

POLICY-IN-CONFIDENCE

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THE BIOLOGICAL SAFETY OF BLOOD: SCREENING FOR RARE VIRAL INFECTIONS

1. The screening of donations for viral and other transmissible infections is one of the important safeguards for ensuring that the blood and blood product supplies are as safe as realistically possible. The range of tests available is gradually being extended but increasingly these are intended to detect very rare infections. Ministers' views are sought on the principle of whether an effective screening test for a very rare transmissible infection should be introduced, just because it is available, even when the cost of general introduction throughout the blood service would cost millions of pounds a year. For such rare infections, it can be argued that it would be more cost effective to provide ex gratia payment for the very small numbers of recipients whose infection was the result of transfusion or use of blood products.

Background

2. Blood and its constituent parts, red cells, platelets and plasma are biological substances collected from humans and as such carry risks of biological infection. Even with the best systems, there can never be an absolute guarantee of freedom from transmission of infection, particularly where the infective agent is either unknown or has not been demonstrated (the classic example was HIV). There are also other risks of the use of blood such as incorrectly cross-matched blood, fluid overload, etc, which cause morbidity and mortality but which are not considered here.

3. Many commercial companies are trying to produce synthetic products which will carry out the function of some of the

constituents of blood. Factor 8, used in the treatment of haemophilia, has recently been manufactured using recombinant technology. This is only licensed in two or three countries, not in the EC, and has additional clinical problems as well as high costs. Other constituents of blood are being tested in clinical trials but it is not known when they will be available for general use.

4. This submission is about screening of blood for markers of infection in the UK. Some tests also apply to plasma and are usually required of any licensed blood products imported into the UK. However, UK decisions not to test for a particular marker are not necessarily reflected in other countries and there are already examples of tests done elsewhere which are not done in the UK. For instance some imported blood products licensed in the UK are made from plasma tested for ALT. The UK can set minimum requirements for tests of imported blood products but any additional tests are a matter for the producer.

Screening and Testing for virological and other biological markers

5. The safety of the blood supply does not depend solely on the laboratory testing of the blood. The exclusion of donors who may be at risk of transmitting infection is an important safeguard. The self deferral and self exclusion system is particularly important, in that some infections, particularly HIV, have a "window period" when the test will not pick up a recent infection. Examples are risk activities for HIV or travel to tropical countries leading to long term self exclusion of donors or temporary self deferral. Currently donors fill in a form covering the relevant points, it is likely that in the near future donors will be individually interviewed prior to giving blood.

6. In the case of fractionated blood products such as albumin and Factor 8, there is an additional safeguard as the manufacturing process is designed to destroy the majority of infectious organisms, particularly HIV, Hepatitis B and Hepatitis C. However, EC and UK guidelines do not differentiate in most instances between plasma and blood in respect of tests that are to be applied to donations.

7. Annex A lists screening tests available on the basis of whether they are deemed compulsory by the EC. It includes brief notes on each test.

COST BENEFIT CONSIDERATIONS

8. The MSBT (The Committee for Microbiological Safety of Blood and Tissues for Transplantation) is the Committee that provides advice to Ministers on the introduction of new screening tests for blood and blood products and organs/tissues for transplantation collected in the UK. The Committee includes virologists, microbiologists, blood transfusion experts and fractionators. The Committee considers each suggested test under several headings:

- (i) Morbidity and mortality
- (ii) Incidence in the general population and donor population
- (iii) Sensitivity of the test (number of false negatives)
- (iv) Specificity (false positives)
- (v) Confirmatory tests
- (vi) Feasibility of use of tests
- (vii) Costs

9. Each test that is added to the repertoire of testing of blood increases the risks of mistakes occurring because of the complexities of handling and processing the larger number of tests. There is the problem of increased chances of missing a positive, increased documentation, the risk of including donations which should have been quarantined etc.

10. Another aspect that needs to be considered is to ensure that the supply of blood and organs is not restricted by testing and excluding donors to such an extent that there is greater morbidity and mortality due to lack of supply than there is saved by non transmission of infection.

11. It is also important to take into account that the recipients of 50% of blood donations will die within 1 year from their primary illness.

12. Additionally the costs of introducing a test must be considered and these include the cost of the kit (which range from 50p to £2.30 for tests currently used by the UKBTS), and any confirmatory tests, staff time and the replacement cost of donors and counselling and possibly treatment of positive donors. The overall cost can be very substantial as over 2 million donations are collected annually in the UK. Annex B contains an example of the cost benefit considerations for testing for an example of a rare virus (HTLVI) which did not support its introduction.

13. If a test is expensive and the number of people who will benefit by the test is very small, then consideration needs to be given to whether some form of recompense to the few individuals who are infected would be more appropriate than carrying out the test. We have payment schemes for those who were infected with HIV through treatment, for their own benefit, with blood products, blood transfusion or tissue transfer. There is a possible parallel with the vaccine damage infants, but in that case infants were vaccinated to generate herd immunity, more than for their own individual benefit.

PRESENT POSITION ON COMPENSATION

14. Apart from the HIV cases, compensation for individuals harmed by blood transfusion or blood products could only be obtained either:

- a. on the basis of product liability, or
- b. by proving negligence

15. Under (a) the individual would not have to prove negligence, simply that the blood (blood product) supplied had been defective

and that it had caused injury. However, suppliers can rely on a 'state of the art' defence and whether the steps taken by the supplier to ensure the safety of the product were in keeping with those generally accepted as reasonable. Our understanding is that under the EC Directive on Product Liability a supplier would not be liable if he acted in accordance with national regulations. If the test were not to be mandatory, it would not, therefore, be certain that a person harmed by blood or blood products would have a case under the product liability law.

16. Under (b) an individual would have to show that a decision not to test for the virus which caused the harm was unreasonable. In determining whether this was the case the Courts would among other factors have regard to the practicalities of testing and the cost benefits of doing so. In the case of a very rare infection, it may be very difficult for an individual to prove negligence simply on the basis that an effective screening test was available but had not been used if the cost/benefit considerations were highly unfavourable.

17. In addition to the above methods of compensation, it is always open to Ministers to make ex gratia or other payments where the special circumstances warrant it, eg those mentioned in para 13.

Case For and Against Special Ex Gratia Payment Arrangements

18. The arguments in favour of such an arrangement are:

- * it would be much less costly than moving towards a policy of screening for every virus for which a test exists, irrespective of the extent of the threat. Against the background of the events in France and Germany and the increased use of litigation, the MSBT may become more reluctant to advise against the use of effective screening tests solely on grounds of cost.

- * decisions not to test for rare infections could be more easily defended if the small number of people harmed by that decision could be certain of recompense.

- * we avoid having a multiplicity of tests which in itself could be a threat to the safety of the blood supply.

The arguments against special arrangements are:

- * public perception about the safety of the blood supply could be undermined. Financial savings could be portrayed as being more important than maintaining safety and the risks could be considered greater than in fact was the case.

- * there would be a two tier system for those treated with blood products which were untested for a particular rare virus. For those harmed as a result of our decision not to test there would be a special payment available; for those harmed by imported blood products also untested there could in logic be no claim to a special payment from DH as

the decisions about not testing would have been made elsewhere. (Individuals harmed by the imported blood product would have to rely on claims for negligence or under product liability.)

- * any extension of Government payment schemes would further encourage groups such as growth hormone/CJD campaigners.

- * pressure could increase for compensation for victims of other medical accidents. Many medical interventions carry a known risk of damage and those who do suffer may not see themselves as different from those knowingly exposed to a low risk from blood. Even though, we might argue in the case of blood that a deliberate decision had been made not to eliminate the risk of viral transmission through testing whereas with other treatments there may be no way of avoiding the risk associated with it.

- * there would in fact be difficulty in deciding where to draw the line. High cost low risk presents little difficulty but there are grey areas where the decision is not so clear cut. Also there is the possibility that EC requirements or public pressure could result in testing where the cost benefit argument was not favourable eg another HIV. In consequence the policy might be perceived to be riddled with anomalies, and therefore difficult to defend publicly.

Implementation

19. If the principle of setting up an ex gratia payment scheme were accepted then the precise details of its operation would need to be fully considered.

SUMMARY

20. Blood transfusion is inherently unsafe. No matter how many tests are applied, transmission of infection will occur and this is something that the public and media seem to have difficulty in understanding. The tests themselves may not be infallible, and there is the risk of human and machine error.

21. However if a test is available for a rare infection but which satisfies all the normal criteria other than its expense, should testing be omitted and infected recipients who suffer clinical harm be recompensed in some form? Is there a difference between such individuals and victims of other treatments known to carry a small risk?

22. At this stage Ministers' views are sought on whether the principle of ex-gratia compensation should be further considered. The alternative will be the introduction of progressively greater numbers of screening tests for all blood donated in the UK, even when the number of recipients at risk of harm for rare and unusual infections transmissible by blood transfusion will be very small. More detailed economic analyses will be worked up if Ministers find the principle of ex-gratia payments acceptable.

23. Officials would be happy to have a meeting with PS(H) to discuss the issues involved.

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ANNEX A

1. TESTS WHICH ARE COMPULSORY ACCORDING TO EC DIRECTIVE 89/381 AND WHICH ARE CARRIED OUT BY THE UK BLOOD TRANSFUSION SERVICES (BTS)

The EC directive covers fractionated blood products, which are pharmaceuticals. It does not cover red cells or platelets or fresh frozen plasma, which are covered primarily by the Council of Europe document on Preparation, Use and Quality Assurance of Blood Components (1992).

(i) HBsAg (antigen)

This is the marker for hepatitis B and the first tests were introduced in the early 1970s. It is not perfect in that a small number of individuals are still infected by blood each year, between 10 and 100 in the UK, although the true figure is likely to be the lower one. Please refer to anti-HBc.

(ii) Anti-HIV 1 and 2 (antibody)

Individuals within the window period are mainly excluded by self exclusion of homosexuals, drug abusers and others participating in at risk activities. It is guessed that despite the exclusion categories and testing of each donation approximately 1 individual in every 1 million transfusions may still become infected by HIV in the UK, taking into account the likely prevalence in the UK population. Such individuals can be paid according to the payment scheme for HIV and blood transfusion/tissue transfer.

(iii) Anti HCV (antibody)

This test for anti-hepatitis C (the major cause of non A, non B hepatitis in the UK) was introduced in September 1991. The UK introduced this test later than some European countries and the US because ACVSB considered that the sensitivity and specificity of the original test were poor, and there were no good supplementary, let alone confirmatory, tests. When these became available, screening was introduced. There is a window period when anti-HCV does not appear and the donor is infected. The BTS relies upon the donor reporting any incidence of jaundice in the period prior to or soon after they have given blood.

(iv) Syphilis antibodies

Testing has been in operation for several decades. The risk of transmission, unless blood is transfused very soon after it has been donated, is small. Interestingly Denmark does not apply this test. This test, as well as antibodies to HIV and HCV are good markers of sexual promiscuity and HCV and HIV for IV drug abuse.

HIV and HCV are destroyed during fractionation of plasma,

and hepatitis B to a slightly lesser extent, and so the risk from blood products is very small indeed.

(v) Creutzfeldt-Jakob Disease

There is no test for this disease, which is primarily diagnosed clinically or at post mortem. However patients known to have the disease have been excluded from donation since 1981, and since 1989 recipients of pituitary derived human growth hormone have been excluded. From 1st September 1993 recipients of pituitary derived gonadotrophin and other pituitary hormones have also been excluded (UK but not rest of EC). These groups have been excluded because of the incidence of CJD in a small number of these recipients. This is despite the lack of any proof of transmission of CJD by blood.

2. TESTS PERFORMED BY SOME OTHER COUNTRIES OUTSIDE THE UK, BUT NOT COMPULSORY UNDER EC DIRECTIVE OR COUNCIL OF EUROPE GUIDELINES

(i) ALT

This is a liver enzyme which was originally used in some countries, primarily the US and Germany, as a surrogate test for non A, non B hepatitis before the availability of the specific anti-HCV test. These countries have continued to do this test, since it is very difficult to stop doing a test once it has been introduced. Some experts have suggested that an elevation in ALT may be an early indicator of HCV infection before the individual becomes positive for anti-HCV. However there are many people who have raised ALT levels, including those who are overweight, have drunk alcohol recently etc. Introducing ALT testing in the UK could lead to the loss of 2% of donors. However BPL, the English fractionator, would like the test introduced, primarily because this would allow a substantial increase in the potential export market for any plasma, intermediates or final products surplus to UK requirements.

(ii) Anti-HBc (antibody)

This topic was the subject of a recent submission to PS(H). This is an additional test for hepatitis B, which may be present when the level of HBsAg is too small to be detected. The MSBT advised the Minister against introducing this test, because of poor specificity, lack of good confirmatory testing and the small number of transmissions that would be prevented at a high cost financially. To our knowledge this test is applied in France, and the US. Several other countries have considered it and decided against introduction primarily Norway and Canada, and we believe Switzerland will soon decide against the test also.

(iii) Anti-HTLV1 (antibody)

This virus may cause acute T-cell leukaemia lymphoma or tropical spastic paraparesis. The virus is endemic in South West Japan and the Caribbean. The risks of infection and long term morbidity and mortality were considered by the ACVSB several months ago. A recent paper and leader

appeared in the BMJ on the topic, confirming that there was no good case for introducing this test in the UK. It also pointed out that targeted screening of donors from the relevant country would miss many of the individuals who were infected. The test is used in the United States, France and Japan.

3. OTHER TESTS NOT ROUTINELY APPLIED, BUT WHICH ARE DONE FOR SPECIFIC INDICATIONS

(i) Antibody to Cytomegalovirus (anti-CMV)

CMV is a common infection in many countries, and CMV testing would exclude 50% of UK donors. Additionally it is difficult to be sure which donors would be infectious. Donors are tested for CMV status and seronegative donations are used principally for neonates and CMV negative bone marrow transplant recipients.

(ii) Malaria (antibody)

Most donors at risk of malaria transmission are excluded on the basis of recent travel to malarial areas, with a period of quarantine during which they cannot give red cells. Since malaria is not transmitted in plasma, well individuals may donate plasma only. Some of the donors may need to be tested for malarial antibodies prior to rejoining the donor panel.

(iii) HIV antigen

This has been considered in several pilot studies abroad, and it is considered that there is no benefit to be gained by testing for the antigen. The number of donors who would be additionally excluded is very small indeed.

4. HUMAN VIRUSES KNOWN TO CAUSE ILLNESS BUT NOT TESTED IN UK OR ELSEWHERE

i. Hepatitis A

Hepatitis A is an infection seen primarily where there is poor sanitation. Consequently many older people have had the infection and have developed immunity. There does not appear to be a chronic carrier state which is infectious. Until recently it was considered that transmission was only by the faeco-oral route. However, in the last two years there have been some transmissions of hepatitis A from Factor 8. There is debate about whether this was due to lack of good manufacturing practice or whether donors who were at risk had not revealed this to the blood centres. Hepatitis A is not usually a serious infection, and it is considered that in the recent episode, there must have been a considerable amount of donors in the active infectious stage contributing to the pool. Pools of plasma from healthy donors usually contain protective antibody to hepatitis A, and normal immunoglobulin has been used to protect against the disease. There are proposals before the EC to ask manufacturers of blood products to validate their process to show inactivation of Hepatitis A.

(ii) Parvovirus B19

This is an infection seen commonly particularly among young children. It usually causes a sore throat and general malaise for a few days. However an important feature is that it can stop the bone marrow producing red cells for several days. This is primarily of interest in patients who have a considerably shortened red cell survival, such as sickle cell patients. More recently it has been suggested that haemophiliacs, particularly those who are HIV positive, may suffer as a result of parvovirus transmission. There is no simple cheap test available, and a suggestion has been made of testing pools of donations initially and then testing fractions of these pools in the case of any positives that are shown up. The topic was considered briefly by the ACVSB and further information will be collected. Experts suggest that using current methods it would be virtually impossible to destroy parvovirus during the fractionating procedures for blood products.

(iii) Yersinia enterocolitica

This causes gastrointestinal upset primarily, but there have been occasional deaths due to this organism which is not a virus. The US considered the problem and felt that the only way of excluding transmission was by reducing the time that blood could be held to 14 days. In the US blood can be kept for up to 42 days (35 in the UK). The US felt that reducing the shelf life of red cells would lead to shortages and consequently pressure to try to find additional donors, with the consequent increase in risk of HIV and other infections. The blood transfusion services in the UK are currently considering the topic. No test is available for the infection.

SUMMARY TABLE

1. Compulsory EC tests carried out by UKBTS

HBsAg
Anti-HIV1 and 2
Anti-HCV
Syphilis
Creutzfeldt-Jakob Disease - growth hormone recipients
(also other pituitary hormone recipients in UK only)

2. Non EC compulsory tests carried out by some countries but not UKBTS

ALT
Anti-HBc
Anti-HTLVII

3. Non-Routine tests performed for specific reasons in UK and elsewhere

Anti-CMV
Malaria
HIV Antigen

4. Viruses or other organisms not tested in UK or elsewhere

Hepatitis A
Parvovirus B19
Yersinia

COST BENEFIT CONSIDERATIONS - HTLV

(Human T-cell leukaemia/lymphoma virus)

(i) Introduction

The question of testing blood donations for HTLV has already been considered on several occasions and Ministers accepted the expert advice that it should not be introduced at present. ACVSB, MSBT's predecessor committee, did not base its conclusion on cost grounds, but on the false positive and false negative rates of the initial screening tests. New combined tests for HIV and HTLV may make testing worthwhile in future but at present the cost/benefit considerations of separate HTLV testing are highly unfavourable. By way of an example of the cost benefits of screening for rare viruses this note outlines the risks associated with HTLV, the costs of screening and the hypothetical cost of ex gratia payments for those who develop HTLV associated disease as a result of a transfusion.

(ii) Cost of screening

In view of the false positive/negative rates with HTLV tests initial screening and confirmatory testing would be required. The cost of the screening programme including confirmatory testing and staff time is estimated at £3.5m a year.

(iii) Ex Gratia Payment

The calculations of the cost of ex gratia payments are based on lifetime risk and in the first years there would be very few actual cases. Based on the North London study, the minimum cost of preventing a single transmission by transfusion, which is not in itself harmful in the vast majority of cases, is about £25,000 and of preventing the risk of HTLVI associated disease developing in a recipient's lifetime, about £1.2 million. This is on the assumption that ATLL can occur after transmission.

Based on the lifetime risk the cost of payments in line with those for HIV infected haemophiliacs and blood transfusion recipients would be as follows:

Cost per case (assuming an infected person married with children)
= £80,500 - the maximum amount paid to any individual.

TSP - 1 case every 5 years	
Annual cost of ex gratia payment	£16,100
Annual cost of screening	£3.5m
Cost to prevent 1 Case	£18m

If ATLL does occur following transfusion of HTLVI positive blood (ie ATLL plus TSP) then the cost of 3 cases of ATLL/TSP per year is estimated at:

Annual cost of ex gratia payment	£257,600
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(ATLL plus TSP)

Annual cost of screening
(ATLL plus TSP)

£3.5m

Cost per case of preventing clinical disease

£1.2m

(iv) Morbidity and mortality

HTLVI is a human retrovirus but is not associated with HIV and does not lead to AIDS. HTLVI is endemic in some parts of the world but not in Europe. The virus can be transmitted by breastfeeding, sexual intercourse and, less commonly, by blood transfusion. HTLVI infection may result in Adult T-cell leukaemia/lymphoma (ATLL) or tropical spastic paraparesis (TSP), both of which are incurable.

There is a similar virus HTLVII but as yet no clinical disease has been generally accepted as being caused by this latter virus.

(v) Incidence of HTLV in the donor population

In early 1991 a survey was carried out by the North London Regional Transfusion Centre to determine the incidence of HTLV among their donor population. Screening tests do not differentiate between HTLVI and II, for which supplementary testing is required. The true incidence of HTLVI was small at 4 donors in 96,720 tested which is 0.004%. (One donor was positive for HTLVII). All 4 of these HTLVI antibody positive donors had sexual partners with connections with endemic areas of the world. Therefore the donors themselves would not have been excluded by applying racial exclusion criteria. The incidence in other parts of the UK is likely to be even less as a smaller proportion of the population comes from endemic areas.

(vi) Risk of Transfusion Transmitted Disease

Clinical studies in naturally occurring HTLVI (ie HTLVI which has not been transmitted through blood transfusion) show life time risks for developing TSP of 0.25% and of developing ATLL of between 2% and 4%. There have been no reports of ATLL developing following HTLV infected blood transfusion. However in our consideration of cost benefit we included ATLL as a risk. Taking the two figures together every year up to 6 people may be put at risk of HTLVI associated disease in their lifetime. This figure is approximately halved by virtue of recipients of half of the blood dying of their primary condition within 1 year of transfusion.