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Report to the Ranking Minority Member, Committee on Commerce, House of Representatives

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BLOOD SUPPLY

Transfusion-Associated Risks

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Program Evaluation and
Methodology Division

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The Honorable John D. Dingell
Ranking Minority Member
Committee on Commerce
House of Representatives

Dear Mr. Dingell:

Widespread concern about the safety of the blood supply has led to many changes in the way blood is collected, processed, and transfused. Consequently, the risks of contracting certain diseases, such as AIDS and hepatitis, are lower today than they were in the mid-1980s, when the public became increasingly aware that blood transfusions are not risk free.

You expressed concern about disparate estimates of transfusion-associated AIDS and hepatitis cases and asked that we determine the current risks, evaluating the content and quality of data collected to assess these risks. In this report, we address the risks of contracting AIDS and hepatitis from blood as well as other known risks of blood transfusion.

You also asked us to evaluate the Food and Drug Administration's (FDA's) layers of safety and its ability to ensure the safety of the blood supply in light of changes in the blood industry. We provide that information in our report entitled Blood Supply: FDA Oversight and Remaining Issues of Safety.[1]

Background

On June 30, 1992, 4,619 persons had been reported with suspected transfusion-associated AIDS, representing about 2 percent of the 222,418 U.S. residents reported with AIDS. The number of suspected transfusion-associated AIDS cases rose every year from 56 for patients transfused in 1978 to 714 for patients transfused in 1984 (Selik, Ward, and Buehler, 1993). Then, in 1985, when HIV antibody screening of donors began, the number declined sharply to 288 cases, and it fell below 20 cases per year from 1986 through 1991.[2] The number of new HIV infections definitively associated with transfusions is even smaller. Only 38 cases of

[1]U.S. General Accounting Office, Blood Supply: FDA Oversight and Remaining Issues of Safety, GAO/PEMD-97-1 (Washington, D.C.: 1997).

[2]Within the human body's disease-fighting capabilities, it can develop antibodies that are specific to each viral infection. The initial HIV-1 tests detected the HIV antibody in blood donated by infected persons.

AIDS have been attributed to transfusions of blood screened negative after March 1985.

Measuring Risk

Meanwhile, researchers at the Centers for Disease Control and Prevention (CDC) and within the blood industry were developing and implementing new methods to measure transfusion-associated risks. As a result, the risk estimates that have been presented in the literature vary considerably, depending on when a study was published, the area of the country it considered, and the assumptions underlying its methods. For instance, early studies employed less-sensitive tests than are currently available, were conducted in high-risk areas rather than nationally, and used measurements that were less precise than those used today.

Moreover, the donor pool is safer today than when early studies were conducted because donors who have tested positive for certain viruses or who have acknowledged risk factors for disease have been removed from the donor pool. Indeed, testing may be the mostly widely cited, and is perhaps the most important, step in protecting the public from the risks of blood transfusions. Tests performed on every unit of blood include tests for antibody to hepatitis B core antigen (anti-HBc), hepatitis B surface antigen (HBsAg), antibody to hepatitis C virus (anti-HCV), human immunodeficiency virus (antibody for HIV-1 and HIV-2, and antigen for HIV-1), human T-lymphotropic virus type I (HTLV-I), and syphilis.[3]

Because the scientific community has focused primarily on the risks of contracting specific diseases from blood transfusion, the state of knowledge is quite advanced for some risks such as hepatitis and HIV. Less is known about bacterial contamination and some noninfectious risks such as circulatory overload. No systematic analysis has been published regarding the overall risks of blood transfusion compared to its potential benefits.

Donated Blood and Its Products

About 8 million people donate approximately 14 million units of whole blood each year. This blood—blood in its natural state—is rarely transfused into patients. Instead, the blood industry separates each unit of

[3]Antibody tests detect antibodies that the human body produces in its immune response to a virus, whereas antigen tests detect a component of the actual virus. Because it takes time to develop antibodies, antigen tests detect infection earlier than antibody tests. HTLV is a retrovirus that can lead to neurologic disease or adult T-cell leukemia and lymphoma. Tests currently available are specific for antibodies to HTLV-I, although there are varying degrees of cross-reactivity with antibodies to HTLV-II. Nevertheless, it is the closest test for HTLV-II at this time. We discuss transfusion-associated diseases further in appendix I.

whole blood into an average of 1.9 specialized products that, in blood-banking terminology, are "components" consisting of various types of blood cells, plasma, and special preparations of plasma.[4] Health care facilities transfuse these components—usually 4 to 5 units at a time—into as many as 4 million patients to treat anemia, bleeding disorders, and low blood volume. Donors give an additional 12 million units of plasma each year, for a total of approximately 26 million annual blood and plasma donations prior to testing for viral infections.

In an increasingly common procedure called apheresis, specifically desired components of a donor's blood are removed and the undesired components are given back to the donor. Whole-blood donors must wait 8 weeks between donations to allow the body to replenish its red blood cells. Apheresis collection of plasma, platelets, or white blood cells (leukocytes) may be performed more frequently, however, if red blood cells are returned to the donor. As we discuss later in our report, apheresis often minimizes transfusion risks for the recipient without compromising safety for the donor.

Results in Brief

The blood supply is safer today than any time in recent history. Improved donor screening and education have removed from the donor pool many persons who are at high risk for disease. Tests used to screen blood for viruses are considerably more sensitive than previous versions. Repeat donors constitute most of the donor pool, which means that they have been tested for viruses on earlier donations. Thus, the window of opportunity for infection is considerably smaller than for first-time donors who have never been tested. Viral inactivation techniques for plasma derivatives eliminate most viruses that may escape detection on testing. And changes in transfusion practices have eliminated some of the circumstances that may have led to unnecessary transfusions in the past.

Nevertheless, because blood is a biological product, some risk remains. Eight of every 10,000 donated units of blood carry some kind of potentially serious risk to the recipient, including allergic reactions, bacteria, reactions to incompatible blood transfusions, and viruses. We calculated

[4]In addition to separating whole blood into component products, other facilities manufacture plasma derivatives by fractionating plasma chemically into concentrated proteins. These include albumin, used for blood volume expansion; immune globulin, used to prevent certain infectious diseases and to treat deficiencies of protein; clotting factor concentrates, used to control bleeding in patients with clotting factor deficiencies, such as hemophilia; and specific immune globulins, prepared from plasmas collected from donors with antibodies to specific diseases and then used to prevent those diseases in others. Derivatives are commonly made by commercial manufacturers from plasma collected from paid donors. Depending on the product, they may pool plasma from as many as 60,000 donors for fractionation in order to produce sufficient amounts of the final concentrated material cost-effectively.

that 4 of every 1,000 patients who receive the average transfusion of 5 units of blood are at risk of receiving an implicated unit amd thus may be exposed to conditions with the potential for the development of serious (chronic, disabling, or fatal) outcomes.[5] While these risks may appear to be substantial when considered outside a medical context, it is commonly understood that transfusion provides substantial benefits. We reasoned that as many as 50 percent, or 500, of the 1,000 recipients would be at serious risk of dying immediately if they did not receive transfusions.[6]

Not all recipients of a contaminated unit acquire the disease it contains. Moreover, many recipients die soon after transfusion from the underlying condition for which the blood was prescribed. Finally, the likelihood that a patient will develop chronic disease or die is small for some diseases. We determined that the overall risk of developing chronic disease or dying as a direct result of a blood transfusion is about 4 in 10,000, which translates into about 1,525 of the 4 million patients who receive transfusions each year.

The risk that a general surgery patient will require blood and develop a chronic disease or die as a result of that blood is 5 in 100,000. For the average person in the United States who has no foreseeable plans for surgery, the annual risk of developing a need for surgery, requiring blood, and developing a chronic disease or dying from the transfusion is 5 in 1 million.

We concluded that in context these risks are very small, particularly considering that many patients would die without blood transfusion. The risks from transfusing blood to recipients in general and surgery patients specifically are considerably smaller than other hospital-related risks. Furthermore, the annual risk to an average person in the United States with no foreseeable plans for surgery is more than 250 times less than the annual risk of hospitalization from accidental poisoning by drugs and other medicines and nearly 600 times less than that of other diseases or events of high public concern, such as heart disease.

[5]We present an overall risk for all types of blood components. Strictly speaking, different blood components carry different risks. This is especially true for a therapeutic dose of apheresis platelets, which, because it contains only 1 donor's platelets, carries a much lower risk to the patient than a typical therapeutic dose of random donor platelets (6 donors) or red blood cells (5 donors). See appendix II for a detailed discussion of these differences.

[6]The ethical concerns surrounding a study of differences in survival rates between groups of patients who have and have not received blood make collecting such data difficult. However, Jehovah's Witnesses who refuse blood on religious grounds are natural case study controls. Research on this population suggests that the mortality rate is between 38 and 53 percent among severely anemic patients who refuse transfusion (Spence et al., 1990 and 1992). Mortality is higher (75 percent) for those with active bleeding who require emergency surgery (Carson et al., 1988).

We took a worst case approach in our analysis. That is, we used the most conservative risk estimates among current comprehensive studies published in the scientific literature. Consequently, the actual risks of transfusion may be somewhat lower, but are not likely to be higher, than the risks we present.

Objectives, Scope, and Methodology

Our objective in this report was to quantify the current risks associated with blood transfusion. To respond to your request, we reviewed data on the current risks of blood transfusion in the United States, evaluating the content and quality of the data. We analyzed the theoretical and research foundations underlying current and past risk estimates and held extensive interviews with industry and government epidemiological experts.

Our analysis assumed that all the layers of safety are working properly. That is, our risk estimates are for units of blood from donors who were properly screened, who were checked on the deferral registry, whose blood was tested for viruses, and so on.

We included risks of receiving units contaminated by eight viruses (HAV, HBV, HCV, HIV-1 and HIV-2, HTLV-I and HTLV-II, non-ABC hepatitis), various bacteria, and one parasite-transmitted disease (Chagas'), as well as four complications of transfusion itself (ABO incompatibility, acute lung injury, allergic reaction, and circulatory overload). We did not include the risks of some diseases that are known to be present in blood but that have very low prevalence rates (such as Leishmaniasis), that have already high prevalence rates in the general population with few complications (such as cytomegalovirus, or CMV, and B19 parvovirus), or that have no scientific proof of transfusion transmission (Creutzfeldt-Jakob disease, or CJD).[7]

[7]No cases of transfusion-transmitted Leishmaniasis have been documented in the United States. In 1991, a new form of the disease, Leishmaniasis tropica, was detected in seven Desert Storm veterans, leading to deferral of individuals who had been in the Persian Gulf in or after 1990. With the absence of any data substantiating transmission of this parasite, the ban was lifted in January 1993. CMV is a type of herpes virus. Estimates suggest that between 60 and 90 percent of the general population have been infected by the time they are adults. Primary infection is usually the result of respiratory or sexual contact, and the acute phase of the virus usually passes without symptoms. Once infected, however, blood carries antibodies for a lifetime. Only blood transfusion recipients with weakened immune systems (such as leukemia patients) and newborns are thought to be at risk for severe complications from CMV-positive blood. Therefore, units for these types of patients are routinely screened for CMV antibodies. Parvovirus, like CMV, causes a clinically mild, short disease state in all but severely immunocompromised patients. It can be severely detrimental to fetuses. About 50 percent of adults show evidence of past infection and no licensed screening test is available. The neurological disease CJD is caused by an unidentified infectious agent and has no cure. However, there is no evidence at this time that it can be transmitted by transfusion.

Unless otherwise noted, our risk estimates are for whole-blood products from unpaid allogeneic donors. Allogeneic donors include volunteer donors for the general supply and directed donors for friends and family.[8] Autologous donors, who donate their blood for their own use, can be infectious but cannot transmit a virus to themselves. A small portion of unused autologous blood is "crossed-over" into the general supply. We included these units.

Limited data are available concerning the risks posed by paid donors of plasma; therefore, we did not include plasma derivatives in our analysis. Although the disease rates of paid donors are thought to be higher than those of volunteer donors, most plasma-derived products undergo viral inactivation processes during manufacturing, which eliminates most but not all viruses. Few cases of disease transmission have been reported since testing and inactivation began. We discuss relevant issues in appendix III.

Our analysis consisted of several estimates for each of the diseases above or complications: (1) risks per donated unit, (2) annual number of infectious or otherwise implicated component units released for transfusion, (3) risks that the transfusion recipient would receive an implicated unit, (4) number of recipients who would contract the disease present in the blood transfusion, (5) number of recipients who would not die from the underlying disease or trauma necessitating the transfusion before problems associated with the blood transfusion manifest, and (6) the number of recipients who would die or develop chronic disease as a result of the disease or other transfusion complication. These numbers are for patients who have a blood transfusion. We also considered the risks for general surgery patients who may or may not require a transfusion and the annual risks for a person in the general population who does not foresee a plan for surgery. In appendix II we provide information on the studies used in our analysis and explain our calculations.

No risk estimate can be properly interpreted in isolation. Therefore, we compared our risk estimate for death or chronic disease from a blood transfusion with other known hospital-related risks, as well as with those for death by other common diseases.

[8]Directed donors are donors who are, for example, relatives or friends of a patient and who donate blood because the patient has asked them to.

Finally, we reviewed means currently or soon to be available by which the risks of blood transfusion may be further reduced.

Wherever possible, we included in our analysis the most recent, nationally representative studies that used state-of-the-art viral tests. For example, we did not include some of the older studies on HIV risk that employed donors from geographical areas that at the time were of high risk and are, therefore, less useful as predictors of current risk at a national level. However, we do recognize their value as the first controlled studies of HIV risk and we note that they are the models upon which newer, more relevant studies are conducted. In appendix I, we discuss the details of the major studies we reviewed, including their relative strengths and weaknesses.

We used one overarching principle when choosing between studies that we considered equally sound and that were a matter of continuing debate in the research community: we chose to include the studies with the higher risk estimates. In other words, ours is a worst-case analysis. Thus, the actual risks for some of the agents and activities we discuss may be somewhat lower but are not likely to be higher given the available research. Using some of the more variable estimates, we conducted sensitivity analyses for our final analysis of the number of recipients likely to die or develop chronic disease; we found the results to be highly robust. That is, even when using different estimates for individual diseases or complications, the resulting final estimate changed very little.[9]

We conducted our review in accordance with generally accepted government auditing standards.

Principal Findings

In the context of other health-related risks, the risks of blood transfusion are extremely small, especially considering the often fatal consequences of refusing a medically necessary transfusion. Moreover, these risks are continually decreasing as a result of advances in donor screening, improved viral tests, viral inactivation techniques, and changes in transfusion medicine practices.

[9]For example, we used a risk estimate of 1 in 4,100 units for HCV based on research suggesting that the anti-HCV screening test misses some infected donors. Using this estimate, we predict that 4 in 10,000 patients will develop serious chronic disease or die. Some researchers do not accept this theory, believing that the risk is closer to 1 in 103,000. Using this estimate changes the prediction only slightly to 2 of every 10,000 patients.

Five Factors That Help Reduce Risk

The risk of contracting a disease from blood transfusion continues to decrease. We identified five factors that have helped reduce the risk of contracting viral diseases from blood transfusions.

First, better donor screening and education efforts have refined the volunteer whole-blood donor pool to one comprising primarily persons with lower risk than those who donated blood before such screening was introduced. The frequency of positive HIV test results among blood donors is now much lower than that of other tested groups, such as military recruits, inner-city emergency room patients, and randomly selected newborns. Moreover, the current rate of positive HIV test results is about 8 per 100,000 blood donors, which is 50 times lower than the rate of 400 per 100,000 in the general population.

Second, state-of-the-art viral screening tests can detect infected blood donations. For example, before anti-HCV testing, the rate of transfusion-associated hepatitis was 4.4 percent. After first-generation anti-HCV tests were introduced, the rate fell to about 1 percent—nearly an 80-percent reduction. Second-generation tests identified an additional 10 percent of infected donors for an overall reduction of 90 percent in transfusion-associated hepatitis C.

Third, because FDA regulations and industry practices prevent the use of blood from infected, behaviorally risky, or test-positive donors, the donor pool comprises primarily repeat donors who have been deemed safe. These repeat donors have a narrower window of opportunity of infection (defined by the interval between tested donations) compared to first-time donors whose blood has never been tested and who, therefore, have a substantially longer window of opportunity of infection.

Indeed, a recent collaborative study by the CDC and the American Red Cross (ARC) revealed that 7 million donations, or 80 percent of all donations collected by ARC in 1991 through 1993, were from repeat donors (Lackritz et al., 1995). Of these donations from repeat donors, less than 2 of every 100,000 donations (142) tested positive for HIV. The remaining 20 percent of the donor pool were first-time donors who provided only about a fourth as much blood, or 2 million donations. Donations from first-time donors were 9 times more likely to be HIV-positive than those of repeat donors: 18 of every 100,000 donations (349) from first-time donors tested positive for HIV.

Fourth, viral inactivation techniques are used whenever possible in the manufacture of plasma derivatives. This is particularly important for the plasma derivatives that hemophiliacs routinely use (see appendix III). Recent research suggests that new inactivation techniques may be available in the future for other blood products, such as red blood cells, that are too fragile to withstand most heat or chemically based inactivation.

And fifth, as physicians have become more aware of changes in the practice of transfusion medicine, they have moved away from routinely prescribing whole blood. Instead, they have moved toward prescribing specific blood components to alleviate specific complications, using plasma volume expanders wherever appropriate, collecting a patient's own blood before an operation, and salvaging and reinfusing a patient's own blood during surgery. See appendix IV for additional discussion of new technology and medical practice changes that could further reduce risk.

Risks of Blood Transfusion

We evaluated the overall risk of blood transfusion by synthesizing the risks of a number of different adverse outcomes that could result from receiving blood (see table 1).[10] Because estimates of risk are better understood in context, we compared them to other known health-related risks.

Appendix II discusses the method of our analysis in detail, including citations for the estimates in table 1.

[10]Our analysis did not include risks associated with plasma products. See appendix III for a discussion of plasma.

Table 1: Individual and Overall Risks of Adverse Outcomes From Allogeneic Blood Transfusion[a]

Agent or activity	1. Risk estimate per unit (12.057 million units donated)	2. Patient risk per transfusion of 5 units
Virus[b]		
HAV	1:1,000,000	1:200,000
HBV	1:63,000	1:12,600
HCV	1:4,100	1:820
HIV-1 and -2	1:450,000	1:90,000
HTLV-I and -II	1:50,000	1:10,000
Non-ABC hepatitis	1:5,900	1:1,180
Bacterium		
Platelet contamination[c]		
Random donor	1:10,200	1:1,700
Apheresis	1:19,500	1:19,500
Yersinia[f]	1:500,000	1:100,000
Parasite[b]		
T. cruzi	1:42,000	1:8,400
Subtotal risk of infection	**5:10,000[g]**	**2.7:1,000[g]**
Transfusion[h]		
ABO incompatible[i]	1:12,000	1:2,400
Acute lung injury	1:10,000	1:2,000
Anaphylaxis	1:150,000	1:30,000
Circulatory overload	1:10,000	1:2,000
Subtotal risk of transfusion reaction	**3:10,000**	**1.5:1,000**
Total		
Risk	**8:10,000[j]**	**4.2:1,000[j]**

3. Annual number of implicated component units if 23.19 million components available and 19.23 million transfusions	4. Number of recipients affected (likelihood of seroconversion)		5. Number of recipients who do not die of underlying disease or trauma first (30% die within 2 years)	6. Number of recipients who develop chronic disease or die as a result of transfusion (likelihood)	
	Number	Percent		Number	Percent
23	21	90%	15	0	0.2%
368	258	70	181	18	10
5,656	5,090	90	3,563	713	20
52	47	90	33	33	100
464	125	27	88	4	4.75
3,931	3,538	90	2,477	372	15
460	460[d]		460[e]	120	26
31[d]	31[d]		31[e]	8	
24	24[d]		24[e]	6	26
552	55	10	39	12	30
11,561	**9,649**		**6,911**	**1,286**	
895[l]	322[k]		322[e]	19	6
1,923	1,923[d]		1,923[e]	96	5
128	128[d]		128[e]	26	20
1,923	1,923[d]		1,923[e]	96	5
4,869	**4,296**		**4,296**	**237**	
16,430	**13,945**		**11,207**	**1,523**	
	3.5:1,000[m]		**2.8:1,000[m]**	**4 :10,000[m]**	

Although donors may carry more than one disease, the likelihood that a unit will escape detection by multiple tests is almost nonexistent. Therefore, the individual risks presented here are independent, and the total risk is calculated by summing individual risks. Numbers may not be exact because of rounding. An example using HIV across columns 1-6 is as follows:

1: The risk of HIV is 1 in every 450,000 donated units. That is, of the 12.057 million units donated, 27 will be HIV positive (12.057 million/450,000 (not shown)).

2: Assuming each patient receives an average of about 5 units of blood (except platelets noted below), then the risk to the patient is 450,000/5, or 1 in 90,000.

3: Each allogeneic unit is made into an average of 1.87 transfused components. Hence, 12.057 million units = 22,583,000 components plus 607,000 apheresis platelets = 23,190,000 total components. The 27 units of HIV-positive blood become 52 different components.

4: Not all recipients will develop the disease present in the blood (seroconvert); 90 percent of the 52 recipients of HIV blood will seroconvert (47 patients). This concept applies only to viruses.

5: Most patients receiving blood are at great risk of dying from their underlying conditions; 30 percent die within 2 years. For HIV, 33 of the 47 patients will survive.

6: Not all agents and activities lead to chronic disease or death. The likelihood that HIV will is nearly 100 percent, so all 33 patients who survive their underlying conditions will die.

[b]The number of virus- and parasite-contaminated units is based on the number of allogeneic units donated (12.057 million) and the number of components made (23.190 million).

[c]A total of 8.330 million individual units of platelets were transfused. Patient risk and available components are based on 4.688 million random donor platelets transfused (56 percent of total platelet transfusions) and 607,000 single donor apheresis platelets transfused (each apheresis unit has 6 individual units collected from 1 donor, totaling 3.642 million platelets, or 44 percent of total platelet transfusions). For example, patient risk for a random donor unit is the risk for each donor unit divided by the average number of units pooled into a therapeutic dose, 10,200/6, or 1 in 1,700 in Morrow's (1991) research on platelet contamination. The number of implicated random donor units is 4.688 million/10,200, or 460 units. The patient risk for apheresis platelets is the same as the per-unit risk (1:19,500) because the platelets are collected at the same time from a single donor. Number of implicated apheresis units is 607,000/19,500, or 31 units.

[d]Seroconversion not relevant. Numbers carried over from column 3.

[e]Not relevant for bacterial contamination or transfusion-related outcomes that are near-term events.

[f]Risk is based on 12.057 million red blood cell units because Yersinia occurs only in these units.

[g]Risk is based on sum of viral risks plus Yersinia risk plus a weighted sum of platelet risks based on proportion transfused ((random platelet risk x 0.56) + (apheresis platelet risk x 0.44)).

[h]The number of units associated with transfusion problems is based on the number of units actually transfused (4.688 million random donor platelets, 607,000 apheresis platelets, 10.741 million whole blood and red blood cells, and 3.194 million other components). Risk is based on 19,230,000 total transfusions. See appendix II for supply and transfusion calculations.

[i]Risk is based on 10.741 million red blood cells and whole blood transfused because compatibility is an issue only for these units.

[j]Assumes a 64-percent chance that a random transfusion to an unintended recipient would be compatible and 100-percent reporting of incompatible erroneous transfusions.

[k]Seroconversion not relevant. Assumes 36-percent incompatible.

[l]Risk is based on sum of viral risks plus Yersinia risk plus a weighted sum of platelet risk based on proportion transfused ((random platelet risk x 0.56) + (apheresis platelet risk x 0.44)) plus transfusion-related risks.

[m]Number of affected patients/total number of transfusion recipients (4 million).

Although the risk of receiving HIV-contaminated blood is the public's greatest fear, other diseases transmitted through blood are far more common than HIV. For example, we found that the risk of contracting HCV infection is more than 100 times greater than that of contracting HIV. After screening and testing, the likelihood that a unit of blood infected with hepatitis C virus would remain undetected and be released for transfusion is 1 in every 4,100 units of blood; for HIV, the likelihood is 1 in every 450,000 units.[11] A more sensitive anti-HCV test that detects more infected units is available in Europe and has been licensed in the United States during the past year. Its use is widespread but not universal.

The likelihood that a unit of blood may become contaminated by bacteria ranges from 1 in 500,000 for red blood cells to 1 in 10,200 for random donor platelets, the blood component used to treat certain bleeding disorders. As we discuss in Blood Supply: FDA Oversight and Remaining Issues of Safety, cited above, bacteria can enter a unit during collection as a result of either poor aseptic technique or donor bacteremia. Bacteria present in a unit can proliferate during storage. Platelets are at high risk because they are stored at room temperature; the risk of their contamination greatly increases over their storage life of 5 days. Bedside tests for bacterial contamination could greatly mitigate this problem and may soon be presented to FDA for approval.

We estimated that about 1 in every 2,000 units may be infected by a virus, bacterium, or parasite.[12] Certain noninfectious risks are also associated with blood transfusion. One such problem is the immune reaction associated with the inadvertent transfusion of blood that contains red blood cells that are incompatible with those in the recipient's blood. Other risks include acute lung injury, circulatory overload, and allergic reactions to certain blood proteins. Some of these risks (for example, acute lung injury) cannot be eliminated without advances in the state of knowledge

[11]Precise numbers such as these are known as point estimates. Their precision is necessary for calculating purposes but should not be construed as definitive. Scientists know that statistical measurement is not perfectly precise. Thus, they calculate a range, or confidence interval, of estimates that is wide enough that they are confident in believing that the real number is somewhere between the two endpoints of the range. For example, the confidence interval for HBV risk ranges from 1 in 31,279 to 1 in 146,662, meaning that the real risk almost certainly lies somewhere in the middle. In the case of HBV, the point estimate is 1 in 63,171 units. We used point estimates in our analyses. We include confidence intervals in appendix I wherever they are available.

[12]See table 1, note g, for calculation method.

about how they occur.[13] The overall likelihood of noninfectious complications is difficult to ascertain, because estimates are based on voluntary hospital reports and because they are likely to remain undiagnosed in the hospital setting. We estimated that some type of noninfectious complication may occur in 1 of every 3,448 units of blood.[14]

Using current risk estimates for individual adverse outcomes, we determined that as many as 8 of every 10,000 units of blood carry a potentially serious risk to the patient, including incompatibility, allergic reactions, bacteria, and viruses. About 11,560 of the 23.19 million components available are infected by bacteria, viruses, or parasites, and about 4,870 of the 19.23 million components that are transfused may lead to an adverse, noninfectious outcome, such as circulatory overload. We calculated that an individual patient's risk of receiving an implicated unit is 4.2 in 1,000, or 1 in 238 patients.[15]

In order to fully understand the risks of blood transfusion, one must consider three additional factors. First, even if a unit of blood is contaminated, the likelihood of acquiring the disease it contains is less than 100 percent, ranging from 10 to 90 percent. Second, blood is typically prescribed for patients who have very serious trauma or disease. Indeed, there is a 30-percent chance that a patient will die within 2 years from the underlying condition for which the blood is prescribed and, therefore, never experience some of the possible negative consequences from the blood transfusion itself.[16]

[13]Graft-vs-host disease is one example of a problem that has been virtually eliminated as scientists discovered how it acts. Donor lymphocytes engraft and multiply in the recipient, who is usually immunocompromised. The donor cells react against the "foreign" tissues of the recipient. The reaction occurs most often in blood received from first-degree family members. These blood donations are now irradiated, thus making graft-vs-host disease from blood transfusion very rare in the United States.

[14]Estimated by summing transfusion-related, noninfectious risks from the second column of table 1: 1/12,000 + 1/10,000 + 1/150,000 + 1/10,000 = 0.00029, or 2.9 in 10,000 units, or 1 in 3,448 units.

[15]The average patient risk is calculated by dividing the per-unit risk by the average number of units in a transfusion. But it must be noted that patient risk depends on the number of units transfused. For example, if the risk per unit for a disease is 1 in 500,000, then a patient who has received an average transfusion of 5 units would have a risk of 1 in 100,000 (500,000 divided by 5). That is, if 1 of every 500,000 units is contaminated, then 1 of every 100,000 patients who receive 5 units could receive a contaminated unit. Similarly, 1 of every 5,000 patients who receive 100 units could receive a contaminated unit (500,000 divided by 100).

[16]This is to say not that there is a causal relationship between receiving blood and dying but, rather, that those who receive a blood transfusion are typically quite ill or traumatized and, consequently, may die from the underlying reason for which the transfusion was administered. The mortality rate may be even higher for platelet recipients, who are often extremely ill with cancer or other life-threatening problems.

Third, only HIV-contaminated blood leads to nearly certain fatal outcomes; the likelihood that a patient would develop clinically serious chronic disease or die as a result of blood transfusion ranges from 0.2 to 30 percent for all other possible complications. When we included all these facts in our analysis, we determined that only 10 percent of exposed recipients are ultimately harmed seriously by their blood transfusions. Indeed, the overall risk of developing chronic disease or dying as a direct result of a blood transfusion is about 4 in 10,000, which translates into 1,523 of the 4 million patients who receive transfusions each year.[17]

Surgery patients numbered 23 million in 1993. Given that there are 3 million surgical transfusion patients annually, we estimated that 13 percent of the surgery patients received blood. Therefore, discounting the fact that some patients had multiple surgeries, a maximum of 9 percent underwent surgery and 1 percent both underwent surgery and received blood among the 260 million in the general U.S. population.[18]

Given these estimates, we calculated that the risk of a general surgery patient's requiring blood and then developing a chronic disease or dying as a result of that blood is 5 in 100,000 (see table 2). For an average person in the general population who does not foresee a plan for surgery, the annual risk that he or she would develop a need for surgery, require blood, and develop a chronic disease or die as a result of that blood is 5 in 1 million.

Table 2: Risks of Surgery and Blood Transfusion[a]

Likelihood of problem if patient	Risk
Receives blood	40:100,000
Is a surgery candidate	5:100,000
Has no plans for surgery	5:1,000,000

[a]Assumes 23 million surgeries in 1993, or 9 percent of the U.S. population, with an estimated 13 percent of the surgeries using blood and 0.012 probability of surgery and blood transfusion occurring together. Assumes further that only 3 million of the 4 million patients who received transfused blood were surgery patients; the remaining 1 million received transfusions for cancer therapy, hemophilia, and other disorders.

[17]The risk for HIV we present does not include the expected reduction resulting from the introduction of the new p24 antigen HIV test. Although no confirmatory data have been collected, it is estimated that the risk of HIV in blood screened by the new test will be 1 in 700,000. When we used this risk estimate in our analysis, we concluded that it would detect an additional 19 of the 52 contaminated components in the supply and ultimately prevent 12 (less than 1 percent) of the 1,523 cases of chronic disease and death associated with transfusion.

[18]Among the estimated 260 million U.S. population, 9 percent underwent surgery (23 million divided by 260 million). Furthermore, 13 percent of those surgery patients received blood (3 million estimated surgery transfusions divided by 23 million surgeries). The likelihood that an average U.S. citizen with no plans for surgery would undergo surgery and receive blood is 1 in 100 (probability of surgery and blood = 0.09 x 0.13 = 0.01).

Blood Transfusion Risks in Perspective

In order to determine whether these risks are small or large, we compared them to other health-related risks. Data from the Medical Practice Study suggest that more than 1 million patients are injured in hospitals each year, and approximately 180,000 die annually as a result of these injuries (Brennan et al., 1991; Leape et al., 1991). A recent study at two large Massachusetts hospitals found that 6.5 percent of admitted patients suffered an injury resulting from medical intervention related to a prescribed drug during their hospital stay (Bates et al., 1995).

The risks to blood transfusion recipients and general surgery patients are considerably smaller than the risk of dying as a direct result of surgery, the risk that a hospital stay will result in death or chronic disability, the risk of suffering an injury from hospital drug therapy, and the risk of developing an infection of unknown cause in intensive care (see table 3).

Table 3: Likelihood of Various Health Outcomes

Outcome	Per 100,000 patients or hospitalizations[a]
Chronic disease or death from blood if	
General surgery patient	5
Received blood transfusion	40
Hospital stay ends in death or disability	600[b]
Death as direct result of surgery	1,333[c]
Injury related to drug therapy during hospital stay	6,500[d]
Infection of unknown cause in intensive care	7,500[e]

[a]We were unable to determine whether some of these figures include the risk of dying from transfusion. However, that risk is a very small proportion of the other risks.

[b]T. A. Brennan et al., "Incidence of Adverse Events and Negligence in Hospitalized Patients: Results of the Harvard Medical Practice Study I," New England Journal of Medicine, 324:6 (1991), 370-76.

[c]C. B. Inlander et al., The Consumer's Medical Desk Reference (New York: Stonesong Press, 1995).

[d]D. W. Bates et al., "Incidence of Adverse Drug Events and Potential Adverse Drug Events: Implications for Prevention," Journal of the American Medical Association, 274:1 (1995), 29-34.

[e]B. N. Doebbeling et al., "Comparative Efficacy of Alternative Hand-Washing Agents in Reducing Nosocomial Infections in Intensive Care Units," New England Journal of Medicine, 327 (1992), 88-93.

Furthermore, the annual risk from transfusion to an average person in the United States who foresees no plan for surgery is the same as or lower than the annual risk of dying from tuberculosis or from accidental

electrocution or drowning, and it is as much as nearly 600 times less than the annual risk of dying from other diseases or events of great public concern (see table 4). These differences are particularly striking considering that the risk estimate for blood transfusion includes both chronic disease and death, whereas some of the other risk estimates include only death; estimates that included chronic disease would be substantially higher. Perhaps most importantly, the risks associated with blood transfusion must be compared to the risk of dying from having refused a blood transfusion that physicians believed to be medically necessary—a risk that could approach 100 percent in some cases.

Table 4: Annual Rates of Various Health Outcomes

Outcome	Condition	Per 100,000 population
Chronic disease or death by transfusion without surgery plans		0.5
Hospitalization for	Septicemia (bacteria infection in bloodstream)	105
	Accidental poisoning by drugs, medicines, and biologicals	128
	Drugs and other pharmaceuticals causing adverse effects in therapeutic use	142
	Infections or parasitic diseases	311
	Cerebrovascular disease	328
	Pneumonia	462
	Malignant tumor	578
	Injury and poisoning	1,060
	Heart disease	1,541
Death from	Electrocution	0.5
	Tuberculosis	0.8
	Drowning	2.8
	Hardening of arteries	9
	Motor vehicle crash	15
	Pneumonia or influenza	32
	Stroke	59
	Cancer	206
	Heart disease	296

Conclusions

We found that the current risks from blood transfusion are small compared to transfusion's overwhelming benefits in saving lives. Blood transfusion is the most common therapy using human tissue in the world. As a tissue, blood retains the medical history of its donor. Because it is a biological product, the risks can approach but may never reach zero.

Medical testing and manufacturing technologies continue to improve blood safety. Medical practice is being transformed to accommodate new knowledge about the risks and benefits of blood transfusion. Ultimately, each patient benefits from these advances. However, because the risks are already so low, incremental increases in safety may be difficult to achieve. Therefore, the potential outcomes of alternatives for reducing blood transfusion risks may require careful consideration in order to identify areas of improvement that would maximize safety with reasonable costs.

The analysis we present here incorporates what is known today about infectious agents in the blood supply. New infectious agents are always emerging, and there is always the possibility that they could be transmitted by blood. Continued safety, therefore, depends on the scientific and medical communities' detecting and identifying new threats to the blood supply.

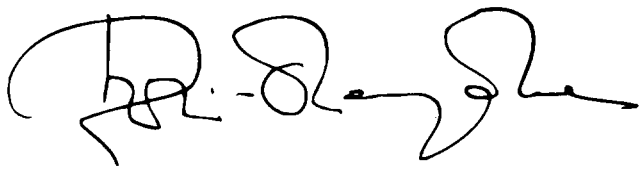
Agency Comments

The Department of Health and Human Services (HHS) generally agreed with the findings and conclusions of our study (see appendix V). HHS also provided technical comments that we have incorporated in the body of the report where appropriate.

As we arranged with your office, unless you publicly announce the report's contents earlier, we plan no further distribution until 15 days after the date of this letter. We will then send copies of the report to the Secretary of Health and Human Services, the Commissioner of the Food and Drug

Administration, and others who are interested. We will also make copies available to others upon request. If you have any questions or would like additional information, please call me at (202) 512-3652. Major contributors to this report are listed in appendix VI.

Sincerely yours,



Kwai-Cheung Chan
Director for Program Evaluation
in Physical Systems Areas

Contents

Abbreviations

ABRA	American Blood Resources Association
ARC	American Red Cross
ATL	Adult T-cell leukemia and lymphoma
CDC	Centers for Disease Control and Prevention
CJD	Creutzfeldt-Jakob disease
CMV	Cytomegalovirus
FDA	Food and Drug Administration
HAM/TSP	HTLV-I-associated myelopathy and tropical spastic paraparesis
HAV	Hepatitis A virus
HBc	Hepatitis B core
HBV	Hepatitis B virus
HBsAG	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDV	Delta hepatitis
HEV	Hepatitis E virus
HGV	Hepatitis G virus
HHS	Department of Health and Human Services
HIV	Human immunodeficiency virus
HTLV	Human T-lymphotropic virus
IGIV	Immune Globulin Intravenous
NIH	National Institutes of Health
TRALI	Transfusion-related acute lung injury

Transfusion-Associated Complications

In this appendix, we discuss factors important for understanding the nature of blood transfusion risks. Specifically, we highlight epidemiological disease factors, present and evaluate the data from blood-supply-risk and transmission-by-transfusion studies, and discuss what is known about the clinical prognosis for each virus, bacterium, and transfusion complication we include in our risk analysis.

HIV-1 and HIV-2

Disease Factors

HIV-1 is widely distributed throughout the world, 21.8 million cases having been reported by July 1996. Sub-Saharan Africa is home to 63 percent, South Asia and Southeast Asia to 23 percent, and North America to 3.7 percent of all reported cases. HIV-2 is endemic only in West Africa, although cases have appeared in other parts of Africa and in Europe, North America, and South America.

The mode of transmission and the course of immunological destruction are similar in HIV-1 and HIV-2. The rate of disease progression, however, may be substantially slower in HIV-2, as may be the likelihood of secondary transmission. HIV-2 is rare in the United States: by 1991, CDC had confirmed only 17 cases, of which 13 had migrated from West Africa, where it was first identified.

HIV cases in the United States were initially clustered among homosexual males, intravenous drug users, prostitutes, and transfusion recipients. However, distribution patterns have changed in the past 10 years to include more cases of infection acquired from heterosexual sex and from perinatal transmission to newborns. CDC reported in July 1996 that 1 in every 300 Americans carries the HIV virus. According to its most recent data, 650,000 to 900,000 Americans were infected by 1992, and 40,000 more become infected each year. More than 325,000 persons had died of AIDS in the United States through 1994; 50,000 more die each year. Experts point to five factors that contribute to HIV's emergence: urbanization, changes in lifestyles, increased intravenous drug abuse, international travel, and blood and tissue transplantation.

In July 1996, CDC announced the discovery in California of the first person in the United States known to carry a rare strain of HIV (group O) that is not consistently detected by current HIV screening tests. Fewer than 100

cases of this virus have been reported worldwide from West and Central Africa, Belgium, France, and Germany. The source of infection of the patient in Los Angeles is not known, but she is originally from Central Africa, and CDC officials believe that she contracted the disease before coming to the United States. The patient has never donated blood, and FDA is working with industry to improve HIV screening tests to detect HIV group O reliably. A second case of HIV-1 group O infection has been identified in the United States under CDC's surveillance activities for unusual HIV-1 variants.

The incubation period from exposure to antibody seroconversion for HIV ranges from days to months before the virus is detectable in blood. It is thought that the average time between infectiousness (when a recently infected blood donor can transmit disease) and seroconversion is 22 days, with a 95-percent confidence interval of 6 to 38 days. It takes an average of 10 years after infection for clinical signs of HIV disease to emerge.

The period of communicability is not well established but is presumed to begin early after the onset of HIV and to extend throughout life. Recent advances in treatment using a combination therapy, which may include new "protease-inhibitors," appear promising. The drugs work by blocking an enzyme critical to HIV replication and can reduce the amount of HIV in the blood to levels that cannot be detected by even the most sensitive tests available. However, success depends on strict compliance with the treatment program.

Prevention and control measures include blood and tissue screening, avoidance of any form of sexual intercourse with persons known or suspected of infection, use of latex condoms and spermicide to reduce risk of sexual transmission, avoidance of shared needles by intravenous drug users, and universal precautions by health care workers.

Blood-Supply-Risk Studies

In a study carried out between 1985 and 1991 in Baltimore and Houston (both areas of high HIV risk), Nelson and colleagues (1992) directly tested the blood of patients before and after cardiac surgery to determine their risk of acquiring HIV from blood donations screened negative for the antibody to HIV. Two cases of HIV were documented in 11,532 recipients after the transfusion of 120,312 units of blood, for an estimated risk of 1 per 60,000 units (upper limit of confidence interval 1 in 19,000). A direct approach was also taken in San Francisco, another high risk area, using donations made between November 1987 and December 1989. Busch and

colleagues (1991) first pooled units of blood that had been screened for HIV antibodies and issued for transfusion and then they tested for evidence of the actual virus. This study estimated the risk of HIV-1 as 1 per 61,171 units, with a 95-percent upper confidence bound of 1 in 10,695. In a subsequent analysis of pools of screened blood donated between October 1990 and June 1993, researchers reported a risk of 1 in 160,000 units (upper bound of 95-percent confidence interval, 1:128,000) (Vyas et al., 1996).

Statistical modeling techniques have replaced most of the direct measurement methods of collecting transfusion risk data. The first such method estimated risk based on data on the incidence of seroconversion among donors (the total number of new infections in a given time period) and assumptions about the sensitivity of tests and the length of the window period. Using this method, Ward and colleagues (1988) estimated the HIV risk at about 1 per 40,000 units.[1] Ward's groundbreaking reasoning was as follows.

From May 1986 to May 1987, 0.012 percent of repeat blood donors and 0.041 percent of first-time donors in the United States had HIV antibody.[2] If we assume that all HIV infections detected in repeat blood donors are new, or incident, infections and that those in firsttime donors are preexisting, or prevalent, infections, then we can estimate the number of persons who are infected with HIV after they have received transfusions screened as negative for antibody. We can do this by assuming the following: a test sensitivity of 99 percent, the development of detectable HIV antibody 8 weeks after infection, an equal probability of infection throughout time, a repeat donation rate of 1.5 times per year (about every 32 weeks), and the collection of 14.4 million of the 18 million components transfused annually (or 80 percent) from repeat donors.In other words,

- for repeat donors, (14,400,000 x [0.00012 x (8/32)]) + (14,400,000 x [0.00012 x (24/32) x 0.01]) = 445.[3]
- For firsttime donors: 3,600,000 x (0.00041 x 0.01) = 15.
- Transmission by HIV seronegative blood: 445 + 15 = 460 units of 18 million = 1 per 39,130, or about 1 per 40,000.

[1]Ward did not report confidence intervals.

[2]Personal communication from Roger Dodd of the American Red Cross.

[3]That is, [number of donors x (the HIV positivity rate x the proportion of the time between donations when the donor could be in the window period)] + [number of donors x (the HIV positivity rate x the proportion of the time between donations when the donor would be outside the window period x the probability that the test result is false negative)], the latter probability being 100 percent minus 99 percent.

Cumming and colleagues (1989) used similar methods but with more refined rates of donor infectivity that accounted for differences between males and females and between firsttime and repeat donors and a lower estimate of test error (0.1 percent). They reported the risk of an HIV positive unit at 1 per 153,000 units if the window period was 8 weeks (as was then thought, using first-generation HIV tests), a 1-in-300,000 risk with a 4-week window period, and 1 in 88,000 with a 14-week window period.

Kleinman and Secord (1988) improved the mathematical model by employing "look-back techniques" to estimate the number of HIV-infected units that would be donated by repeat donors in the window period. That is, they looked back at recipients who had received test-negative donations from repeat donors who later gave test-positive donations. With this technique, Kleinman and Secord calculated the rate of recipient infection from these preseroconversion donations, estimated the duration of the window period, and found the HIV risk in Los Angeles in 1987 to be 1 per 68,000.

Petersen and colleagues (1994) used the lookback method to refine the estimate of the window period. They evaluated the HIV status of recipients who had received screened negative donations from 182 repeat donors who later tested positive for HIV. The study reflected donations from a large portion of the United States and conditions from 1985 to 1990. These researchers found 20 percent of recipients of preseroconversion units infected. Moreover, the rate of disease transmission in recipients was found to be higher as the interval between the negative and positive donations decreased. Mathematical modeling showed that the infectious window period averaged 45 days (95-percent confidence interval, 34 to 55 days).[4] Subsequently, Petersen combined the 45-day window period with measures of the rate of seroconversion among repeat donors in a large donor population with estimates of seroconversion rates for firsttime donors to arrive at the first national HIV risk estimate of 1 in 225,000.

Today, newer HIV antibody tests have reduced the window period to between 22 and 25 days. Using the 25-day window estimate and nationally representative data from a total of 9 million ARC donations in 1992 and 1993, Lackritz and colleagues (1995) used a laboratory error rate of 0.5

[4]By 95-percent confidence interval, we mean that the researchers have established a range of values for which they are confident that in 95 out of every 100 measurements (in this case of the window period), the true value would fall somewhere between the two endpoints of the stated interval. These researchers found preliminary evidence suggesting that antibody tests used after March 1987 had a smaller window period of 42 days, a finding that was later confirmed.

percent, which predicted the erroneous release of 1 in every 2.6 million positive donations. An additional factor in this model was the elimination of the window period units that would have been discarded because they were positive on other test results, such as hepatitis, syphilis, and liver enzymes. Indeed, 15 percent of HIV preseroconversion (HIV test-negative) donations from repeat donors and 42 percent of HIV test-positive donations were positive on other tests. This study concluded that there was a residual risk of HIV transmission in 1 of every 450,000 to 660,000 transfusions of a unit of screened blood.[5]

In discussing the implications of their findings, the researchers noted several limitations. First, scientists are unable to measure directly the number of window-period donations that are discarded for positive results on other screening tests, and it is not known what pattern of positivity on other tests window-period donors might display. Second, because current data on the incidence of HIV among firsttime donors is unavailable, researchers must rely on 1985 data collected when HIV testing began that showed that the prevalence among firsttime donors was 1.8 times higher than the prevalence among repeat donors. It was assumed that the incidence rates would show a similar relationship. Whether this has changed in the past 11 years is a question still outstanding. Third, although the study is based on a large sample of donations from 42 different ARC regions that together collect nearly half of the nation's blood, it is not certain that they represent non-ARC centers.

Schreiber and colleagues (1996) studied the donations of 586,507 repeat donors who donated 2,318,356 units at five metropolitan blood centers between 1991 and 1993. Using a window estimate of 22 days, the researchers estimated the likelihood that a repeat blood donor would donate a unit in the window period at 1 in 493,000 (95-percent confidence interval, 202,000 to 2,778,000).[6] Schreiber did not adjust for the firsttime donors who constituted 20 percent of the donor pool or for laboratory error. When we did so, using the method that Lackritz and colleagues published, we calculated the risk at 1 in 412,000. Our revised estimate is higher than Lackritz's. However, the study population for Schreiber's research is in Baltimore, Detroit, Los Angeles, Oklahoma City, and San Francisco—metropolitan areas that collect only 9 percent of the nation's

[5]No point estimate is reported.

[6]Schreiber's calculation of the window period is 3 days less than that of Lackritz. They are considered equally valid estimates. The choice of one over the other does not significantly change the outcome of the calculations.

blood and that would be expected to pose higher risks than the national average.[7]

To date, no cases of transfusion recipients infected with HIV-2 have been reported in the United States and only 2 HIV-2 positive units have been detected among nearly 60 million screened units. In Europe, however, a sizable number of infected blood donors have been detected on screening, and some cases of transfusion transmission have been documented. Thus, the United States may see cases of transfusion-transmitted HIV-2 in the future.

Transmission-by-Transfusion Studies

Donegan and colleagues (1990) retrospectively tested 200,000 blood component specimens stored in late 1984 and 1985 for HIV antibody and contacted recipients of positive donations to determine their status. Of the 124 recipients with no known risk factors for HIV, 111 (89.5 percent) were positive for HIV. The recipients' gender, age, underlying condition, and type of component did not influence infection rates. The rate of progression to AIDS within the first 38 months after infection was similar to that reported for homosexual men and hemophiliacs. A later study by Donegan and Lenes (1990) suggested that washed red blood cells and red blood cell units stored more than 26 days had lower transmission rates than other components. Rawal and Busch (1989) have demonstrated that filtering leukocytes from blood components reduces HIV infectivity.

Clinical Prognosis

Despite the encouraging findings of recent research on AIDS treatment, it is currently believed that 50 percent of persons testing positive for HIV will develop AIDS within 10 years after contracting the virus and, because AIDS is currently incurable, it is expected that all will succumb to it eventually.

Hepatitis A

HAV is almost always transmitted by the fecal-oral route. Commonly reported risk factors among patients with HAV include household exposure (about 24 percent of all patients), contact with young children in daycare (18 percent), homosexual activity (11 percent), foreign travel in endemic areas (4 percent), and illicit drug use (2 percent), but in about 40 percent of cases no risk factors can be identified. The infection does not lead to

[7]For similar reasons, we did not use Schreiber's estimates for HTLV-I risk (1 in 641,000, confidence interval from 1 in 256,000 to 1 in 2,000,000) or for HCV (1 in 103,000, confidence interval from 1 in 28,000 to 1 in 288,000). But we did use his estimate for HBV despite the lack of adjustment for testing sensitivity and errors, because it was more conservative than the estimate that did.

chronic disease and mortality is 0.2 percent or less. A vaccine was introduced in 1995.

HAV is very rarely found in donated blood because the virus circulates in blood for only 7 to 10 days before an infected person becomes symptomatic. The risk of hepatitis A by blood transfusion is estimated at 1 per 1 million, and only 25 cases of transfusion transmission had been reported in the literature by 1989.[8]

Hepatitis B

Disease Factors

HBV, a DNA virus, has a worldwide distribution. In the United States, an estimated 1 to 1.25 million persons have chronic HBV infection, with 200,000 to 300,000 new infections each year. HBV is diagnosed by elevated levels of certain liver enzymes and by serological antigen and antibody tests, such as those used in blood donor screening. Antigen tests are 99.9-percent sensitive; antibody tests are 99-percent sensitive. Antibody tests remain positive even after infectious viremia has subsided, and positivity is considered a surrogate for persons with lifestyle behaviors that place them at risk for HIV or hepatitis C.

Symptoms include the gradual onset of anorexia, abdominal pain, or jaundice (yellowing of the skin as a result of decreased liver function). Sometimes, patients experience joint pains, a rash, or itching. HBV is acquired when the virus enters the body through breaks in the skin or mucous membranes. The virus has been isolated in many different body fluids but has been shown to be at infectious levels only in blood, semen, and saliva. The virus is spread by sharing contaminated needles, sexual contact, occupational exposure to blood or body fluids, transmission from an infected mother to her newborn during the perinatal period, and blood transfusions. Although 30 percent of all infected persons have no identifiable risk factor, most have other high risk characteristics (that is, history of other sexually transmitted diseases, noninjection drug use, incarceration) or belong to minority populations of low socioeconomic levels.

[8]HAV is a very stable virus capable of withstanding considerable heat in dry conditions. In 1992, hemophiliac patients receiving factor VIII concentrates of plasma were exposed to HAV because the method used for inactivating viruses (solvent-detergent washing) did not affect HAV in the plasma. The outbreak led to swift recall of this product. A heat-inactivation process should eliminate this risk.

Blood-Supply-Risk Studies

Transfusion-associated HBV infection has not been studied to the same extent as transfusion-associated HIV. Few direct measures exist. Most estimates are based on statistical modeling of the window period or on mathematical modeling of the incidence rates and test sensitivities.

The current estimate of the window period for detecting HBV is 59 days, with a range of 37 to 87 days. Blood containing the virus is infective many weeks before the clinical onset of symptoms and remains infective during the acute phase of the disease. Chronic carriers who may exhibit no symptoms are also infectious. Often, the amount of virus is too low to be detected on the antigen test; therefore, positivity on antibody tests (anti-HBC) also helps detect chronic carriers.[9]

Transmission-by-Transfusion Studies

No direct measures of HBV transfusion risk exist. In the ARC system, 100 cases per year are reported among 2 million recipients. Surveillance studies indicate prior transfusion as a factor for 1.1 percent of the 23,000 cases of hepatitis B reported each year, or 250 cases.

M. J. Alter of CDC (1995) estimates the transfusion risk of HBV at about 1 per 200,000 units. Her analysis is based on the theory that a certain proportion of infectious cases of HBV (and other hepatitis viruses as we discuss below) among blood donors are not detected by current tests. In the case of HBV, the relevant figures are as follows: HBV is found in 0.03 percent of blood donors (3 in 10,000). The antigen test is 99.9-percent sensitive and the antibody test is 99-percent sensitive, meaning that as many as 1 percent of infected individuals test false negative. After testing, 1 in 233,000 units (0.00043 percent) are still infectious.[10] The risk from transmission of missed units is 100 percent.[11] Among patients who receive 4 units of blood, 1 in 58,000 are at risk.

[9]Delta hepatitis (HDV) is an incomplete virus that requires the help of HBV to replicate in the human body. Persons coinfected with HBV and HDV may have a more severe acute illness and a higher risk of fulminant hepatitis than others infected only with HBV. No direct measure of the incidence of HDV is available, but CDC's models suggest that HDV accounts for 7,500 infections annually. Its prevalence among HBV infected donors is estimated at between 1.4 and 8 percent. Hepatitis B immunizations prevent HDV infections, too.

[10]After antigen screening, 0.00003 percent of units are infectious; after antibody screening, 0.0004 percent. In sum, 0.00043 percent, of all units are infectious. Note that Alter rounds this last figure to 0.00040 percent in table 2 of her article. We use 0.00043 percent, which changes the estimate slightly.

[11]The risk of transmission among donors who test positive on the antibody test alone is 4 percent, because in most cases a positive antibody test indicates an old, resolved infection.

More recently, Schreiber and colleagues (1996) used data on 2,318,356 allogeneic blood donations from 586,507 donors who had donated more than once between 1991 and 1993 at five blood centers. Among donors whose units passed all screening tests, the risks of giving HBV-contaminated blood during the infectious window period was estimated to be 1 in 63,000 units (confidence interval from 1 in 31,000 to 1 in 147,000).

Clinical Prognosis

M. J. Alter (1995) assumed that half of the 4 million annual transfusion recipients die of their underlying disease.[12] Using these assumptions, Alter predicts 34 HBV infections among the 2 million transfusion recipients who survive long enough to develop HBV.

The development of chronic infection occurs in 5 percent to 10 percent of HBV-infected adults (M. J. Alter, 1995). An estimated 15 percent of persons with chronic HBV acquired after early childhood die of either cirrhosis or liver cancer. There is no treatment for HBV. Factors that facilitate the emergence of the virus are increased sexual activity and intravenous drug abuse.

Interferon treatment of adults with HBV-related chronic hepatitis has been shown to achieve long-term clearance of infection in upward of 40 percent. Routine hepatitis B vaccination of infants and adolescents and vaccination of adolescents and adults in high-risk groups has begun to prevent transmission of HBV.

Hepatitis C

Disease Factors

HCV, a flavi-like virus, has a worldwide distribution and is relatively common among dialysis patients, hemophiliacs, healthcare workers, and intravenous drug users. In 1995, CDC estimated that there are 35,000 to

[12]The 50-percent fatality rate for transfusion is based on a study by Ward et al. (1989) that traced back selected recipients of transfusions and found that 50 percent of a transfusion control group that had not received HIV-infected blood had died within a year and that 63 percent of recipients of HIV-infected blood had died by the time investigators could locate them. However, other researchers have noted that these study participants were not representative of a general surgery population as they were often referred from a subspecialty surgical area and had a poorer prognosis for survival. In a more recent study, Vamvakas and Taswell (1994) enrolled all residents of a U.S. county who underwent transfusion in 1981. While this group cannot be directly generalized to all U.S. surgeries, the enrollment of all transfusion patients without any selection bias better characterizes actual transfusion practices. These researchers found a 30-percent fatality rate within 2 years following surgery.

180,000 (average 120,000) new HCV infections each year in the United States. Diagnosis is by an antibody test that is 90- to 95-percent sensitive. Symptoms include gradual onset of anorexia, nausea, vomiting, and jaundice. Its course is similar to that of HBV but more prolonged.

Most HCV is acquired in the community and much needs to be learned about modes of transmission. CDC reports among documented cases in 1992 that 2 percent were associated with health care occupational exposure to blood, 4 percent with blood transfusion, 12 percent with exposure to a sexual partner or household member who had hepatitis or multiple sexual partners, 29 percent with injection drug abuse, 46 percent with low socioeconomic level, and 6 percent with other high-risk behavior (that is, noninjection illegal drug use, history of sexually transmitted diseases, imprisonment, sexual partners or household contacts who inject drugs, or no identifiable risk factors).

Blood-Supply-Risk Studies

Before an antibody-specific test for HCV was implemented, blood donors were tested for surrogate markers of the disease using tests to detect antibody to HBV (anti-HBc) and elevated alanine aminotransferase, a liver enzyme that, when levels are high, may indicate liver problems such as those associated with HCV. Donahue, Nelson, and other colleagues in Baltimore and Houston evaluated the risk of HCV at four different phases of blood donor screening in 12,146 cardiac surgery patients who had been transfused (Donahue et al., 1992; Nelson et al., 1992, 1995). Prior to surrogate testing, these researchers estimated the risk of transfusion-associated HCV at 1 in every 222 units of blood. When surrogate testing was implemented, the risk decreased to about 1 in every 525 units. The first-generation anti-HCV test further reduced the risk to 1 in 3,333 units. When the second generation HCV test was introduced in 1992, these researchers found 15 cardiac surgery patients infected with HCV among a study population who together had received 22,008 units of blood for a per-unit risk of about 1 in 1,470.

In another study, Kleinman and colleagues (1992) concluded that second generation HCV tests reduced HCV risks to between 1 in 2,000 and 1 in 6,000 component units.

The current estimate of the window period is 82 days with a range of 54 to 192 days. Blood containing the virus is infective from 1 week after exposure into the chronic stage. Screening is inhibited by several factors: current second-generation tests may not detect 10 percent of persons

infected with HCV; acute, chronic, and resolved infections cannot be distinguished on the basis of test results; the window period can be quite prolonged; and in populations with low prevalence (such as blood donors), the rate of false positives is high.

Two factors currently contribute to the risk of HCV in the blood supply. First, donors in the window period do not yet have any antibodies to be detected on screening tests. Schreiber and colleagues estimate that the risk posed by these donors is 1 in every 103,000 units (95-percent confidence interval, 28,000 to 288,000).

A much bigger risk stems from the possibility that the relatively low sensitivity of current antibody tests results in false negative tests in 10 percent of donors actually infected by HCV. Assuming that the prevalence of HCV among donors is 0.244 percent and test sensitivity is 90 percent, M. J. Alter (1995) at CDC estimates that 0.0244 percent of all units (1 in 4,100) are HCV infectious after screening.[13] Using the 50-percent mortality rate for transfusion, M. J. Alter predicts 1,955 infections in the 2 million surviving recipients.

M. J. Alter's estimate is based on observations in community acquired hepatitis, identified as a result of active surveillance. It has not been independently confirmed, it is based on second-generation tests, and it is unclear whether it applies to asymptomatic blood donors. Nevertheless, because it represents the most conservative risk estimate in the current literature, we chose to use it in our overall risk analysis.

Transmission-by-Transfusion Studies

Studies from around the world suggest that between 80 and 90 percent of transfusion recipients who receive antibody positive blood seroconvert to HCV.

Clinical Prognosis

Approximately 25 percent of persons infected with HCV become acutely ill with jaundice and other symptoms of hepatitis, and each year more than 4,000 patients require hospitalization. About 600 die of fulminant disease.[14]

[13]No confidence interval reported.

[14]These figures include all cases of HCV, not transfusion-associated cases alone.

Much still needs to be learned about the long-term effects of HCV infection. Eighty-five percent or more develop persistent HCV infection, and while about 70 percent of infected individuals develop chronic hepatitis, long-term follow-up studies suggest that only 10 to 20 percent develop clinical symptoms of their liver disease over a 20-year period following transfusion. (Farci et al., 1991; Seeff et al., 1992; Koretz et al., 1993; Iwarson et al., 1995). Many persons who are affected suffer no symptoms.

Until recently, no treatment was available for hepatitis C. Recent evidence now suggests that interferon may be helpful in treating chronic hepatitis C. Studies by DiBisceglie and colleagues (1989) and Davis and colleagues (1989) demonstrated marked improvement of liver enzyme activity in about half of all treated patients. In many, the liver itself improved. However, liver enzyme activity was sustained in only 10 to 51 percent of patients, and the effect of long-term therapy had not been determined.

Other Hepatitis Viruses

Disease Factors

Hepatitis E has been identified in developing nations around the world. Like HAV, it is transmitted by the fecal-oral route (and also by contaminated water) and its course of symptoms parallels that of HAV. HEV, however, is associated with a high rate of fulminant hepatic failure among pregnant women, in whom the death rate may be as high as 20 percent.

In 1995, researchers announced the discovery of a new hepatitis virus not previously identified as hepatitis A, B, C, D, or E. Labeled hepatitis G virus (HGV), it is not yet known if this strain is associated with acute and chronic hepatitis. Between 0 and 16 percent of cryptogenic (non-A,B,C,E type) hepatitis patients and between 28 and 50 percent of patients with fulminant hepatitis were HGV-positive. HGV may also lead to aplastic anemia (decreased bone marrow mass); 3 of 10 such patients were HGV positive (Alter, 1996). Persistent infection has been observed for up to 9 years. In 1995, the National Institutes of Health (NIH) reported that 3 of 13 hepatitis patients (23 percent) enrolled in an ongoing study had acquired HGV from their blood transfusion. In the NIH study, HGV was also detected in 12 percent of transfusion recipients who had minor symptoms that were not clinically identified as hepatitis, in 10 percent of those with HCV-related hepatitis, in 8 percent of those with no symptoms, but in only 0.6 percent of the 157 nontransfused patients enrolled as study controls.

Blood-Supply-Risk Studies

The prevalence of HGV in blood donors as measured by HGV RNA detected by PCR is higher than that of HCV. The HGV virus was identified in the blood of 24 of 1,478 (1.6 percent) of the NIH donors, and a small study of 200 Midwestern blood donors found that 4 (2 percent) were reactive for HGV ("New Hepatitis G Virus," 1995; "Abbott Announces Discovery," 1995). Although no antibody tests have been developed to detect HGV, HGV frequently coexists with HBV or HCV; therefore, tests that detect either of the latter viruses help eliminate HGV from the blood supply.

Both HBV and HCV tests help detect non-ABC hepatitis in blood donors. Using the same methods and assumptions as for HCV, M. J. Alter (1995) estimates the risk of transfusion-transmitted non-ABC hepatitis at 1 per 5,925 units.

Transmission-by-Transfusion Studies

Despite the relatively high risk estimates of hepatitis in the blood supply, hepatitis researchers assert that the residual risk of hepatitis from transfusion is very small and no different from the risk of background hepatitis found in nontransfused hospitalized patients. For example, analyses from two large transfusion-related hepatitis studies conducted in the United States in the late 1970s and in Canada in the 1980s suggest that the risk of non-ABC hepatitis from transfusion (3.6 percent of patients) is similar to that of control groups of nontransfused hospital patients (3 percent) (Aach et al., 1991). The Canadian Red Cross found the same rate of non-ABC hepatitis (0.6 percent) between patients receiving volunteer supply blood and patients receiving their own blood.

HTLV-I and HTLV-II

Disease Factors

HTLV-I is endemic in southern Japan, the Caribbean basin, and Africa. Populations in Japan have rates of HTLV-I infection ranging from a low of 1.1 percent in Tokyo to a high of 37.5 percent in males and 44 percent in females from Okinawa. Populations native to the Caribbean basin have HTLV-I seroprevalence rates of 2 percent to 12 percent. HTLV-II, which is detected by the HTLV-I-based laboratory tests currently used to screen the blood supply, is endemic among Indian populations in the Americas, including populations in Florida and New Mexico (Levine et al., 1993; Hjelle et al., 1990) and among intravenous drug users in the United States and Europe. The rate of infection in the United States blood donor

population has been estimated to be between 0.009 and 0.043 per cent (Williams et al., 1988; Lee et al., 1991; Sandler et al, 1990). Dodd reports that the ARC observes a donor seropositivity rate of 0.006 percent to 0.008 percent.

The most common modes of transmission are from mother to child by breast feeding, by transfusion of contaminated cellular blood products, by needle sharing among intravenous drug users, and through sexual activity.

Blood-Supply-Risk Studies

The current estimate of the window period for HTLV-I and HTLV-II is 51 days with a range of 36 to 72 days (Manns et al., 1992). When blood screening for HTLV was introduced in 1988, nearly 2,000 U.S. donors were found to be positive. The HTLV infections among blood donors in the United States are nearly evenly divided between types I and II.[15] Most HTLV-I positive donors were born in or report sexual contact with a person from the Caribbean or Japan, while nearly all HTLV-II positive blood donors report a past history of intravenous drug use or sex with an intravenous drug-using partner. Because the current blood screening tests use HTLV-I antigens to detect both types, the sensitivity of detection of HTLV-II is lower than that for HTLV-I antibodies. Hjelle and colleagues (1993) reported that the screening ELISA test misses 20 percent of HTLV-I infections and 43 percent of HTLV-II infections. Thus, low test sensitivity, especially for HTLV-II, is the primary reason that infected blood remains in the blood supply.

Schreiber and colleagues (1996) estimate that the risk of receiving an HTLV-contaminated unit from a repeat donor in the infectious window period is 1 in 641,000 (confidence interval from 1 in 256,000 to 1 in 2,000,000).

Dodd (1992) has calculated the residual risk of transfusion transmission at 1 in 50,000 units based on current seroprevalence rates among donors and screening test sensitivity.[16]

Transmission-by-Transfusion Studies

Data from the Transfusion Safety Study (Donegan et al., 1994) show that, overall, 27 percent of recipients who received anti-HTLV-positive blood became infected. The rates of infectivity varied by blood product and

[15]More than 80 percent of HTLV-I and HTLV-II seropositivity among intravenous drug users stems from HTLV-II infection. HTLV-II also appears endemic among North American Indians in Florida and New Mexico.

[16]No confidence interval reported.

storage time. Only cellular blood products (red blood cells and platelets) appear to transmit HTLV; no plasma products have been implicated in disease transmission. Moreover, the longer the blood was stored, the less likely it was to transmit HTLV: the transmission rate for products stored 0 to 5 days was 74 percent; 6 to 10 days, 44 percent; 11 to 14 days, 0 percent. The transmission rate in the United States appears to be much lower than in other countries, where rates of 45 to 63 percent have been reported. The most likely explanation for the lower infectivity of U.S. blood is its typically longer storage time.

Clinical Prognosis

Two diseases have been associated with HTLV-I: adult T-cell leukemia and lymphoma (ATL) and a chronic degenerative neurologic disease called HTLV-I-associated myelopathy and tropical spastic paraparesis (HAM/TSP).

ATL is a malignant condition of T lymphocytes, a form of white blood cell produced by the lymph nodes and important for immunity. The clinical features of ATL include leukemia, swelling lymph nodes, enlarged and impaired functioning of the liver, enlarged spleen, skin and bone lesions, and increased calcium in the blood. Conventional chemotherapy is not curative, and the median survival after diagnosis is 11 months.

ATL occurs in 2 to 4 percent of individuals infected with HTLV-I in regions where the disease is endemic and early childhood infection is common. The typical patient is 40 to 60 years old, which suggests that several decades may be required for the disease to develop. Only one case of ATL has been documented as having been acquired by transfusion (CDC, 1993).

HAM/TSP is characterized by slowly progressive chronic spastic paraparesis (slight paralysis of the lower limbs), lower limb weakness, urinary incontinence, impotence, sensory disturbances (tingling, pins and needles, and burning), low back pain, exaggerated reflexes of the lower limbs, and impaired vibration sense. Fewer than 1 percent of persons infected with HTLV-I develop HAM/TSP. The interval between infection and disease is much shorter than that for ATL, and cases of HAM/TSP as a result of blood transfusion have been documented with a median interval of 3.3 years between transfusion and development of the disease.

Despite sporadic case reports, HTLV-II had not been definitively associated with any disease until recently. In November 1996, Lehky and colleagues (1996) reported on the clinical and immunological findings of 4 HTLV-II positive patients with spastic paraparesis, whose disease progression

resembles that of HTLV-I-infected patients with HAM/TSP. HTLV-II was first isolated in 2 patients with hairy cell leukemia, although no virus has been isolated from additional cases of this disease.

Parasites

Disease Factors

Several bloodborne parasites can be present in donated blood. Few direct measures of risk exist; therefore, estimates are based on reported cases. With the exception of one parasite, the risk of transfusion-associated parasite transmission is less than 1 in 1 million.[17]

Chagas' disease is caused by the parasite T. cruzi. Typically, humans become infected following the bite of a reduviid bug, otherwise known as the kissing bug. The bug favors poverty conditions, particularly in rural areas where wood and adobe housing is cracking or decaying. Infected bug feces either contaminate the bite wound or enter by other mucous membranes. Chagas' disease is endemic in large parts of South America, Central America, and Mexico. Estimates are that as many as 100,000 T. cruzi-infected persons are in the United States (Shulman, 1994).

Blood-Supply-Risk Studies

Four cases of transfusion-transmitted Chagas' disease have been reported in the United States and Canada. Risk of blood donors infected with T. cruzi varies in the United States, depending on the number of Hispanic immigrants in a given area. Brashear et al. (1995) reported that 14 of 13,309 (10.5 percent) donors in Texas, New Mexico, and California had evidence of infection. Kirchhoff et al. (1987) reported that as many as 5 percent of the Salvadoran and Nicaraguan immigrants in the Washington, D.C., area

[17]Malaria is caused by the bite of an infected mosquito in endemic areas. An average of 3 cases a year that were acquired by transfusion are reported in the United States. Donor history questions are designed to defer donors who are at risk of malaria as a result of travel. Viscerotropic Leishmaniasis is caused by the bite of an infected sandfly in endemic areas, such as the Persian Gulf. Viscerotropic Leishmaniasis affects the internal organs of the body. Veterans of Desert Storm were deferred from donating blood when 7 cases were discovered among military personnel serving in Desert Storm and Desert Shield. While cases of cutaneous Leishmaniasis have been reported in Texas, this variant of the disease in not thought to be a risk for blood transfusion. No cases of transfusion-transmitted viscerotropic Leishmaniasis have been reported in the United States. Babesiosis is caused by the bite of an infected tick, a problem found mostly in endemic areas of the northeastern United States. To date, CDC reports 15 cases of transfusion-transmitted babesiosis in the United States. Toxoplasmosis is caused by infection with a parasite whose usual host is the domestic cat. The parasite is transmitted through handling of infected cats or cat litter. Other means of transmission include eating raw or undercooked pork, goat, lamb, beef, or wild game. Recent preliminary data from CDC indicate that about 20 to 25 percent of the U.S. population has been infected. Most cases pass unnoticed. Cases have been reported as transmitted by transfusion only to immunocompromised patients.

may be infected. In some U.S. areas, about 1 in 600 eligible blood donors who have Hispanic surnames and 1 in 300 eligible blood donors who are Hispanic immigrants or refugees might be infected (Kerndt et al., 1991; Pan et al., 1992).

Most blood banks now ask donors whether they have a history of Chagas' disease and questions about risk factors that are linked to possible infection with T. cruzi. ARC has conducted seroepidemiological studies of blood donors in Los Angeles and Miami, where 8 percent and 12 percent of prospective donors reported having been born in or having traveled for more than 4 weeks to areas in which Chagas' disease is endemic.[18] Additional screening questions ARC asked these donors included a history of sleeping in rural areas where the bugs are prevalent, a history of transfusion in an endemic area, and a history of a positive test for Chagas' disease. Of those at risk, 0.1 percent tested positive for the antibody to T. cruzi. Dodd estimates that 1 in about 8,500 units in Miami and Los Angeles may contain T. cruzi.

Furthermore, about 2.4 percent of donors nationally report risk factors, or about one fourth the risk in Miami and Los Angeles, where large numbers of Hispanic immigrants reside. If the same rate of seroprevalence (0.1 percent) exists among all U.S. donors who report behavioral risk, then Dodd estimates that the national risk for T. cruzi-contaminated blood is 1 in about 42,000.

Transmission-by-Transfusion Studies

Schmunis (1991) reports that the risk of transmitting T. cruzi through infected blood ranges from 14 to 49 percent in South America. ARC has found no evidence of transmission among 15 recipients of infected blood, suggesting that transmission rates in the United States are no higher than 10 percent.[19]

Clinical Prognosis

Following the bug bite, a characteristic lesion may form but usually passes unnoticed. If the bug feces falls onto mucous membranes directly, the classic Romana sign (conjunctivitis and swelling of the eye area) develops. During the acute phase, the parasite can be seen in the blood for a few weeks. Acute infection with T. cruzi can be asymptomatic, or it can be fatal. More typically, after a 10-to-14-day incubation period, fever, swollen lymph nodes, and enlarged spleen and liver develop.

[18]Interview with Roger Y. Dodd, American Red Cross, Jerome H. Holland Laboratory.

[19]Interview with Roger Y. Dodd, American Red Cross, Jerome H. Holland Laboratory.

Between 20 and 30 percent of infected individuals develop chronic Chagas' disease, often years to decades following infection. Rapid and erratic heart beats signify cardiac involvement. The parasite has an affinity for cardiac cells and for the smooth muscle of the esophagus and colon. As the disease progresses, the heart, esophagus, and colon (and occasionally, the stomach, gall bladder, and bladder) enlarge (Shulman, 1994).

Treatment of acute infections with the drugs nifurtimox and benznidazole is successful in at least 70 percent of cases. In July 1996, Venezuelan scientists announced success in eradicating Chagas' disease in 70 percent to 90 percent of infected laboratory mice using the antifungal drug DO870 (Urbina et al., 1996).

Bacteria

Disease Factors

Bacteria can enter donated blood at one of several points (Yomtovian, 1995). Bacteria can be introduced during the manufacture of the bag used to collect blood. During collection, bacteria from the skin can contaminate blood, especially if the donor's arm is not disinfected properly. Donors who are suffering from a bacterial disease—even common food-induced digestive infections—can unknowingly donate a contaminated blood unit. In a review of the research on transfusion-associated bacterial sepsis, Wagner and colleagues (1994) point to several reports of bacteria already present in the collection bag proliferating during processing or storage of the blood. Finally, bacteria can be introduced while preparing for transfusion, particularly if the entry port of a thawing container for a frozen blood component comes in contact with contaminated water in the warming bath. Although fresh plasma and cryoprecipitate can harbor bacteria, contamination of red blood cells and platelets is the most significant problem. Bacterial contamination is one complication that cannot be eliminated by donating blood for self use.

Red blood cells are refrigerated, which reduces the viability of most bacteria, such as the one that causes syphilis. However, certain cold-loving bacteria, such as Yersinia enterocolitica and Pseudomonas florescens, thrive under refrigerated conditions. Yersinia is present in the digestive tract or lymph nodes of humans and can cause diarrhea and other gastric symptoms that may be mild enough to be overlooked by blood donors.

Pseudomonas florescens is one of several common skin bacteria that can enter blood during collection.

Platelets run a greater risk of bacterial contamination because they are stored for up to 5 days at room temperature. Skin contaminants, such as staphylococcus epidermidis, are the most frequently isolated bacteria from platelets. In the United States, platelets can be administered as either apheresis single-donor units or pooled random donor units collected from 6 to 10 donors. Bacterial sepsis can occur if any of the pooled units are contaminated. Indeed, Morrow and colleagues (1991) found that the rate of sepsis was 12 times higher for pooled units than for single-donor units. Today, single-donor units are increasingly replacing pooled units.

Blood-Supply-Risk Studies

Wagner and colleagues (1994) report that the frequency of bacterial contamination is measured three ways—through laboratory culture, hospital surveillance programs, and fatalities. Laboratory culture techniques measure bacteria directly but are subject to lapses in sterile techniques that can introduce bacteria into samples. In addition, many quality control studies reporting bacterial contamination have found that the number of bacteria in the sample was far below the level that would be expected to cause problems to the recipient. Nevertheless, culture methods of bacterial detection suggest that blood component units—particularly platelets—run a significant risk of contamination.

Most episodes of bacterial sepsis are associated with platelets late in the storage period. Yomtovian (1995) conducted a 4-year hospital-based surveillance program in which platelets were cultured for bacteria. The reported contamination rate of platelets 4 days old or less was 1.8 per 10,000 units, whereas the contamination rate for 5-day-old platelets was significantly higher, at 11.9 per 10,000 ($p < .05$). Morrow et al. (1991), also found that the contamination rate was five times higher in 5-day-old platelets than in 1-4-day-old platelets (Morrow et al., 1991). Earlier findings such as this led FDA in 1985 to reverse its 1983 decision to extend the shelf life of platelets from 5 to 7 days.

In 11 percent of all reported patient fatalities (10 of 89 deaths) between 1986 and 1988, bacteria in the patient's blood matched that of the donated units. During this period, about 60 million units of blood components were transfused. Thus, about 1 death per 6 million transfused units was definitively caused by bacterial sepsis. However, researchers acknowledge that bacteria-induced transfusion fatalities are only rarely diagnosed and

reported, because physicians fail to attribute patients' deaths to the possibility of bacteria in blood transfusions.

Similarly, nonfatal outcomes of sepsis are believed to be greatly underdiagnosed and, therefore, underreported. Common, nonthreatening reactions of a patient's immune system to transfusion include fever and chills that may mask underlying bacteremia. Morrow and colleagues of Johns Hopkins Medical Institutes (1991) reported platelet transfusion-associated sepsis in 1 out of every 4,200 platelet transfusions. Bacterial contamination associated with fever following transfusion occurred once in about 1,700 pooled platelet units or once in 19,519 single-donor platelets. This is undoubtedly an underestimate because only patients exhibiting clinical symptoms were evaluated.

More recently in Hong Kong, Chiu and colleagues (1994) conducted a 3-year prospective study of bone marrow transplant recipients for clinical evidence of platelet transfusion reactions. These researchers found 10 episodes of symptomatic bacteremia with 4 leading to septic shock. A total of 21,503 random-donor platelet units were pooled into 3,584 doses administered to 161 patients. Each patient received an average of 20 pools. The frequency of bacteremia was calculated three ways: 1 in every 2,100 platelet units, 1 in every 350 transfusions, and 1 in every 16 patients.[20] Again, this is probably an underestimate, because Chiu and colleagues looked only for symptomatic bacteremia.

In sum, there is no reliable estimate of the frequency of bacterial sepsis among transfusion recipients across the United States. Culture methods probably yield overestimates while reporting mechanisms probably yield underestimates of clinically relevant bacterial contamination. CDC is initiating a prospective incidence study in collaboration with AABB, ARC, and the Navy in an attempt to quantify this risk. For the purpose of our analysis, we include the Morrow estimate of documented bacterial sepsis (not all febrile reactions) because the researchers prospectively monitored patients and obtained bacterial cultures from implicated units in the United States.

Although it is now well documented that refrigerated red blood cells can harbor bacteria, we could find no studies that directly estimated the likelihood that red blood cells are contaminated by bacteria. Dodd

[20]No confidence intervals were reported.

(1994) estimates that 1 in every 500,000 red blood cell units may be contaminated by Yersinia or other bacteria.[21]

Transmission-by-Transfusion Studies

Many surgical patients who are otherwise healthy can sustain a small amount of bacteria introduced by transfusion. However, immunocompromised patients, such as those with leukemia, are very susceptible to foreign organisms. Unfortunately, these patients are the primary users of platelets.

Clinical Prognosis

In transfusion-associated bacterial sepsis, the onset of symptoms usually occurs within the first few hours following transfusion but may occur during the transfusion or following an extended delay (Greene, 1995). The initial signs are typically fever and chills and may include nausea, vomiting, diarrhea, chest or back pain, low blood pressure, rapid heartbeat and breathing, and cyanosis from lack of blood oxygen. Patients with advancing bacterial sepsis rapidly progress to acute renal failure, respiratory distress, disseminated intravascular coagulation (uncontrolled internal bleeding), and death. Death may occur from 50 minutes to 17 days following transfusion (Morduchowicz et al., 1991; Tipple et al., 1990). Goldman and Blajchman (1991) reported that 26 percent of identified transfusion-associated sepsis cases ended in death.

Noninfectious Complications of Transfusion

Transfusions can result in serious or fatal complications as a result of serological or clerical errors in blood typing, mismanagement of the transfusion, or unanticipated reactions in the recipient to elements of the donor's blood. Many of the unanticipated reactions are unavoidable within current understanding and practice of transfusion medicine. Few comprehensive assessments of the incidence of such outcomes can be found in the literature. Thus, estimates of the frequency of noninfectious transfusion risks are based on studies by a small number of transfusion services, summation of the number of such occurrences reported in the literature, or from regulatory reports of errors, accidents, and deaths (Dodd, 1994).

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) has only recently been recognized as a potential complication of blood transfusion. No known risk factors have been identified among recipients who develop TRALI.

[21]No confidence interval was reported.

Cases have been evenly distributed between males and females and among recipients of all ages. No underlying conditions necessitating transfusion have been identified, and most patients have no prior history of transfusion reactions.

Implicated blood components include whole blood, red blood cells, fresh frozen plasma, and cryoprecipitate. It is the plasma portion of the blood that causes TRALI, and even red blood cells contain small residual amounts of plasma.

In TRALI, specific white blood cell antibodies present in the donor's blood react with the entire circulation of the recipient's white blood cells. The result is the release of various components that cause severe damage to lung tissue, which in turn leads to acute respiratory crisis. Most cases of TRALI have been traced back to blood donated by women who have been pregnant more than once, because pregnancy causes the mother's blood to develop specific antibodies to elements of the fetus's blood that her body considers foreign (Popovsky and Moore, 1985).

Walker (1987) estimated the risk of TRALI to be 1 in 10,000 units.[22] However, Popovsky argues that TRALI is rarely diagnosed and reported. Therefore, Walker's figure is probably an underestimate. Popovsky et al. (1992) report that, prior to 1985, only 31 cases of TRALI had been reported. By 1992, additional reports involving over 40 recipient reactions had been published. At the time of their publication, Popovsky and colleagues were aware of an additional 35 unreported cases.

TRALI presents with acute respiratory distress within about 2-4 hours following transfusion (Boyle and Moore, 1995). Fever, low blood pressure, chills, cyanosis from lack of blood oxygen, nonproductive cough, and shortness of breath or difficulty breathing are common symptoms. In most instances, TRALI improves within 48 to 96 hours, provided that prompt diagnosis and respiratory support is initiated. For those who recover, there appear to be no long-term consequences. Death may be the outcome in approximately 5 percent of cases.

ABO Incompatibility

ABO incompatibility is the result of improper serological typing or clerical recording of the major blood groups in donor or recipient blood, mislabeling of donor units, or improper verification of donor or recipient blood type.

[22]No confidence interval was reported.

A study of errors reported to New York State in 1990-91 found 104 cases of erroneous transfusions out of 1,784,641 (0.006 percent) red cell transfusions, over half of these (54, or 0.003 percent) related to ABO incompatibility (Linden, Paul, and Dressler, 1992). This is important because transfusion of ABO-incompatible blood is one of the major causes of serious noninfectious risks for transfusion recipients. Most of the 50 other errors were related to the transfusion of a wrong unit of blood that was fortuitously ABO-compatible with the recipient's blood type and transfusion of ABO-incompatible fresh-frozen plasma.

It was also found that 61 incidents (59 percent of the 104 cases) were the result solely of errors outside the blood establishment. The majority of these stemmed from the failure of the person administering the transfusion to verify the identity of the recipient or the blood unit. However, there were 25 incidents (25 percent) in which the errors were attributable to the blood establishment and 18 cases (17 percent) in which both the blood bank and hospital service made errors in administering incorrect blood or in giving blood to someone other than the intended recipient.

From this information, the study's authors calculated an incidence rate of ABO-incompatible errors of 1 in every 33,000 transfusions (0.003 percent). The study concluded that three persons died from acute transfusion reactions, for a death rate of 1 per 600,000 red cell transfusions. The overall true rate of ABO errors, accounting for instances in which errors were made but the blood was fortuitously compatible, was calculated at 1 in 12,000 units.

Transfusing ABO-incompatible blood usually—but not always—leads to a hemolytic transfusion reaction (HTR), the result of the immune system's destruction of red blood cells. It presents with fevers, chills, low blood pressure, destruction of red blood cells, kidney failure, blood in the urine, uncontrolled internal bleeding, shock, and death. Occasionally, initial symptoms are deceptively mild with the patient experiencing a vague sense of unease or an aching back. There are no known long-term effects. In the Linden study, death occurred in 6 percent of cases.

Anaphylaxis

Anaphylaxis is a serious allergic reaction that can occur in recipients who are deficient in IgA, a type of antibody normally present in humans. Approximately 1 in 700 individuals are IgA-deficient, but anaphylaxis occurs only in those who have developed antibodies to IgA as a result of

pregnancy or prior blood transfusion and then receive a blood transfusion that contains IgA. Therefore, cases of transfusion-induced anaphylaxis are generally unanticipated and unavoidable. Walker (1987) estimates that 1 in 150,000 blood units transfused results in anaphylaxis in the recipient.[23]

Anaphylaxis occurs immediately after transfusion begins, sometimes after the infusion of only a few milliliters of blood or plasma. The onset is characterized by coughing, bronchospasm, respiratory distress, vascular instability, nausea, abdominal pain, vomiting, diarrhea, shock, and loss of consciousness. We found no estimates of the likelihood of death as a result of anaphylaxis. Because of its seriousness and the possibility that it can be overlooked or not diagnosed rapidly, we used a fatality rate of 20 percent in our analysis. Patients with a history of anaphylaxis should receive plasma from an IgA-deficient donor.

Circulatory Overload

Rapid increases in blood volume are not tolerated well by patients with poor cardiac or pulmonary functioning. Even the transfusion of small amounts of blood can cause circulatory overload in infants. Patients with chronic anemia or active hemorrhaging are also susceptible. Walker estimates that 1 in 10,000 transfused units leads to circulatory overload.[24]

Circulatory overload presents with rapid breathing, severe headache, swelling of hands and feet, and other signs of congestive heart failure. Other symptoms include coughing, cyanosis from lack of blood oxygen, discomfort in breathing, and a rapid increase in systolic blood pressure. No long-term effects have been noted when transfusion is stopped promptly at the first signs of circulatory overload. We found no estimates of the likelihood of death. Because the symptoms typically develop over the course of the transfusion, we assume that most instances are diagnosed before permanent damage ensues. We used a fatality estimate of 5 percent in our analysis.

[23]No confidence interval was reported.

[24]No confidence interval was reported.

Our Methods and Analysis

Here we discuss the methods we used in conducting our analysis on transfusion risks. We also include supporting information for the risk estimates on which our analysis is based, as well as other information that is important for understanding transfusion risks.

The Evaluation of Transfusion-Risk Studies

In recent years, many estimates of transfusion risks have been published in the scientific literature. As more becomes known about how viruses are transmitted through blood transfusion, the methods used to evaluate these risks continue to evolve. In this report, we sought to provide insight into the changing nature of the field and how methodological developments have affected estimates of transfusion risk.

We considered the following factors as we evaluated the scientific research:

- who the study participants were (donors or recipients),
- what was measured (which generation test was used),
- when the study was conducted (before or after the widespread use of screening tests),
- where the study was conducted (in a geographic area with high disease incidence or among geographic areas representative of the United States), and
- how risk was estimated (using direct measurement of disease status or statistical modeling).

The studies in our analysis differ by whether they were based on positive viral tests among blood donors or recipients and whether they involved the direct measurement of disease or statistical modeling. Ideally, direct measurement of disease among recipients both before and after transfusion yields the most valid estimate of transfusion risks. However, such studies are difficult and costly to conduct, particularly for diseases with low incidence rates. Most of the recent studies used statistical modeling of the window period and blood donor seroconversion rates.

By window period, we mean the period of time between viral infection and when blood tests can detect either the presence of the virus itself or the body's antibody response to the virus. By seroconverting donors, we mean donors who change from test-negative at one donation to test-positive at the next. The risk estimate on HCV that we used is based on the sensitivity of the viral test itself and the possibility that some positive donors are missed.

Appendix I provides detailed findings from many published scientific articles. We could select only one study for each part of our analysis. We used one overarching principle when choosing between studies that we considered equally sound and that were a matter of continuing debate in the research community: we chose to include the studies with the higher risk estimates. In other words, ours is a worst-case analysis. Table II.1 provides the research citations for the risk estimates we used, including information about the methods used in each study and their relative strengths.

Table II.1: Scientific Studies Used as Source of Our Risk Estimates

Complication	Source	Study type[a]	Strength[b]	Risk per unit	Risk of seroconversion	Risk of chronic disease or death
HAV	Dodd (1994)	C	6	1:1,000,000		
	GAO estimate				90%[c]	
	Institute of Medicine (1995)	C				0.2%
HBV	Schreiber et al. (1996)	M	1,2,3,5	1:63,000		
	M. Alter (1995)	C			70	10
HCV	M. Alter (1995)	M	1,2,4,5	1:4,100		
	Aach et al. (1991)	R	2		90	
	Koretz et al. (1993)	P	1,3,4			20
HIV-1 and -2	Lackritz et al. (1995)	M	1,2,3,4	1:450,000		
	Donegan et al. (1990)	R	4		90	
	Merck Manual (16th ed.)	C[d]				100
HTLV-I and -II	Dodd (1992)	C		1:50,000		
	Donegan et al. (1994)	R	1,2,3		27	
HTLV I	CDC (1993)	C				4
HTLV II	CDC (1993)	C				<1
Non-ABC hepatitis	M. Alter (1995)	M	1,2,4,6	1:5,900	90	15
Yersinia	Dodd (1994)	C	6	1:500,000	Not relevant	
	Goldman and Blajchman (1991)	R	6			26
Platelet contamination	Morrow et al. (1991)	P	3,4	Random = 1:10,200; apheresis = 1:19,500	Not relevant	
	Goldman and Blajchman (1991)	R	6			26
T. cruzi	Dodd (GAO interview)	P	1	1:42,000		
	Dodd (GAO interview)	R	1		10	

(continued)

Complication	Source	Study type[a]	Strength[b]	Risk per unit	Risk of seroconversion	Risk of chronic disease or death
	Shulman (1994)	C				30
ABO incompatibility	Linden et al. (1992)	R	1,4,5	1:12,000	Not relevant	6[e]
Acute lung injury	Walker (1987)	C		1:10,000	Not relevant	
	Boyle and Moore (1995)	C				5
Anaphylaxis	Walker (1987)	C		1:150,000	Not relevant	
	GAO estimate					20[f]
Circulatory overload	Walker (1987)	C		1:10,000	Not relevant	
	GAO estimate					5[f]

[a]C = compendium source; M = statistical model; P = prospective direct measure; R = retrospective direct measure.

[b]1 = current time period; 2 = state of art tests; 3 = representative sample; 4 = valid measures, including test sensitivity and test errors where possible; 5 = most conservative estimate; 6 = only estimate available.

[c]Extrapolated from HCV seroconversion data.

[d]Where data were derived from compendium sources, we did not evaluate strengths.

[e]Calculated from data presented.

[f]Estimate based on clinical presentation of symptoms and prognosis as discussed in R. Berkow (ed.), The Merck Manual of Diagnosis and Therapy (Whitehouse Station, N.J.: Merck and Co., 1996).

The United States Blood Supply

Our analysis differs on several dimensions from the analyses in the literature. Other studies have considered only volunteer donations screened in the United States to calculate the number of implicated units available for transfusion. We sought to simulate the total allogeneic blood supply and delivery system as accurately and completely as possible from the most recent and complete data we could obtain. Thus, we calculated the number of units donated by U.S. volunteers and directed donors, subtracted the number of units rejected on testing, and then added autologous units that were crossed-over into the general supply and units imported from Europe. We also calculated the total number of allogeneic blood products that were available for transfusion and the total number of allogeneic blood products that were transfused (Wallace et al., 1995). (See table II.2).

Table II.2: Estimate of Total Allogeneic Blood Supply and Transfusions

Item	Total units	Percent
Volunteer donations	12,035,000	87.3%
Autologous donations	1,117,000	8.1
Directed donations	436,000	3.2
European imports	206,000	1.5
Total blood collected	13,794,000	100.0
Rejected on testing	625,000	4.5
Total U.S. blood supply	**13,169,000**	
Volunteer supply (total U.S. minus directed and autologous donations)	11,616,000	
Directed donations	436,000	
Autologous donations crossed over	5,000	
Total allogeneic blood supply	**12,057,000**	
Whole blood and red blood cell allogeneic transfusions	10,741,000	
Untransfused allogeneic whole blood and red blood cells	1,316,000	10.9
Other allogeneic transfusions		
Random donor platelets (average 6 donors per unit)	4,688,000	56
Apheresis platelets (1 donor per unit)	607,000[a]	44
Plasma	2,255,000	
Cryoprecipitate	939,000	
Untransfused allogeneic nonred blood cell components	2,644,000	
Total allogeneic blood products		
Available	**23,190,000**	
Transfused	**19,230,000**	
Available allogeneic supply not transfused	3,960,000	17.0

[a]A total of 8,330,000 individual units of platelets were transfused. One therapeutic unit of apheresis platelets is equivalent to 6 individual platelet units. Therefore, 3,642,000 individual units (or 44 percent of the total platelets transfused) were transfused as 607,000 therapeutic units of apheresis platelets.

Source: E. L. Wallace et al., "Collection and Transfusion of Blood and Blood Components in the United States, 1992," Transfusion, 35:10 (1995), 802-11.

By dividing the number of available products by the number of donations, we determined that, on the average, allogeneic blood products are divided into 1.9 transfused components.[1] We used the number of components available wherever possible to determine the available number of implicated units. We used the number of units donated to calculate bacterially contaminated red blood cells with the assumption that all units donated were made into red blood cells. For complications that are directly related to transfusion (for example, ABO blood group incompatibility and circulatory overload), we used the number of units transfused.

We could not estimate the total number of platelets available, so we used the number of platelets transfused to calculate bacterially contaminated platelet units. Because unit and patient risks differ for random donor and apheresis platelets, we considered these separately, noting that 56 percent of transfused platelets are random donor platelets using an average of 6 donors per therapeutic unit and the remainder are apheresis platelets consisting of 1 donor per therapeutic unit. Our analysis is based on transfusions of a therapeutic unit of platelets that totaled 5,295,000 in 1992 (4,688,000 pooled concentrates from random donors and 607,000 apheresis units).

Table II.3 illustrates how we conducted the remainder of our analysis. For example, patient risk depends on the risk per unit and the number of units transfused. If, as in HAV, the risk per unit is 1 in 1,000,000, then a patient who has received an average transfusion of 5 units would have a risk of 1 in 200,000 (1,000,000 divided by 5). That is, if 1 of every 1,000,000 units is contaminated, then 1 of every 200,000 patients who receive 5 units could receive an HAV-contaminated unit. We must emphasize, however, that we used the "average" transfusion of 5 units. Many trauma and surgery patients require massive transfusions of 100 or more units of blood. Patient risk—and, therefore, each subsequent step of the analysis—is entirely dependent on the number of units transfused. For example, among patients who receive 100 units of blood, 1 of every 10,000 patients could receive a HAV-contaminated unit (1,000,000 divided by 100).

[1]Our estimate of 1.9 components per donated allogeneic unit is somewhat higher than the 1.8 commonly cited in the literature. This is because we did not include autologous units, which are usually transfused as whole blood or red blood cells, the platelets and plasma being discarded.

Table II.3: Calculations for Individual and Overall Risks of Adverse Outcomes From Allogeneic Blood Transfusion

Agent or activity	1. Risk estimate per unit (12.057 million units donated)	2. Patient risk per transfusion of 5 units
Virus		
HAV HBV HCV HIV HTLV-1 and -2 Non-ABC	1:1,000,000 1:63,000 1:4,100 1:450,000 1:50,000 1:5,900	Risk from col. 1 divided by average transfusion of 5 units. For example, for HAV, (1,000,000/5) = 200,000, or 1 in 200,000 patients. Total sum of risks to patients for viruses is (1/200,000 + ... 1/1,180) = 0.0023, or 1 in 435
Bacterium		
Yersinia	1:500,000	For Yersinia, risk from column 1 divided by average transfusion of 5 units = 1:100,000.
Platelet contamination	Random donor 1:10,200 Apheresis 1:19,500	For random donor platelets, risk from column 1 divided by average donors in a pooled unit (6) = 1:1,700 For apheresis platelets, which have one donor per unit, risk from column 1 = 1:19,500
Parasite		
T. cruzi	1:42,000	Risks from col. 1 divided by average transfusion of 5 units. Total risk to patient for parasite = 0.00012, or 1 in 8,400
Subtotal infection risk	Sum of virus risks and yersinia (1/1,000,000+...1/500,000) plus weighted sum of platelet risk [(1/10,200 x 0.56) + (1/19,500 x 0.44)] = 0.0005 or 5:10,000	Same method as column 1 using patient risks = 2.7:1,000

3. Annual number of implicated units if 23.19 million components available and 19.23 million transfusions	4. Number of recipients affected (likelihood of seroconversion)		5. Number of recipients who do not die of underlying disease or trauma first (30% die within 2 years)	6. Number of recipients who develop chronic disease or die as a result of transfusion (likelihood)	
	Number	%		Number	%
Total components available divided by no. of units in sample expected to contain one implicated unit from col. 1. For example, no. of HAV units is 23.19 million/1,000,000 = 23. Total virally contaminated units = 10,494	No. of implicated units from col. 3 multiplied by seroconversion rate in col. 4. For example, for HAV, 23 x 0.90 = 21 recipients	90% 70 90 90 27 90	No. of seroconverted recipients from col. 4 multiplied by likelihood of survival. For example, for HAV, 21 x 0.70 = 15 seroconverted recipients who survive beyond 2 years	No. of surviving patients from col. 5 multiplied by the likelihood of chronic disease or death in col. 6. For example, for HAV, 15 x 0.002 = 0 recipients who develop chronic disease or die	0.2% 10 20 100 4.75 15
Same as above, based on total red blood cell units = 12.057 million/500,000 = 24 bacteria-contaminated red blood cells	Seroconversion not applicable to bacteria. Totals carried over from col. 3		Not relevant for bacterially contaminated units that harm in the near term. Totals carried over from col. 4	Same as for viruses	26
Same as above, based on platelet transfusions = 4,688,000 as random donor units and 607,000 as apheresis units = (4,688,000/10,200 + (607,000/19,500 = 491 bacteria-contaminated platelets	Seroconversion not applicable to bacteria. Totals carried over from col. 3		Not relevant for bacterially contaminated units that harm in the near term. Totals carried over from col. 4	Same as for viruses	26
Same as above, based on number of available components = 23.19 million/42,000 = 552 parasite-contaminated units	Same as for viruses (55)	10	Same as for viruses	Same as for viruses	30
11,561	9,649		6,911	1,286	

(continued)

Agent or activity	1. Risk estimate per unit (12.057 million units donated)	2. Patient risk per transfusion of 5 units
Transfusion		
ABO Incompatible	1:12,000	Risks from col. 1 divided by average transfusion of 5 units. Total sum of patient risks of transfusion complication = (1/2,400 + ... 1/2,000) = 0.0015, or 1 in 666
Acute lung injury Anaphylaxis Circulatory overload	1:10,000 1:150,000 1:10,000	
Subtotal transfusion reaction risk	3:10,000	1.5:1,000
Total		
Risk	Sum of all risks: 1/450,000 + ... 1/10,000 = 0.0008, or 8:10,000, or 1:1,250	Sum of all risks: 0.0042, or 4.2:1,000, or 1:238

3. Annual number of implicated units if 23.19 million components available and 19.23 million transfusions	4. Number of recipients affected (likelihood of seroconversion)		5. Number of recipients who do not die of underlying disease or trauma first (30% die within 2 years)	6. Number of recipients who develop chronic disease or die as a result of transfusion (likelihood)	
	Number	%		Number	%
Same as above, based on total red blood cell and whole blood transfusions = 10.741 million/12,000 = 895 incompatible units	Seroconversion not applicable to transfusion-related complications. Totals carried over from col. 3		Not relevant for transfusion-related complications that harm in the near term. Totals carried over from col. 4	Same as for viruses	6
Same as above, based on total transfusions of all components. For example, for acute lung injury, 19.23 million units/10,000 = 1,923	Seroconversion not applicable to transfusion-related complications. Totals carried over from col. 3		Not relevant for transfusion-related complications that harm in the near term. Totals carried over from col. 4	Same as for viruses	5 20 5
4,869	4,296		4,296	237	
16,430	**13,945**		**11,207**	**1,523**	
	% of recipients who seroconvert = 13,945/4,000,000 = 0.0035 = 1:287		% of recipients who seroconverted and survived more than 2 years = 11,207/4,000,000 = 0.0028 or 2.8:1,000, or 1:357	% of recipients who develop chronic disease or die = 1,523/4,000,000 = 0.0004, or 4:10,000, or 1:2,500	

It is important to note that although we present a composite risk estimate for a unit and a patient, these risks actually vary depending on the type of component transfused. This is most apparent for apheresis platelet recipients who are exposed to only one donor per therapeutic unit rather than the average of 5 donors for red blood cell or fresh frozen plasma recipients and 6 donors for random donor platelet recipients.

Table II.4 presents our calculations for specific blood components, contrasting them with the overall per-unit and per-patient risk estimates we present elsewhere in the report. Note that only the per-patient risk for apheresis platelet recipients is substantially different from the combined risk estimates. Indeed, on a per-patient basis, the risk for apheresis platelet recipients is an order of magnitude lower than the risks for the other patients.

Table II.4: Estimated Risks for Specific Blood Components

Blood component	Risk per unit	Risk per patient
Red blood cells[a]	7.7:10,000	3.8:1,000
Fresh frozen plasma[b]	7.5:10,000	3.7:1,000
Random donor platelets[c]	7.8:10,000	4.7:1,000
Apheresis platelets[c]	7.3:10,000	7.3:10,000
Red blood cells and platelets combined[d]	8.0:10,000	4.2:1,000

[a]Includes risks for all viruses, Yersinia, T. cruzi, and all transfusion related risks.

[b]Includes risks for all viruses except HTLV-I and -II, T. cruzi, ABO incompatibility, acute lung injury, anaphylaxis, and circulatory overload.

[c]Includes risks for all viruses, platelet contamination, T. cruzi, acute lung injury, anaphylaxis, and circulatory overload. Per-patient risk for random donor platelets based on 6 individual donor units. Per-patient risk for apheresis platelets based on 1 individual donor unit.

[d]Includes risks for all viruses, Yersinia, platelet contamination, T. cruzi, ABO incompatibility, acute lung injury, anaphylaxis, and circulatory overload.

Risk Estimates and Their Confidence Intervals

As we discussed earlier, estimates that are commonly quoted in the media are point estimates. The nature of our analysis required that we use precise risk estimates, but confidence intervals give a better sense of possible risk. Precise numbers such as the ones we use in our analysis are known as point estimates. Their precision is necessary for calculating purposes but should not be construed as definitive. Scientists know that statistical measurement is not perfectly precise. Thus, they calculate a range, or confidence interval, of estimates that is wide enough that they are confident in believing that the real number is somewhere between the

two endpoints of the range. Appendix I includes the confidence intervals for the different estimates of risk where we could find them in the scientific literature.

Point estimates are artificially precise in the sense that they do not take into account factors that introduce error. Factors that can affect the measurement of transfusion risks include the sensitivity and specificity of the tests used to detect viruses and the window period of undetectability. Table II.5 provides the sensitivity (likelihood of detecting truly infected persons) and specificity (likelihood of testing positive only if persons have the disease in question) and estimates of the window period of undetectability for a sample of tests used to detect viruses in donors' blood.

Table II.5: Test Sensitivity and Specificity Rates and Window Period Estimates

Test characteristics	HTLV-I	HIV-1 and -2	HBsAG	HCV	HBcore
Sensitivity	98.17-99.87%[a]	99.15-100%	99%	65-91%[b]	100%
Specificity	99.58-99.85%	99.83-99.94%	99.9%[c]	99.84%	99.73%[c]
Days in window period (range)	51 (36-72)	22 (6-38)	59 (37-87)	82 (54-192)	Not relevant

[a]The HTLV-I test is considered to have lower sensitivity for HTLV-II infections.

[b]Sensitivity data based on reactivity in patients with acute (65 percent) and chronic (91 percent) nontransfusion associated non-A, non-B, hepatitis. The only available data for transfusion-associated non-A, non-B, hepatitis suggest that second-generation HCV tests detect seroconversion to anti-HCV earlier than do first-generation HCV tests in 73.3 percent of patients.

[c]Calculated from manufacturer's test kit insert. (Total donations screened - no. repeat reactive/total donations screen - no. confirmed) x 100 = specificity.

Source: HTLV-I data from Summary Basis of Approval for Abbott HTLV-I 2.0 EIA (92-0318). HIV-1 and -2 data from package insert for Abbott HIVAB HIV1/HIV2 (rDNA) EIA (83-9848/R8). HBsAg sensitivity data from FDA summary basis of approval for Ortho Antibody to HBsAg ELISA Test System (85-372). HBsAg specificity data from package insert for ORTHO Antibody to HBsAg ELISA test system 2 (631-20-086-6). HCV data from package insert for ORTHO HCV 2.0 ELISA Test System (631-20-226-7). Specificity data based on reactivity in patients with nontransfusion-associated non-A, non-B, hepatitis. Sensitivity was 65 percent in acute cases and 91 percent in chronic cases. HBcore sensitivity data from Hepatitis B Virus Core Antigen (Recombinant) ORTHO ELISA Test System (631-20-132-3). HBcore specificity data from FDA summary basis of approval for the same test (90-0731 and 91-0109).

Plasma Products

In this appendix, we describe some of the ways in which the manufacturing of plasma differs from that of blood. We give particular attention to differences that stem from volunteer versus paid, or commercial, donors. We note viral inactivation processes. Finally, we discuss what little information we could find on the differences in viral seropositivity rates of paid and volunteer donors.

Plasma Product Uses

More than 40 million hospital patients use plasma products each year. Plasma is the liquid portion of blood, containing nutrients, electrolytes (dissolved salts), gases, albumin, clotting factors, hormones, and wastes. Many different components of plasma are used, from treating the trauma of burns and surgery to replacing blood elements that are lacking as a result of disease such as hemophilia. Table III.1 describes plasma components and their uses.

Table III.1: Uses for Plasma Components

Component	Use
Albumin	To restore plasma volume in treatment of shock, trauma, surgery, and burns
Alpha 1 proteinase inhibitor	To treat emphysema caused by genetic deficiency
Antihemophilic factor concentrate	For prophylaxis and treatment of hemophilia A bleeding episodes
Anti-inhibitor coagulant complex	To treat bleeding episodes in presence of factor VIII inhibitor
Anti-thrombin III	To prevent clotting and thromboembolism associated with liver disease, anti-thrombin III deficiency, and thromboembolism
Cytomegalovirus immune globulin	For passive immunization subsequent to exposure to cytomegalovirus
Factor IX complex	For prophylaxis and treatment of hemophilia B bleeding episodes and other bleeding disorders
Factor XIII	To prevent and treat bleeding in factor XIII-deficient persons
Fibrinolysin	To dissolve intravascular clots
Hepatitis B immune globulin	For passive immunization subsequent to exposure to hepatitis B
IgM-enriched immune globulin	To treat and prevent septicemia and septic shock stemming from toxin liberation in the course of antibiotic treatment
Immune globulin: intravenous and intramuscular	To treat agamma- and hypogamma-globulinemia; for passive immunization for hepatitis A and measles

(continued)

Component	Use
Plasma protein fraction	To restore plasma volume subsequent to shock, trauma, surgery, and burns
Rabies immune globulin	For passive immunization subsequent to exposure to rabies
Rho(D) immune globulin	To treat and prevent hemolytic disease of fetus and newborn infant stemming from Rh incompatibility and incompatible blood transfusions
Rubella immune globulin	For passive immunization subsequent to exposure to German measles
Serum cholinesterase	To treat prolonged apnea subsequent to the administration of succinylcholine chloride
Tetanus immune globulin	For passive immunization subsequent to exposure to tetanus
Vaccinia immune globulin	For passive immunization subsequent to exposure to smallpox
Varicella-zoster immune globulin	For passive immunization subsequent to exposure to chicken pox

Source: Adapted from American Blood Resources Association, "Basic Facts About the Commercial Plasma Industry."

Plasma Donors

Plasma is typically collected from paid donors in a commercial setting. Donors receive between $15 and $20 for the 2 hours required to remove whole blood, separate the plasma from the cells and serum, and reinfuse the latter back into the donor. People may donate once in 48 hours but no more than twice a week. Prospective paid donors, like volunteer donors, are screened for medical history and risk behaviors, and each one must pass an annual physical examination and tests for total protein and syphilis in the blood every 4 months.

The American Blood Resources Association (ABRA)—a trade association for plasmapheresis collection centers and plasma derivative manufacturers—maintains a national donor deferral registry. Only first-time donors are checked against the registry of known donors deferred for positive test results, disease history, or risky behavior. Repeat donors' records are checked at the plasmapheresis center where the plasma is removed. Most centers ensure that donors are not migrating from one center to another over the 48-hour minimum donation interval.[1]

[1]For example, centers may mark the donors' finger with florescent dye. Nearby centers use different colors.

As with whole blood donated by the volunteer population, firsttime donors are known to carry higher viral test positivity rates than repeat donors. One manufacturer reported success with its program to detect and remove firsttime donor blood that was found to have positive viral markers (Philip, 1995).

Plasma Fractionation and Product Manufacture

Plasma collected at plasmapheresis centers is shipped in separate collection containers to pharmaceutical manufacturing plants. There the plasma is pooled into processing lots of as many as 60,000 units. A chemical fractionation process separates the various active components of plasma, which are further manufactured into clotting factor products for hemophiliacs, albumin for burn victims, and immunoglobulin preparations for immune-deficient persons.

Most plasma derivatives undergo viral inactivation or removal. The two main methods are heat treatment and solvent-detergent washing. Heat treatment is accomplished either by exposing the lyophilized (freeze-dried) product to dry heat or suspending it in a solution. Alternatively, the completely soluble liquid product is heated with the addition of various stabilizers such as sucrose and glycine. Extensive research has carefully calculated specified temperatures and times for different heat treatment processes.

Another method in use today exposes the product to an organic solvent such as N-Butyl phosphate and a detergent such as Triton X-100 or polysorbate 80 to dissolve the lipid coat of viruses, rendering them inactive. Solvent detergent inactivation cannot eliminate non-lipid-coated viruses such as HAV or parvovirus B-19.

A delicate balance maintains between disabling viruses and retaining adequate concentrations of the unstable components in the plasma. Heat and chemicals are particularly damaging to the plasma. Gentle but potentially safe methods still under investigation include nanofiltration to remove virus particles on the basis of molecular size; monoclonal antibody affinity chromatography to capture the protein of interest while the viruses and unwanted components are washed away; irradiation to inactivate viruses; virucidal agents that, having killed viruses, can then be removed during further manufacturing; and exposure to ultraviolet light.

Genetic engineering techniques are now used to produce recombinant factors VIII and IX, meaning that the genes to produce the proteins have

been cloned and can be harvested from genetically engineered Chinese hamster ovary cells in the laboratory. These products have, so far, been found free of human viruses.

History of Disease Transmission From Plasma Products

In the 1980s before the etiology of HIV transmission was understood, many hemophilia patients used plasma products infected with HIV, with 63 percent of all hemophilia patients in the United States becoming infected as a result. Many more contracted HBV and HCV.

Disease has been transmitted in many fewer cases since the introduction of antibody tests and viral inactivation and removal processes for plasma derivatives.

In January 1996, CDC reported the transmission of HAV by plasma derivatives factor VIII and factor IX, which are used to treat hemophilia patients. Both products had been virally inactivated by solvent detergent, but this technique is not completely effective in inactivating HAV or other nonlipid viruses such as parvovirus.

Clinical trials have demonstrated that current heat treatment and solvent detergent viral inactivation techniques are effective against HBV, HCV, and HIV. (Colombo et al., 1985; Horowitz et al., 1988; Kernoff et al., 1987; Manucci et al., 1988; Schimpf et al., 1987.)

In February 1994, Baxter Healthcare announced a voluntary withdrawal of its Immune Globulin Intravenous (IGIV) following reports that the product may have transmitted HCV to 14 patients in Spain, Sweden, and the United States. In July 1994, CDC confirmed 112 reports of possible cases of acute HCV infection from Baxter's IGIV (111 cases) and that of the American Red Cross (1 case). Because these products had maintained a longstanding safety record, they had not been virally inactivated with FDA-approved methods. In the 74 cases in which risk-factor data were available, 68 (92 percent) had receipt of IGIV as the only risk factor for infection.

In December 1994, FDA notified manufacturers of immunoglobulin products that it would begin testing for HCV in all products that had not undergone a validated virus inactivation or removal step. FDA further required manufacturers to submit their plans to incorporate the steps into their manufacturing plan. The immune globulins affected by this policy include Rho(D) immune globulin for Rh-negative pregnant women and

specific immune globulins for HBV, tetanus, and varicella-zoster. No new cases of HCV transmission by IGIV have been reported to date.

A similar product, immune globulin for intramuscular administration (IGIM), is not virally inactivated. Although no cases of HCV transmission by this means have ever been reported, concerns have been raised about this product, and FDA allows only the manufacturing lots that have been tested for HCV to be distributed.

HIV is a delicate virus in that it is readily inactivated. In 1988, CDC reported on a worldwide survey of 75 suspected cases of HIV transmission by heat-treated factor concentrates. Among the 75 recipients, 18 met the strict criteria for a probable association, including 8 who had received U.S.-manufactured concentrates. Subsequently, the manufacturer withdrew the product and modified its viral inactivation technique (Centers for Disease Control and Prevention, 1988). No cases of HIV transmission by plasma products inactivated according to current standards have been reported.

Rates of Viral Test Positivity Among Commercial and Volunteer Donors

Despite the evidence that viral inactivation and removal processes make today's plasma products safer than ever, the fact remains that the paid commercial plasma donor pool has higher rates of viral infectivity than the volunteer whole blood donor pool.

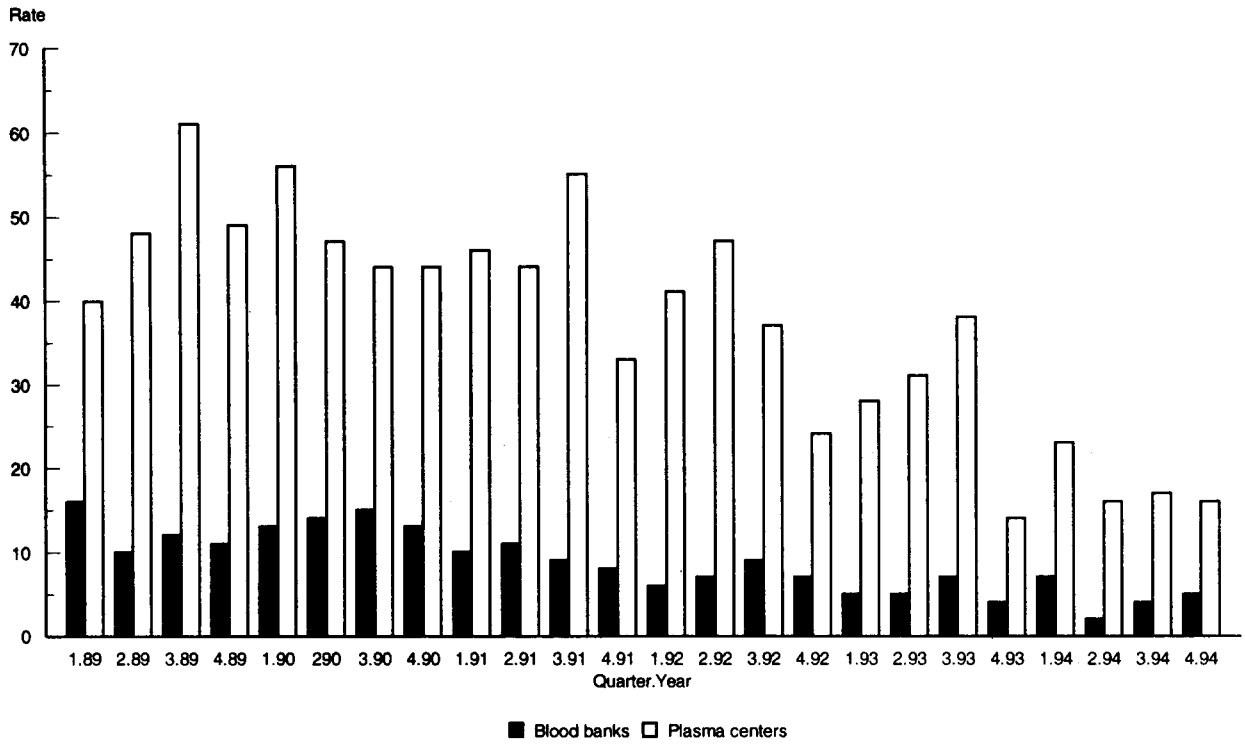
In 1978, FDA required that each blood unit be labeled as either volunteer or paid. In the regulations, FDA concluded that paid blood donors were more likely to transmit hepatitis to recipients than were volunteer donors. Its conclusions were based on the following research evidence: higher rates of HBsAG positivity in commercial donors; higher rates of HBV and non-A, non-B, hepatitis in recipients of paid donor blood; and a highly researched cohort of transfusion recipients in which the elimination of commercial blood resulted in substantially fewer cases of posttransfusion hepatitis.

While the commercial donor pool for whole blood is all but nonexistent in the United States today, the plasma industry continues to rely on paid donors to supply the raw plasma for further manufacturing into plasma derivatives.

We were unable to obtain national data on the viral test positivity rates among paid plasma donors compared to volunteer blood donors. We did, however, find several sources of information pertaining to this issue. First,

we found that California requires the reporting of initial and confirmed HIV prevalence rates for both blood banks and plasma collection centers. Figure III.1 shows that the confirmed HIV prevalence rates per 100,000 commercial plasma donations has decreased in recent years but remains substantially higher than those same rates in volunteer whole blood donations.

Figure III.1: Reported Confirmed HIV Prevalence Rates Among Donations in California, 1989-94[a]



[a]Reported Western Blot Confirmed HIV prevalence rates per 100,000 commercial plasma donations and volunteer whole blood donations in California (1989-94).

Source: California Department of Health Services, Office of AIDS, HIV/AIDS Epidemiology Branch, Sacramento, California, August 1995.

Plasma donors can donate much more frequently than blood donors, so fewer plasma donors are needed to collect 100,000 units. Moreover, several plasma units could be donated during the window period, whereas it is unlikely that more than one whole blood unit could be donated in the window period. Comparing donors to donors would probably show an even greater discrepancy.

Second, we analyzed the clinical data that manufacturers submitted to FDA during the approval process for a sample of viral tests. As table III.2 shows, the test-positive rates for commercial plasma donors are substantially higher than those of volunteer whole blood donors.

Table III.2: Viral Test Antibody Positivity Rates: Clinical Trial Data[a]

Donor trial sample	HIV-1 and -2		HCV 1st generation (1990)	
	Sample size	% positive	Sample size	% positive
Blood volunteer	13,059	0.09%	9,998	0.6%
Plasma paid	3,995	0.15	10,523	6.7

HTLV-I[b]							
2nd generation (1994)		1st generation (1990)		2nd generation (1994)		HBcore	
Sample size	% positive	Sample size	% positive	Sample size	% positive	Sample size	% positive
14,068	0.5%	13,690	0.12%	6,510	0.29%	2,969	1.1%
6,005	10.6	3,850	0.55	[c]	[c]	10[d]	20.0

[a]Rates are for repeatedly reactive results. That is, initial test positives are retested.

[b]HTLV-I is not present in plasma

[c]Not evaluated.

[d]Note the small sample size. Also, subjects were designated "paid donors" but some may have donated whole blood rather than plasma.

Summary

Clearly, most commercial plasma donors are healthy and free of disease. However, monetary incentives such as those offered by commercial plasma-collection centers may be tantalizing to those who are known to be at risk for infectious diseases, such as intravenous drug users and prostitutes. Screening questions address these risk behaviors, but there is no definitive way to screen out all risky donors, and current tests may not be sufficient to catch all infected units. For example, more than 80 percent of HTLV-I and HTLV-II infections among intravenous drug users stem from HTLV-II, but the HTLV-I antibody test is somewhat less sensitive for HTLV-II infections.

Newly emerging and yet unknown viruses often enter the population through high-risk individuals. Viral antibody tests may not yet exist, and current viral inactivation and removal techniques may be ineffective for new viruses. It is not known for sure whether HTLV-II is present in plasma. Moreover, one infectious donation can contaminate an entire pool of as many as 60,000 units.

Without national data on the differences in prevalence and incidence rates between paid and volunteer donors, it is not possible to draw firm conclusions about potential risks posed by plasma derivatives. Such data would be valuable because they could be used to monitor the blood industry in its entirety.

Further Reducing Risk

This appendix covers a number of different approaches used to further reduce the risk of blood transfusion. These include drug therapies to reduce the need for transfusion, alternative products, reducing the use of transfusions, and reducing the risks directly by controlling the sources of donation, extending viral inactivation techniques, genetic engineering, or improving viral testing.

Drug Therapies to Reduce the Need for Blood Transfusion

Physicians are increasingly considering alternatives to blood transfusion. Recombinant human erythropoietin—a growth factor that stimulates the body's manufacture of red blood cells—has been shown to decrease the need for blood as well as increase the yield from patients donating preoperatively for themselves. Clinical studies of anemic patients undergoing long-term hemodialysis who use erythropoietin show hematocrits and hemoglobin levels that are high enough to preclude further transfusions (Stack and Snyder, 1991). U.S. patients with anemia now use 200,000 to 400,000 units of red blood cells a year (Menitove, 1991). Similarly, the antidiuretic hormone, DDVAP, when given preoperatively has been shown to be effective in decreasing blood loss in cardiac and orthopedic surgery as well as reducing the need for postoperative platelet transfusions. For white blood cells, physicians are prescribing granulocyte, granulocyte-macrophage colony-stimulating factors, and multilineage colony-stimulating factor (interleukin-3) to prevent chemotherapy-induced neutropenia (abnormally low numbers of circulating neutrophils) and to accelerate recovery from this condition. The recently discovered thrombopoietin is rapidly advancing through clinical trials and will undoubtedly reduce the need for platelet transfusions.

Alternatives to Blood

Researchers are also working to develop substitutes for blood. One synthetic red blood cell substitute is made from outdated blood. The product, known as stroma-free hemoglobin solution, has been successful at supporting life for baboons with dangerously low hematocrits with no significant changes in heart rate, cardiac output, oxygen consumption, or mean arterial blood pressure (Gould et al., 1986, 1990).[1] However, recent experiments in Scotland using mice suggest that it may increase susceptibility to bacterial infections (Griffiths, 1995). It appears that bacterial sepsis results when hemoglobin provides bacteria with a source of iron that enhances the bacteria's ability to replicate.

[1]Stroma is the structural portion of erythrocytes. The hematocrit is the percentage of the volume of a blood sample occupied by cells.

If clinical trials can establish that stroma-free hemoglobin can be a safe and effective treatment for anemia, it will have the advantage over red blood cells of being universally compatible, having a long shelf life, and being free of infectious agents.

Perhaps more promising are recombinant red blood cell substitutes that are artificial in the sense that they are not derived from blood. These products are limited by their short shelf life and as yet undetermined toxicity. A double-blind, controlled Phase III clinical trial of a recombinant red blood cell substitute, HemAssist, is under way for patients suffering from blood loss and shock caused by trauma. The clinical trial will compare the outcomes of accident and trauma victims resuscitated under the current standard of care with those treated with HemAssist plus the current standard of care. It is not clear that HemAssist will substitute for blood at all. The anticipated outcome is survival. At this time, this product is not planned to be used as a substitute for blood in patients with anemia caused by other than acute blood loss. Another blood substitute, PolyHeme(R), is expanding its Phase II clinical trials from infusing the equivalent of 6 units of blood to 10 units, or the equivalent of replacing the total adult blood volume. At the same time, the manufacturer is pursuing FDA approval for Phase III trials of the blood substitute.

Reducing the Use of Transfusions

Avoiding unnecessary transfusions is a primary goal of transfusion medicine specialists. "Transfusion trigger" refers to the clinical events and laboratory data that lead physicians to transfuse blood to patients. In a 1985 study, Ali concluded that 11 percent of red blood cell transfusions were probably of doubtful benefit to the patients (Ali, 1988). The most overprescribed blood component, however, is probably fresh-frozen plasma. In 1986, Blumberg and colleagues indicated that as many as 73 percent of fresh-frozen plasma transfusions were unjustified (Blumberg et al., 1986). Yet, transfusions of plasma numbered 2.056 million in 1987 and increased by nearly 10 percent in 1992 to 2.255 million units (Wallace et al., 1993, 1995).

It is the responsibility of the prescribing physician to evaluate the patient's specific needs and to transfuse only appropriate blood components. This requires a scientific approach based on clinical laboratory results and careful consultation with the resident transfusion medicine specialist. Because many physicians lack knowledge about the specific indications for the use of blood products, many blood banks are tightening their control over the prescription of blood products. Hospital transfusion

committees (now required for accreditation by the Joint Commission on Accreditation of Healthcare Organizations) routinely review and control transfusion practices.

Intraoperative blood salvage—a procedure in which patients' own blood is collected during surgery and later reinfused—is becoming a more frequent practice. In 1992, an estimated 427,000 patients had their blood collected and reinfused during surgery. However, little is known about the potential risks associated with this procedure.

Other ways to reduce transfusions include preoperative and intraoperative hemodilution; improving the scrutiny of laboratory tests among premature and newborn infants; improving supportive care (for example, close monitoring of the use of fluids); and expanding the use of crystalloids and colloids for the treatment of acute blood loss in surgery, obstetrics, and trauma.

Controlling the Sources of Donation

Nonemergency patients can theoretically reduce the risks of receiving virally contaminated or incompatible blood by donating their own blood prior to surgery. However, a recent industry survey of 1,829 institutions indicated that autologous transfusion errors occur in nearly 20 percent of all blood banks. In most of these cases, the hospital transfused a regular or directed donor unit before using the patient's own blood. The most serious error—giving an autologous unit to an unintended recipient—occurred in 1.2 percent of responding hospitals.

Only about 60 percent of the surveyed facilities test autologous donations for viruses, and about 40 percent permit the transfusion of autologous units that test positive for viruses. The risk of patients' receiving bacterially contaminated blood that they have donated for their own use is equivalent to that risk within the general blood supply. Moreover, breakage or damage during handling of autologous units was reportedly high. Among 599 question respondents, 201 (34 percent) reported breakage of 308 units during laboratory processing or shipping and 195 of 605 (32 percent) respondents reported the unavailability of 368 autologous units from breakage or damage outside the laboratory. Of the 368 units, 182 were damaged by faulty refrigeration.

Consequently, the overall risk of receiving potentially virally infected, bacterially contaminated blood or blood not tested at all may actually be increased by a procedure designed to decrease risk.

Similarly, some patients request that the blood they receive come from directed donations, believing that this will reduce their risk. However, studies indicate that blood donated by the volunteer population can be safer than blood donated by relatives and friends, who may feel social pressure to donate and therefore do not divulge risk behaviors or disease status.

Also of major importance for reducing risk is the increased use of single-donor apheresis platelets, which is slowly replacing the practice of pooling units from 6 to 8 donors. Exposing patients to fewer donors is clearly a way to minimize risk.

Extending Viral Inactivation to Cellular Components

Promising advances in the inactivation of viruses for plasma have been discussed in appendix III. Research on the viral inactivation of cellular components of blood has been more difficult. Extending storage time, washing, platelet removal, or leukocyte reduction—the elimination of white blood cells— for red blood cells reduces but does not eliminate some circulating viruses. Mild temperature elevation irreversibly destroys red blood cells. Chemical approaches, such as using ozone, has shown variable results.

Photochemical approaches to reduce viruses in red blood cells and platelets have shown more promise. Hypericin, a naturally occurring antiviral agent found in the St. John's wort plant, has shown preliminary success at destroying HIV and other viruses in donated blood ("VIMRx Pharmaceuticals Expects," 1995). More importantly, both viral inactivation and improved cell recovery and survival have been demonstrated using psoralen derivatives and ultraviolet light, particularly when used with the "quencher" rutin, a naturally occurring flavonoid obtained from buckwheat.

Closing the Window Period

The majority of virally contaminated units are donated by persons who have recently contracted a virus and whose immune systems have yet to produce the blood antibodies that allow screening tests to detect infection. New screening tests are constantly narrowing this period of undetectability; however, the costs of implementing them throughout the blood supply are considerable while their predicted effect appears to be quite small. For example, current estimates suggest that the full implementation of a new HIV screening test would eliminate 24 cases of transfusion-transmitted HIV among the 21.6 million transfusions conducted

each year. This translates into a cost of $2.3 million dollars per life-year saved compared to the median cost of $19,000 per life-year saved for other medical life-saving interventions (Tengs et al., 1995). In comparison, traditional antibody tests prevent 16,000 cases of transfusion-transmitted HIV per year at a cost of about $3,600 per life year saved ("HIV-1 Antigen Test," 1995).

FDA recommended the use of this test when it became commercially available in early 1996. We were unable to find any studies that systematically compared the likely outcomes of targeting similar funding levels toward other avenues of reducing risk, such as improving donor education and screening or viral inactivation techniques.

In September 1996, Stramer reported the one and, to date, only documented case of HIV that has been detected by the p24 antigen test that was not also positive on the traditional antibody test among nearly 8 million donors tested since March 1996 ("Red Cross Reports," 1996). Researchers have speculated that the models predicting the detection of more donors may have overlooked the possibility that acute illness during the early window period may keep donors from giving blood temporarily.

Remaining unanswered is the possibility that the new antigen test has attracted recently infected "test-seekers" for a more sensitive HIV test that is not available at HIV testing and counseling sites and who actually increase the risks of HIV in the blood supply.

Summary

The risks of transfusion will continue to decrease as a direct result of pharmaceutical advances, changes in medical practice, improved selection of donors, viral inactivation techniques, and improved viral tests. Because the risks of transfusion are already so low, any incremental reductions in that risk will come at some cost either to the blood supply or to the health care system. A rapidly progressing medical field such as that of blood transfusion warrants careful consideration of the costs and benefits of different approaches to reducing risk.

Comments From the Department of Health and Human Services

Note: GAO comments supplementing those in the report text appear at the end of this appendix.

DEPARTMENT OF HEALTH & HUMAN SERVICES — Office of Inspector General

Washington, D.C. 20201

NOV 27 1996

Mr. Kwai-cheung Chan
Director of Program Evaluation
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Dear Mr. Chan:

The Department has carefully reviewed your draft report entitled, "Blood Supply: Transfusion-associated Risks." The comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

The Department also provided extensive technical comments directly to your staff.

The Department appreciates the opportunity to comment on this draft report before its publication.

Sincerely,

Michael Mangano
for June Gibbs Brown
Inspector General

Enclosure

The Office of Inspector General (OIG) is transmitting the Department's response to this draft report in our capacity as the Department's designated focal point and coordinator for General Accounting Office reports. The OIG has not conducted an independent assessment of these comments and therefore expresses no opinion on them.

COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE GENERAL ACCOUNTING OFFICE (GAO) DRAFT REPORT, "BLOOD SUPPLY: Transfusion-associated Risks (GAO/PEMD-97-2)

GENERAL COMMENTS

The Department of Health and Human Services is in general agreement with the principal findings and conclusions of the GAO draft report (GAO/PEMD-97-2) on "Blood Supply: Transfusion-associated Risks." Specifically, the Department concurs that the U.S. blood supply is currently safer than it has ever been. This level of safety largely reflects improvements in the areas of donor screening and education; serologic screening tests for viral pathogens; and viral inactivation techniques. However, recent experiences with hepatitis C transmission from intravenous immunoglobulin and hepatitis A transmission from clotting factor concentrates illustrate the need for continued vigilance.

In this report, the GAO estimates the risk of adverse events, including transmission of viral and bacterial pathogens, associated with the transfusion of screened blood. Such estimates can assist public health officials, industry, clinicians, and consumers in making informed therapeutic and programmatic decisions to reduce the risks associated with transfusion. Because many of these risks are already low, new interventions will likely be of decreasing benefit. We concur with GAO that new interventions will "...require careful consideration in order to identify areas of improvement that would maximize safety with reasonable costs."

The Department has reviewed the report and provided GAO with extensive technical comments. In addition, the Department believes that information derived from estimates in this report should be substantiated by scientific references whenever possible.

The following are GAO's comments on the HHS November 27, 1996, letter.

GAO Comments

We agree with the department's belief that our estimates should be referenced. We point to table II.1 as well as to the scientific citations throughout the draft. We regret that the bibliography included in the final report was not available at the time of the department's review.

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