disease to six of 43 hamsters receiving unfiltered red cells but none of 35 hamsters given filtered cells. Gregori *et al.* [36•] report removal of all but 0.01% infectivity from leucodepleted human red cells spiked with scrapie from hamster brain. These studies indicate that infectivity is not intrinsic to red cells or that if infectivity is associated with red cells it is loosely bound and removed by the filtration process. These data, if transferable to the human situation, provide a means of securing the safety of red cell transfusions in countries where the population has been exposed to BSE. Neither study, however, precisely mimics the human situation and so it is necessary to consider the suitability of hamster scrapie as a model for BSE and the similarity between the blood cells of hamsters and humans.*

Of hamsters and men

As it is extremely difficult to design experiments that directly address the biology of vCJD in human blood, most of the data available relate to animal red cells and transmission of scrapie rather than BSE. Whole blood transfusions between sheep have demonstrated transmission of BSE but these experiments have not yet been extended to transfusion of the individual components of blood [37].

As described above, available evidence suggests that prion disease cannot develop in the absence of PRPc. It is therefore reasonable to ask what is the distribution of PRPc in human blood cells and how does it compare with PRPc distribution in blood cells of animals used for investigation of blood-borne TSE infectivity, since differences in PRPc expression may occur and be relevant to disease progression. Holada and Vostal [38] report flow cytometric experiments demonstrating low levels of PRPc on human red cells and absence of PRPc from hamster red cells. Experiments of this type, which utilize a single monoclonal antibody to PRPc, may give erroneous information if the relevant PRPc epitope is not accessible on the cell type examined because of differences in posttranslational modifications like glycosylation [39]. If hamster red cells differ from human red cells in lacking PRPc expression, however, are hamsters a relevant model with which to study the infectivity of human red cells?

If hamster scrapie strain 237K PRPsc does not bind to human red cells does this necessarily mean that BSE/vCJD PRPsc does not bind either? Nishina *et al.* [40•] reported that diglycosylated hamster brain PRPc is required for the amplification of hamster PRPsc strain 237 *in vitro* whereas unglycosylated mouse brain PRPc is required for the amplification of RML PRPsc, a clear indication that different sources of PRPsc have different requirements for glycosylation of PRPc. Earlier work [41] also demonstrated that the glycosylation profile of PRPc can influence the amount of PRPsc bound.

The same protein can have different glycosylation profiles in different tissues from the same animal [42,43]. Clearly, such tissue-specific differences in glycosylation of PRPc could result in tissue-specific differences in binding and replication of PRPsc and account for heterogeneity of PRPc isoforms observed in different regions of mouse brain and for different patterns of PRPsc deposition by different PRPsc strains [44].

These considerations lead to the conclusion that expression of PRPc on a given cell or tissue is not, of itself, an indication of susceptibility to PRPsc binding. Consequently, the glycosylation profile of PRPc on red cells may influence the ability of different strains of PRPsc to bind to red cells and may account for the lack of PRPsc binding observed in animal experiments described above. The same reasoning applies to the interpretation of animal experiments examining the infectivity of blood platelets. Hamster platelets lack PRPc whereas human platelets express PRPc at high levels [45]. Platelets were found to lack infectivity in the blood of hamsters infected with hamster scrapie [46]. The glycosylation profile of the complement regulatory protein CD59 on human red cells and platelets has been determined in detail. The protein on both cell types is extensively glycosylated but the glycosylation profiles of the protein on the two cell types are distinct [43]. If PRPc on red cells and platelets is glycosylated in a similar manner this may account for absence of PRPsc binding because large N-linked oligosaccharides at Asn181 and Asn197 could shield large parts of the surface of the prion protein and sterically hinder protein–protein interactions [47]. This could also explain why murine red cells which express PRPc [38] lacked infectivity when derived from animals infected with mouse-adapted vCJD [48]. Nevertheless, it would be prudent to investigate binding of BSE PRPsc to human red cells and platelets before assuming that these cells do not carry vCJD infectivity, since the glycosylation profile of a protein can differ between species [49,50].

Human red cell PRPc and hamster brain PRPc may differ in the structure of the GPI anchor. On human red cells, GPI-linked proteins CD59 and acetylcholinesterase are unusual in that the GPI anchor is palmitoylated in a way that renders it resistant to phospholipase C [43,51]. If as Rudd *et al.* [43] point out this is likely to be a feature of all GPI-linked proteins on the red cell, then red cell PRPc would have the same anchor. The GPI anchor found on PRPc from Syrian hamster brain is not palmitoylated in

* Since this manuscript was submitted for publication a fourth case of probable transfusion-transmission of vCJD by non-leukodepleted red cell preparations has been reported in the UK (http://www.hpa.org.uk) and a further study demonstrating removal of endogenous TSE infectivity from leukodepleted scrapie-infected hamster whole blood by filtration through prion-specific affinity resins has been published (Gregori L, Gurgel PV, Lathrop JT *et al.*, 2006 Lancet 368:2226–2230).

this way [47]. This difference may influence the location of PRPc in lipid rafts and thence accessibility to PRPsc [20,52].

Finally, there is also the possibility that human red cells could bind PRPsc independently of PRPc. PRPsc binds with high affinity to plasma lipoproteins [32•]. Plasma LDLs have been reported to bind red cells, albeit with low affinity [53].

Conclusion

Recent reports show there is a high probability that human red cell preparations have transmitted vCJD. Experiments carried out with rodent TSEs indicate that infectivity in red cell preparations is not associated with the red cells themselves but with other constituents of the product such as residual leukocytes and plasma. Lack of intrinsic red cell infectivity may result from posttranslational modifications of the structure of red cell PRPc which prevent PRPsc binding. If it can be shown that the causative agent of vCJD fails to bind human red cells and in the absence of a suitable screening test for PRPsc in blood, it may be prudent for blood services in countries where vCJD occurs to consider processing red cell preparations by washing or filtration to remove fluid phase infectivity prior to transfusion.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 291).

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研究報告の概要

○輸血と変異型クロイツフェルト・ヤコブ病
変異型クロイツフェルト・トヤコブ病(vCJD)は血液を介して感染する可能性がある。血液成分を介した二次感染を予防するため、複数の国で輸血歴のある供血者の除外が開始されている。Dynamic age-structured modelを用いて、この措置の効果を検討した。これは1) 供血者の行動、2)CJDの症例対照試験、3)受血者の年齢分布、4)受血者の死亡の疫学的データに基づくモデルとしては初めてのものである。当該モデルから、食肉からヒトに伝播したvCJDは、輸血のみにより感染が拡大する可能性はないこと、また、輸血歴のある供血者を除外することにより感染を免れるのは1%未満の症例にすぎないことが予測された。

使用上の注意記載状況・その他参考事項等

赤血球M・A・P「日赤」
照射赤血球M・A・P「日赤」
赤血球濃厚液-LR「日赤」
照射赤血球濃厚液-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
血液を介したvCJD感染予防の目的で行われている輸血歴のある供血者の除外措置の効果を検討したところ、食肉からヒトに伝播したvCJDは、輸血のみにより感染が拡大する可能性はないこと、また、輸血歴のある供血者を除外することにより感染を免れるのは1%未満の症例にすぎないことが予測されたとの報告である。	日本赤十字社は、輸血感染症防止のため輸血歴のあるドナーを無期限に献血延期としている。vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴(旅行及び居住)を確認し、欧州36ヶ国に一定期間滞在したドナーを無期限に献血延期としている。また、英国滞在歴を有するvCJD患者が国内で発生したことから、平成17年6月1日より英国滞在歴1日以上の方からの献血を制限している。さらに、血液製剤の保存前白血球除去を順次導入し、平成19年1月16日からは全ての輸血用血液に保存前白血球除去を実施している。今後もCJD等プリオン病に関する新たな知見及び情報の収集に努める。

MedDRA/J Ver.12.0

Blood Transfusion and Spread of Variant Creutzfeldt-Jakob Disease

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Variant Creutzfeldt-Jakob disease (vCJD) may be transmissible by blood. To prevent secondary transmission through blood components, several countries have started to exclude as donors persons who have received a blood transfusion. We investigated the effectiveness of this measure by using a dynamic age-structured model. It is the first such model based on epidemiologic data: 1) blood donor activities, 2) a case-control study on CJD, 3) age distribution of recipients, and 4) death of recipients of blood transfusions. The model predicts that an infection like vCJD, which has been introduced into the population by the alimentary route, could not become endemic by transfusion alone and that only <1% of cases would be avoided by excluding from blood donation those persons who have received a transfusion.

Recent studies of variant Creutzfeldt-Jakob disease (vCJD) indicate that this disease is transmissible by blood. One case of probable transfusion-transmitted vCJD infection has been reported, and 1 case of subclinical infection has been detected (*1,2*). On February 9, 2006, a third case was announced by the UK Health Protection Agency (www.hpa.org.uk/hpa/news/articles/press_releases/2006/060209_cjd.htm). Each of the 3 patients had received a blood transfusion from a donor who subsequently developed clinical vCJD, which indicates that transfusion caused the infection. However, a policy to exclude potential donors who had received a transfusion would not have prevented at least the first 2 cases because the corresponding donors had not received any blood transfusion. Diagnostic tools to detect prions in blood are under development (*3*), but no routine test for the presence of the infectious agents of vCJD is available. Therefore, the questions arise as to whether an infection like vCJD could become endemic through blood donation alone and to what extent exclusion of potential donors with a history of transfusion would influence the transmission of such an infection (i.e., how many deaths due to the infection could be prevented?). The following mathematical model is the first to address these questions on the basis of epidemiologic data and realistic and epidemiologically justified assumptions.

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Methods

Model Structure

Figure 1A shows the transitions of a person through the basic states of potential donor activities and receipt of blood transfusion. After birth a person is in the state of not having received any transfusion and not yet being an active donor (S_{00}). The first index refers to the person's state as a transfusion recipient; the second index, to the person's status as a donor. Persons in state S_{00} can change to state S_{01} by becoming a donor or to state S_{100} or S_{101} by receiving a blood transfusion. The third index indicates whether a person with a transfusion history can actually be identified and excluded from donating blood (deferred) (index 1) or not (index 0). The states S_{111} and S_{110} can be reached by either transfusion recipients who start donating blood or active donors who receive a blood transfusion. Blood donors who become inactive are transferred into the states of ex-donors S_{02} and S_{12}, depending on their transfusion history. Ex-donors can also become transfusion recipients; i.e., they are transferred from S_{02} to S_{12}. Donor exclusion transfers a certain proportion of transfusion recipients into

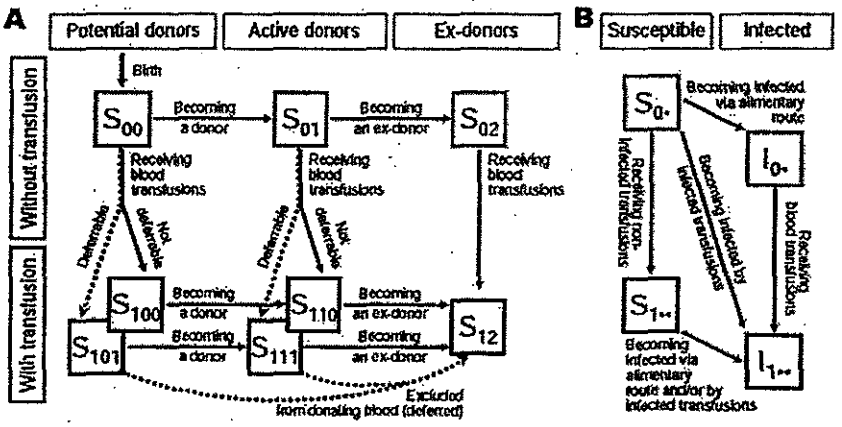

Figure 1. A) States and transitions for the model of blood transfusion in the absence of an infection. B) Routes of infection. The arrows representing deaths out of all states are omitted. Paths of donor exclusion are plotted by dotted arrows. S_{00}, nonrecipients who do not donate; S_{01}, nonrecipients who donate; S_{02}, nonrecipients who are excluded from donating; S_{100}, recipients who do not donate; S_{101}, recipients who become excluded from donating; S_{110}, recipients who donate; S_{111}, recipients who become excluded from donating; S_{12}, recipients who are excluded from donating. Indices replaced by a dot (panel B) represent all other possible states (e.g., $S_{0\cdot}$ represents S_{00}, S_{01}, or S_{02}).

the state of ex-donors. For all susceptible states, Figure 1B shows the transitions to the corresponding infected states. Table 1 provides a list of all input parameters together with descriptions and sources. The details of the model with all the numerical parameter estimates and the equations are given in the online Appendix (available from www.cdc.gov/ncidod/EID/13/1/89-app.htm). The computer program is available upon request. This article summarizes the major features of the model, the data sources, and the estimation of the model parameters.

Demography

To simplify the model, we did not attempt to describe the demographics of the population during the next 150 years. Doing so would involve predicting changes in rates of birth, death, and immigration. It is assumed that in the absence of infection, the population is demographically stationary. We assumed a constant inflow of newborns and an age-specific death rate. The latter was estimated as a weighted mean of the age-specific female and male death rates. Because this study was initiated in Germany, we used the corresponding demographic data. To start the simulation in a demographically stationary state, the model was run for 100 years without infection. Thus, the age distribution of the population was identical to the life table of Germany 2002/2004 averaged over both sexes (www.destatis.de/download/d/bevoe/sterbet04.xls).

Modeling Blood Donors

Blood donors in Germany are ≥18 and <68 years of age. The rates for becoming a new donor and terminating the period as an active donor are age dependent. The corresponding parameters were estimated by using data from 262,071 donors registered with the German Red Cross

Table 1. Summary of input parameters for the model*

Parameters	Description	Source
Age-specific mortality rates	U-shaped, with minimum at age 10.	Federal Statistical Office of Germany
Donor recruitment	Donors ages 18–67 y. Maximum recruitment rate at age 18, lower plateau ages 25–50; further decrease until age 67.	Age-distribution of first-time donors at DRK Blood Service and age structure in population
Proportion of donors	3% of population.	DRK Blood Service West
Duration as active donor	Donors ages 18–40 y, mean duration as active donor 10–14 y, decreases linearly to 0.	Age distribution of active donors at DRK Blood Service West, by age at first donation
Risk of receiving transfusions	Bimodal, with peaks for newborns and aged persons. Multiple transfusions possible.	Data collected from 4,867 patients March 2003, University Hospital Essen, Germany
Transfusion-associated risk for death	Increases according to a sigmoid function, ≈17% at birth to ≈48% in old age. For those with transfusion-associated risk for death, life expectancy is ≈2.5 years at birth and decreases to ≈0.5 y in old age.	Follow-up of ≈3,000 transfusion recipients for ≈7.5 y in Newcastle, UK (*4*)
Alimentary infection	Constant over an initial period of 10 y.	Arbitrary assumption
Incubation period†	Gamma distributed with mean 16 y, SD 4 y. Sensitivity analysis with mean = 50 y and same coefficient of variation.	Models fitted to the UK incidence of vCJD (*5,6*)
Donor exclusion	Either 0 or 95% of those with transfusion history.	Arbitrary assumption

*DRK, German Red Cross; SD, standard deviation; vCJD, variant Creutzfeldt-Jakob disease.
†Time between infection and death, i.e., duration of infection.

(DRK) Blood Service West in Hagen, Germany, including age, sex, age at first donation, number of donations, and date of last donation.

The age-specific prevalence of active donors peaks at ≈24 years of age and subsequently declines monotonically to zero by age 68. The overall prevalence in the population is 3%, i.e., 2.4 million donors in a population of ≈80 million.

Modeling Transfusion Recipients

The model takes into account that persons may receive >1 transfusion throughout their lifetime, but it does not track the number of transfusions received per person. Persons with ≥1 transfusion continue to be at risk for infection from further transfusions. The age-specific risk of receiving a transfusion was estimated from data for all patients hospitalized at the University Hospital in Essen during March 2003. Of 4,867 patients, 1,343 (27.6%) received ≥1 transfusion. The number of persons receiving a blood transfusion in each 5-year age group was divided by the corresponding number of persons in the general population. The observed rates were fitted with a simple model that assumes initially an exponential decline and subsequently a unimodal peak, which is proportional to the density function of the normal distribution. These age-specific ratios were properly scaled to balance the yearly number of transfusions per capita. To limit the complexity of the model, we did not take into account persons in subgroups, such as those with hemophilia, who obtain blood products from pools of donors. Because for medical reasons these subgroups are excluded from donating blood, they cannot contribute to persistence of the infection.

Independence of Receiving and Donating Blood

The events of receiving a blood transfusion and of donating blood are assumed to be independent of each other. This assumption is supported by the results of a case-control study of potential risk factors for CJD, which was coordinated by the Clinical Surveillance Centre for CJD, Department of Neurology in Göttingen, Germany (*7*). Table 2 shows the joint distribution for the control group of having received and donated blood. According to the Fisher exact test, the p value for the hypothesis of no association is 0.43.

Heterogeneity in the risk of receiving a blood transfusion is modeled by the assumption that only a proportion of the population are at risk, whereas the remaining proportion never receives a transfusion. This assumption was introduced to be consistent with data from the case-control study, in which ≈18% of the population reported having ever received a blood transfusion. Without this assumption, the model would predict that eventually 100% of a cohort would receive a blood transfusion because the average annual risk of receiving a blood transfusion is about 5%, i.e., ≈4 million in a population of 80 million.

Table 2. Joint distribution of transfusion history and blood donation

Received blood	Donated blood, no. observed (no. expected if events are independent)		
	No	Yes	Total no. (%)
No	401 (404)	104 (101)	505 (82)
Yes	93 (90)	19 (22)	112 (18)
Total no. (%)	494 (80)	123 (20)	617 (100)

Modeling Transfusion-associated Death Rates

The transfusion-associated death rate has been described in detail by Wallis et al. (*4*). A good fit to the data assumes that at all ages a certain proportion of transfusion recipients have a higher rate of dying and the remaining proportion has a survival rate that corresponds to that of persons of the same age group in the general population. This age-dependent proportion of transfusion recipients with an increased risk for death is described by a generalized logistic function with a positive value at birth and an asymptote <100% for old age. The transfusion-associated death rate increases linearly with age. The increased death rate appears to be concentrated in the first 2 years after a transfusion. Wallis et al. report that 2,888 patients were observed as long as 7.4 years after transfusions received in June 1994 (*4*). The sex-specific rates were averaged for the simulation model.

Modeling the Infection

Usually the incubation period refers to the time between the infection and disease. In the context of CJD, however, disease can refer to onset, diagnosis, or death. Like Bacchetti, we also focused on death rates (*8–10*). The incubation period is assumed to be gamma distributed with a mean duration of 16 years and a standard deviation of 4 years, which conforms to estimates of Valleron et al. and Ghani et al. (*5,6*). Because of great uncertainty about the length of the incubation time, we also considered a much higher value of 50 years in the absence of the competing risk for death. The coefficient of variation is assumed to be the same, such that the standard deviation is 12.5 years. Because of competing risks, the actual sojourn in the incubation period is 15.3 for an incubation period of 16 years and 34.0 years for an incubation period of 50 years. The proportions of infected persons who would die with disease symptoms are 79% and 37% for the incubation periods of 16 and 50 years, respectively. This means that for an incubation time of 50 years, nearly two thirds would die without disease symptoms. Hereafter we refer to these values of 15 and 50 years as short and long incubation periods.

We distinguish between 2 modes of transmission. Initially, the infection is introduced into the population by the alimentary route. In the United Kingdom the number of infected animals entering the food supply peaked in 1989; most were concentrated within a period of 10 years (*11*), which we take as the assumed period of alimentary infection. After this period, this mode of transmission was interrupted so that further transmissions are possible only through blood transfusions.

A study to detect the presence of abnormal prion protein in appendix and tonsil tissues has suggested a prevalence of 235 infections per million in the United Kingdom (*12*). We arbitrarily assumed the prevalence of infections in Germany to be ≈1 order of magnitude lower, yielding a cumulative incidence of 25 per million, which was the value used for the simulations.

We made 2 contrasting assumptions about the infectivity of blood preparations and evaluated the results of these 2 simulations: each transfusion (100% infectivity) or no blood transfusion (0% infectivity) from an infected donor leads to infection of the recipient. In the model the infection probability (probability of receiving blood from an infected donor) is proportional to the proportion of infected donors among all donors. Thus, we can calculate the number of infections from blood transfusions compared with the number of infections from alimentary transmission alone.

Modeling Donor Exclusion

The model distinguishes between persons with and without transfusion history, termed recipients and nonrecipients; these terms are applied to persons whether they have or have not donated blood. The model allows recipients to be excluded from donating blood. In modeling the exclusion of recipients, we took into account that this measure may be imperfect and that a certain proportion of recipients may not be excluded.

Results

For the parameter estimates obtained from the sources described above, the infection cannot become endemic (Figure 2). If we assume no further spread through blood transfusions after 10 years of infections by the alimentary route, the maximum prevalence reached is ≈1,860 (1,434 for nonrecipients plus 426 for recipients) because some of the infected persons die of other causes during the incubation period. If transmission is assumed to be possible through blood transfusions (100% infectivity), then the maximum prevalence among recipients is increased by ≈78 infections after 4 more years for the short incubation period and by 193 infections after 23 more years for the long incubation period.

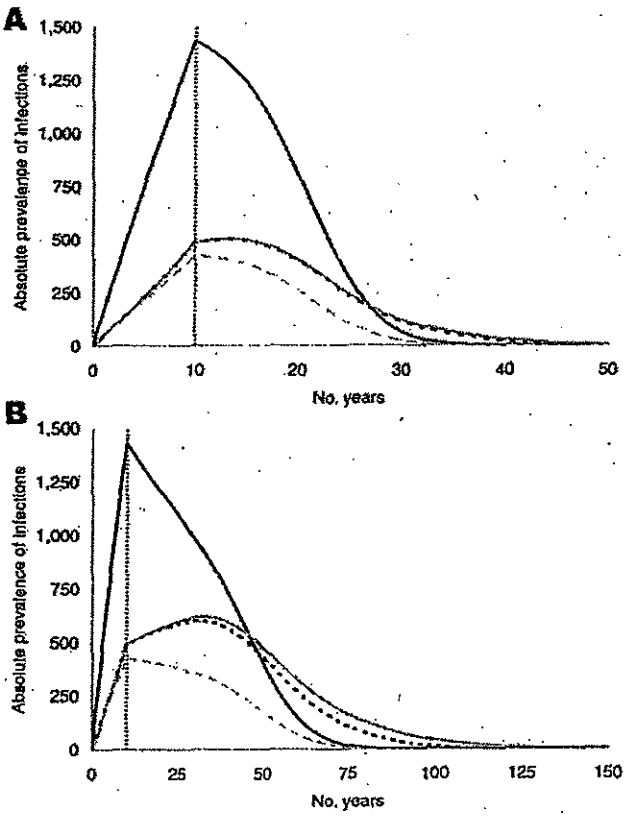

Figure 2. Absolute prevalence of infection for an incubation period of 16 (A) and 50 (B) years, for nonrecipients of blood transfusion (solid, black), recipients under the assumption of no infectivity (dashed, gray), of 100% infectivity without donor exclusion (dotted, black), and 100% infectivity with donor exclusion (solid, gray). The prevalence declines after the alimentary route of transmission is interrupted, i.e., after 10 years. Prevalence differs only slightly if the infection probability of a transfusion from an infected donor is increased from 0% to 100%. Donor exclusion produces negligible reductions.

We assumed that donor exclusion is implemented immediately at the beginning of the alimentary infection risk period, which reduced the original number of 2.55 million donors by ≈20% to a value of 2.05 million donors. Because the model does not account for the stock of blood donations, this reduction in the number of donors must be compensated for with an increased rate of donations per donor to satisfy the demand; i.e., the average number of donations would have to increase from 1.6 to 2 per donor per year. Figure 2A shows that donor exclusion has almost no effect when the incubation period is assumed to be 16 years. The absolute prevalence (i.e., the actual number of infected persons) differs at most by 9. For a long incubation, differences are visible (59 persons at most) but small in view of the long time intervals and the size of the total