Prevention of transfusion transmitted infections.
Donor screening and characteristics of recipient populations

Elsa Tynell

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ABSTRACT

Minimising the risk for transfusion transmitted infections (TTIs) relies on selection of safe donors, including microbiological screening, and avoidance of unnecessary transfusions. Blood donor screening for HTLV-I and II, was introduced in Sweden in 1994. The first year six HTLV-I and no HTLV-II positive donors were found, which meant a prevalence of 2 per 100 000. The transmission rate at transfusion is estimated at 15% but only five percent of infected individuals will develop serious disease during their lifetime: tropical spastic paraparesis (TSP) after three to four years or adult T-cell lymphoma (ATL) after several decades. TTIs should be prevented but cost effectiveness needs to be considered. We estimated the cost for prevention of one death, due to transfusion transmitted HTLV disease (ATL), to $540 million when every donation was tested and $36 million when only new donors were tested. The number of prevented deaths would be almost the same (1/180 versus 1/210 years). As a result of this study only new donors are now tested in Sweden. The age and expected survival of blood transfusion recipients will affect the expected damage caused by transmitted infections, i.e. the development of clinical disease and the risk for secondary spread to infants and sex partners. Survival rates of transfusion recipients in Stockholm and Örebro counties in 1993 were found to be 66% after one year, 51% after 40 months and 39% after seven years for those in Örebro. The median age of recipients was 70 years and 21% were 80 years or older. Adequate indications for transfusion are essential. Donated blood is a limited resource and a small risk of infection will always remain, in spite of rigorous safety. Among patients transfused in Örebro County in 1993 and 2000 survival rates were higher in operated patients, in younger patients and in females. Lower survival rates were seen in patients with cancer and in those receiving more than ten units. Overall one year survival rate in 2000 was higher than in 1993 despite higher age among recipients. Many donors are deferred temporarily or permanently because of false-reactive test results. A survey was performed in 19 blood centres in 11 counties. The viral screening tests showed between 0.01 and 0.2% false-reactive results and the variation for each test was about tenfold. There was also a great variation in deferral rates between counties. In a questionnaire study only 37% of deferred donors found the information at notification sufficient and over 80% were worried by their test result. There is need for a more standardised approach to the microbiological screening of donors, with the aim to minimise the number of false-reactive results, and need for better information and support to deferred donors.

Keywords: HTLV-I and II, blood donor screening, transfusion recipients, case-mix, survival rates, false-reactive test results, cost effectiveness.

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ORIGINAL PAPERS

This thesis is based on the following papers. They will be referred to by their Roman numerals:

Screening for human T cell leukaemia/lymphoma virus among blood donors in Sweden: cost effectiveness analysis.
*British Medical Journal* 1998;316:1417-1422

II. Tynell E, Norda R, Shanwell A and Björkman A.
*Transfusion* 2001;41:251-255

III. Tynell E, Norda R, Montgomery SM and Björkman A.
Diagnosis and procedure specific survival among transfusion recipients in 1993 and 2000, Örebro County, Sweden.
*Vox Sanguinis* 2005:88:181-188

IV. Tynell E, Norda R, Ekermo B, Sanner M, Andersson S and Björkman A.
ABBREVIATIONS

AIDS  Aquired immuno deficiency syndrome
ALT  alanine amino transferase
anti-HBc  antibody against hepatitis B core antigen
anti-HBs  antibody against hepatitis B surface antigen
anti-HCV  antibody against hepatitis C virus
anti-HTLV I+II  antibody against human T-lymphotropic viruses I and II
ATL  adult T-cell lymphoma
Au-antigen  Australia antigen = HBsAg
CMV  cytomegalovirus
CUE  confidential unit exclusion
EBV  Epstein-Barr virus
HBsAg  hepatitis B surface antigen
HBV  hepatitis B virus
HCV  hepatitis C virus
HHV 6,8  human herpes virus types 6 and 8
HIV  human immuno deficiency virus
HTLV-I+II  human T-lymphotropic virus types I and II
ICD IX, X  international classification of diseases, 9th and 10th editions
LD  leucocyte depletion
NANB  Hepatitis non-A, non-B
NAT  nucleic acid technology /testing
QALY  quality adjusted life year
RBC  red blood cells
TSP  tropical spastic paraparesis
TTI  transfusion transmitted infection
vCJD  variant Creutzfeldt-Jakob disease
WB  Western blot
WNV  West Nile virus
WHO  World Health Organisation
General introduction

History of blood transfusion

Transfusion of blood without great danger for the patient became possible after the discovery of the AB0-system in 1900 and the first transfusion in Sweden was described in 1916 (Swedish Association for Transfusion Medicine. Manual for Blood centres, 2002). The use of sodium citrate to stop collected blood from clotting and later refrigeration were also important innovations that made transfusions on a larger scale possible (www.blood.co.uk). Transfusions became common during World War I and even more so during World War II, when blood donation became a patriotic duty in many countries. Later on blood transfusions made open cardiac surgery possible and the development of such extensive surgery and the use of the cardio-pulmonary by-pass machine further increased the demand for blood. Similarly the development of platelet collection and transfusion was a necessary condition for the development of aggressive cancer treatment, especially in blood malignancies.

In Sweden the increase in yearly consumption of blood was more than fourfold between 1949 and 1968 (Gullbring 1969). In the US blood collection increased during the 1960s to 1980s but fell again and was found in 1994 to be the lowest since 1971 and the transfusions were then on the same level as in 1979 (Wallace, Churchill et al. 1998). However, it is generally expected that the need for donated blood will continue to be high (Ferriman 1998). Artificial blood will probably not be an alternative for many more years. Treatment with erythropoietin, in patients undergoing cancer chemotherapy, in order to increase their production of erythrocytes, has been shown to be much more expensive, more than $100 000 per quality adjusted life year (QALY), than transfusion of human blood (Barosi, Marchetti et al. 1998).

Early history of iatrogenically transmitted blood borne infections

The first recognised description of iatrogenically parenterally spread disease was published in 1885, when mass vaccination against smallpox in a shipyard in Bremen, Germany gave rise to large number of jaundice (“ikterus”) cases (Lurman 1885). More descriptions of hepatitis spread by injection or blood testing were published thereafter, one from Serafimerlasaretetin Stockholm (Lindstedt 1923) and one among diabetics in Lund (Flaum 1926). Perhaps because of the language barrier (these articles were written in German) they had been overlooked in England (MacCallum 1972).
Table 1. Highlights from the history of blood transfusion*

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1492</td>
<td>Pope Innocentius VIII had a blood transfusion because of coma after a stroke</td>
</tr>
<tr>
<td>1628</td>
<td>William Harvey described the functions of the heart and the circulation of blood</td>
</tr>
<tr>
<td>1665, 1667</td>
<td>Experiments with blood transfusions between dogs and from animals to humans in England and France</td>
</tr>
<tr>
<td>1818</td>
<td>First blood transfusion because of postpartum hemorrhage performed in England</td>
</tr>
<tr>
<td>1867</td>
<td>First use of antiseptics to control infection during blood transfusions in England</td>
</tr>
<tr>
<td>1900</td>
<td>Karl Landsteiner, an Austrian physician, discovered the human blood groups: A, B, and O.</td>
</tr>
<tr>
<td>1914-1918</td>
<td>Sodium citrate, to prevent the blood from clotting, and refrigeration together make longer storage of blood possible.</td>
</tr>
<tr>
<td>1921</td>
<td>The first voluntary Red Cross blood service started in Britain</td>
</tr>
<tr>
<td>1932</td>
<td>The first blood bank established in Leningrad</td>
</tr>
<tr>
<td>1939-40</td>
<td>The Rh blood group system discovered by Karl Landsteiner</td>
</tr>
<tr>
<td>1943</td>
<td>Morgan and Beeson published the first descriptions of transfusion transmitted hepatitis from England and the US</td>
</tr>
<tr>
<td>1950s to 1970s</td>
<td>Glass bottles gradually replaced by plastic bags for the collection of blood</td>
</tr>
<tr>
<td>1953</td>
<td>Refrigerated centrifuge enables component therapy</td>
</tr>
<tr>
<td>Mid-1950s</td>
<td>Open heart surgery</td>
</tr>
<tr>
<td>1961</td>
<td>Platelet therapy for hemorrhage in cancer patients</td>
</tr>
<tr>
<td>1962</td>
<td>Antihemophilic factor concentrate developed</td>
</tr>
<tr>
<td>1971-72</td>
<td>HBsAg testing of blood donors introduced</td>
</tr>
<tr>
<td>Early 1980s</td>
<td>SAGMAN solution, invented by Claes Högman, makes longer storage of blood possible</td>
</tr>
<tr>
<td>1981</td>
<td>First case of AIDS reported</td>
</tr>
<tr>
<td>1984</td>
<td>HIV identified as the cause of AIDS</td>
</tr>
<tr>
<td>1985</td>
<td>HIV testing of blood donors introduced</td>
</tr>
<tr>
<td>1990</td>
<td>HCV testing of blood donors introduced</td>
</tr>
<tr>
<td>1999</td>
<td>Nucleic acid testing (NAT) for HIV and HCV started in USA</td>
</tr>
</tbody>
</table>

*from (www.aabb.org) (www.blood.co.uk) (www.bloodbook.com/trans-history).
With the increasing use of blood transfusions, reports on the spread of infections by transfusion (transfusion transmitted infections - TTIs) began to appear. In 1943 jaundice after blood transfusion was described in one British (Morgan 1943) and one American publication (Beeson 1943). In the latter the recipient’s risk to contract a bloodborne (viral) infection was judged to be correlated to the number of donors he/she was exposed to, rather than to the volume of blood transfused. Bacterial contamination of blood and its effect on the recipient also became a concern (Raigorodsky 1946; Braude, Sanford et al. 1952). The emergence of the HIV epidemic in the 1980s however had a greater impact on blood collection, transfusions and the public interest in the matter than any of the transfusion transmitted infections recognised before that time. Table 1 shows some important events in the history of blood transfusion and TTIs.

**Strategies to prevent transmission**

Theoretically all infectious agents that can exist in the bloodstream, be it only for a short while, can be transmitted by transfusion although many do not cause TTIs. One reason for this may be that donors feel unwell and do not attempt to donate during acute viremia, bacteremia or parasitemia. A list of infectious agents that can cause TTI is presented in table 2.

Ways to prevent the spread of TTIs are selection of the right donors by interviews and questionnaires, microbiological screening, leucocyte depletion (LD), inactivation of possible residual infectious agents in blood components, avoiding “unnecessary” transfusions (guidelines) and autologous blood transfusions.

**Selection of donors**

Sixty percent of healthy adults in the rich part of the world are qualified to be blood donors but only a maximum of ten percent volunteer for donation. In the developing countries the frequency is less than one percent (Hurley 1995).

**Paid or unpaid donors**

Unpaid donors were long ago recognised as more safe (Titmuss 1970). Titmuss´s book “The gift relationship” had a strong impact on blood donation in the US, where at that time 25% of the blood collection system was commercial. Donors were paid in money or given one or two
**TABLE 2. Agents transmitted by transfusion*** (the most important in bold letters)

<table>
<thead>
<tr>
<th>Viruses:</th>
<th>Parasites:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>Malaria (all species)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Trypanozoma cruzi</td>
</tr>
<tr>
<td>Hepatitis D (delta)</td>
<td>Babesia</td>
</tr>
<tr>
<td>HIV 1 and 2</td>
<td>Leischmania</td>
</tr>
<tr>
<td>HTLV I and II</td>
<td>Toxoplasma gondi</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>Filaria</td>
</tr>
<tr>
<td>Parvo B19</td>
<td></td>
</tr>
<tr>
<td><strong>West Nile virus</strong></td>
<td>Treponema pallidum</td>
</tr>
<tr>
<td>Epstein Barr virus (EBV)</td>
<td>Pseudomonas spp</td>
</tr>
<tr>
<td>Hepatitis G GBV-C/HGV</td>
<td>Staphylococci</td>
</tr>
<tr>
<td>HHV 6</td>
<td>Streptococci</td>
</tr>
<tr>
<td>HHV 8</td>
<td>Salmonella spp</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Yersinia enterocolitica</td>
</tr>
<tr>
<td>Colorado tick fever</td>
<td>E.Coli</td>
</tr>
<tr>
<td>Prions (?) - agent of variant Creutzfeldt-Jakob disease</td>
<td>Diphteroids</td>
</tr>
<tr>
<td></td>
<td>Bacteroides</td>
</tr>
<tr>
<td></td>
<td>Serratia liquefaciens and marescens</td>
</tr>
<tr>
<td></td>
<td>Bacillus spp</td>
</tr>
<tr>
<td></td>
<td>Brucella spp</td>
</tr>
<tr>
<td></td>
<td>Clostridium perfringens</td>
</tr>
</tbody>
</table>

* (Morduchowicz, Pitlik et al. 1991; Hurley 1995; Mandell 2005)

Days off from work. A prisoner donor could even get a remission of sentence. There was also a sort of insurance system where the donor “paid” by one or two donations per year. This ensured the availability of a certain number of free transfusions for the donor and his/her family if needed during that year. Fees could be charged by the blood bank if donations were not made according to the agreement, and this meant a motivation to be untruthful about one’s health. Such donors were an example of “individual responsibility donors” as opposed to “community responsibility donors” that can be viewed as the true altruists (Piliavin 1991).
The influence of paying donors on the blood collection system was shown in a study in New Mexico where there was an almost 100% turnover in the donor population after a changeover to non-paid donors (Surgenor and Cerveny 1978). There was no significant change in the incidence of hepatitis B surface antigen (HbsAg - the only viral disease marker used at that time) in the blood supply, but the quality of blood services was improved and the cost for patients reduced. A concrete example of the risk with paid donors is described in a report from the US in 1973. An unemployed 50 year old man, healthy besides “intermittent ethanolism”, donated plasma twice a week for two years and took several courses of antibiotics and other medications during the period of donation. Seven recipients got salmonella septicaemia transmitted by platelets from this donor, who was later shown to have a salmonella osteomyelitis (Rhame, Root et al. 1973).

In countries where blood collection was organised by the Red Cross, donors were always unpaid. This was the case for example in Britain, Australia and Finland. In Finland blood collection was first organised by the scout organisation but later on by the Red Cross. In Finland during and shortly after the second world war donors would receive ration cards that gave them the right to buy milk or butter, later coffee and sometimes they would get a drink of brandy after donation “against postdonation weakness” (www.blodtjanst.fi 2004).

In Sweden blood collection was organised by public hospitals and donors were paid from the start. The fee in Stockholm and Uppsala in 1951 was 28 and 30 Skr respectively. It has not been raised since then, which means that the fee has almost completely lost its economic value. A Swedish study of blood donors’ motives for donation showed that the proportion of donors willing to continue donation, even if they were not paid, increased from 34% in 1951 to 72% in 1968 (Gullbring 1969). Presently, in many parts of Sweden only gifts like mugs, socks or t-shirts are offered to donors.

Many countries experience difficulties to attract a sufficient number of new young donors. Different strategies are used. In an anonymous mail survey of donors small incentives, gifts of minimal value and also medical tests, were shown not to attract unsafe donors whereas money did. (Sanchez, Ameti et al. 2001). In another also anonymous US study, young donors more frequently than other donors came to the blood centre in order to have an HIV test performed and also reported more other risk behaviours that would have led to deferral (Damesyn, Glynn et al. 2003).
A pre-donation interview with new donors and a health questionnaire at every donation are important tools for finding the right donors. However, most deferrals of unsuitable donors occur after laboratory screening, more often because of too low hemoglobin content (Axelsson and Sojka 1998; Halperin, Baetens et al. 1998) than because of infectious disease screening test results.

Confidential unit exclusion (CUE) means that the donor after donation can communicate to the blood centre staff that his/her blood should not be used for transfusion. It had its greatest significance after the identification of AIDS as a TTI but before the introduction of HIV-screening. It may still prevent transfusion of window phase donations (see below) and although its use has declined, it is still used in many blood centres in the US (Chamberland 2001). CUE is not used in Sweden.

Microbiological testing

Until recently screening of blood donors has relied mostly on testing for antibodies against the different infectious agents, except for Hepatitis B virus (HBV). This implies that there is a “window period”, i.e. a period of time from infection until antibodies against the infectious agent can be detected in the blood. In order to shorten this period of possible unsafe donations, conventional p24 antigen testing and/or nucleic acid technology/ testing (NAT) can also be used. Raised liver enzymes, alanine amino transferase (ALT), can also be used as an indirect so called “surrogate” marker for hepatitis.

Leucocyte depletion (LD)

LD is accomplished by filtration of collected units. LD can diminish the risk for transmission of leucocyte associated viruses and perhaps prions. It may also decrease the risk for transmission of bacterial infection since contaminating bacteria may be phagocytised and killed by donor granulocytes, which then can be removed by LD a few hours after collection (Williamson 2000). Leucocytes can survive in the recipient up to one and a half years after a transfusion (Lee, Paglieroni et al. 1999). An immunomodulatory effect is seen after transfusion and this was shown already in 1973 as an improved renal allograft survival after transplantation in transfused compared to non-transfused patients. (Opelz, Sengar et al. 1973). This immunomodulatory effect is believed to be due to donor leucocytes. Many studies have been performed to investigate whether transfusion leads to an increased risk for cancer.
recurrence or postoperative infections (Houbiers, van de Velde et al. 1997). Such an effect, if there is one, could be attributable to donor leucocytes and comparisons between the outcome of patients receiving LD or non-LD components have been made (Jensen, Kissmeyer-Nielsen et al. 1996; Llewelyn, Taylor et al. 2004). Results from meta-analyses including many studies did not manage to show a definite beneficial effect of LD on cancer recurrence or postoperative infections (Vamvakas and Blajchman 2001). However, even a very small decrease in postoperative infections would have a great economic impact. The total cost for universal LD in the UK would be balanced by a 1-2% decrease in postoperative infections (Williamson 2000). A recent British study that compared the situation before and after implementation of universal LD did not show any difference in elective orthopaedic and cardiac surgery (Llewelyn, Taylor et al. 2004).

Universal LD is used in several western European countries and in Canada, in the UK and Ireland mainly as a precaution towards variant Creutzfeldt-Jakob disease (vCJD), elsewhere rather as a precaution towards presently unknown infectious agents, possible negative effects due to immunomodulation and for the prevention of Cytomegalovirus (CMV) transmission. However, 31 authors from 26 institutions in the US signed a letter to “Transfusion” in which they strongly opposed measures to implement LD of components for all patients in the US until there were more reliable data showing a health benefit (Thurer, Luban et al. 2000). In Sweden LD is performed in practically all platelet units and in an increasing proportion of all red blood cell (RBC) units transfused (97% and 61% respectively in 2003) (Report on Sweden’s blood supply 2003).

**Pathogen inactivation**

There are various methods for inactivation: heat treatment and solvent detergent treatment for HCV in plasma, nucleic acid targeted pathogen inactivation aimed at residual donor leucocytes mainly for cellular components, psoralens and photodynamic methods for pathogen inactivation in platelets, photodynamic methods and nucleic acid targeted processes for components from CMV-seronegative donors for RBCs (Corash 2000).
Transfusion transmitted infections and blood donor screening

The history of infectious disease blood donor screening in Sweden is presented in table 3.

Table 3. Blood donor screening in Sweden

<table>
<thead>
<tr>
<th>Test</th>
<th>Year of implementation</th>
<th>Present use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis</td>
<td>1948-1954</td>
<td>For new donors and when required by plasma purchasers</td>
</tr>
<tr>
<td>HBsAg</td>
<td>1970-1972</td>
<td>For new donors and at every donation</td>
</tr>
<tr>
<td>Anti-HIV</td>
<td>1985</td>
<td>For new donors and at every donation</td>
</tr>
<tr>
<td>Anti-HIV 1+2</td>
<td>1991</td>
<td>For new donors and at every donation</td>
</tr>
<tr>
<td>Anti-CMV</td>
<td>1985-85</td>
<td>No longer in use routinely, leucodepleted blood used instead</td>
</tr>
<tr>
<td>p-ALT</td>
<td>1989</td>
<td>When required by plasma purchasers</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>1991</td>
<td>For new donors, on re-entry after a long period and after “risk events”</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>1992</td>
<td>For new donors and at every donation</td>
</tr>
<tr>
<td>Anti-HTLV-I + II</td>
<td>1994</td>
<td>For new donors only</td>
</tr>
<tr>
<td>HCV-RNA</td>
<td>1999</td>
<td>Required for plasma fractionation</td>
</tr>
<tr>
<td>HIV-RNA</td>
<td>2001</td>
<td>When required by plasma purchasers</td>
</tr>
</tbody>
</table>

Comparisons between different screening tests presently used for blood donors in Sweden are presented in paper IV. The total number of confirmed positive test results in Sweden in 2003 is presented in table 4.
Table 4. Confirmed positive test results in Sweden 2003

<table>
<thead>
<tr>
<th>Infectious agent</th>
<th>Donations</th>
<th>New donors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tests performed</td>
<td>Nº positive</td>
</tr>
<tr>
<td><strong>Anti-HIV</strong></td>
<td>633059</td>
<td>2</td>
</tr>
<tr>
<td><strong>Anti-HCV</strong></td>
<td>633059</td>
<td>3</td>
</tr>
<tr>
<td><strong>HBsAg</strong></td>
<td>633059</td>
<td>2</td>
</tr>
<tr>
<td><strong>HTLV-I+II</strong></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*From report on Sweden’s blood supply 2003*

**Lues**

Transfusion transmitted syphilis was a serious problem during the first half of the 20th century because of direct donor to recipient transfusion (Bruce-Chwatt 1985). The problem almost disappeared after the start of refrigerating blood (Ravitch 1948) but reappeared with the use of fresh blood components (platelets)(Chambers, Foley et al. 1969). In Sweden screening was introduced between 1948 and 1954 and is now performed in all new donors, and whenever required by plasma purchasers. Since 1969 there has been no identified case of transfusion transmitted syphilis in the US and it is unclear whether donor screening has an impact on transmission today (Dodd 2000). When platelets from donors with reactive screening test results for syphilis were further tested by polymerase chain reaction (PCR), no treponemal DNA or RNA was found (Orton, Liu et al. 2002). There is no general requirement for screening within the European Community (Hurley 1995).

**Hepatitis B and C**

The Australia antigen (Au-antigen), later called hepatitis B surface antigen (HbsAg) was first described in 1967 (Blumberg, Gerstley et al. 1967), mainly in patients with Down’s syndrome but also in leukaemia, hepatitis, hemophilia and thalassemia patients. Testing of blood donors started in 1970-72 in Sweden like in many other countries.
Anti-hepatitis B core-antigen (anti-HBc) is another marker of hepatitis B that develops during the course of HBV infection and there is a life long expression of anti-HBc together with antibodies against HBsAg (anti-HBs) after a cleared infection. Many countries do not screen blood donors for anti-HBc. However, in Sweden anti-HBc testing is used in new donors and after a “risk event” such as tattoo, piercing, surgery or blood transfusion. Persons with signs of earlier HBV infection are not accepted as blood donors. “Anti-HBc only” is an intriguing finding in donors, especially since there is no accepted confirmatory test, although there are ways to rule out an actual true or cleared infection from unspecific reactions (Allain, Reeves et al. 1995; Hughes, Barr et al. 1995). However, in low-endemic areas about 10-20% of individuals with any HBV markers are known to be anti-HBc positive in spite of being negative in all other hepatitis B markers. This pattern is more common in HIV or HCV positive individuals (Alhababi, Sallam et al. 2003). During the “tail end” of HBsAg carriage “anti-HBc only” can also be present (Barbara 1994).

However, after HBV testing had been introduced, cases of post-transfusion hepatitis still occurred that were Au-antigen negative. This group of hepatitis patients were diagnosed as hepatitis “non A non B” (NANB). In a Canadian study from 1984-85, 92 out of 1000 blood product recipients developed post transfusion hepatitis of which 31 were hepatitis C (HCV) (Feinman, Berris et al. 1988) (Feinman 1991). ALT and later anti-HBc were introduced and used in some countries as surrogate markers for hepatitis NANB, until anti-HCV testing of donors became available, and similarly for HIV (Korelitz, Busch et al. 1996) and window period HIV (Dodd and Popovsky 1991). In a Canadian prospective study (Blajchman, Bull et al. 1995) screening for anti-HBc and ALT was shown to reduce the risk for hepatitis C by 70% (p<0.05) before introduction of HCV antibody screening in 1990. However, a fall in incidence of HCV was seen, between 1984-85 and 1988-90, even without this surrogate testing, probably due to improved selection of donors.

In an American study ALT screening, used as a surrogate test for HCV in blood donors, was calculated to reveal 1800 HCV-infectious units per million before the introduction of HCV screening but only three infectious units per million donations thereafter. The cost of continued ALT screening was then estimated at $7,931,000 per quality-adjusted year of life saved (Busch, Korelitz et al. 1995). Indirectly, exclusion of donors at risk for HIV and anti-HIV screening of donors also became a tool against hepatitis NANB before a test directed against the agent itself was introduced since both infections have the same modes of transmission.
The hepatitis C virus was first described in 1988-89 (Choo, Kuo et al. 1989; van der Poel, Cuypers et al. 1994) and found to be the main etiologic agent of hepatitis NANB. The first generation of anti-HCV tests became available (Kuo, Choo et al. 1989). Due to a high rate of false positive results and poor clinical correlation, blood donor screening was postponed in some countries. A second generation of anti-HCV tests was developed and started to be used in 1991 and a third generation in 1993. In 1991-92 most industrialised countries started blood donor screening (Allain 1998). In Sweden screening became mandatory in 1992.

**Human immunodeficiency virus (HIV)**

Transfusion associated AIDS was described in 1983 in an infant (Ammann, Cowan et al. 1983). Individuals from groups with already identified higher risk for HIV (mainly homosexual men) had been instructed, even before a test was available, not to donate blood. This resulted in a fall in the per donation risk from 1.2% to 0.2% in California where the incidence of HIV was high (Busch, Young et al. 1991). HIV, at first called HTLV III, was isolated and recognised as the etiological agent of AIDS in 1983-84 (Barre-Sinoussi, Chermann et al. 1983; Gallo, Salahuddin et al. 1984). Commercial antibody tests were developed and screening of blood donors was implemented in 1985-86. In France in 1992 persons from the National Centre of Blood Transfusion were even sentenced to prison after being accused of having caused a delay in the implementation of general HIV screening of blood donors by an American test (Abbott) in favour of a French test (Pasteur) and also of having caused a delay in the implementation of only allowing distribution of heat treated clotting factors and as well as of continuing to collect blood from prisoners (Le Monde) (Dumay 1999). In 1999 three French former ministers were tried in court, also because of the “blood scandal”, but no sentence was imposed (Whitney 1999). Several other countries have also had their “AIDS scandals” (www.news.bbc.co.uk 2001).

The first generation of anti-HIV-1 tests mostly also discovered HIV-2 thanks to cross reactivity, but in 1991 a test for both HIV-1 and 2 was introduced. Later HIV type O was described and current licensed assays all discover type O.

Despite a dramatic decrease in the transmission of HIV by transfusion, five to ten percent of HIV transmissions in the world are still due to transfusion and 25% of the blood transfused in Africa is not screened for HIV (WHO 2001) (Field 2004).
Antigen (p24) can be discovered earlier than antibodies and such testing was used early on for diagnosis in patients. Later on “combo-tests” for detection of both antigen and antibodies were introduced and these “combo tests” are also being used in some places for blood donor screening although some, but not all, have a high frequency of false-reactive results (paper IV).

**Nucleic acid technology/testing (NAT)**

In 1990 the window period for HIV was calculated to be 45 days (Petersen, Satten et al. 1994). Improvement in the sensitivity of tests reduced the period to 22 days. New studies suggested that the window period would be shortened by another six days by p24 antigen testing and by still another five to six days by NAT. However, observations showed that the yield of additionally detected HIV positive donations by additional testing with p24 was only one in nine million donations, possibly because those with antigenemia are in the initial acute phase of the infection and likely to be ill and will therefore not donate blood (Dodd 2000) whereas a positive NAT can be discovered before the onset of symptoms.

In order to handle the enormous amount of tests and the cost for these, minipool NAT became the rule, although the number of samples included in the pool varies greatly. The minipool technique means that the possible amount of virus will be diluted proportionate to the number of samples included in the pool.

Pooled NAT discovered one extra HIV infectious unit in 3.1 million donations (0.33 per million) and one extra HCV infectious unit in 230,000. Only two out of 12 such HIV-NAT positive but antibody negative donations discovered were p24 antigen positive (Stramer, Glynn et al. 2004)

HIV p24 antigen and ALT testing have been discontinued in the US after the introduction of NAT for HIV and HCV. Although the expected yield of HCV-NAT is greater than that of HIV-NAT, the yield observed by introducing pooled NAT compared to earlier screening in France was 0.41 per million donations for HIV and 0.20 per million donations for HCV (Pillonel and Laperche 2004).

In 2000 the first case of HCV transmission despite negative NAT was reported from Germany (Schuttler, Caspari et al. 2000) and in 2002 the first of HIV transmission despite negative NAT from France (Renaudier 2002) followed by one from the US in 2004 (Delwart, Kalmin et al. 2004).

Some countries that have introduced minipool testing are now discussing whether individual NAT should be used to close the window even further. According to a recent estimate, again
from the US, replacing minipool NAT by individual NAT would reduce the HCV and HIV risk from one per two million units to one per three to four million units (Busch, Glynn et al. 2005) and close the window by another four days for both HIV and HCV (Busch and Dodd 2000). Tables 5 and 6 show the impact on the length of window period and risk for viral transmission (HIV and HCV) of different screening tests.

NAT in the European Union
The yield of additional NAT is dependant on the incidence in the population. It also depends on the number of days by which the window period can be shortened and can therefore be expected to be higher for HCV, since HCV has a long window period. In a Eurosurveillance report the yield by antibody testing compared to NAT in six countries that recently had implemented NAT for HIV and HCV, was presented (Laperche 2005). A decrease in residual risk for HIV and HCV was observed but this trend started already before the implementation of NAT and was judged to be due to better selection of blood donors. For HCV the yield was found to be smaller in northern than Mediterranean countries. For HIV concurrent antigen testing also diminishes the yield of NAT. Testing for HBV-DNA (NAT) is routinely only used in Germany (Laperche 2005). Such a screening would probably prevent most acute phase window period related infections but revealed fewer probable cases of transmission of HBV from chronic carriers than anti-HBc in a British study (Allain, Hewitt et al. 1999).

The cost effectiveness of NAT has been debated. Studies have estimated it not to be cost effective but no country has decided to withdraw this screening after having introduced it. A wish for harmonisation within the union is expressed. A report on the “NAT situation” in 18 European countries is to be published in June this year (Laperche 2005). By now implementation of minipool NAT for HCV and HIV is taken for granted in most high income countries (Laperche 2005). This is however not the case in Sweden and Denmark.

In Sweden NAT for HCV is used for all plasma for fractionation since 1999 and for HIV when required by the plasma purchaser, but no universal blood donor screening with NAT is performed. Instead combined antigen-antibody testing for HIV is beginning to be used as an alternative for NAT. A combined antigen-antibody test for HCV is under development.
Table 5. HIV. Effect of different methods of blood donor screening on length of window period and estimated risk for TTI

<table>
<thead>
<tr>
<th>Screening test</th>
<th>Year (country)</th>
<th>Length of window period</th>
<th>Risk for TTI per unit</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Antibody (anti-HIV 1)</em></td>
<td>1990 (US)¹</td>
<td>45</td>
<td>1:40 000 to 1:153 000¹</td>
</tr>
<tr>
<td></td>
<td>1996 (US)¹</td>
<td>22</td>
<td>1:450 000 to 1:660 000¹</td>
</tr>
<tr>
<td></td>
<td>2000-02 (France)²</td>
<td></td>
<td>1:1 400 000²</td>
</tr>
<tr>
<td><em>p24 antigen testing</em></td>
<td>1996 (US)¹</td>
<td>16</td>
<td>1:676 000¹</td>
</tr>
<tr>
<td><em>Minipool NAT</em></td>
<td>1999 (US)¹</td>
<td>10-11</td>
<td>1:990 000 to 1:1.100 000¹</td>
</tr>
<tr>
<td></td>
<td>2000-02 (France)²</td>
<td></td>
<td>1:2 500 000²</td>
</tr>
<tr>
<td><em>Individual NAT</em></td>
<td>(US)</td>
<td>6</td>
<td>1:5-6 000000¹</td>
</tr>
</tbody>
</table>

¹Figures from the US (AuBuchon, Birkmeyer et al. 1997), (Dodd 2000), (Busch and Dodd 2000), (Busch, Glynn et al. 2005)

²Figures from France (Pillonel and Laperche 2004)

Table 6. HCV. Effect of blood donor screening on length of window period and risk for TTI

<table>
<thead>
<tr>
<th>Screening test</th>
<th>Year country</th>
<th>Length of window period</th>
<th>Risk for TTI per unit</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Antibody 3rd generation</em></td>
<td>2000-2002² France</td>
<td>70</td>
<td>1:1000 000²</td>
</tr>
<tr>
<td><em>Antigen testing</em></td>
<td>Under development</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>2000-2002² France</td>
<td></td>
<td>1:6 650 000²</td>
</tr>
<tr>
<td><em>Individual NAT</em></td>
<td>US</td>
<td>6</td>
<td>1:5-2.5 000000¹</td>
</tr>
</tbody>
</table>

¹ (Dodd, Notari et al. 2002), (Busch and Dodd 2000), (Busch, Glynn et al. 2005)

² (Pillonel and Laperche 2004)

³ Only repeat donors
**Cytomegalovirus (CMV)**

CMV is found in peripheral blood leucocytes of seropositive individuals (Hillyer, Lankford et al. 1999). Immunocompromised patients, for instance those undergoing transplantation, have a high risk of developing serious CMV disease. Blood components from seronegative donors have therefore often been used for this category of patients. Its high seroprevalence in the adult population (40-100%) (Jong 1998) implies that excluding all seropositive individuals from donation is not an option. LD of collected units has been used and shown to be efficient for the prevention of CMV disease and is therefore becoming an increasingly common alternative to the use of blood components from CMV seronegative donors (Pamphilon, Rider et al. 1999). In Sweden blood donors are not routinely screened for antibodies against CMV.

**HTLV-I and II**

HTLV-I and II (human T-lymphotropic viruses, or human T-cell leukaemia viruses I and II) are two closely related blood borne viruses. HTLV-I is found in well defined populations like in certain islands in Japan, certain areas in Central Africa, the Northeast of Iran (Safai, Huang et al. 1996), parts of South America and the Caribbean. HTLV-II exists in Central Africa, South America - especially in the Amazon area, the Caribbean and in North America mostly in Amerindian populations. The introduction of HTLV-II among intravenous drug users has affected the epidemiology of HTLV-II and it is now common among drug users in the US, Vietnam and Southern Europe (Roucoux and Murphy 2004). HTLV continues to bring confusion due to its name, since HTLV-III was the name used for HIV during the first years of the HIV-epidemic. However, the risks for development of disease and for transmission by transfusion of infected blood are widely different for HTLV-I, II and HIV (table 6).

Blood donor screening for HTLV-I and II was first introduced in 1986 in Japan, which is highly endemic for HTLV-I. Table 7 shows data about HTLV-I and II blood donor screening in different countries. In Sweden general screening was introduced in 1994 and in 1995 this was changed to screening of new donors only. In the UK universal screening was introduced in 2002.
Table 6. Comparison of frequency of transmission and pathogenity between HTLV-I and HIV-1

<table>
<thead>
<tr>
<th>Risk for:</th>
<th>HTLV-I</th>
<th>HIV-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission by transfusion of infected blood</td>
<td>15% (13-63%)</td>
<td>Almost 100%</td>
</tr>
<tr>
<td>Development of clinical symptoms in infected individuals</td>
<td>2-5%</td>
<td>Almost 100% if not treated</td>
</tr>
<tr>
<td>Death from transfusion transmitted infection</td>
<td>1 death in 200 years in Sweden (without screening of blood donors)</td>
<td>Almost 100% if not treated</td>
</tr>
</tbody>
</table>

1 (Okochi, Sato et al. 1984), (Sullivan 1991), (Donegan, Lee et al. 1994).
2 (Inaba, Okochi et al. 1999), (Hollsberg and Hafler 1993; Tosswill, Taylor et al. 2000).
3 Paper I

The need for HTLV-I and II donor screening is not evident. In Australia the Red Cross National Transfusion Committee recommended universal screening in 1989 and again in 1991 whereas the National Health and Medical Research Council did not agree because the costs were judged to exceed by far the possible public health benefit. The Red Cross maintained their view and had introduced screening in all blood banks in 1993 (Kaldor 1997; Whyte 1997). In Sweden a cost effectiveness analysis of HTLV-I and II screening in Sweden was requested by the National Board for Health and Welfare and the results are presented in paper I. A Norwegian study (Stigum, Magnus et al. 2000) showed that the cost per saved life rapidly falls with increasing prevalence and screening was not judged to be reasonable unless the prevalence was 8 per 100 000 or higher. A decision had already been made not to screen blood donors in Norway, where the prevalence was even lower than in Sweden.

In Europe the majority of HTLV positive donors discovered were HTLV-I except in Norway where only one HTLV-II and no HTLV-I positive donor was found in 55 000 tested (Taylor 1996; Samdal, Skaug et al. 1999). In USA on the other hand HTLV-II was responsible for more than half of HTLV positive donors (Lee, Swanson et al. 1991; Boulware, Ratner et al. 2002) and for nine out of ten in a study from New Mexico (Hjelle, Scalf et al. 1990).
The first generation of the test relied on cross-reactivity with HTLV-II and there was also a problem with many false-reactive results.

Table 7. HTLV-I and II screening in different countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Year of implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>1986</td>
</tr>
<tr>
<td>USA</td>
<td>1988</td>
</tr>
<tr>
<td>Canada</td>
<td>1990</td>
</tr>
<tr>
<td>France</td>
<td>1991</td>
</tr>
<tr>
<td>Australia</td>
<td>1989-93</td>
</tr>
<tr>
<td>Netherlands</td>
<td>1993</td>
</tr>
<tr>
<td>Denmark</td>
<td>1994¹</td>
</tr>
<tr>
<td>Sweden</td>
<td>1994²</td>
</tr>
<tr>
<td>Finland</td>
<td>1995³</td>
</tr>
<tr>
<td>Portugal</td>
<td>1995</td>
</tr>
<tr>
<td>Greece</td>
<td>1995</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>2002</td>
</tr>
</tbody>
</table>

¹Testing performed on all donations for 3.5 years, after that only on new donors
²Testing performed on all donations the first year, after that only on new donors
³Testing performed on all donations for 4 years, after that on new donors and on repeat donors every third year

The risk for HTLV-I and II transmission can also be reduced by universal LD. However, a British study showed that about 30% of HTLV-I infectious donations would enter the blood supply even after LD (Pennington, Taylor et al. 2002).

Parvo virus B19

Parvo virus B19 has long ago been shown to be transmitted by clotting factor (Mortimer, Luban et al. 1983) and is fairly resistant to inactivation. Transmission by transfusion can cause serious disease in immunocompromised patients. Again its high seroprevalence, 50% in the adult population (Fiebig and Busch 2004), would make exclusion of all seropositive
donors impossible and both donors and recipients often have protective antibodies. Transmissions due to single donor components are rare (Fiebig and Busch 2004). General screening for this virus is not being performed currently.

**Hepatitis viruses Non A-E**

GB virus C (earlier called hepatitis G), although it is closely related to HCV, has not been shown to cause disease in humans (Feucht, Zollner et al. 1997; Halasz, Weiland et al. 2001). It is spread in the same way and is found in groups with risk factors for parenteral transmission in seven to 35% but also in as many as 1.9% of healthy individuals without risk factors (Feucht, Zollner et al. 1997) and has accordingly been found in healthy blood donors (Tacke, Schmolke et al. 1997). The consensus is that presently there is no reason for blood donor screening. Other viruses that have been discussed in this context are TT-virus and SEN-V.

**Bacteria**

Today most TTIs and TTIs leading to death are caused by bacteria (Williamson 2002), in most cases following transfusion of platelets. In the UK seven deaths out of nine due to a TTI between late 1995 and 2003 were caused by bacterial infection (SHOT 2003). TTIs caused by bacteria are under-diagnosed and under-reported since especially recipients of platelets are often already febrile and treated with antibiotics (AuBuchon and Kruskall 1997). The bacteria can come from the donor’s blood, the donor’s arm or from the blood collection bag. Since platelets need to be stored in room temperature, they represent the highest risk for bacterial contamination. Long storage of platelets has been associated with a higher risk which is in contrast to viral infections where longer storage means less infectivity (Donegan, Lee et al. 1994).

As many as ten percent of platelet components have been reported to harbour bacteria (Wagner, Friedman 1994). In another study the frequency of bacterial contamination was estimated to be 0.4% per platelet concentrate (Blajchman 1997) (Corash 2000) and a prospective study of almost 3600 platelet units transfused to 161 patients found a risk of symptomatic bacteremia to be one per 16 patients, one per 350 transfusions and one per 2100 platelet units (Chiu, Yuen et al. 1994). Improved cleansing of the donor’s arm together with diversion of the first aliquot of blood had a dramatic effect in a British study (McDonald, Roy et al. 2004). LD, which is efficient as a tool against CMV transmission, might also decrease the risk of bacterial infection. Platelets are routinely screened for bacteria in the Netherlands,
Belgium and Wales but screening is presently not mandatory in Sweden. Several methods for pathogen inactivation are also being tried.

**Malaria**

Deliberately induced malaria had been used for treatment of neurosyphilis, but the first case of accidentally transfusion transmitted malaria was described by Woolsey in the US in 1911. Malaria transmitted to pregnant women, splenectomised and other immunocompromised patients is particularly serious (Bruce-Chwatt 1985). Travel history, i.e. history of short or long term stay in endemic areas or clinical episodes of malaria are used as exclusion criteria in non-endemic areas (Dodd 2000). In Sweden origin from or long term stay (more than three years) in endemic areas lead to deferral for five years whereas short term stay leads to six months deferral after leaving the endemic area. Those who have had malaria are not accepted. This implies that some infected donors may not be identified and many more non-infected are deferred. Serological testing of donors is not performed in Sweden. New test systems for detection of antibodies, antigen and NAT are presently being developed (Fiebig and Busch 2004).

Due to increased travelling and migration, an increasing number of malaria cases are diagnosed in transfusion recipients also in non-endemic areas. One such a case was recently reported from the UK. The infectious donor originated from West Africa but had not visited the area for seven years, and was therefore according to current guidelines not tested or deferred (SHOT 2003). This case has led to a discussion of introducing serology for all donors that have stayed in endemic areas (Kitchen, Mijovic et al. 2005). In endemic countries prophylactic treatment of the recipient and sometimes even of the donor is often used to prevent malaria in the recipient (Bruce-Chwatt 1985; Dodd 2000).

**Chaga’s disease**

Screening for its causing agent, Trypanosoma Cruzi, is performed in several countries in Latin America where the disease is endemic in many areas. In other parts of the world e.g. in Sweden, life long geographical exclusion is used for all persons who have lived in endemic areas for more than three years. Six transfusion transmitted cases of the disease in the US and Canada have been described since 1989. All but one were caused by platelet transfusions (Fiebig and Busch 2004).
*West Nile virus (WNV)*

This is a virus from the old world isolated already in 1937 with birds as the major reservoir and mosquitoes as vectors. It was not until a few years after it had first been found in North America in 1999, that it was recognised as a TTI with 23 confirmed cases and several deaths in 2002 (Pealer, Marfin et al. 2003). Blood donor screening with minipool NAT was implemented at full speed, and was carried out over the whole of the US already in the beginning of the following summer, i.e. the following mosquito season. Breakthrough of viral transmission in six confirmed or probable cases in spite of negative minipool NAT led to implementation of single donation NAT in high risk areas (Fiebig and Busch 2004).

*Variant Creutzfeldt-Jakob disease (vCJD)*

The causative agent is probably a prion and the same that causes bovine spongiform encephalopathy (BSE) or “mad cow disease”. Transmission by transfusion has been shown between sheep (Houston, Foster et al. 2000). Such transmission has not been proven in man but one vCJD patient in Britain was found to have received blood from a donor who died of vCJD three years after the donation. Another 46 recipients of blood from donors who later developed vCJD have not yet developed the disease (Llewelyn, Hewitt et al. 2004). One recipient died five years after the transfusion but without any signs of neurological disease. At autopsy prion protein was detected in the spleen and a lymph node but not in the brain (Peden, Head et al. 2004).

No screening test is presently available. Persons who have stayed for more than six months in the UK between 1980 and 1996 are not accepted as donors in Sweden and other countries. In the US donors are also excluded if they have stayed more than five years in Europe during this period (Fiebig and Busch 2004). Questioning donors about the consumption of mammalian brains is also being considered in the US (Schreiber, Sanchez et al. 2004). Since 1998 no British plasma is used for fractionation (Provan 1999) and universal LD has been carried out in the UK since 1999 as a precaution against vCJD. In an experiment with prion infected hamster blood, LD was shown to remove 42% of the infectivity (Gregori, McCombie et al. 2004). After identification of the first possibly transfusion transmitted case of vCJD, all previously transfused donors are deferred (Stainsby, Williamson et al. 2004).
Problems for donors with reactive screening test results

Although volunteer donors most often give blood for altruistic reasons and although we depend on their good will, this altruistic act may have negative implications for the donors. HTLV-I or II infection may be detected, an also sexually transmitted infection that most people even in the health care sector do not know much about, for which there is no treatment available and which is sometimes misunderstood as something similar to HIV and therefore causing problems in the donors’ private life. Severe psychological distress was seen significantly more often among HTLV positive compared to seronegative donors in an American study (Guiltinan, Murphy et al. 1998).

In a US study of donors that were notified by letter and deferred because of positive HBsAg positive test result, 74% understood that the test was abnormal and 78% that they were infected (Moyer, Shapiro et al. 1992). This means that a substantial proportion did not understand the information they were given. In a large US study, where 1500 deferred donors answered a questionnaire, 81% were confused and 75% had questions after receiving the notification letter and those notified of test results that were confirmed negative or indeterminate were the most confused (Kleinman, Wang et al. 2004). False-reactive test results are much more common than confirmed positive test results and they are extremely difficult to explain to donors without evoking worry. A quotation from a letter to “Transfusion” can illustrate this: “There is scant enlightenment, let alone consolation, for the donor deferred with a “false positive” result and given the explanation that the predictive value of the screening tests for antibodies to human immunodeficiency virus type 1 is only 10-30 percent when the seroprevalence of the antibodies is 0.04 percent.” (Sayers 1992). Try to explain that to a donor in every day language! A questionnaire study of donors deferred because of false-reactive test results is presented in paper IV.

The future of blood donor screening

Because of the existence of a window phase for the different already known agents and as a precaution against not yet recognised agents, pre-donation interviews and questionnaires continue to be important tools in order to reduce the risk of infected donors in Sweden as well as in other countries.

New candidate viruses and other infectious agents should be of low prevalence, persistent and pathogenic, for blood donor screening to be implemented. Also transmission by blood and blood products needs to be proven (Allain 1997). Cost benefit aspects also need to be considered. The importance of minimising the risk for transmission of TTIs to recipients is
obvious. However, there is also a responsibility towards the donors, that new tests that are introduced have a high specificity and that confirmatory tests are licensed almost at the same time as the screening tests (Sayers 1992). Only a minimum of false-reactive and indeterminate test results should be acceptable for a screening to be introduced in blood donors.

The greatest risk associated with transfusion today
Great progress has been made in the prevention of viral transmission by transfusion. However, the most common reason for transfusion related death is transfusion of a component intended for another patient. According to a publication from 1992 about 25 patients are killed every year in the US (AuBuchon and Kruskall 1997) and 64% of all serious hazards reported in the UK from 1996 to 2002 were due to transfusion of incorrect components (Stainsby, Williamson et al. 2004). According to an estimate in 1994 the risk for death due to patients receiving the wrong blood was at least 30 times higher than the risk for a patient being infected with HIV through transfusion (McClelland and Phillips 1994). As many as 60 -70 steps are required to get the correct unit of blood from a donor to a patient (McClelland, McMenamin et al. 1996). Bar code technology for matching the donated unit and the recipient is being tried in some places (McClelland, McMenamin et al. 1996). In Sweden bar code technology is not used for this purpose so far. However, the unique personal identification numbers for all permanent residents in Sweden, used both in the health care sector and elsewhere, decreases the risk for this kind of errors.

Survival studies
To evaluate costs and benefits of blood donor screening it is necessary to perform an analysis of the presumptive recipients. Knowledge about their expected survival is crucial since infectious agents with a long incubation period will not have time to develop in the majority of patients. Data on survival can be found in “lookback” studies, although the primary aim of these studies is to study transmission rather than survival, and in population based studies where the survival of all recipients of blood in a certain area is investigated.

Lookback
"Lookback” implies identifying patients having received blood from donors later found to be infected with a TTI. A reason for lookback can be either to inhibit further spread of an agent in the population (HIV in 1980s), to study the transmission frequency and long term
pathogenity of a TTI (Kenny-Walsh 1999; Wiese, Berr et al. 2000) or to enable treatment or economic compensation for iatrogenically infected patients (HCV in the 1990s and later). A lookback can be general, where all persons that have been transfused a certain number of years before screening was introduced are invited through information campaigns to be tested. A lookback is directed when as many as possible of recipients of donations from donors, later found to be infected, are identified and contacted.

Both general and directed lookbacks can be restricted to certain age categories for instance children, diagnostic groups like hemophiliacs or certain operations like cardiac surgery. Young recipients may be targeted because of their longer expected survival and therefore higher risk to develop disease if infected and/or to give rise to secondary cases of infection caused by the transmitted agent. They may also have a greater chance to benefit from treatment. Certain diagnoses or operations may be targeted because of a recognised higher probability of being transfused with many units of blood components. The case of hemophiliacs is special since they both have a high proportion of infected persons due to exposure to a large number of donors through clotting factors and are expected to have many years of survival due to young age.

An advantage with directed lookbacks is a high yield of infected among tested recipients and a limited number of persons that need to be tested. A drawback is that infected donors who did not donate after the test was introduced are not identified and therefore not their recipients either unless they are approached by general lookback. A drawback of using only general lookback is that specific groups of patients such as infants may be unaware of having been transfused and therefore not tested. General lookback also means testing a large number of recipients and a low yield.

A comprehensive directed lookback for HIV was made in Sweden in 1985. In Stockholm 30 former donors were identified at the HIV clinics and another five at the blood centres by the newly implemented HIV screening program for donors. Fifty seropositive recipients were traced, all transfused between June 1982 and November 1985 (Berglund, Beckman et al. 1988). A similar directed lookback was performed for HTLV I/II in Sweden after the screening was introduced in 1994 and is described in paper I.

HCV lookback was initiated in many countries shortly after the anti-HCV testing of donors had been introduced: 1990 in Holland (Vrielink, van der Poel et al. 1995), 1994 Scotland (Ayob, Davidson et al. 1994), 1995-97 England (NBS 2002), 1996 Denmark, 1994-99 Canada
So far only a limited directed HCV lookback has been performed in Sweden (Norda, Duberg et al. 1995; Foberg, Ekermo et al. 1996). Directed lookback for HCV whenever a seroconversion of a donor occurs is mandatory since 2001. A more complete lookback for hepatitis C in Sweden is under discussion.

Because of their exposure to many donors, recipients of many units are more likely to be traced in a lookback investigation. Recipients of many units have been shown to have a poorer outcome than others (paper II), (Vamvakas and Goldstein 2002). This means that overall survival rates from lookback studies are usually lower than in other studies of patients’ survival and they are therefore not representative of the majority of transfusion recipients.

**Population based studies**

Well known population based studies on general survival of patients that were transfused in the early 1980s are Whyte’s study from Canterbury, New Zealand (Whyte 1988) and that by Vamvakas and Taswell from Olmstead county, Minnesota, USA (Vamvakas and Taswell 1994). All these transfusions took place before the HIV epidemic was recognised and before HIV testing of blood donors had been implemented so they are historically important but not applicable to the situation of today.

Later studies are Wallis study from the North of England of patients transfused in 1994 (Wallis, Wells et al. 2004), Kleinman’s from the US of patients transfused in 1995 (Kleinman, Marshall et al. 2004) and and our own studies (papers II and III).

In conclusion survival rates of patients transfused in the 1990s are generally lower than of those transfused in the early 1980s. This probably reflects an increased reluctance towards transfusion after the start of the HIV epidemic implying that only the most severely ill patients are transfused.

**Transfusion practice**

To improve transfusion safety, avoiding inappropriate transfusion is necessary. This means that knowledge about transfusion practices, the number of units transfused, diagnoses and operations of transfused patients and transfusion triggers is needed. Transfusion practice varies largely between and even within countries and over time. A large study of transfusions in certain elective operations in 43 European hospitals in 1994 showed a great variation between hospitals even within the same country. There were also regional differences where more autologous transfusions were given in the Mediterranean area and more albumin and
artificial colloids in central-northern Europe (Sirchia 1994). Capraro showed that the likelihood of being transfused in Finland for a certain operation could vary as much as six-fold between different hospitals (Capraro 2001). It is also clear that the number of blood components transfused per inhabitant is not the same in the different Nordic countries (Report on Sweden´s blood supply) (2002, 2003).

Transfusion practice often relies on tradition and general guidelines are not always followed, although after intervention practice did change in some places. This was shown in another Finnish study where the proportion transfused out of all patients undergoing coronary artery bypass surgery decreased from 76% to 48% between 1994 and 1999 (Capraro and Syrjala 2001). A Canadian article (Wilson, MacDougall et al. 2002), in which a systematic review is made of nine different intervention studies performed between 1988 and 2000 in eight countries, also showed that practice could be changed by intervention.

A study of transfusion practice in Örebro County, Sweden is presented in paper III.

**Autologous blood transfusions**

Autologous blood includes transfusion of your own preoperatively donated blood, intra- and postoperative blood salvage. The purpose is to avoid transfusion of allogenic blood. Recipients of the two latter kinds cannot be traced through the registers of the blood centres.

Preoperative autologous blood donation was first described in 1921 (Grant 1921) in a patient who was to undergo an operation of the cerebellum and was expected to benefit from a post-operative transfusion. However, he could not afford to pay for a blood donor and was therefore bled the day before his operation and then transfused with his own blood postoperatively.

There was an increasing interest in autologous transfusion in the 1970s, when transmission of hepatitis became a concern, but it was not until the 1980s and the emergence of the HIV epidemic that it became more widely used especially in the US. Survey data show a 30-fold increase in number of autologous units donated between 1982 and 1990 (AABB). In a study from the US by Vamvakas of patients transfused perioperatively in 1986 (Vamvakas and Moore 1997) as many as 18% received autologous blood and autologous transfusions constitute five percent of the total blood use in the US (Provan 1999) A reason for the very high proportion of autologous transfusions may be that the US was struck much harder by the AIDS epidemic also by transfusion than Europe was at this early stage, but also lack of awareness of this alternative to allogenic transfusion among patients and surgeons in Europe (Provan 1999). In Sweden there was a five-fold increase in autologous donations between
1991 and 1994, but since then rates have steadily decreased so that autologous units now only constitute 0.11% of all transfused units (Report on Sweden’s blood supply) (2003).

It has also been argued that autologous transfusion could be a way to avoid the immunomodulatory effect of allogenic blood just like LD and that this would lead to a reduced incidence of postoperative infections and cancer recurrence. An effect on postoperative infections was suggested in two studies one of patients undergoing colorectal surgery (Heiss, Mempel et al. 1993) and one of hip replacement (Murphy, Heal et al. 1991). Other studies did not come to the same result (Busch, Hop et al. 1993; Vamvakas, Moore et al. 1995). A meta-analysis of two randomised controlled studies that had come to opposite results (Busch, Hop et al. 1993; Heiss, Mempel et al. 1993) did not show a benefit of autologous compared to allogenic transfusion for prevention of postoperative infection or cancer recurrence (Vamvakas and Pineda 2000).

However, if autologous transfusions would lead to even a small decrease in postoperative bacterial infections their otherwise extremely high cost per QALY would decrease substantially (Sonnenberg, Gregory et al. 1999; Vamvakas 2000).

Intraoperative blood salvage

Intraoperative blood salvage can only be used for “clean” operations, i. e. without bacterial infection. Cancer surgery has also been a contraindication for intraoperative blood salvage, since a concern has been that this might lead to the spread of cancer. However, the risk for this is considered to be minimal according to British guidelines (Napier, Bruce et al. 1997).

Directed donations

Directed donation means that the donor gives blood to a special patient often a family member. This approach can be used for medical reasons for instance in cases with unusual blood groups. Such donations have become increasingly popular in the US as an alternative to autologous donations because of fear following the HIV epidemic. However, such donations have not been shown to be safer, especially not if the donor has never donated before and donors of units for directed donation cannot always be categorised as volunteer donors (Yomtovian 1992). Interestingly, in a Greek study only 17% of donations were meant for an anonymous recipient, all others were directed. This specifically Greek situation is perhaps due to the large number of patients (3-5000 in a population of ten millions) with transfusion
dependent thalassemia (Chliaoutakis, Trakas et al. 1994). In developing countries directed or replacement donations are also common as a means to ensure blood supply (Chamberland 2001). In Sweden directed transfusions are uncommon.

**Comparison with other risks in life**

Figure 1 shows a comparison between the risk for transfusion transmitted HCV or HIV infection and other risks in life.

![Figure 1. Comparison between different risks](image)

* Risks for HCV and HIV infection from Swedish data, other risks from Calman (Calman 1996).
Rationale for studies I – IV

The key background elements for the studies presented in this thesis may be summarised as follows:

The newly introduced HTLV-I and II screening represented an interesting model for cost effectiveness analysis for blood donor screening but required in depth analysis of several parameters. Knowledge about recipient characteristics such as age and survival are necessary for performing such an analysis. “Patient mix”, i.e. diagnoses and operations of patients as well as age strongly affect survival figures. In order to avoid shortage of blood and to minimise the the number of adverse events after blood transfusion no more than an optimal number of transfusions should be carried out. False-reactive test results of infectious disease screening tests are the cause of worry for donors and threaten the blood supply in several ways.

AIMS OF THE STUDY

To assess cost effectiveness of HTLV-I and II screening in blood donors (I).
To assess survival of transfused patients (II) and trends in survival and transfusion practices over time (III).
To assess the frequency of false-reactive test results in blood donor screening and the effect of temporary or permanent deferral on donors (IV).

Materials and methods

Collection of data on microbiological screening
Screening was carried out at the local or regional laboratories and the outcomes of HTLV- and II screening on all new and repeat donors in Sweden 1994 were reported to the Swedish Institute for Infectious Disease Control where all confirmatory procedures took place.
Blood donor screening for HTLV-I and II was performed using commercially available enzyme linked immuno assays (ELISA). Reactive test results were confirmed by Western blot (WB). Those found positive (all except one) or indeterminate by WB were further investigated by polymerase chain reaction (PCR) (I).
Lookback investigations of recipients of blood from donors proved to be HTLV-I or II positive were carried out by the Regional Centres for Communicable disease Control in each county where a positive donor had been discovered or where a recipient of blood from such a
A data sheet to be completed was sent to all blood centres in the region. We asked for total number of tests performed for each infectious agent, which assays that had been used and their outcomes: negative, repeatedly reactive but not proved to be positive by confirmatory testing - thus classified as false-reactive - and how many of these false-reactive test results that led to deferral of the donor. The numbers of confirmed positive results were also collected (IV).

Collection of data on donors

The names and addresses of all deferred donors (temporarily or permanently) from the same period of time were collected. A preliminary questionnaire was tested on three donors at a personal meeting and on eight by mail. The final version of the questionnaire including an information letter was sent by ordinary mail to all other deferred donors in the region and a reminder after two weeks to those who had not yet responded (IV).

Collection of data on transfused patients

1) From the data bases of the blood centres:

The date of birth of randomly selected patients transfused in the county of Stockholm in 1992 for a pilot study of survival (I).

The date of birth of randomly selected patients transfused in the county of Stockholm in April 1993 (II) and all patients transfused in Örebro county in March to May 1993 (II and III) and all patients transfused in March to May 2000 (III).

2) From the hospital administrative records and the national census file:

The date of death if applicable (I, II and III)
3) From the hospital administrative records:

The type of clinic where the patients were treated (II and III) and diagnoses and operations (III).

All data were entered into a register using JMP statistical software. Diagnoses were classified according to the chapters of the International Classification of Diseases (ICD IX and X). Operations were classified according to Nordic classification standards. Only the first diagnoses and operations registered were used in the analyses.

Results and discussion

Blood donor screening for HTLV-I and II

During the first year of HTLV-I and II blood donor screening 1625 screening reactive test results were found (0.25%). Only six of these were confirmed positive by WB and five out of these further confirmed by PCR. However, as many 49% of a subset of 571 repeatedly screening reactive were WB indeterminate but PCR negative. The seroprevalence in Swedish donors was 2:100,000. This meant a very high frequency of false-reactive test results leading to the deferral of donors and loss of blood components. Lookback revealed three infected recipients out of 35 tested, a transmission rate of nine percent.

A cost effectiveness analysis was performed based on certain assumptions gathered from the literature, from observations from the Swedish blood donor screening, lookback investigation of recipients exposed to infectious blood components and from the pilot study of survival of transfusion recipients in general.

The cost to prevent one death from transfusion caused HTLV-I or II disease was $540 million or $36 million depending on whether all donations or only new donors were tested, a 19-fold difference. Still the difference in number of deaths prevented was small: one prevented death in 180 and 210 years respectively, depending on whether donors were tested every time or only upon registration to become a donor.

The low yield of the screening was dependant on the very low seroprevalence in the population, the relatively low transmission rate of the virus at transfusion, the low proportion
of infected individuals that develop clinical symptoms and even if they do, the long incubation period from being infected to developing symptoms. Therefore the high age of most Swedish transfusion recipients decreases this risk even more. The analysis led to the discontinuation of screening of every donation. Since 1995 only new donors are screened for HTLV-I and II.

Table 8. Estimated costs and benefits of HTLV-I and II screening of blood donors

<table>
<thead>
<tr>
<th>Testing model</th>
<th>Every donation tested</th>
<th>Only new donors tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs each year ($ million)</td>
<td>3.02</td>
<td>0.17</td>
</tr>
<tr>
<td>Total costs ($ million) for:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Each positive donor found</td>
<td>1.9</td>
<td>0.13</td>
</tr>
<tr>
<td>Each death prevented</td>
<td>540</td>
<td>36</td>
</tr>
<tr>
<td>Prevented events per year:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donors identified positive</td>
<td>0.54</td>
<td>0.39</td>
</tr>
<tr>
<td>each year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>0.0056 (1/180 years)</td>
<td>0.0047 (1/210 years)</td>
</tr>
</tbody>
</table>

If the analysis was to performed again this year the costs would be altered, firstly because of much improved screening tests. In our survey of blood centres 2002 to 2003 eight false-reactive test results from HTLV-I and II screening (0.04%) were obtained compared to the 0.25% found during the first year of the screening. The lower percent of false-reactive test results and even more the better performance of WB has led to that a large part of the cost for confirmatory testing now can be avoided.

In the analysis we assumed that deaths from transfusion transmitted HTLV disease would be due to adult T-cell lymphoma (ATL). However, according to a fairly recent Japanese study, the morbidity in 102 cases of transfusion transmitted HTLV-I infection was only about one percent and no ATL case was found (Inaba, Okochi et al. 1999). Maybe ATL can only develop after congenital infection or after transfusion during the first year of life. This implicates an overestimate of the risk in our cost effectiveness analysis although there are also reports of development of ATL after transfusion in patients treated for blood malignancies (Chen, Wang et al. 1989) (Pennington, Taylor et al. 2002).
Our cost effectiveness analysis however may also represent an underestimate of the risk. We did not calculate with any mortality due to the other main HTLV-associated disease, tropical spastic paraparesis (TSP), although indirectly complications thereof might perhaps also cause the death of patients since many have sensory disturbances, that could lead to ulcers, and urinary bladder problems (Farid-hosseini 2001). HTLV-I and II are found in the lymphocytes and have not been found to be transmitted by cell free blood components (Donegan, Lee et al. 1994), (Okochi, Sato et al. 1984). Virus in 30% of infectious units would escape leukocyte depletion (LD) according to a British study (Pennington, Taylor et al. 2002). However, that implies that 70% of units would be safe after LD which is now performed increasingly often in Sweden. LD would therefore decrease the yield of HTLV-I and II screening if the analysis was to be repeated now.

Eleven years have passed since universal HTLV-I and II screening was implemented and ten years since the decision to screen only new donors. During that period a major part of the whole blood donor population can be expected to have been exchanged. Fourteen new cases of HTLV-I or II infection in new donors have been diagnosed from 1996-2000, a prevalence of 3 per 100 000 among new donors to be compared with 2 per 100 000 during the first year when all donations were screened. New donors from some HTLV-I and II endemic areas will be subject to geographical exclusion for other reasons: risk for malaria for those from central Africa and for Chaga’s disease for those from large parts of Latin America. However the large group of well educated immigrants from the Middle East, where there are areas endemic for HTLV-I, are likely to present as new donors and will not be excluded for geographical reasons. A continuation of the present screening policy therefore seems adequate.

Survival of transfused patients in general

Our cost effectiveness analysis presented above, relied on data from a pilot study of survival in 255 transfused patients in the county of Stockholm in 1992. Their median age was 70 years and 30% were younger than 40. Survival rates were 67% and 49% after one and three years respectively (I).

The next survival study (II) was undertaken in order to see if these data could be verified in a large scale study of 1734 transfused patients in the counties of Stockholm and Örebro. The results were quite similar: mean age 71 years, 66% and 51% alive after one year and 40 months respectively (paper II). This survival rate was lower than in the New Zealand study by Whyte (Whyte 1988) the US study by Vamvakas and Taswell of patients transfused in 1981.
(Vamvakas and Taswell 1994). In a letter to the editor of the journal “Transfusion” by Vamvakas we were invited to make a comparison between our surgical patients (from Örebro county) and his study of patients transfused perioperatively in 1986 (Vamvakas and Moore 1997). The HIV epidemic has had a great impact on transfusion policy and attitudes towards transfusion among patients, the public in general and those who work in the health care sector. An advantage of comparing with data from his later study was that those patients, just like ours, were transfused after the start of the HIV epidemic. Nevertheless the survival rate in our population was still lower and this could not be explained by the higher age of our patients, since correction for age did not alter the rate of patients surviving up to 40 months after transfusion (Vamvakas 2001) (reply).

In paper III seven year survival rate of our patients was also lower than in Vamvakas study of patients transfused in 1981. However, five year survival rate of our patients was very similar to that of two newer studies: one from northern England (Wallis, Wells et al. 2004) and one from the US (Kleinman, Marshall et al. 2004) where patients were transfused in 1994 and 1995 respectively. A comparison of different survival studies is presented in table 5 in paper III.

Transfusion practice - diagnoses and operations

In the comparison above we included all patients treated in surgical departments in the county of Örebro (Vamvakas 2001) (reply) and they were, unlike those like in Vamvakas study (Vamvakas and Moore 1997), not all perioperatively transfused. In paper III we once more studied all transfused patients in the County of Örebro from March to May 1993 including diagnoses and operations in the analysis. We also studied all patients transfused from March to May 2000 and compared these two populations in terms of one year survival, number of units received, diagnoses and operations. We found both in paper II and III that recipients of many units had a poorer outcome which has also been shown in other studies (Whyte 1988; Vamvakas and Goldstein 2002). In paper III we found a higher survival rate among operated patients compared to non-operated (fig 2). This was also observed previously (Whyte 1988; Vamvakas and Taswell 1994; Vamvakas and Goldstein 2002; Wallis, Wells et al. 2004).

Our comparison revealed that the relative risk of death within one year adjusted for diagnoses, operations and other possible confounders was 0.78 (CI 0.66-0.91) in 2000 compared to 1993 in spite of higher age among patients transfused in 2000 (III).
The relatively higher survival rates of patients transfused in the 1980s, lower in the 1990s and perhaps again higher of those transfused in the first decade of 2000, like we observed in paper III, might be a sign of the reluctance towards transfusion following the start of the HIV epidemic now possibly being reversed. Another explanation can be the increasing life expectancy of the population as a whole in our society so far. Further studies of patients transfused in the first decade of 2000 will clarify if this represents a steady trend over time.

**Screening of blood donors and false-reactive test results**

In order to if possible avoid shortage of blood, transfusion of the “right” patients is necessary. Although guidelines exist there is a great variation in transfusion practice (Sirchia 1994; Capraro 1998; Capraro 2001). However, retention of both new and repeat donors and recruitment of a sufficient number of new donors are also important issues. Even temporary deferral of donors, because of false-reactive test results in microbiological screening or for other reasons, causes worry among donors, diminishes the chance of their return further on (Piliavin 1987; Halperin, Baetens et al. 1998) and means the loss of already collected units. Paper IV includes both a survey of blood centres and a questionnaire to deferred donors in Mid-Sweden.
Out of a total of almost 450,000 samples tested in 2002 and 2003, 1059 test results were false reactive causing 259 deferrals. Some 117 confirmed positive test results were also reported. The number of donations and new donors corresponded to over 30% and 25% respectively of those in the whole country during that period of time.

Six different anti-HIV-1 and 2 screening tests, four anti-HCV tests, five HBsAg tests, four anti-HBc tests, four anti-HTLV-I and II tests and five syphilis antibody tests were used in ten counties. The frequency of false-reactive test results varied ten-, sixteen- and nine-fold for anti-HIV-1 and 2, anti-HCV and HbsAg tests respectively.

The rate of deferred donors varied even more between the counties from 63 to 1.3 false reactive test results leading to the deferral of one donor. One donor may have given rise to more than one of the false-reactive test results in some instances. All the same this can not explain such an extensive variation, which instead must be explained by different policies, for instance regarding additional testing further on with alternative screening tests, also licensed for blood donor screening. If such an analysis gives a repeatedly negative result the donor is allowed to continue. Such an approach is discussed in detail in a recent Australian article (Kiely and Wood 2005).

Some 204 deferred donors in nine counties were contacted and 88% responded to the mail distributed questionnaire they were offered to participate in. Deferred donors were older than all donors in the counties involved but female to male ratio was the same. Most donors were informed by letter only (46%) but in contrast to foreign studies many were also informed by telephone only (29%). Only about one third (37%) of donors found the information at notification “absolutely sufficient” or “fair enough”, 63% would have liked to know more and over 80% were worried.

Similarly high response rates have been seen in earlier studies of Swedish blood donors (Gullbring 1969; Sanner 1996; Axelsson and Sojka 1998; Nilsson Sojka and Sojka 2003) but not in many other questionnaire studies of blood donors (Moyer, Shapiro et al. 1992; Oswalt and Gordon 1993; Thomson, Bethel et al. 1998; Sanchez, Ameti et al. 2001; Kleinman, Wang et al. 2004).

Some 87% of notified deferred donors had talked privately about their test results, most often with their husband/wife/partner. However, as many as 28% of all respondents had talked privately to four or more categories of persons. The high response rate and the fact that so many had talked privately about their test results illustrate the importance of the subject to the
donors. Some free comments among the answers revealed great fear and even personal tragedy.

It may be concluded that minimising the number of false-reactive test results and thus of donors confronted with such a complex message is critical. An obvious reason for this is also that the positive predictive value of a screening reactive test result among healthy blood donors, especially in areas not endemic for the infectious agent in question, is much lower than in a patient population.

**General conclusions**

Sweden has a low steady prevalence of HTLV-I and II among donors: 2-3 per 100,000. The cost for prevention of death due to HTLV-I or II infection transmitted by transfusion is therefore extremely high, especially if all donations are screened. Screening only new donors will prevent almost the same number of deaths. A small and rather constant number of new donors are found to be HTLV-I or II positive each year. Continued screening of only new donors therefore seems adequate.

Survival data are needed for cost effectiveness analyses of blood donor screening, and for comparability, survival studies need to contain data about case-mix. Patients transfused in Örebro County in 2000 had a higher one year survival rate than those transfused in 1993 even after adjustment for possible confounders and in spite of higher age. Operated patients showed higher survival rates. Seven year survival of those transfused in 1993 was 39%.

The proportion of false-reactive test results varied about ten-fold between four to six different screening assays used for each infectious agent and deferral rates varied extensively between counties. There is potential for a standardisation in Sweden of screening and confirmation algorithms for blood donor screening. The notification procedure for donors with false-reactive test results could also be better standardised and improved. Training of the staff in charge of this very difficult task is important.
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