e.g. blood donors, raises a number of unresolved ethical questions. For instance, how should reactive test results be handled when obtained with the first available test, which cannot be confirmed or clarified by another method?

## 13. Exclusion of persons from donating blood

Donor selection criteria based on the history of the donor must still be used for risk prevention; an overview can be found in Appendix (E) of [1]. The regulations applicable in Germany have been adopted in Haemotherapy Guidelines [75].

In the past few years it has been discussed whether potential transmission by transfusion could lead to perpetuation of vCJD among humans, even though transmission through the food chain has been stopped, and whether an exclusion of transfusion recipients could essentially influence the course of the vCJD epidemic. In several European countries including the UK, the Netherlands, Switzerland and France—there albeit as early as 1998 under the impression of virus transmissions—the exclusion of transfusion recipients from donating has meanwhile been laid down.

In order to obtain a scientific database, a model calculation based on very pessimistic assumptions was prepared. The epidemiological model describes the spreading of an infection, in this case vCJD, due to blood donations based on the demographic situation in Germany. It assumes that 2,000 individuals were infected by contaminated food during a limited period of 10 years. The total population comprises 80 million people. The parameters for the model were estimated on the basis of four data sets:

1. Donations from 262,071 donors at the blood donation services of DRK (DRK-Blutspendedienst) West Hagen, Germany;
2. 617 controls of a case control study on Creutzfeldt–Jakob Disease at Göttingen University, Germany;
3. age distribution of 1,343 transfusion recipients at the University Hospital of Essen, Germany; and
4. a longitudinal study from Newcastle on the survival of 2,888 patients after a blood transfusion in June 1994.

The age structured model uses 2-month intervals and takes into account the following conditions:

- The mandatory age limit for blood donors is between 18 and 68 years. Each blood donor undergoes an active phase of donor activity the duration of which depends on age.
- The risk of receiving a blood transfusion strongly depends on age and has its peak at approx. 70 years.
- Survival after a blood transfusion also strongly depends on age. The increased mortality rate of transfusion recipients reduces the risk of spreading by blood donations.
- The model takes into account the current mortality rates in the Federal Republic of Germany.
- A mean incubation period of 16 years with a standard deviation of 4 years was assumed for the infection.

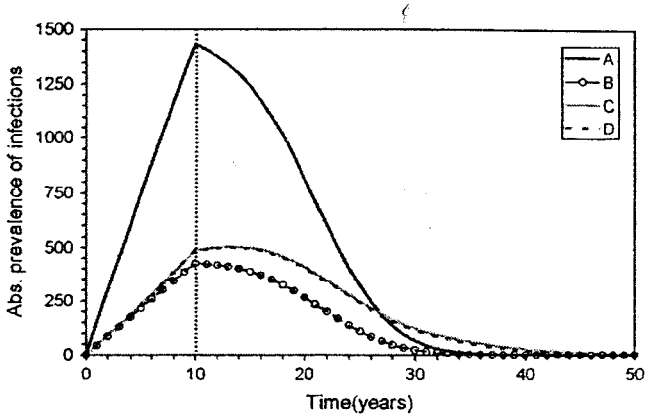


Fig. 3. Prevalence of vCJD. The vertical line shows the end of the phase of introduction of the infection by food. The curves show prevalence with the denominator of 80,000,000 German population, for the following cohorts: Curve A: Non-recipients (individuals *without* transfusion history, infection is therefore only possible by food). Curve B: Recipients (individuals *with* transfusion history), if transmission by transfusion is excluded (infection risk 0%, therefore—as in Curve A—infection possible only by food). Curve C: Recipients, if infected blood donations always lead to infection of recipients (infection risk 100%). The difference between Curve C and Curve B shows that the majority of infections was not caused by blood donations but by food. Curve D: as Curve C, but excluding donors with transfusion history. Reproduced from Fig. 2A in "How much would the exclusion of transfusion recipients from donating blood reduce the spread of vCJD?" *Emerging Infectious Diseases*, Vol. 13 No. 1, 2007.

- The model permits exclusion of donors with a history of blood transfusions. It is assumed that 95% of the donors with a history of blood transfusions can be excluded.

Fig. 3 shows the absolute infection prevalence as a function of time predicted by the model. Prevalence increases during the 10-year period of food related infection and leads to a maximum of 1,434, infected individuals in the portion of the population without transfusion history (Curve A). In the portion of the population with transfusion history, depending on whether no risk of infection is assumed (0%, Curve B) or, in the most unfavorable case, an absolute infection risk is assumed (100%, Curve C) by blood donations from infected donors, 426 or 504 infected individuals, respectively, are to be expected. Maximum prevalence in the German population is 1,860 or 1,921 infected individuals respectively, corresponding to approx. 24 infected individuals per 1 million inhabitants. (The maximum value of 1,921 is slightly smaller than the total of 1,434 plus 504, since the maximum values of the individual curves are reached at different times.) The majority of infections caused by transfusions cannot be prevented by the exclusion of donors with a transfusion history, since they were infected by blood from food infected donors without a transfusion history. Thus, an exclusion of transfusion recipients would bring about only a minor contribution to prevention (Curves C and D can hardly be distinguished).

Given the initial rate of introduction of the infection, no further spreading occurs after that period of time, and, due to decreased life expectancies of vCJD infected individuals, the prevalence during the subsequent 20–30 years has a tendency

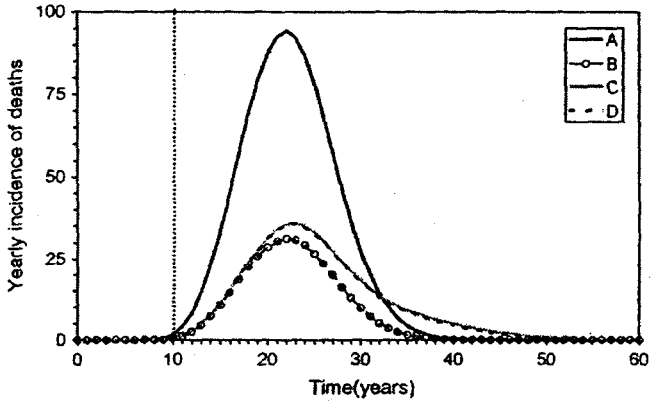


Fig. 4. Mortality from vCJD. The vertical line shows the end of the phase of introduction of the infection by food. The curves show incidence of deaths (Fig. 4) with the denominator of 80,000,000 German population, for the same cohorts A–D shown in Fig. 3. Reproduced from Fig. 3A in "How much would the exclusion of transfusion recipients from donating blood reduce the spread of vCJD?" *Emerging Infectious Diseases*, Vol. 13 No. 1, 2007.

towards zero again. Even if it is assumed that infected blood donations will always lead to infection of the recipient (infection risk = 100%), no further spreading occurs. In addition, the decrease in prevalence is only delayed due to the incubation period of the individuals infected (Curve C). An exclusion of transfusion recipients, even in the latter most pessimistic scenario, can bring about only a minor contribution to prevention (Curve D). This is also shown in Fig. 4, in which the annual incidence of deaths due to infection is shown. The maximum number of vCJD associated deaths occurs not before 23 years after the beginning of the onset of infection due to the long incubation period.

Fig. 5 compares the incidence of deaths of individuals infected by food (Curve E) with those that may be caused by blood donations with maximum risk of infection (Curve F). Due to the incubation period, transfusion associated deaths

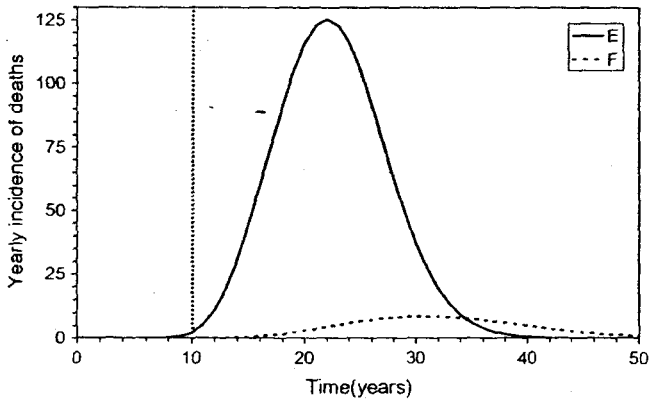


Fig. 5. Curve E: Deaths due to vCJD infections that could only be caused by food (totals of Curves A and B in Fig. 2). Curve F: Deaths due to vCJD caused by blood from infected donors (infection risk 100%) (difference between Curves C and B in Fig. 2). The vertical line marks the end of the phase of infection by food. Reproduced from Fig. 4A in "How much would the exclusion of transfusion recipients from donating blood reduce the spread of vCJD?" *Emerging Infectious Diseases*, Vol. 13 No. 1, 2007.

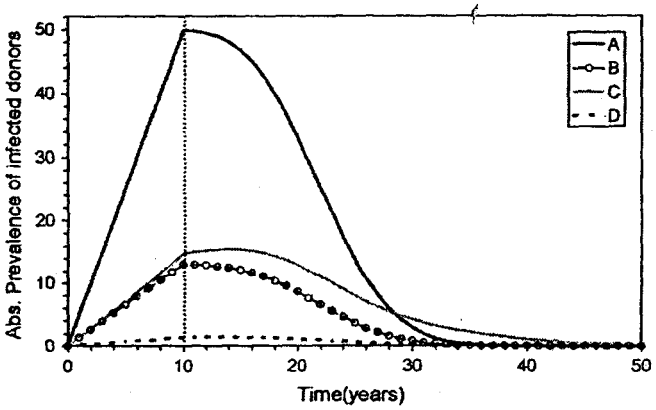


Fig. 6. Curve A: Prevalence of infected donors *without* transfusion history (infection possible only by food). Curve B: Prevalence of infected donors *with* transfusion history, if transmission by transfusion could be ruled out (infection risk 0%, therefore—as in A—infection possible only by food). Curve C: Prevalence of infected donors *with* transfusion history, if it is assumed that infected blood donations always lead to infection (infection risk 100%). The difference between Curve C and Curve B show that the majority of infections are not caused by blood donation but by food. Curve D: As Curve C, but excluding donors with transfusion history. This curve shows 5% of the donors with transfusion history, who were not excluded according to the model assumptions. The vertical line shows the end of the phase of infection by food. Reproduced from Fig. 5A in "How much would the exclusion of transfusion recipients from donating blood reduce the spread of vCJD?" *Emerging Infectious Diseases*, Vol. 13 No. 1, 2007.

occur markedly later than deaths caused by food infections. Within the displayed 50 years, 172 transfusion associated deaths have to be expected. During this period, however, a maximum of 15 cases could be prevented if donors with a transfusion history were excluded, equivalent to 1 case in 3–4 years. Out of the 2,000 individuals infected by food, we expect 1,557 vCJD cases if the infection risk of infected donors is 0%, and 1,729 cases if the infection risk is 100%. If approx. 20% of the donors were excluded, less than 1% of the cases would be prevented. Fig. 6 explains why the exclusion of donors with a transfusion history only slightly influences the incidence of deaths:

- The majority of the infected donors were infected by food and reveal *no* transfusion history (Curve A). This group is not covered by the exclusion criterion "donors *with* a transfusion history" and is able to continue to transmit the disease.
- Infected donors *with* a transfusion history can be excluded, but represent only a minor portion of infected donors (Curve B or C, respectively). The portion of donors infected by transfusions is very small (difference between Curve C and Curve B).

The assumptions chosen here present a considerable overestimation of the real risk of infection in Germany. Since an infection introduced by food cannot be sustained in the population, there is no further long-term risk after this route of transmission has been interrupted. Because of the low prevalence of approx. 24 infected individuals per 1 million (see above), linear reduction can be performed on predicted

developments if markedly lower prevalences are assumed. The actual prevalence of individuals infected by food in Germany is probably lower by at least a factor of 10. Therefore, the above mentioned figures can probably be reduced by the corresponding factor. A detailed description of the model with all parameters and figures for the data sources on which this calculation is based has been published [105].

## 14. Impact of deferrals on the blood supply

Before introducing any donor deferrals, their effects should be quantified and a risk/benefit assessment (safety vs. blood supply) performed. It can be added to the discussion of the above model that an exclusion of transfusion recipients would not have prevented the three probable transmissions in the UK, since those donors were not transfusion recipients themselves. Moreover, it can be expected that an undetermined number of donors would not remember transfusions and continue to donate blood. On the other hand, as the French example shows, an exclusion of transfusion recipients is possible in principle, but would entail serious problems and disadvantages, would require major efforts and could therefore only be implemented over a longer period of time.

Examples from Germany may illustrate the impact of new exclusion criteria in general. With the 2000 update of guidelines, a rise of Hb limit for men from 125 to 135 g/l was introduced, which had a serious effect on the donor population. The deferral rate (Table 5) initially rose by approx. 2.5%, and after the male donors with Hb between 125 and 135 g/l had been deferred, decreased again to its initial level.[9] Deferral rates tended to be rising from 322,312 in 2002 to 345,906 in 2003 (8.25% vs. 8.87% of the population prepared to donate). Since winter 2000/2001—despite intensive encouragement to donate blood—the demand for blood components, especially RBC, has not always been met so that, e.g., planned operations have to be postponed. Also, stricter donor exclusion criteria for the sake of improved safety may lead to a loss in donors, as anti-HBc testing [106] has led to permanent exclusion of approx. 0.6–1% of blood donors. New reasons for exclusion frequently are not understood by those concerned and require great educational efforts. As experience with the deferral due to a cumulative stay in the UK of more than 6 months between 1980 and 1996 has shown, considerable uncertainties remain despite numerous dialogues due to the lack of possibility to explore the donor's individual risk or to obtain a confirmatory/exclusion test. Exclusion of transfusion recipients could even be perceived as a signal that, despite all efforts, blood supplies are not sufficiently safe.

To secure blood supplies, new donors would have to be recruited to a considerable extent. According to the German data on epidemiology collected by the Robert Koch-Institut, the prevalence of virus infections in new blood donors is higher than in long-term donors. While special promotion campaigns (cf. bone marrow/stem cell donors for children with leukemia) motivate many people to donate in the short-term, it is the continued reliability of donor preparedness in connection with the constantly required readiness to act that is important in blood donor promotion campaigns. The following possible approaches could secure continued donor preparedness and the supply of blood components:

- Economical use of blood and blood products: All measures that result in optimal use of blood and blood products will not only minimize the possible transmission risk but will also contribute to safeguarding the supply of blood and blood products. The activities in Germany and the European Union have been described above.
- Sustained recruitment measures: The GRC blood donation services are currently spending approx. €20 million a year on maintaining their existing donor base. Additional recruitment campaigns (approx. €3 million annually) have been aimed at the approx. 1–2% donor increase required to compensate for the annual rise in demand due to the increasing average age of the population. The GRC has been able to fulfill this goal with a relatively low budget, since advertising space in various media has generously been made available free of charge. In the case of donor exclusion due to transfusion history, just below 18,000 additional donors per month would be needed in the first half-year, and more than 11,800 additional donors per month in the second. Altogether, approx. 4 first-time volunteers would have to be recruited for each deferred donor (compare Appendix (E) of [1]). Such an additional recruitment campaign requiring more financial means could no longer be carried out by the blood donation services.
- Increasing the social prestige of the blood donors: It might be helpful to provide donors with a non-material reward in the form of increasing the social prestige attached to the act of giving blood. A professional study should explore the possibilities and develop suggestions for raising the esteem in which blood donors are held.

Table 5
Main reasons for deferral according to an analysis by the Institut für Transfusionsmedizin (Institute for Transfusion Medicine) Münster of the German Red Cross blood donation service West in 2004 (in % of volunteer donors)

| | |
|---|---|
| Hemoglobin | 2.21% |
| Operations, interventions | 1.30% |
| Blood pressure | 1.17% |
| Infectious diseases | 1.24% |
| Suspected/risk of infection | 0.78% |
| Current donation situation (e.g. unease, fear, communication problems) | 0.73% |
| Medication | 0.72% |
| Traveling | 0.28% |

According to statistics from the German Red Cross blood donation services, the deferral rate among all volunteer donors in 2003 was 8.87%. There is a strong fluctuation in the deferral rate between the various blood donation services, which ranged

[9] German Red Cross (GRC) blood donation centre West, figures from North Rhine-Westphalia.

from 5–14% and is now 7–12%. No correlation can be detected between the deferral rate and the degree of conurbation. These differences can certainly not solely be explained by differences in the donor population of the German Red Cross blood donation services. An improvement could be the introduction of uniform interpretation aids throughout Germany.

## 15. Summary and conclusions

So far 162 cases of vCJD in the UK, 20 in France, 4 in Ireland, 2 in the Netherlands, 2 in the USA, and one case each in Canada, Italy, Japan, Portugal, Saudi Arabia, and Spain have been observed. Twenty-seven of these patients resided outside the UK and had not spent considerable time in the UK; a connection with stay in the UK is questionable in the case in Japan. It must not be ruled out that vCJD will be diagnosed in more countries. Recent model calculations in the UK [50] have resulted in lower than previously published estimates of the overall number of clinical vCJD cases, however, with considerable confidence intervals. A fundamental assumption is that new infections from the food chain have been effectively stopped. On the basis of new estimates, the number of up to 600 cases of vCJD for Germany indicated in the report of this group in 2001 can be considered as too pessimistic.

Three cases published in the UK since 2004 must be regarded as evidence for the transmissibility of the vCJD pathogen by blood. One of the recipients died from an unrelated disease. However, autopsy revealed the vCJD pathogen in the spleen and lymph nodes, pointing to a subclinical or not yet symptomatic infection. Unlike all other previously observed vCJD cases, this patient was heterozygous M/V at codon 129. This observation and the results from a serial investigation of appendix tissue in the UK could indicate that there are a considerable number of infected persons who might not develop vCJD, or in whom its manifestation is delayed. At present, it is not possible to ascertain whether infectivity is present in the blood of these persons, and if so, at what time and to what extent. Precautionary measures should therefore not be based exclusively on the number of already manifested vCJD cases and the forecast of future numbers of cases derived thereof.

A possible transmission of the vCJD pathogen by plasma products still cannot be entirely ruled out, but it seems unlikely since various experimental systems have shown that prions are largely removed during the manufacture of these blood products. Examining the effectiveness of these steps, however, should be continued in a product-oriented manner. A Note for Guidance was published in 2004 by the European Medicines Agency (EMEA) for this purpose [88].

Transmissibility of vCJD by transfusion had been assumed already in 2001; precautionary measures for minimizing the risk had been taken. As an additional measure, the exclusion of transfusion recipients from donating blood has to be considered in order to break a hypothetical chain of further spread and possible perpetuation of vCJD by blood products. Such exclusion has been introduced in the UK, the Netherlands, Switzerland, and as early as 1998—to prevent viral transmissions—in France. A model calculation took these considerations into account; to be on the safe side, still a worst case scenario was dealt with. For Germany, the group concluded that such exclusion is not warranted. The evaluation of the potential gain in safety regarding vCJD, based on the above mentioned model calculation, was not considered to outweigh the drawbacks of such a measure.

The secondary route of infection by blood could largely be stopped as soon as a suitable test could be introduced into routine donor screening. No such test is currently available; developing and optimizing test methods should have high priority.

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