. There will also be urgent interest in the use of the test to investigate risk factors for infection (or possible infection) by comparison of test-positives with test-negatives. Unlike most blood-borne infections that have been major problems for blood transfusion, vCJD is unlikely to be associated with the same "high risk" groups that are now asked to not give blood. Blood donors have been an important population for initial investigation of risk factors for other infections e.g. HCV, but the selective nature of donors has meant these studies have been biased away from the more common risk factors in the population and have therefore been limited in their ability to inform public health. Blood donors are expected to be more representative of the general population with regard to their diet than with regard to their exposures to other blood borne infections. This makes the donor population a more suitable population for the investigation of risk factors for vCJD present in the general population than has been the case for other infections, for example, HCV and HIV. Also, in contrast to HCV and HIV, risk factors for vCJD seem to be less easy to identify by the epidemiology of the clinically diagnosed cases than has been true for HIV and HCV (to be expected if the risk factor is a relatively common dietary factor, and/or long past). It may therefore be the case that a test becomes available before good risk factor information is available for donor selection - and the test will be the tool (via epidemiological studies) for obtaining this information. The blood service may therefore be able to contribute to public health, and to blood safety through donor selection, by conducting a prompt study of risk factors associated with positivity to the first (and subsequent) tests for vCJD. Work on the design and methods of such possible studies could be done now,

to allow preliminary peer-review and preparation in advance of the time they are needed.

In order to improve the availability of safer blood, and prepare for any sudden drop in eligible donors (e.g. in case of poor specificity vCJD testing) and a need to recruit more donors and, or, relax some selection criteria in order to meet demands for blood, donor recruitment policy and donor selection criteria need to be evaluated. This requires combining knowledge about the response to recruitment drives and about the frequency of donor characteristics in potential donors, with knowledge of the risk (i.e. the prevalence and incidence) of blood-borne infections in sections of the population that are targeted for recruitment and in potential donors with characteristics leading to exclusion. This work is beginning. Factors used by the NBS to monitor the success of recruitment (and so determine recruitment policy) are being added to the variables used to describe infection rates so that recruitment can consider infection rates as well as donation yields when targeting advertising and incentives to donate.

PTI surveillance describes instances of recognised TTI and identifies the circumstances under which they occur. Whilst the SHOT system has the potential to observe any novel symptom or syndrome occurring post-transfusion, its power to detect late-onset, chronic, or atypical symptoms of infections transmitted by transfusion is likely to be weak. For example, a rare malignancy associated with a viral agent not yet recognised to be an etiological factor for the malignancy. Studies of recipient mortality, and if possible morbidity, - ideally linked to stored samples from donations - could be used not only to test hypothesis about disease caused by transfusion transmissible agents, but also be used to data-dredge for any indication of unrecognised hazards of transfusion, and then for any infectious cause.

Blood components that are not transfused because they are visibly contaminated with bacteria should be returned to the blood service for investigation of the source, and any further spread, of the contamination. These events are not eligible for reporting to the PTI surveillance as there is

no transfusion and so no post-transfusion infection. However, these events can be just as informative about the source of contamination of blood components as a case of transmission and should be monitored. Surveillance of contaminated components (not transfused) could be seen as comparable – with regard to informing blood safety - to the surveillance of infections in donors, or the exercise performed by the SHOT system that has monitored "near-miss" events such as the transfusion of the "wrong" blood group that does not happen to cause a reaction.

Reconciliation of data in the TTI system and other CDSC information sources could be strengthened. For example, health care associated infections, and hospital-acquired bacteraemias are often reported as suspected transfusion associated infections. Different investigations concerning the same infection can currently be monitored by different departments of CDSC without awareness and exchange of information. Matching of records from different sources (e.g. laboratory reports, and infected donor reports) may become more difficult if personal identifiers collected by surveillance systems are further restricted. The ability to match reports should be retained so that information can be completed and updated from different sources and duplicate reports for a single infection can be identified.

The risk estimation methods are now being used to contribute to the evaluation of some transfusion service practices. Initial work on the evaluation of proposed new tests has been described (chapter 5). Further work will include the use of these methods in the evaluation of donor selection criteria. For example, the effect of accepting men who have had sex with men as blood donors on the risk of HIV and HBV entering the blood supply can be estimated using data and assumptions about the prevalence and incidence of HIV and HBV in this currently excluded group.

Overview of elements of a comprehensive (ideal) TTI surveillance system/programme for England and Wales and conclusion

The surveillance system for transfusion-transmissible infections in England and Wales is now relatively comprehensive. However, limitations and omissions can be identified when working with the data provided, or comparing the system with that in other countries.

The following components are proposed for a full and comprehensive TTI surveillance system for England and Wales. This is based on the system now in place. Other strategies could be combined to construct equivalent, alternative, total systems. For example, in France, where the current strategy is to actively follow-up every transfusion recipient, the benefits of a long-term recipient study would be far less and other supplementary strategies may be envisaged.

	Components of comprehensive TTI surveillance and epidemiology	***In England & Wales***
1.	Surveillance of infections in the population – including vigilance for mutant/variants of known infectious agents and for new infectious agents.	Currently conducted by PHLS & CDSC
2.	Surveillance of behaviours associated with infections in the population	Currently conducted by CDSC/ONS/special surveys e.g. the sexual lifestyles survey
3.	Surveillance of donation testing, infected donors and of (diagnosed, reported) post-transfusion infections.	Currently conducted by NBS/PHLS CDSC – as described in this thesis.
4.	Surveillance of non-infectious complications of transfusion	Currently conducted by SHOT.
5.	Infected recipient natural history studies.	Currently conducted for HCV infected recipients by PHLS CDSC.
6.	Infected donor risk factor investigations/studies	Routine investigations conducted by PHLS CDSC for HIV infected donors. Pilot study underway for HBsAg and anti-HCV seroconverting donors.
7.	Regular studies or routine monitoring of the frequency of characteristics proposed as donor selection criteria amongst potential and actual donors.	No routine. Several ad hoc surveys have been conducted by the NBS.
8.	Regular studies or routine monitoring of recipient characteristics and transfusion practices and outcomes.	No routine. Development of one study now in progress in NBS.
9.	Regular studies or routine monitoring of the morbidity and mortality of transfusion recipients.	No routine. Development of one study of mortality now in progress in NBS.
10.	An archive of donation samples and linked recipient samples for the testing of hypothesis regarding the prevalence of new/emerging infections in blood donations and their transmission by transfusion. Ideally, this would be linked to 8 and 9 so that hypotheses about morbidity and mortality could also be tested.	No routine.

The surveillance of transfusion-transmissible infections forms a relatively small component of the surveillance of blood-borne infections, just as blood donation testing forms a relatively small component of the control of the

transmission of these infections in the population. Targeted HBV immunisation, needle-exchange schemes and safer sex practices do far more to reduce the transmission of HIV, HBV and HCV by addressing the more common routes of transmission of these viruses. Data from the surveillance of blood donors in England and Wales has not identified new high priorities for national public health work: it has informed public health about the frequency of infections in low risk, healthy adults (and in transfusion recipients) and thereby clarified the elevation of risks experienced by some other groups in the population and perhaps indirectly contributed to the setting of priorities for infection prevention.

The documentation of, and publicly available information about, transfusion-transmitted infections may actually adversely affect the perception of blood safety amongst at least some of the public. The identification and description of risks can lead to public worry, without the expected reassurance from the quantification of the risk. Further work is needed on risk communication and understanding how risks are perceived.

Infectious risks are no longer the major cause of preventable, serious, complications, however this remains a key area. This may be partly because the potential for damage to recipients is there, as has been revealed by HIV and HCV in the past two decades, and this danger – of known infections and of new and, or, unknown ones - is perhaps better perceived and more dreaded than the known risks of non-infectious complications. Several attempts have been, and continue to be, made to examine transfusion risks in a broader context and to improve communication of the risks of transfusion to the general public.

Chapter 6 references

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Appendices