SUMMARY

In Greece a policy to defer donors who have lived in the UK for longer than 6 months between 1980 and 1996 has been implemented in order to avoid the transmission of variant Creutzfeldt–Jacob disease (vCJD) via blood transfusion and therefore to reduce the theoretical risk of transmitting vCJD through the blood supply. The objective of this study was to evaluate blood donor loss due to vCJD deferral and to refine estimates of the possible risks and benefits of donor-deferral strategies that are aimed at avoiding transmission of vCJD. Records of all pre-donation deferrals over a 12-month period were studied. As many as 11,936 pre-donation screening interviews were conducted. There were 1,473 (12.3%) deferrals for multiple reasons. The risk of transmitting vCJD accounted for 61 (4.1%) of all deferrals. The rate of deferral of voluntary donors was significantly different from that of replacement donors (67.2% vs. 32.8%, \( p = 0.001 \)). The vCJD deferral was also associated with ages 36 through 48 years and with male gender. Monitoring and evaluating deferral rates and reasons could be used to assess the magnitude of blood donor loss due to vCJD deferral in Greece.

KEYWORDS

blood donation, variant CJD deferral
BACKGROUND AND OBJECTIVES

Creutzfeldt-Jacob Disease (CJD) is one of a group of diseases called Transmissible Spongiform Encephalopathies (TSE) or prion diseases. Variant Creutzfeldt-Jakob disease (vCJD), first described in 1996, is a “new” disease, linked with the outbreak of Bovine Spongiform Encephalopathy (BSE) in cattle. These diseases, in general, have long incubation periods and are characterized by severe and irreversible damage to the central nervous system eventually resulting in death. The diseases are caused by prions. Prions exist in our body in a normal, harmless state (PrPC). However, prions become deadly infectious agents once they experience a conversion into a misfold state. Normally, PrPC is composed mostly of alpha-helix structure with a minority of beta-sheets. In a pathological prion PrPSc, beta-sheet conformation dominates. Abnormal PrPSc accumulation leads to amyloid plaque deposits, neuronal apoptosis, vacuolation of the brain (sponge – like appearance) and eventually death. So far there are no clinically effective treatments for CJD. One form of this disease, variant CJD (vCJD), first identified in 1996, is known to be caused by ingesting beef contaminated with Bovine Spongiform Encephalopathy (BSE), and is more commonly known as the human form of “mad cow” disease. Collaborative projects have findings that strongly suggest that vCJD may be transmitted via blood transfusion, thus establishing beyond reasonable doubt that blood transfusion is a transmission route. While the risks of transmission, of known viruses HBV, HCV and HIV are now extremely low, unfortunately other infectious diseases such as vCJD have emerged as a new transfusion risk. The absence of a screening test for vCJD in blood donations emphasizes the need for precautionary measures to be taken in order to exclude donors, who may have already been incubating vCJD, from donating. In reaction to various scientific reports, the Ministry of Health & Social Solidarity of Greece issued a regulation in February 2001 banning any potential donor who spent accumulated time of at least six months in the United Kingdom between 1 January 1980 and 31 December 1996. Moreover, as is stated in the European Blood Directive in order to avoid iatrogenic CJD transmission the following measures are implemented: potential donors must not donate if they are recipients of dura matter grafts, corneal, scleral or ocular tissue grafts and recipients of pituitary derived extracts. Finally, any donor who has been diagnosed with any form of CJD, or other associated disorder or has had two or more blood relatives develop a prion-associated disease is also deferred from blood donation. Particularly overseas, in Canada, while there have been no cases of vCJD attributable to the use of blood or plasma derivatives, lack of experience with this condition and the causative agent suggest that vCJD may have the potential to spread through blood or blood derivatives. People are not eligible to donate blood or plasma if they have had a blood transfusion or have received medical treatment with a product made from blood in the UK, France or Western Europe since 1980. Furthermore, according to previous FDA recommendations and to the latest ones, stated in the AABB 2012, donors who have spent a total of three months or more in the UK from the beginning of 1980 through the end of 1996, donors who have spent a total of five years or more in Europe from 1980 to the present, current or former US military personnel, civilian military employees and their dependents who resided at US military bases in Northern Europe (Germany, UK, Belgium and the Netherlands) for a total of six months or more from 1980 through 1990, or elsewhere in Europe (Greece, Turkey, Spain, Portugal and Italy) from 1980 through 1996 and any donors who have injected bovine insulin since 1980, unless it is possible to obtain confirmation that the product was not manufactured after 1980 from cattle in the UK, are also deferred indefinitely from donating. As a result of these restrictions, we have created an array of precautions based on our present knowledge of the disease in order to reduce the risk for infectious contamination of blood by CJD via transfusions especially as there is no specific screening blood test available. In considering this potential risk and measures to deal with it, the principle has been adopted that one must seek to apply measures which will reduce the targeted risk without jeopardizing the safety of the blood system in other ways. In Greece, approximately 600,000 units of blood are collected annually mainly from healthy non – compensated voluntary blood donors and from family members and friends of the patients in need of a blood transfusion (replacement donors). This is achieved by 9 National Blood Transfusion Centers and 101 National Blood Transfusion Services throughout the country. To encourage blood donation, blood collection sessions are organized at various places, where there are a lot of determined volunteers, such as churches, schools, community centers, private companies and associations on the Greek mainland and at various Greek islands. Thereby, according to the Greek National Data of 2007–2009 the source of blood donations origins from 45% voluntary blood donors, 48.5%
family members and friends (replacement donors), 2.4% Armed Forces personnel and 4.1% from the Swiss Red Cross [Figure 1], the data are comparable for all three years. As far as the provision of blood concerns, 78.1% is transfused to patients of Hospitals and Private Clinics, 17.5% to thalassemic patients and 4.4% is discarded. Moreover, according to the recent summary report of Coordinating Haemovigilance Centre of Greece (SKAE), the total number of tested blood units for 2010 was 609,735 and 582,187 for 2011. The annual average of the National collection of whole blood units and plateletpheresis during the SKAE study period 2007-2011 was 615,000 and 22,000 respectively. In our Blood Transfusion Service during the year 2011, 11,936 blood donor candidates were evaluated through pre-donation screening interviews. Of the donations that were collected, 2,616 units of red cells, 402 therapeutic units of fresh plasma and 678 therapeutic units of platelets were transfused in patients of our hospital, while the rest of the collected units were transfused in patients of other hospitals or private clinics. Thus, the objective of this study was to evaluate blood donor loss due to CJD deferral and to refine estimates of the possible risks and benefits of donor-deferral strategies that are aimed at avoiding transmission of vCJD.

MATERIALS AND METHODS
During the year 2011, 11,936 candidates for blood donation were evaluated through pre-donation screening interviews. In particular, 7,336 were volunteer donors, 315 were personnel from the Armed Forces and 4,285 were replacement donors as shown in Figure 2 in comparison with the above National Data. The proportion of male blood donor candidates was 65% and 35% were female, with a mean age of 34.8 years. 7,651 (64.1%) were volunteers and 4,285 (35.9%) were replacement donors. Data were collected from two categories of donors: those who appeared at the Blood Service (27.1%) and those who went to donate to our sessions (72.9%). Donor selection was done by having the blood donor answer a questionnaire followed by physical examination (blood pressure, heart rate) and hemoglobin estimation. During the blood donor interview, attention was given to all questions relative to CJD infection. A retrospective study of pre-donation deferral of prospective blood donors potentially infected with CJD was conducted. Records of all pre-donation deferral reasons over a period of one year (1 January 2011 to 31 December 2011) were analyzed to quantify the deferral rate. Deferred donors were also stratified according to gender, age and category (volunteer or replacement donor). Deferred persons were categorized by age, gender and reason for deferral by retrospective evaluation of the donor questionnaires. Proportions were compared for significance using Pearson’s correlation coefficient on the SPSS statistics computer programme.

RESULTS
Total number of candidates for blood donation, in the year 2011, at our Blood Transfusion Service was 11,936. 7,651 (64.1%) were volunteers and 4,285 (35.9%) were replacement donors. 1,473 donors were deferred from donation. The total deferral rate was thus 12.3% for all reasons. The strategy of deferring donors who have lived in the UK for 6 months or longer between 1980 and 1996 to avoid possible vCJD transmission, led to the loss of 61 donations accounting for 4.1% of all deferrals [Figure 3]. None of the donors referred to any known risk factors for occurrence of familial (hereditary) or iatrogenic CJD. The mean age of the donors deferred for vCJD was 42 years of age. Females were found to have lower deferral rates than males (18% vs 82%, p=0.01) and also volunteers to have higher rates regarding vCJD deferral as compared to replacement donors (67.2% vs 32.8%, p=0.01).
FIGURE 2
Source of blood donors of our Blood Transfusion Service during the year 2011 as compared to the National data for all Blood Centres and Services for the years 2007–2009.

FIGURE 3
Distribution % of reasons of deferral of 1,473 potential blood donors in our Blood Transfusion Service (2011).
DISCUSSION

Variant CJD is a subset of a broad range of prion diseases. More specifically, vCJD is one of four types of CJD: Sporadic (sCJD) which accounts for the vast majority (85%) of CJD cases, Familial or Genetic regarding inherited cases of CJD, iatrogenic (iCJD) caused by contaminated transplants and medications and lastly variant CJD (vCJD) acquired mainly through consumption of contaminated cattle. However, in 2004 the possibility of human to human transmission of vCJD through blood transfusion arose. Since 2004, four suspected cases of vCJD infection through blood transfusion were reported, all in the United Kingdom, providing empirical support that vCJD is transmissible by blood transfusion. In these four cases, the donors developed vCJD, 17–40 months after blood donation, and the recipients developed vCJD about 7 years after transfusion. A further transmission of vCJD was described in February 2009. The patient suffered from haemophilia and had received batches of factor VIII to which a donor, who subsequently developed vCJD, had contributed plasma. The patient died of other causes but was found to have evidence of prion accumulation in his spleen. The possibility of vCJD transmission by blood has implemented precautionary measures such as indefinitely deferring donors who have spent more than 6 months in the UK between 1980 and 1996. This is the most direct solution to the problem, but public health policy must be conservative and cautious. Moreover, if there should be more cases of vCJD transmission by blood transfusion, the public would lose faith in the blood transfusion system, resulting in more losses of blood donations. In order to balance the costs and benefits of public health policy regarding vCJD and blood supply some solutions of the problem must be considered. Firstly, a blood test is the most direct solution to the problem, this could identify the contaminated with vCJD blood units. On the other hand, maybe screening people’s blood would reveal the true magnitude of the problem especially in certain countries where the majority of cases have clustered. Secondly, component processing of leukocytes and plasma can offer a combination or an alternative to the above. According to some scientists it is likely that host B lymphocytes are involved in the transport of prions from the periphery to the central nervous system. In addition, plasma seems to be another transmission route for PrPSc, while rejecting the hypothesis that red blood cells carry PrPSc. These results suggest that reduction of leukocytes can lower the risk of vCJD transmission by blood. Furthermore there are prion removal devices under development that would significantly decrease the infectivity of the contaminated blood. The FDA does not recommend deferral of Source Plasma donors who have lived or traveled elsewhere in Europe, in contrast to deferral of donors of Whole Blood and blood components intended for transfusion, Source Leukocytes, and recovered plasma. This difference in deferral criteria between source plasma donors and others takes into account that, in contrast to whole blood and other components used for transfusion, plasma derivatives made from source plasma are highly processed materials. Also the FDA has taken into consideration the estimated low prevalence of vCJD infections in Europe compared to the UK, the likely ability of plasma fractionation processes to reduce TSE (Transmissible Spongiform Encephalopathy) infectivity and the uncertain effect of a deferral upon the supply of plasma derivatives. Risk reduction measures within the UK are more problematic. All adults (except strict vegetarians) are considered to have been at risk of vCJD through the food chain. An early risk assessment (February 1999) made two firm recommendations on risk reduction. The switch to non-UK plasma for fractionation was achieved over the second half of 1998. Leukodepletion was achieved in a progressive program completed by 1 November 1999. To reduce further the risk, exclusion of donors who had themselves received a blood transfusion in the UK since 1980 was implemented in April 2004. Nothing however is without cost, figures from the National Health System of the UK in 2007, show us that leukodepletion costs £70 million annually and there was additional substantial cost of importing plasma from the USA. The development of specific prion reduction filters for RBCs offer the potential of a further substantial reduction in infectivity of the blood supply and the risk of transfusion transmission. The UK Blood Services evaluated then that these filters and their introduction was likely to add another £100 million annually to the blood supply bill. On the other hand, several cases of prion transmissions have been reported in the United Kingdom in patients who contracted CJD years after having received non-leukodepleted blood products from asymptomatic donors. In October 1997, the UK Spongiform Encephalopathy Advisory Committee advised that universal leukodepletion must be considered. The UK Departments of Health commissioned an independent risk assessment by Det Norske Veritas Consulting (DNV) asked the Blood Services to consider the feasibility (Comer & Spouge, 1999). Implementation was recommended in July 1998 and completed by the autumn of
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1999 (Department of Health, 1998). The measure was predicted on studies suggesting that B lymphocytes were likely to be involved in the initial phases of disease and that leukocytes were an important locus of infectivity in the peripheral blood.[31] Hitherto, no case of transfusion-transmitted vCJD has been reported from the UK in any patient who received blood after the implementation of universal WBC reduction in October 1999.[32] However, the possible benefits of leukodepleted red blood cell concentrates (LD–RBCs) use with regards to the vCJD transmission risk remains unclear. Data obtained in rodent models indicated that only 40% of the infectivity seemed to be associated with the white blood cells (WBC), while plasma would contain 60%.[33] Based on these results, and the fact that around 10 mL of plasma remains in each RBC unit, it could be expected that leukodepletion alone might be unable to provide a significant prion infectivity reduction. In that context, one company (MacoPharma, Tourcoing, France) developed a prion removal device (P-Capt) to reduce the plasma associated infectivity from RBCs by incorporating a prion-specific resin into a biocompatible filter.[34]

CONCLUSION
Current evidence indicates that it is possible to effect vCJD transmission through blood transfusion. No incidence of vCJD has been reported in Greece until now. It is advisable that public health measures be as conservative as possible and restrict potentially risky blood donors from donating but on the other hand blood supply in Greece is already limited and short blood supply may threaten the health of many that need the transfusions. A blood test for screening is the most direct solution to the problem, as this could identify the blood units that are contaminated. Also leukodepletion by itself reduces about half of the infectivity which if combined with future prion removal devices might give us an acceptably safe product.

The data from our analysis suggest that donor deferral due to vCJD criteria in our Blood Transfusion Service is 0.51% (61/11,936) of all donations. A certain profile donor to be deferred for possible vCJD transmission emerged from our study matching to a male, volunteer, aged between 36 and 48 years old who had resident in the UK the phobic period of time, mainly for studies. Females were found to have lower deferral rates than males (18% vs 82%) because they represent significant lower proportion of the whole number of blood donors as compared to men. Moreover, the proportion of men blood donors in Greece varies between 70–75% while the corresponding one of women donors is 25–30%.

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