

Transfusion transmission of vCJD: a crisis avoided?

In this issue of *The Lancet*, three reports examine issues about the iatrogenic transmission of variant Creutzfeldt-Jakob disease (vCJD). In a Research Letter, Alexander Peden and colleagues report autopsy evidence of possible transfusion transmission of vCJD in an individual who is a codon 129 methionine-valine heterozygote. Luisa Gregori and colleagues report on the effectiveness of leucoreduction to prevent transfusion transmission of prions. In the third paper, Guillaume Fichet and colleagues identify a new technique for disinfecting prion-contaminated medical devices. Together, these reports provide further insights into the challenges of managing the iatrogenic transmission of prion diseases. The papers should also serve as an illustration of the benefits of precautionary policy-making and as an example of the appropriate integration of science into the policy process.

Precautionary responses to risk of vCJD transfusion transmission

Concerns about the potential transfusion transmissibility of vCJD emerged soon after the discovery of the disease in 1996.¹ These concerns prompted three large UK recalls of blood products that originated from individuals who later developed vCJD.² Precautionary measures were subsequently introduced by several nations to protect against transfusion transmission of vCJD, including the institution of leucoreduction and the introduction of donor-deferral policies for individuals who had travelled to regions endemic for bovine spongiform encephalopathy (BSE).^{3,4} The UK has been the most aggressive in managing the risk, instituting such policies as importing plasma to manufacture fractionated products and deferring donations from some individuals who have received a transfusion.^{5,6} At the time these policies were introduced the risk of vCJD was considered to be theoretical on the basis of existence of the prion in reticuloendothelial tissue and the demonstration of peripheral transmission via the oral route.⁷

Increasing evidence has emerged to suggest that vCJD is indeed transfusion transmissible. The report by Peden and colleagues further adds to this growing literature. In addition to being only the second reported case of transfusion-associated vCJD infection, the case reported is unique for two main reasons: it presents autopsy evidence of infection, presumably resulting from transfusion transmission from a preclinical case; and it provides evidence of vCJD-related infection in a codon-129 heterozygous individual. There are some important caveats that must be considered when interpreting these results. Primarily, the prion load was limited, which could be a general feature of infection in codon-129 heterozygotes. Non-clinical infection has been previously reported in animal models.⁸ As such, the true clinical and public-health significance, with respect to the issue of whether the individual would have subsequently developed clinically evident vCJD or whether this individual poses a risk for iatrogenic transmission of the disease, remains uncertain.

Nevertheless, combined with the animal studies by Houston and Hunter and their colleagues^{9,10} showing transfusion trans-

mission of the disease in preclinical models, and the previous case report¹¹ of probable transfusion transmission, there now appears to be sufficient evidence that individuals without clinical signs of vCJD harbour, and therefore potentially transmit, the infection (table). This accumulating evidence is a vindication of the precautionary policies introduced by several nations to manage what was, at the time, a theoretical transfusion-transmission risk of vCJD.¹⁵ This approach to policy-making represents an important shift from the traditional evidence-based policy making model. Evidence-based approaches would have required clear evidence provided by well-designed epidemiological studies before the institution of protective policies. The introduction of policies to protect against a theoretical risk, which would reduce blood availability and incur important costs, would have been viewed as irrational. However, important lessons had been learned from the application of such strict evidence-based models to the risk of BSE and transfusion transmission of hepatitis C and HIV. In both those instances, by the time the evidence arrived, large numbers of individuals had been infected. Consequently the precautionary principle, which essentially states that complete evidence of risk does not have to exist before measures are taken to protect against the risk, has been advocated as an alternative model to strict evidence-based policy making. By using this principle and by acting in advance of complete certainty, policy makers have potentially protected against vCJD emerging as a new large-scale blood-borne epidemic.

However, it is important to recognise that the policy response to vCJD was not successful for simply applying precaution, but for the manner in which it was applied. Precautionary-based decisions have had serious negative outcomes; the refusal of some African nations to accept genetically modified foods in the presence of famine and the banning of DDT for malaria prophylaxis being two cases in point.^{16,17} The fundamental difference between the response to the threat of vCJD transfusion transmission and these

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Level of evidence	Evidence	Year
Cohort studies	None	..
Case-control studies	None	..
Ecological evidence	None	..
Case series	None	..
Case reports	Case report of vCJD infection identified in autopsy of patient who received transfusion from donor with preclinical vCJD	2004
	Human case report of vCJD in recipient of transfusion from donor with preclinical vCJD	2004 ¹¹
Animal evidence	In primates, efficiency of BSE transmission via transfusion shown to be at least as efficient as by oral route	2004 ¹²
	Sheep-to-sheep transfusion transmission shown in animal models of preclinical and clinical disease	2000 ⁹
	Animal-model evidence of transfusion transmission of TSE	2002 ¹⁰
		1998 ¹³
Biological models	Prion identified in lymphoid tissue	1997 ⁷
	Theoretical transfusion-transmission risk suspected on basis of demonstration of oral transmission of prion	1996 ¹⁴

TSE=transmissible spongiform encephalopathy.

Scientific evidence for possible transfusion transmission of vCJD

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Prion protein

C and N are carboxy and amino terminals.

precautionary responses was that the vCJD response was proportional to the potential risk, and took into consideration negative health-effects of the policy. Additionally, the policies were constantly re-evaluated and modified as further evidence of the risk of transfusion transmission of vCJD was obtained and by the measured effect of the policies on blood availability. Furthermore, whereas precautionary decision-making has been previously accused of not appropriately using science, the opposite has been the case with managing transmission risks associated with vCJD.

Ongoing policy challenges

The fundamental challenge to policy making that emerges out of the two case reports of vCJD transfusion transmission is the significance of preclinical cases of vCJD and how to manage their risk of iatrogenic transmission of vCJD. Without a test for vCJD, measures need to be introduced to provide broad protection to all potentially contaminated substances. The second and third papers in today's *Lancet* provide some insight into the scientific developments feeding policy responses to this challenge. The experimental evidence that a large proportion of prion infectivity might be attached to white cells

meant that leucoreduction was a potential strategy for reducing transfusion risk from blood obtained from individuals with preclinical disease. The strategy has been introduced on a precautionary basis without clear evidence of benefit for human transmissible spongiform encephalopathies (TSE). Gregori and colleagues' paper now suggests that the process might only result in partial clearance of prions. Their study is well designed and scientifically sound; however, it is not clear that a hamster model is applicable to human beings, particularly as the cellular distribution of prions varies widely among species and strains of TSE agents. Assuming the results could be translated to human blood products, an appropriate use of precaution would, were there not other forces operating, require re-evaluation of the evidence and potential removal of the policy. However, leucoreduction confers other benefits, including a reduction of non-haemolytic febrile reactions, and has therefore also been introduced in countries where the risk of vCJD is immeasurably low.¹⁸

Asymptomatic infected individuals could also pose a risk to others if surgical equipment that is used on them is then used on other individuals without appropriate decontamination. A model for this form of transmission already exists with the transmission of sporadic CJD via reused stereotactic electrodes and neurosurgical equipment, and has required, from the earliest assessments, the use of measures to mitigate the risk of transmission through surgical procedures.¹⁹ In the UK, the policy response has included upgrading disinfection facilities in hospitals, the development of a CJD incidents panel, and identification and tracking of surgical instrument sets.^{20,21} The potential risk for such transmission of vCJD would presumably be greater, given the higher prion load in these individuals and the distribution of the prions through a wider range of organs, including lymphatic tissue, than seen in sporadic CJD.²² However, the sterilisation of prions from equipment through standard infection-control procedures has been a continuing challenge because of the resistance of the prion to denaturing and the damage that sufficiently rigorous measures have on the equipment. The paper by Fichet and colleagues identifies a new strategy to potentially decontaminate prion-infected equipment without damaging delicate, expensive, and reusable diagnostic and interventional equipment. If preclinical cases are risks for iatrogenically transmitting the infection, in areas where there is suspected to be a sufficient proportion of these individuals an approach to protect surgical instruments from contamination would have to be considered.

Lessons

The potential risk of transfusion transmission of vCJD provides a useful model for decision-making in the presence of scientific uncertainty. The key lesson from this policy-making experience is that lack of definitive evidence should not preclude action for serious potential exposures. However, if precautionary action is taken, the measures should be proportional to the risk and consider the harms associated with the response. The policies should be constantly re-evaluated as new science emerges on the question, and policy makers and the scientific community should work closely to ensure that the important gaps in

knowledge facing policy makers are being investigated. To manage the ongoing threat of vCJD, policy makers will have to continue to formulate policy in this manner. Other public-health domains addressing risk of a similar nature could also learn from the vCJD experience.

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Mean times in transfusion—carrots and sticks for practice in England

On July 22, 2004, a document entitled *Emergency Planning—development of an integrated plan for the management of blood shortages* was issued by the UK Department of Health.¹ This report sets out a plan for managing any future shortages in supply of blood to hospitals and outlines how blood will be directed to where it is most clinically appropriate. A more detailed action plan for hospitals is expected to follow soon. This development has come as a result of deliberations within a working group of the Chief Medical Officer's National Blood Transfusion Committee, which includes in its membership representatives from hospitals, the National Blood Service, the Department of Health, the medical Royal Colleges, and specialist societies.

Why is this important? The supply chain for blood in the UK starts with blood donated by voluntary donors (5.5% of the population). In England the donations are processed by the

National Blood Service and issued to hospitals on demand. The UK is self-sufficient in blood apart from fresh-frozen plasma imported from USA for use in children born after 1996. These children will not have been affected by variant Creutzfeldt-Jakob disease (vCJD) from the food chain and the use of non-UK fresh-frozen plasma will avoid potential exposure to vCJD from UK donors. In April, 2004, concerns about human transmission of vCJD by blood transfusion² led to exclusion of donors who have been previously transfused. The projected loss of donors because of this exclusion is 3.2% of the current base of donors (HIV-related attrition of donors peaked in 1982 at 6%). When a screening test for vCJD becomes available, it is predicted that the donor base could fall further.

Because of the crisis related to transfusion-transmitted HIV infection in the 1980s, transfusion services in high-income countries introduced processes that improved the virological

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