population (Figure 2B). The reason for these small differences is described below.

The cumulative numbers of deaths from the infection are given in Table 3. The numbers are considerably smaller for the long than for the short incubation period because a long incubation period implies more deaths from other causes. The numbers are given separately for cases in patients with and without a history of blood transfusion. The route of infection for nonrecipients is alimentary only, whereas the route of infection for recipients is unclear. If we compare the simulations at 100% and 0% infectivity of blood transfusions, we observe 172 and 224 additional cases for the short and the long incubation periods, respectively. These numbers represent 11% of 1,557 and 31% of 725 cases, which would be expected for 0% infectivity for the short and long incubations periods, respectively. For the short incubation period we expect a higher absolute number of alimentary cases but a smaller proportion of transfusion cases than for the long incubation period. The exclusion of donors would prevent only 15 and 50 cases, i.e., ≈15 (0.9%) of 1,729 and 50 (5%) of 949, respectively, at the end of the epidemic. The epidemic lasts for ≈50 or ≈150 years for the short and the long incubation periods, respectively.

The predicted yearly incidence of deaths due to vCJD, separated by transfusion history, is shown in Figure 3. The yearly peak incidence of total deaths would be 128 and 29 for the short and the long incubation periods at 23 and 51 years after the beginning of the epidemic, respectively. For 0% infectivity the peak incidence would be only 5 and 3 cases less for the short and long incubation periods, respectively, which implies that the exclusion of donors with a transfusion history does not effectively prevent infection.

Figure 4 shows the predicted yearly incidence of deaths according to the route of infection. The time lags between the peaks of deaths due to alimentary infection and due to transfusion clearly differ and are 9 and 20 years for short and long incubation periods, respectively.

Finally, we considered the absolute prevalence of infected donors according to their history of blood transfusion (Figure 5). Most infected donors do not have a transfusion history, which explains the negligible effect of a policy excluding transfusion recipients from donation.

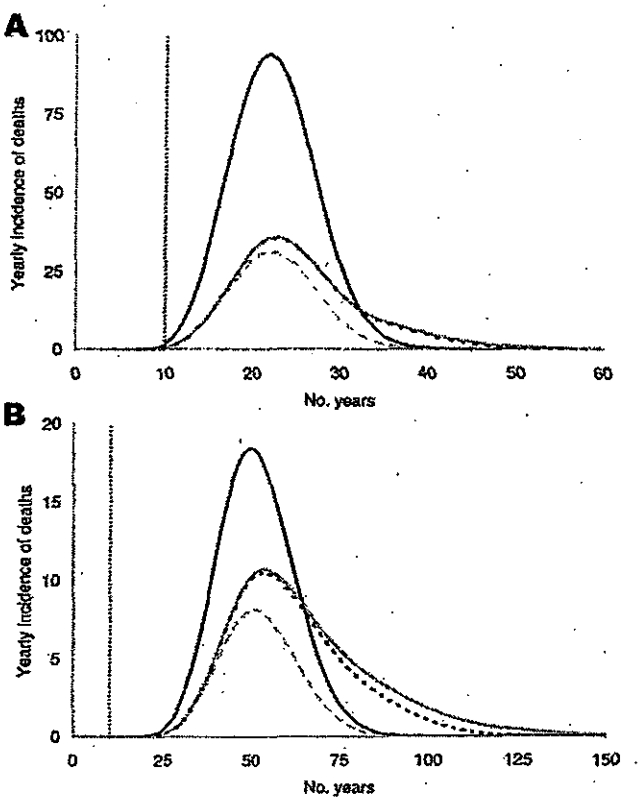

Figure 3. The yearly incidence of deaths for an incubation period of 16 (A) and 50 (B) years. The black curves show nonrecipients of blood transfusion who were infected only by the alimentary route. These curves are independent of the infection probability and the rate of donor exclusion. The lower 3 curves represent the deaths of recipients originating from 0% infectivity of blood transfusions (dashed gray), 100% infectivity without donor exclusion (solid gray), and 100% infectivity of blood transfusions with donor exclusion (dotted black, almost indistinguishable from solid gray line in A). The differences between the solid and dashed gray curves represent the cases due to blood transfusion.

To determine whether the same model could also predict transition into a positive endemic equilibrium of the infection, we made the unrealistic assumptions that the rates of donor recruitment and donor loss are constant between the ages of 18 and 67 and that the rate of receiving a blood transfusion is constant throughout life. Then the model showed an extremely long time (>2,000 years)

Table 3. Cumulative numbers of deaths from variant Creutzfeldt-Jakob disease at the end of the epidemic

Incubation period	Donors excluded	Infectivity (%)	Without transfusion	With transfusion	Total no. cases
Short	No	0	1,167	390	1,557
	No	100	1,167	562	1,729
	Yes	100	1,167	547	1,714
Long	No	0	503	222	725
	No	100	503	446	949
	Yes	100	503	396	899

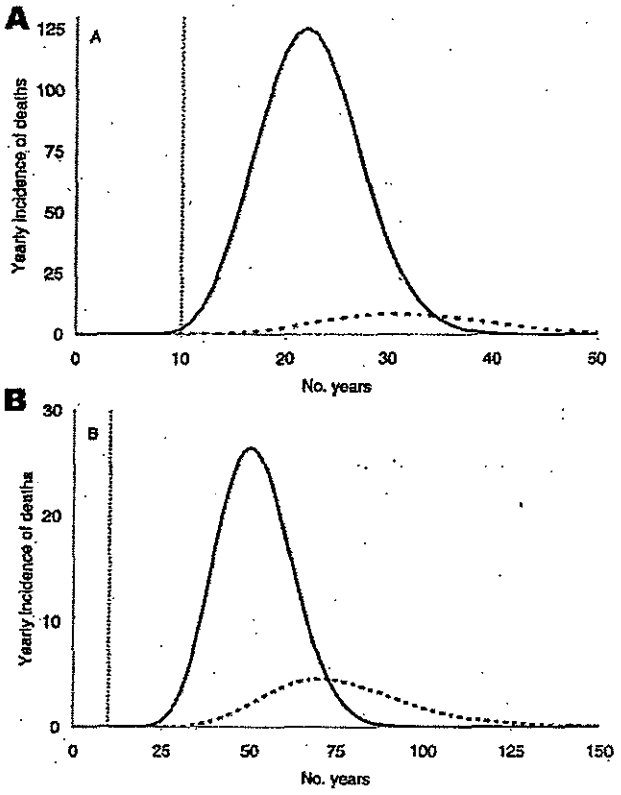

Figure 4. Yearly incidence of deaths caused by alimentary transmission (solid line) and by blood transfusion (dashed line).The 2 peaks differ by 9 and 20 years, depending on the incubation period: 16 (A) and 50 (B) years, respectively.

before positive equilibrium would be reached (results not shown).

Discussion

Our model is the first attempt to describe in a realistic way the transmission of infections through blood transfusions. In 1994, Velasco-Hernández proposed a model for the spread of Chagas disease by vectors and blood transfusion (*13*). His model was used by Roberts and Heesterbeek to introduce their new concept to estimate the effort to eradicate an infectious disease (*14*). Huang and Villasana included transmission through blood transfusion in an AIDS model (*15*). All these models have in common what Inaba and Sekine state about their extension of Velasco-Hernández's Chagas model: "...here we assume that blood donors are randomly chosen from the total population, and so there is no screening and the recipients of blood donations are donating blood themselves at the same rate as anybody else. This is an unrealistic assumption, but we will use it." (*16*). These models implicitly describe transmission through blood transfusion exactly like person-to-person transmission by droplet infections.

The key innovation in our model is the simultaneous incorporation of 6 functions that all depend explicitly on the age of a person: 1) natural death rate, 2) rate of receiving a blood transfusion, 3) rates of donor recruitment, 4) donor loss, 5) death rate associated with transfusions, and 6) proportion of transfusion recipients at increased risk for death. The age-dependent effects of these processes cannot be ignored. Peak ages of donor activity (≈22 years) and of receiving a blood transfusion (≈70 years) are quite distinct and ≈50 years apart. This age pattern does not favor the spread of infection by blood transfusion. Another factor that acts against the infection becoming endemic is the transfusion-associated death rate. The good quality of the follow-up data of nearly 3,000 patients helped to incorporate realistic assumptions about the survival probabilities of transfusion recipients (*4*). The only data available about the joint distribution of blood donor activity and history of a blood transfusion was the CJD case-control study performed in Göttingen, Germany (*7*).

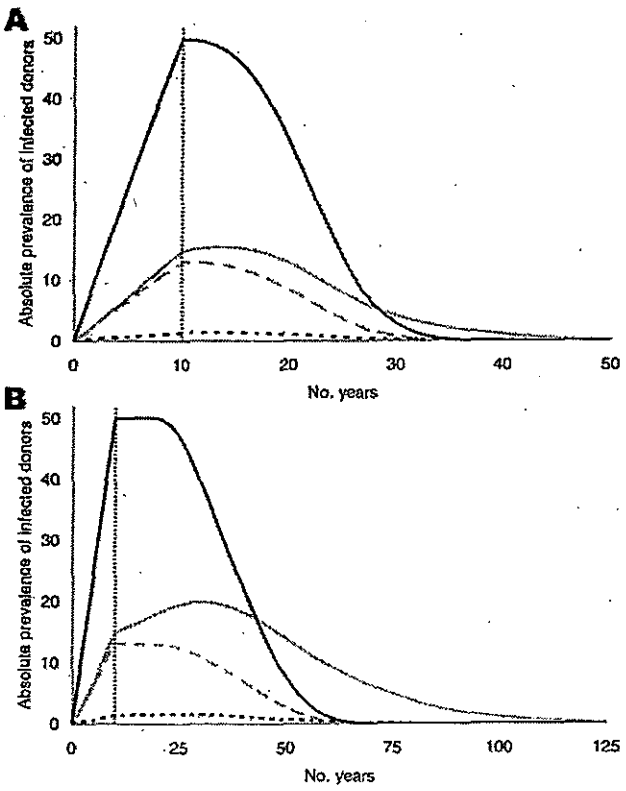

Figure 5. Absolute prevalence of infected donors for an incubation period of 16 (A) and 50 (B) years. The solid black curves show the infected donors without transfusion history. These curves are identical for 0% and 100% infectivity and are independent of donor exclusion. The gray curves show infected donors with transfusion history for 100% (solid) and 0% (dashed) infectivity, respectively, without donor exclusion. The dotted black curves show the effect of donor exclusion starting at the beginning of alimentary risk. Most infected donors have no transfusion history and cannot, therefore, be excluded from blood donation.

The length of the incubation period plays a major role in transmission dynamics and hence was subject to a sensitivity analysis. The model does not account for possible changes of infectivity during the incubation period. The model represents a worst-case scenario because it assumes 100% infectivity throughout the period of infection. Even under this extreme assumption, donor exclusion can prevent only 0.9% (or 5%) of the expected deaths, assuming the incubation period has a mean duration of 16 (or 50) years. The main explanation for this surprising result is that most infected donors have been infected by the alimentary route and never received any blood transfusion and, therefore, are not eligible for donor exclusion.

The present simulations have arbitrarily assumed a cumulative incidence of alimentary infection, about 25 per million (2,000 per 80 million). With pessimistic assumptions, the model predicts either 19.5 deaths per million for the short incubation period or 9 deaths per million for the long incubation period in the absence of spread through blood transfusion. This corresponds to at least 9 (36%) of 25 deaths attributable to the infection, which is ≈2 orders of magnitude higher than expected for vCJD in the United Kingdom. As of July 2006, the number of vCJD cases in the United Kingdom was 160. If we assume that the total number of cases will be 200, then our assumption corresponds to about 3.3 cases per million. Thus, at most, 1.4% of infected persons would die from the infection (unless a second wave of vCJD cases with a long incubation period occurs). According to our model, 0.9% of the deaths could be prevented by donor exclusion under the assumption of the short incubation period. In absolute numbers this would be ≈2 cases.

In France, the total number of vCJD cases recorded through July 2006 is 18. Even under the assumption that this number represents only 35% of the total number of cases (*17*), the absolute expected number of prevented cases would be <1. In 1998, France decided to exclude donors with a transfusion history, primarily to reduce the spread of viruses. The present model could be modified to assess the effectiveness of excluding donors with transfusion history for preventing emerging infections with different modes of transmission and additional epidemiologic states, e.g., latent or immune.

Our worst-case scenario assumptions of the epidemiology might seem similar to the situation in the United Kingdom. In Germany, no case of vCJD has been reported, which indicates that the expected number of cases in Germany is at least 2 orders of magnitude less than that in the United Kingdom. This latter aspect was considered in the interpretation of our model by a working group commissioned by the German Federal Minister of Health, which recommended in April 2006 that persons with a transfusion history not be excluded from donating blood (*18*). Our analysis enables different countries to perform their own risk assessment and choose a strategy according to the absolute number of cases observed or expected.

The German CJD Surveillance study was supported by a grant from the German Ministry of Health (Az 325-4471-02/15 to Inga Zerr and H. A. Kretzschmar). Helpful discussions about previous versions of the model took place with the Working Group Overall Blood Supply Strategy with regard to vCJD, Germany (Chairman R. Seitz).

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医薬品　研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
一般的名称	－		研究報告の公表状況	http://www.fda.gov/cber/blood/fxivcjdqa.htm	公表国：米国	
販売名（企業名）	－					

研究報告の概要

変異型クロイツフェルトヤコブ病（vCJD）が血漿由来の血液凝固第 XI 因子製剤（pdFXI）投与により患者に伝播するリスクが問題となっている。米国では 1989 年から 2000 年にかけて約 50 名の患者に英国供血者血漿由来の pdFXI が投与された。
米国公衆衛生局（PHS）は、vCJD のリスクは小さいものだと考えている。リスク評価にコンピュータモデルを使用したが、多くの未知の要因があるため、正確なリスク評価は行えない。供血時に英国供血者が気付かずに vCJD を保持していた可能性があるため、この pdFXI 製剤を投与された患者には有意なリスクがあるかもしれない。
これまでのところ、英国供血者からの血漿分画製剤を長期にわたり投与された患者も含め、血友病患者や FXI 欠乏症などの血液凝固異常患者に vCJD が発症したという事例は世界的にも知られていない。
2003 年 12 月から 2007 年 4 月までの間に赤血球輸血を通じて vCJD 因子が伝播したとされる 4 例はすべて英国での報告であり、いずれも pdFXI などの血漿分画製剤は関与していなかった。
今のところ、健康な供血者や受血者の vCJD を検出するための検査はない。

使用上の注意記載状況・その他参考事項等

重要な基本的注意
現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的な vCJD 等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

報告企業の意見	今後の対応
pdFXI の vCJD 伝播リスクは非常に小さいと考えられるとの情報である。 本情報にもあるとおり、現時点まで血漿分画製剤からの vCJD 伝播の報告はなく、血漿分画製剤の製造工程でプリオンが除去できるとの情報もある。 なお、本報告で問題とされている英国供血者血漿は弊社では使用していない。	今後とも vCJD に関する安全性情報等に留意していく。

Potential Variant Creutzfeldt-Jakob Disease (vCJD) Risk

From Investigational Factor Eleven (FXI) From Donors In The United Kingdom

Summary Information

Key Points:

- In recent years, questions have been raised concerning the risk from variant Creutzfeldt-Jakob disease (vCJD), a rare but fatal brain infection, in patients who received plasma-derived investigational Factor Eleven (pdFXI) made from plasma obtained in the United Kingdom (UK) where vCJD has occurred.
- Approximately 50 individuals in the US, between 1989 and 2000, received pdFXI made using plasma from donors in the UK. This product was used to prevent or treat bleeding due to a rare problem, a deficiency of FXI.
- The US Public Health Service (PHS) believes that the risk of vCJD is likely to be small based on a number of considerations. We used a computer model to help determine the risk but we recognize that many unknowns prevent us from accurately determining the risk. The model raised the possibility that those who received this pdFXI product could potentially be at significant risk due to the possibility that a UK blood donor unknowingly carried vCJD at the time of donation. However, we believe the risk is small based on additional considerations. ***To date we are not aware of any cases of vCJD having been reported worldwide in patients with hemophilia or other blood clotting disorders, including pdFXI deficiency, who have received large amounts of plasma-derived products manufactured from UK plasma. This includes patients who received these products over a long period of time.***
- Contacting a specialist in bleeding disorders, e.g. a healthcare provider specializing in hemophilia, and/or a Hemophilia Treatment Center is a good way to learn about any new information as it becomes available.

Additional Information:

- Between December 2003 and April 2007, there have been four reports of people, all in the UK, who probably acquired the vCJD agent through red blood cell transfusions. This has increased concern about the potential transmission of vCJD by blood products, particularly those made from UK blood donors. ***None of the reported cases involved any plasma-derived product, including pdFXI.***
- However, because of the finding that red blood cells can transmit vCJD, FDA used a computer model to conduct a risk assessment to try to estimate the possible risk that might occur from the UK investigational pdFXI.
- The actual risk of acquiring vCJD is unknown and is likely to be small. Because so much is unknown about vCJD and its prevalence, the risk assessment performed by FDA has a lot of uncertainty, making it impossible to precisely estimate the risk of vCJD in general, or the actual risk to individual FXI deficient patients. There is no test yet available to detect vCJD in healthy donors or recipients. The US Public Health Service believes the risk of vCJD is likely to be small. There have been no reports of vCJD in patients using any plasma-derived blood product in the UK or anywhere else in the world.
- At this time, PHS does not believe there is a need for UK pdFXI recipients to inform their surgeons or dentists about the recipient's potential exposure to vCJD. Also, there is no recommendation for surgeons and dentists to take any special precautions based on such potential exposures. This belief is based on the very large degree of uncertainty in the FDA risk assessment and the lack of known cases of vCJD transmitted by plasma-derived clotting factor products in the UK, where risk is considered greatest, or anywhere else in the world. Also, relatively few patients were exposed to the pdFXI product in the US compared to the number of recipients of plasma-derived clotting factors, of which pdFXI is only one of many, in the UK.
- vCJD originally came from a disease in cattle called "mad cow disease" or BSE (bovine spongiform encephalopathy). Transmission of the BSE agent to humans, leading to vCJD, is believed to occur primarily from eating beef and beef products contaminated with the BSE agent. Both BSE and vCJD are invariably fatal brain diseases with incubation periods typically measured in years.
- From 1995 through April 2007, 202 individuals with vCJD were reported worldwide, with 165 in the United Kingdom (UK), and three in the United States. Two of the individuals in the United States had lived in the UK from 1980-1996 during a key exposure period to the BSE agent. The third US individual with vCJD most likely acquired the infection in Saudi Arabia. The reported incidence of vCJD in the UK, based on disease onset, peaked in 1999 and has been declining thereafter. In the UK, where most cases of vCJD have occurred, the current risk of acquiring vCJD from eating beef and beef products appears to be negligible.
- More information about vCJD is available on these government websites:
  - FDA: Potential Risk of Variant Creutzfeldt-Jakob Disease (vCJD) From Plasma-Derived Products
  - Centers for Disease Control and Prevention: vCJD (Variant Creutzfeldt-Jakob Disease)
  - US Department of Agriculture
- Information also may be obtained from these non-government sources:
  - Committee of Ten Thousand
  - Hemophilia Federation of America
  - National Hemophilia Foundation and/or HANDI
  - World Federation of Hemophilia

Updated: May 30, 2007

Questions and Answers

Variant Cruetzfeldt-Jakob Disease (vCJD) and Factor XI (pdFXI)

Index

Q. What is vCJD and how is it spread?

A. Variant Creutzfeldt-Jakob disease, or vCJD, is a very rare, fatal disease that can infect a person for many years before making them sick by destroying brain cells. Eating beef and beef products contaminated with the infectious agent of bovine spongiform encephalopathy (BSE) is the main cause of vCJD.

Most cases of vCJD have occurred in the United Kingdom (UK). Individuals in the UK are at a greater risk for this rare disease than are individuals elsewhere because of the previous higher risk of potential exposure to contaminated beef in the UK diet. From 1995 through April 2007 there have been 202 individuals with vCJD reported worldwide, 165 of them in the UK. In the United States (US), there have been three reported cases of vCJD. Two of these individuals had lived in the UK during 1980-1996, a key exposure period to the BSE agent. The third US individual with vCJD probably acquired the infection in Saudi Arabia.

The reported incidence of vCJD in the UK, based on disease onset, peaked in 1999 and declined thereafter. In the UK, where most cases of vCJD have occurred, the current risk of acquiring vCJD from eating beef and beef products appears to be negligible.

Only three cases of BSE have been found in US cattle, and safeguards are in place to help prevent infected beef products from entering our food supply. These safeguards include restricting importation of cattle and beef products from almost all countries with BSE, a surveillance program to detect BSE in the US, prohibiting the use of high-risk animal-derived proteins in cattle feed, prohibiting meat from sick cattle to be used for human consumption, and requiring the removal of high-risk materials from carcasses of cattle over a certain age.

While vCJD is primarily due to eating infected beef and beef products, four people in the UK became infected with the vCJD agent after receiving red blood cells from three donors who later developed vCJD. Three of the red blood cell recipients developed typical vCJD and died from the disease. A fourth died of an unrelated illness but had evidence of infection. To date, there have been no reports of vCJD transmission by close personal contact (such as being in the same room with someone who has vCJD, hugging, kissing, or having sexual relations).

Q. How does vCJD differ from Creutzfeldt-Jakob disease (CJD)?

A. Both vCJD and CJD cause progressive degeneration of the brain leading to death. However, the variant form—never seen before 1994—usually affects persons much younger than other forms of CJD. Unlike CJD, vCJD has been acquired by food exposure and transmitted by blood transfusion. vCJD also has somewhat different clinical symptoms, a longer survival after onset of illness (the majority of illnesses lasting more than one year), and produces a characteristic abnormality in brain tissue called "florid plaques" rarely if ever seen in the other forms.

Q. Is it known that pdFXI can transmit vCJD?

A. No. However, pdFXI is made from plasma. Plasma is the liquid part of blood remaining after the cells are removed. Animal studies show that if blood carries the vCJD agent, so can the unprocessed plasma.

Manufacturing steps used in making pdFXI have been shown to help remove infectious agents, including agents similar to that causing vCJD. The manufacturing steps may reduce or eliminate most risk even if a vCJD-infected donor contributed plasma.

Q. What is the likelihood that a patient who received pdFXI could have become infected with vCJD?

A. The US PHS believes the risk of developing vCJD infection from pdFXI is likely to be small. Many unknowns prevent us from accurately determining the risk using a computer model, and we believe the risk is likely to be smaller than the modeling predicts. However, we do not know this with certainty. Right now, there is no test available to detect vCJD in blood donors or recipients. There is no way of knowing whether a person is infected if