LEUCOREDUCTION

UNE MESURE ENVISAGEABLE DANS LE CADRE DE LA POLITIQUE NATIONALE DE SECURITE DES TRANSFUSIONS SANGUINES

KCE reports vol.4B

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
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LEUCOREDUCTION

Une mesure envisageable dans le cadre de la politique nationale de sécurité des transfusions sanguines

KCE REPORTS VOL.4B

IRINA CLEEMPUT
DIRK RAMAEKERS
MARK LEYS
LUC BONNEUX

FEDERAAL KENNISCENTRUM VOOR DE GEZONDHEIDSZORG
CENTRE FÉDÉRAL D'EXPERTISE DES SOINS DE SANTÉ
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Auteurs : Cleemput, Irina
Ramaekers, Dirk
Leys, Mark
Bonneux, Luc

Conflict of interest : none declared

External validators and assisting experts : Prof. Dr. Sondag, Prof. Dr. Vandekerckhove, Dr. Vanopdenbosch, Dr. van der Poel

Layout : Nadia Bonnouh, Patrice Chalon

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Federaal Kenniscentrum voor de Gezondheidszorg - Centre Fédéral d'Expertise des Soins de Santé.
Résidence Palace (10de verdieping-10ème étage)
Wetstraat 155 Rue de la Loi
B-1040 Brussel-Bruxelles
Belgium
Tel: +32 [0]2 287 33 88
Fax: +32 [0]2 287 33 85
Email : info@kenniscentrum.fgov.be info@centredexpertise.fgov.be
Web : http://www.kenniscentrum.fgov.be http://www.centredexpertise.fgov.be

Introduction

La leucoréduction est une technique de filtration qui permet de réduire de 99.99% la quantité de globules blancs contenus dans le sang. Les avantages de la leucoréduction sont connus depuis longtemps, mais ne sont pas encore suffisants pour justifier la filtration de toutes les transfusions (leucoréduction universelle). La Croix Rouge de Belgique réserve actuellement cette technique aux transfusions destinées aux patients à haut risque de réaction négative aux globules blancs (leucoréduction sélective). La plupart des pays d' Europe ont instauré la leucoréduction universelle en 2004. La raison principale en est le risque de transmettre la maladie de Creutzfeldt-Jakob (vCJD) via une transfusion sanguine; la vCJD est causée par le même agent pathogène que la maladie de la vache folle (BSE). La Croix Rouge de Belgique est confrontée d'une part, à une augmentation notable des coûts engendrée par le leucoréduction universelle, et d'autre part à l'augmentation des primes d'assurance et au risque réel quoique minime de démélés judiciaires longs et pénibles. C'est pourquoi, la Croix Rouge de Belgique a donc demandé au Ministre de la Santé Publique de prendre en charge ce problème.

Mr Rudy Demotte, Ministre de la Santé Publique a à son tour demandé au Centre Fédéral d'Expertise des Soins de Santé d'évaluer les fondement scientifiques de la leucoréduction universelle à partir de la littérature afin d'étayer les décisions relatives à l'implémentation de cette technique.

Ce rapport est le résultat d'une collaboration multidisciplinaire entre des experts internes au Centre d'Expertise et des experts externes. Remerçions tout d'abord les experts externes et les validateurs: le Prof Dr Sondag (Croix Rouge), le Prof Dr Vandekerckhove (Rode Kruis), le Dr Vanopdenbosch (CODA, expert-BSE) et le Dr van der Poel (Sanquin, Centre de transfusion néerlandais). Leur aide nous a été très utile dans la rédaction de ce rapport.

Nous voulons également remercier le Dr Ralph Crott, expert du Centre d'Expertise, pour son aide, ainsi que le Dr Baeten et ses collègues du centre de transfusion sanguine d'Anvers pour l'accueil et la qualité de l'information transmises au cours de la visite de leur centre.

Un mot de remerciement particulier sera adressé à tous les donneurs de sang volontaires. Personne ne peut oublier que c'est leur don généreux à la société qui permet de garantir la grande sécurité transfusionnelle que nous connaissons en Belgique.

Jean-Pierre Closon
Directeur Général Adjoint

Dirk Ramaekers
Directeur Général

CELLULE STRATEGIQUE DU
MINISTRE DES AFFAIRES
SOCIALES ET DE LA SANTÉ
PUBLIQUE

tél.: 02 220 20 11
fax: 02 220 20 67
personne de contact: Annette KOENIGS
e-mail: annette.koenigs@minsoc.fed.be

Monsieur Dirk RAMAEKERS
Directeur général du Centre fédéral
d'Expertise des Soins de Santé

Rue de la loi, 155
1040 - BRUXELLES

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URGENT

Monsieur le Directeur général,

Je vous saurais gré de bien vouloir examiner la situation des pays européens en matière d'implémentation de la déleucocytation des produits sanguins.

Je souhaiterais également que vous procédiez à l'évaluation du rapport coût-utilité qui découlerait de la déleucocytation de tous les produits dérivés sanguins, ainsi qu'à une comparaison entre les prix pour les produits déleucocytés en Belgique et dans les autres pays européens.

Les résultats de cette étude devraient être connus pour la fin du mois d'août 2004.

Je vous remercie pour votre collaboration.

Renaud WITMEUR
Directeur du Secrétariat du Ministre et
de la Cellule stratégique Santé Publique

Service Public Fédéral
Santé Publique et Sécurité Sociale

.be

Avenue des Arts, 7
B - 1210 BRUXELLES
Accessible par les transports en commun : station de métro Madou
http://socialsecurity.fgov.be.

Résumé du rapport

Leucoréduction universelle : généralités

Garantir la sécurité des transfusions sanguines constitue l'un des objectifs principaux de la gestion de ce processus. En Belgique, le risque de transmission d'infections virales via transfusion sanguine, comme l'hépatite B, l'hépatite C et le SIDA, est très faible: il varie de 1 sur 200 000 pour l'hépatite B à 1 sur quelques millions pour le SIDA. La mortalité consécutive aux infections transmises par transfusion est encore beaucoup plus faible. La morbidité et la mortalité consécutives aux infections transmises par transfusion sont également beaucoup plus faibles que celles dues à d'autres causes: les erreurs administratives qui aboutissent à l'administration de sang non-compatible, restent le plus grand problème (comme dans tous les pays du monde). Outre le risque de transmission d'infections virales, il existe un risque de contamination bactérienne, surtout des plaquettes sanguines (celles-ci doivent être conservées à température ambiante, ce qui favorise la prolifération bactérienne). En Belgique, ce risque est minimalisé par un dépistage systématique de tous les concentrés de plaquettes sanguines. Le fait que le donneur qui est volontaire et non payé, fournisse généralement un sang très pur reste le principal facteur préventif. Le risque de maladie grave due à une transfusion sanguine est ainsi extrêmement faible.

La leucoréduction, déleucocytation ou leucodéplétion consiste à réduire, entre autres par filtration, le nombre de leucocytes (globules blancs) d'un facteur > 1000 dans le sang à transfuser. Les leucocytes sont pour le receveur des cellules étrangères à activité immunitaire, responsables d'une série de complications après la transfusion sanguine, sans présenter d'avantage clinique pour le patient. La leucoréduction a des effets cliniques positifs prouvés pour des patients spécifiques, à savoir les patients qui doivent subir souvent des transfusions sanguines, les patients présentant une résistance réduite (y compris les nouveau-nés), les candidats à une transplantation et les donneurs d'organe. En Belgique, ces patients reçoivent déjà du sang déleucocyté. L'option stratégique porte donc sur le choix entre la politique actuelle de leucoréduction sélective pour certains groupes de patients ou une politique de leucoréduction universelle de toutes les transfusions.

La présente étude qui répond à une demande du Ministre de la Santé, Rudy Demotte, a pour but d'évaluer les connaissances scientifiques concernant les avantages et les inconvénients médicaux et économiques de la leucoréduction. Plusieurs pays voisins ont mis en place une politique de leucoréduction universelle. Cependant, quoique les avantages médicaux de la réduction soient connus depuis longtemps, ils sont également contestés depuis le début. L'instauration de cette technique s'est faite généralement en réaction au danger - alors hypothétique - de la

transmission de la variante de la maladie de Creutzfeldt-Jakob (vCJD, variante humaine de la maladie de la vache folle) via transfusion sanguine.

Maladie de Creutzfeldt-Jakob (vCJD)

La maladie de Creutzfeldt-Jakob (vCJD) est la variante humaine de l'encéphalopathie spongiforme bovine (ESB), la tristement célèbre maladie de la vache folle. Les affections à prions chez l'homme et l'animal sont qualifiées du terme d'EST (encéphalopathie spongiforme transmissible) parce qu'elles se caractérisent par une destruction du cerveau. Il ne fait plus aucun doute que vCJD et ESB sont une même affection, transmise par un même prion anormal, dit 'conformer'. En outre, il existe des indices expérimentaux qui permettent de supposer qu'il pourrait exister un rapport entre la forme classique et sporadique de cette affection (sCJD) et l'ESB. Les prions sont des protéines normales produites par le génome humain. Les prions anormaux sont des protéines avec les mêmes chaînes protéiques, mais qui s'enroulent de manière différente. Ces prions enroulés différemment font que les prions normaux commencent à s'enrouler eux aussi de façon différente. Ces protéines anormalement enroulées sont exceptionnellement résistantes à toutes les formes de dégradation, de dénaturation et de dégénérescence. Cela fait qu'elles s'accumulent, surtout dans le système nerveux, ce qui provoque la destruction de ce dernier.

Le mode de transmission de l'ESB de la vache à l'homme reste inconnu pour l'instant, bien qu'il est probable que ce soit par consommation de viande contaminée par des prions. Au Royaume-Uni (et ailleurs, par les exportations de viande en provenance d'Angleterre), 1.6 millions de vaches contaminées se sont retrouvées dans la chaîne alimentaire. En avril 2004, on relevait 151 cas de vCJD, dont 141 au Royaume-Uni. En-dehors du Royaume-Uni, la France compte 6 cas reconnus (et un septième qui est très suspect), soit 1 par 10 millions d'habitants au cours des dix dernières années. Jusqu'ici (6 septembre 2004), aucun cas de vCJD n'a été identifié en Belgique.

Des modèles animaux montrent que l'ESB est transmissible par transfusion sanguine même si l'animal contaminé ne présente pas encore de symptômes. Au Royaume-Uni, un seul cas clinique de contamination consécutive à un transfusion a été identifié récemment. Il s'agit d'un patient qui a reçu du sang provenant d'une personne ayant développé par la suite la vCJD. Un autre cas (subclinique) a été découvert lors d'une autopsie après un décès par ailleurs dû à une autre cause. Le risque de transmission de vCJD via transfusion sanguine est ainsi établi, bien qu'il faille faire remarquer qu'un seul cas clinique de transmission sur des millions de transfusions sanguines représente encore un risque extrêmement faible. Il est difficile d'imaginer que le risque de transfusion en-dehors du Royaume-Uni puisse être autre chose qu'extrêmement faible.

On ignore si la leucoréduction constitue une mesure efficace pour prévenir la transmission du vCJD via transfusion sanguine. Le chiffre souvent cité de 90% de réduction du risque est spéculatif et n'est basé sur aucune étude expérimentale, chez l'homme ou chez l'animal. Des études très récentes chez le hamster ont montré que chez les animaux infectés par l'EST dumouton (scrapie), l'effet de leucoréduction restait limité à 42% de réduction de la 'charge d'EST' et 35% du risque d'infection. Il est probable que le bénéfice soit plus lié à l'action de filtrer qu'à la réduction du nombre de globules blancs; les prions sont adhérents et restent collés aux surfaces. De ce fait, la recherche des meilleurs filtres est une option souhaitable.

Toute politique de précaution est basée sur les principes de bon sens et de proportionnalité en cas d'incertitude sur les risques. La situation effrayante de l'Angleterre à la fin des années 90 ne s'est pas confirmée, mais dans ce cas, la leucoréduction universelle était raisonnable et proportionnelle en rapport au très grand risque potentiel. Cinq ans plus tard, la leucoréduction universelle semble difficile à défendre du point de vue médico-scientifique en-dehors de l'Angleterre. La leucoréduction universelle a un effet modéré sur un risque purement hypothétique avec des donneurs sanguins sains, d'autant plus que ce risque ne s'est pas (encore) matérialisé en Belgique dix ans après le début de l'épidémie au Royaume-Uni.

Avantages médicaux prouvés de la leucoréduction

La leucoréduction réduit la transmission des maladies infectieuses, l'allo-immunisation HLA et les conséquences immunologiques des transfusions sanguines.

La seule maladie infectieuse cliniquement pertinente dont la transmission soit empêchée avec certitude par la leucoréduction est le cytomégalovirus (CMV). Environ 1% des donneurs de sang sont porteurs du cytomégalovirus (CMV) et peuvent le transmettre au receveur de leur sang. Le CMV provoque une morbidité et une mortalité élevées chez les patients CMV-séronégatifs ayant une immunité affaiblie. La prévention d'autres maladies infectieuses, comme l'HTLV I/II et l'EBV, est peu pertinente sur le plan clinique.

Les globules blancs contiennent des antigènes tissulaires (ce qu'on appelle le système HLA), qui peuvent avoir un effet immunisant. Cela peut avoir des conséquences cliniques très graves pour le patient, surtout pour les patients polytransfusés (qui sont exposés à plusieurs transfusions). La leucoréduction réduit de 70% le risque de développer une immunisation HLA et est donc très efficace pour prévenir ces réactions graves à la transfusion. En outre, la leucoréduction joue un rôle important quand on veut éviter que des transfusions de plaquettes deviennent inefficaces à cause des antigènes HLA développés par le patient.

Le fait que la leucoréduction puisse prévenir d'autres conséquences immunologiques des transfusions n'est pas certain. Il existe des indices selon lesquels la

leucoréduction offre de meilleurs résultats chez les patients opérés, tant en termes de réduction de la durée d'hospitalisation que des effets de l'opération, mais ces résultats ne vont pas tous dans le même sens. Cela s'explique par la grande hétérogénéité qui existe entre les études, les systèmes de soins de santé, les techniques utilisées et la réduction des risques dans diverses populations de patients. La seule chose qu'on puisse dire avec assez de certitude est que la qualité du sang filtré contenant mille fois moins de globules blancs est meilleure que celle de sang non filtré. La pertinence clinique de cette amélioration qualitative reste incertaine.

Inactivation pathogénique

Une alternative à la leucoréduction est l'inactivation pathogénique. Cette technique encore en développement semble prometteuse et est déjà disponible pour une utilisation sur le plasma et les concentrés de plaquettes sanguines. On ne sait pas encore à quel moment l'inactivation des pathogènes deviendra disponible pour les concentrés d'érythrocytes. Cette technique se base sur le principe de la dénaturation spécifique des acides nucléiques (ADN et ARN). Les globules rouges et les plaquettes ne contiennent ni ADN ni ARN, ce qui en principe, les épargne des prions. L'inactivation pathogénique ne peut pas neutraliser les prions, étant donné qu'il s'agit de protéines (d'ailleurs exceptionnellement résistantes) et non d'acides nucléiques, mais est en principe capable d'inactiver tous les virus et bactéries connus et inconnus, ainsi que les globules blancs. L'expérience avec cette technique est cependant encore fort limitée. Les premières études cliniques ont révélé une réduction de la viabilité des plaquettes sanguines traitées, ce qui augmente le besoin en transfusions. Etant donné que les risques infectieux ne constituent qu'une part réduite de tous les risques des transfusions, cela augmente l'incertitude. En attendant des résultats plus nombreux et plus concluants, l'inactivation pathogénique reste prometteuse mais incertaine. En outre, comme les risques réels des transfusions sont très faibles, il est nécessaire, pour rester dans un rapport raisonnable de coût-bénéfice, que le coût ne soit pas trop élevé.

Aspects économiques de la leucoréduction

Coût de la leucoréduction

En Belgique, une unité de globules rouges coûte 67.85 €; une unité de globules rouges déleucocytée coûte 25.14 € de plus. Ce montant est probablement une bonne indication du coût additionnel réel de la leucoréduction, et est très comparable avec la pratique dans d'autres pays.

En Belgique, on applique actuellement une leucoréduction sélective: 35% des concentrés de globules rouges sont déleucocytés. La leucoréduction sélective limite l'utilisation de sang filtré aux indications pour lesquelles l'efficience clinique est

prouvée raisonnablement. Ces indications sont fixées par Arrêté Royal (12 mars 1998). Il existe suffisamment de preuves pour dire que la leucoréduction utilisée dans ces indications spécifiques est efficiente en termes de rapport coûts-bénéfices .

Leucoréduction universelle

Le principe de la leucoréduction universelle est d'étendre la leucoréduction à tous les dons de sang. L'impact budgétaire de la leucoréduction universelle en Belgique est évalué à 7.71 millions € supplémentaires par an, en plus des 4.25 millions € dépensés actuellement à la leucoréduction sélective. On s'attend à ce que ces coûts additionnels diminuent, grâce à l'expérience croissante des opérateurs sanguins et à la concurrence industrielle pour des filtres meilleur marché. En outre, ce calcul ne tient pas compte des économies potentielles réalisés en évitant les complications associées aux globules blancs après transfusion sanguine. Etant donné l'incertitude quant à la pertinence clinique pour les groupes de patients qui ne relèvent pas des indications connues de leucoréduction sélective, il n'est pas possible de chiffrer ces économies.

Dans l'optique des centres de transfusion sanguine, la leucoréduction universelle offre des avantages indéniables, permettant notamment d'économiser de l'argent: en simplifiant la gestions des stocks, en standardisant les procédures, en réduisant potentiellement le nombre de procès et en réduisant ou en stabilisant les primes d'assurance en responsabilité civile. Les primes d'assurance élevées que la Croix Rouge paie actuellement en responsabilité civile représentent une perte importante pour les soins de santé belges. Il existe une disproportion entre les primes et les indemnisations. Cela entraîne une réduction de l'efficience des soins de santé en général et des transfusions sanguines en particulier.

Il est un fait établi que la qualité du sang filtré est meilleure que celle du sang non filtré. Il n'est pas certain que cela compense l'investissement consenti pour offrir cette meilleure qualité à tout un chacun.

Aspects juridiques

En tant que producteur des produits sanguins, la Croix Rouge est responsable des produits livrés. Cette responsabilité a entraîné une augmentation énorme du niveau des primes d'assurance en responsabilité civile au cours des cinq dernières années. Cette explosion des coûts est complètement disproportionnée par rapport aux risques réels des transfusions sanguines, lesquels se réduisent actuellement. La leucoréduction universelle pourrait réduire le risque de poursuites judiciaires – étant donné que l'argument de ne pas avoir tout fait pour prévenir le dommage devient sans valeur - et par conséquent l'importance des primes d'assurance. Cela semble incertain, étant donné qu'il n'existe aucun rapport entre les primes d'assurance et le niveau de sécurité atteint objectivement par les transfusions.

La législation européenne n'est pas adaptée aux raisonnements modernes en matière de nécessité médico-éthique de définir des priorités pour les investissements dans les nouvelles technologies médicales. Les raisonnements modernes sont résumées dans le concept "accountability for reasonableness". Les opérateurs de banques de sang doivent rendre des comptes sur la sécurité sanguine dans des limites raisonnables, non sur tous les risques imaginables. Ce qui est raisonnable doit être fixé après une information suivie d'un débat démocratique avec les représentants de la nation.

Pour faire participer le public à la décision politique, il est indispensable d'organiser une communication adéquate sur le risque minime actuel des transfusions sanguines, aussi bien que sur l'impossibilité d'éliminer tout risque résiduel. C'est d'autant plus important dans ce cas que la sécurité du sang est garantie surtout par des donneurs de sang désintéressés.

La législation actuelle favorise la mise en œuvre des procédures de sécurisation en fonction des technologies disponibles et non en fonction des besoins objectifs. Ceci a pour conséquences que des moyens destinés à améliorer les soins de santé sont perdus en primes d'assurance, en procès et en technologies inefficaces.

Si la législation ne change pas, les banques du sang resteront dépendantes d'une interprétation arbitraire du principe de "précaution" par les tribunaux. L'argument selon lequel les pays voisins ont introduit cette tevchnique reste difficile à contrer dans les milieux juridiques. Actuellement, les opérateurs des banques du sang estiment que le risque d'être condamné reste insupportablement élevé.

Conclusions

Grâce au recours à des donneurs de sang volontaires et non rémunérés et au contrôle de qualité strict, le sang livré par la Croix Rouge belge est de haute qualité et extrêmement sûr. Les globules blancs contenus dans une transfusion sanguine sont cependant des cellules étrangères à l'organisme superflues, et peuvent provoquer des effets indésirables. Le sang non filtré coûte 68 €; l'élimination des globules blancs par filtrage coûte 25 € par unité en Belgique. L'utilité d'éliminer les globules blancs est connue depuis longtemps, et prouvée pour des indications spécifiques. La politique actuelle en Belgique, la leucoréduction sélective pour les transfusions sanguines à des populations spécifiques de patients, est donc efficace et permet de réduire les coûts.

On ne connaît pas l'amélioration d'efficacité et le gain en terme d'économie liés à une extension de la leucoréduction à toutes les transfusions de sang. Le sang traité présente une meilleure qualité que le sang non traité, mais il n'est pas clairement démontré que cette augmentation de la qualité puisse compenser l'augmentation des coûts. Il est raisonnable de s'attendre à ce que les coûts de la leucoréduction

continuent à baisser dans l'avenir. Les pouvoirs publics doivent maintenir le prix des systèmes filtrants le plus bas possible par des négociations efficientes avec l'industrie.

Il est important d'éviter les transfusions sanguines superflues dans le cadre de la prévention de leurs conséquences indésirables. La politique actuelle, qui vise une utilisation plus parcimonieuse des transfusions sanguines, doit être poursuivie. Les comités de transfusion sanguine mis en place dans les hôpitaux belges doivent surveiller activement l'utilisation optimale du sang et des produits sanguins. Pour ce faire, les groupes professionnels doivent continuer à développer et à mettre en œuvre des directives pour une utilisation optimale du sang et des produits sanguins.

La prévention de la maladie de Creutzfeldt-Jakob (vCJD), variante humaine de la maladie de la vache folle (ESB) a été à la base de la décision de leucoréduction universelle du sang dans plusieurs pays. La décision d'appliquer la leucoréduction universelle qui a été prise au Royaume-Uni à la fin des années '90, était raisonnable et proportionnelle à la menace. L'instauration de la leucoréduction universelle dans d'autres pays en-dehors du Royaume-Uni ne peut cependant pas être motivée sur la base de cette menace de vCJD. Dix ans après ses débuts, l'épidémie de vCJD reste limitée au Royaume-Uni ainsi qu'en France (1 habitant sur 10 millions en France). L'efficacité de la leucoréduction dans la prévention de la transmission de prions par le sang était basée sur des spéculations. Des études récentes confirment que la leucoréduction avec les filtres existants n'entraîne qu'une élimination médiocre des prions. Cela pourrait changer avec des filtres plus performants.

Le problème social sous-jacent est mieux cerné par l'augmentation considérable des frais d'assurance des banques du sang. Ces coûts sont totalement disproportionnés par rapport à la sécurité toujours croissante des transfusions sanguines. Pour les banques du sang, ces dépenses d'assurance sont essentielles pour leur survie, mais pour les soins de santé belges, ils constituent une utilisation inefficiente des moyens. La législation actuelle en Europe n'est pas adaptée au besoin de définir des priorités pour les investissements dans l'amélioration de la qualité. Cela a pour conséquence que les investissements sont dominés par l'offre technologique croissante, et pas par le besoin objectif.

Nous concluons qu'il n'existe pas d'arguments scientifiques pour exprimer une nette préférence entre le système existant en Belgique - leucoréduction sélective - et la leucoréduction universelle reprise par la plupart des autres pays après le Royaume-Uni. La leucoréduction universelle entraîne une majoration des coûts pour fournir un produit de meilleure qualité à tous les patients. La leucoréduction universelle présente en théorie l'avantage de prévenir la transmission de virus nouveaux ou liés aux cellules pour lesquels il n'est pas encore effectué de tests. La pertinence clinique de cette amélioration reste limitée et discutable. L'argument vaut tout autant pour les dépenses supplémentaires consenties.

L'interprétation vague du principe de 'precautionary policy' dans la réglementation européenne risque de favoriser une politique d'investissements médicaux dictée par la technologie existante, et non par les besoins objectifs. Nous recommandons des études juridiques supplémentaires, avec pour but d'adapter la législation nationale et européenne aux principes modernes de l'éthique médicale, basée sur 'accountability for reasonableness'. Les investissements en une sécurité accrue doivent être raisonnables et proportionnés à la menace. Aussi longtemps que l'actuelle incertitude légale continue à subsister, l'instauration d'un nombre croissant de mesures de sécurité et les frais y associés – indépendamment d'arguments médico-scientifiques convaincants - est inévitable.

Un rapport sur la sécurité sanguine n'est pas terminé sans un grand merci aux innombrables donneurs de sang désintéressés. Ils représentent la meilleure garantie de la sécurité du sang. C'est pourquoi il est important qu'ils soient impliqués dans la politique de transfusion: ils ont le droit à une utilisation optimale du sang donné volontairement, à la meilleure qualité et un prix abordable. Une communication adéquate sur les risques est donc essentielle.

Aperçu des points principaux

A propos de la sécurité sanguine en Belgique

Les transfusions sanguines en Belgique sont extrêmement sûres, grâce à un contrôle de qualité strict et à l'utilisation de sang de donneurs volontaires et non rémunérés.

Les investissements pour une amélioration additionnelle de la sécurité sanguine doivent rester proportionnels aux bénéfices attendus, ceux-ci sont peu importants, vu le haut niveau de sécurité déjà atteint.

A propos de l'ESB (maladie de la vache folle) et de vCJD

L'agent infectieux qui provoque la maladie de la vache folle est identique à celui de la maladie de Creutzfeldt-Jakob. Il s'agit d'un prion, une protéine présentant une très grande résistance à toutes les formes de dénaturation, qui détruit le cerveau par accumulation.

Le prion qui provoque l'ESB/vCJD est transmissible par transfusion sanguine; deux cas de transmission probable de vCJD par transfusion de sang contaminé sont connus en Angleterre. Il n'est pas possible de prévoir le risque exact par transfusion sanguine en Angleterre, mais il semble actuellement encore fort réduit.

Dix ans après le début de l'épidémie de vCJD en Angleterre, celle-ci se limite presque complètement à ce pays. Le risque en France, le seul pays avec plus de quelques cas, est de 1 habitant par 10 millions en 10 ans.

L'élimination des globules blancs du sang à transfuser ne présente qu'une efficacité médiocre pour prévenir l'infection. En théorie, l'utilisation de filtres plus performants pourrait permettre de retenir plus de prions.

En Angleterre, l'élimination des globules blancs du sang à transfuser était une mesure parfaitement défendable au vu de la grande incertitude quant à l'importance de l'épidémie. Cinq ans plus tard, et surtout dix ans après le début de l'épidémie, cette mesure constitue une réaction dont l'utilité est sans aucun doute limitée en-dehors de l'Angleterre.

Au sujet des avantages médicaux de la leucoréduction

Les globules blancs contenus dans le sang à transfuser sont des cellules étrangères à l'organisme et à immunité active. On sait depuis longtemps qu'ils peuvent entraîner des effets indésirables chez le receveur.

Les patients ayant une immunité réduite, ou qui courent le risque de recevoir plusieurs transfusions sanguines, profiteront des globules rouges accompagnés d'un minimum de globules blancs.

C'est pourquoi la Belgique a adopté une politique de leucoréduction sélective. Les patients avec une immunité réduite, les femmes enceintes, les patients transplantés, les nouveau-nés, les patients polytransfusés et les patients ayant un risque élevé de réactions de transfusion, ou qui ont présenté de telles réactions dans le passé, reçoivent du sang sans globules blancs.

Il existe des rapports contradictoires portant sur le fait que la leucoréduction offrirait également des avantages pour d'autres groupes de patients, plus particulièrement par une amélioration des résultats après intervention chirurgicale.

Au sujet de l'inactivation pathogénique

L'inactivation pathogénique se base sur le principe de la dénaturation sélective de l'ADN et de l'ARN. Elle inactive les virus, les bactéries et les protozoaires. Elle n'a pas d'effet sur les prions, qui sont des protéines.

A l'heure actuelle, les accidents par transmission d'agents infectieux via une transfusion sanguine sont extrêmement rares: cela limite l'utilité d'une telle technologie, qui doit d'ailleurs prouver qu'elle est extrêmement sûre.

L'inactivation pathogénique est une technologie prometteuse, mais encore expérimentale. Il subsiste encore des questions sur la qualité des plaquettes sanguines et globules rouges traités par inactivation pathogénique.

L'utilisation de la technique d'inactivation pathogénique en-dehors d'études cliniques soigneusement effectuées est à déconseiller.

Au sujet de l'efficience de la leucoréduction

En Belgique, le sang non traité (c.-à-d. du sang non filtré) est remboursé à 68 € par unité. Lors de la leucoréduction, actuellement réservée à certains patients, 99.99 % des globules blancs sont éliminés par filtration. Cela est remboursé à 25 € de plus. En Belgique, le remboursement du sang est remarquablement bas, comparé aux pays voisins. Le coût de la leucoréduction est très comparable aux estimations dans les pays voisins.

La leucoréduction sélective, l'actuelle politique menée en Belgique, fournit une meilleure qualité de sang aux patients qui en profitent le plus. Cela permet de réduire les coûts. La leucoréduction universelle, la politique proposée, propose cette qualité supérieure à tout un chacun. Les bénéfices cliniques de la leucoréduction universelle et les économies associées sont incertains.

Du point de vue scientifique, on ne peut exprimer de préférence pour la leucoréduction universelle ou sélective. La leucoréduction universelle produit incontestablement une meilleure qualité de sang et prévient la transmission de virus liés aux cellules nouveaux ou connus (pour lesquels on ne teste pas encore). Il n'est

pas clairement démontré que les bénéfices cliniques compensent le coût supplémentaire de la procédure.

Du point de vue des banques du sang, le coût d'assurance additionnel lié à la leucoréduction sélective par rapport à la leucoréduction universelle est cependant non négligeable. Comme les primes d'assurance ne sont pas proportionnelles au faible risque des transfusions sanguines, le coût réel de la leucoréduction sélective pour le système de soins de santé est sans doute plus élevé que ce qu'on admet généralement.

Au sujet des aspects sociaux

Ces dernières années, le coût des assurances pour la Croix Rouge est passé de moins de 300 000 € par an à plus de 900 000 € par an. Cette augmentation du coût est tout à fait disproportionnée par rapport à la sécurité sanguine très élevée et croissante du sang livré par la Croix Rouge de Belgique.

La pratique législative européenne est vague et trop susceptible d'interprétations diverses. La jurisprudence suggère que la sécurité sanguine doit être maximale. Cela conduit à des investissements dans les technologies disponibles, dont l'utilité marginale ne peut pas toujours être démontrée clairement.

L'imprécision de la législation et la possibilité d'arbitraire juridique qui en découle, font que les banques du sang se sentent responsables du point de vue financier et judiciaire. Les considérations sur le bien-fondé médical deviennent dès lors accessoires. Si la responsabilité des banques du sang n'est pas transférée, elles doivent envisager toutes les mesures disponibles afin de maintenir au niveau le plus bas, le risque d'une condamnation coûteuse sur le plan humain et financier.

Une politique de prévention dans une perspective médico-éthique signifie que la sécurité doit être optimale. Cela signifie que les mesures de sécurité à instaurer doivent être raisonnables et proportionnelles à la menace.

Ce qui est raisonnable et proportionnel est fixé par une information suivie d'un débat démocratique avec les acteurs concernés.

Etant donné que la meilleure garantie de la sécurité sanguine est constituée par la participation de donneurs volontaires et non rémunérés, il est extrêmement important de conserver leur confiance. Il va sans dire que la confiance dans la qualité et la sécurité du sang est importante pour les patients et leurs médecins traitants. Cela vaut autant pour la garantie d'une sécurité sanguine optimale que pour la garantie de coûts acceptables de sang transfusé.

Messages clés et recommandations politiques

- **D'un point de vue scientifique**

Sur le plan médico-scientifique, il n'est pas possible d'exprimer de préférence en faveur d'une politique de déleucocytation sélective ou universelle : La déleucocytation universelle fournit une meilleure qualité de sang, mais les bénéfices cliniques de cette pratique, ne sont démontrés que pour certaines populations à risques. Grâce à la provenance du sang (sang de donneurs volontaires) et au fait que la prévalence de la maladie de Creutzfeld-Jacob est très basse dans notre pays, les risques transfusionnels sont également très bas .

- **D'un point de vue économique**

Sur le plan économique, les économies associées à la déleucocytation universelle grâce à la diminution des complications post-transfusionnelles sont inconnues. Le procédé simplifie toutefois la procédure de distribution du sang à la fois pour les centres de transfusion et pour les hopitaux. La déleucocytation génère une augmentation de coût brut de 25 € par unité.

- **D'un point de vue juridique**

L'actuelle législation européenne ne favorise pas une utilisation judicieuse des moyens. Des études supplémentaires sont nécessaires pour améliorer la pratique législative (européenne) dans le sens d' une politique préventive. Une politique de prévention dans la perspective médico-éthique favorise une sécurité optimale, mais il est difficile d'évaluer si les investissements additionnels consentis pour mettre en œuvre les mesures de sécurité sont raisonnables et proportionnels à la menace.

Les banques du sang et leurs opérateurs sont exposés à une incertitude juridique croissante. Cela entraîne une forte augmentation des coûts d'assurance, ceux-ci sont totalement disproportionnés par rapport aux efforts fournis pour garantir la qualité et la sécurité maximales du sang. Des études supplémentaires sont nécessaires pour améliorer la sécurité juridique des banques du sang et de leurs opérateurs.

- **Recommendations politiques**

Le cœur du problème est la responsabilité juridique et financière liée à chaque risque potentiellement évitable, quelle que soit la hauteur du risque et quel que soit le coût de son évitement. Si la politique choisit de ne pas instaurer une leucoréduction universelle, la question se pose de savoir si le pouvoir exécutif ne devrait pas couvrir le risque financier et juridique des banques du sang.

Une politique de prévention doit se baser sur l'information des acteurs concernés et sur leur participation aux décisions, depuis le donneur de sang volontaire et désintéressé et le patient jusqu'à et y compris le médecin traitant et les hôpitaux. Comment rendre cette participation effective? La question reste actuellement ouverte.

Table des matières

1 Introduction

1.1 Blood transfusion safety

While the safety of transfused blood increased drastically, the inevitable dangers of a transfusion with a heterologous human product became paradoxically more clear. In the recent past, Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) caused many victims among blood recipients, causing great interest in the control of viral transmission through blood products. Now, viral transmission through blood products is a small, but existing risk ranging from 1 in 200 000 for Hepatitis B Virus (HBV), to 1 in 1 million for HCV and 1 in several million for HIV in Belgium (Table 1).[1 2] In the UK, 12 incidents of viral transmission were recorded over more than 12 million blood units delivered.[3] Mortality caused by blood transmitted viral infections is even lower, in the order of one in several million blood units.

Bacterial contamination of blood products is actually a more serious hazard than viral contamination. Particularly platelets, to be stored at ambient temperature, are at risk. Mortality can be very high. The haemovigilance system of the UK (Serious Hazards of Transfusion, SHOT), estimated the risk of bacterial contamination as 1 in 400 000 units and the risk of death due to transfusion-related bacterial contamination as 1 in 2 000 000 units.[3] This may be somewhat optimistic; the infant haemovigilance system of the Netherlands identified 3 incidents of bacterial contamination in 158 000 units.[4]

Between 1996 and 2000, SHOT registered 62 transfusion-related deaths (all causes) in more than 16 million transfused units (four in one million).[5] The transfusion risks are therefore to be classified as minimal.[6] Indeed, playing football is a more hazardous activity.[6]

Table 1: Estimated transfusion risks in Belgium

	Estimated frequency
Acute haemolytic reactions	probably of a similar magnitude as in UK, France and US
Hepatitis B Virus	5 per million units[7]
Hepatitis C Virus	1.43 per million units[7]
Human Immunodeficiency Virus	0.17-0.25 per million units[7]
Bacterial contamination of red blood cells	0.1 per 100 units*
Bacterial contamination of thrombocytes	0.45-0.6 per 100 concentrates**
Fatal reaction to red blood cells transfusion	± 0.4 per million units
Septic reaction to platelet transfusion	< 1 per 100 000 units**
Fatal reaction to platelet transfusion	0 per million units

* extrapolation of results in platelets
** systematic screening for bacterial growth prevents almost all transfusion transmitted bacterial infections

The blood transfusion process is complex and crosses many disciplines and professions. One study identified over 40 steps between the patient and their transfusion, all of which involve potential human error.[8] In the US, UK and the Netherlands, 70% of all reported adverse events were due to avoidable errors; in the US, transfusion error incidence was between 1 in 12 000 and 1 in 19 000 cases,[9] in the UK this was 1 in 16 000,[3] in the Netherlands 1 in 20 000.[4] The risk of serious injury was 1 in 67 000 in the UK.[3] The risk of dying as a result of a transfusion error was 1 in 600 000 to 1 in 800 000 in the US, 1 in 600 000 in the UK and probably of a similar order of magnitude in the Netherlands.[3 4 9] Belgium has as yet no haemovigilance data on transfusion error incidence, but the similar results found in the very different health care systems of US, UK and Netherlands suggest that these results may be similar for Belgium too.

An undesirable consequence of the pursuit of zero transfusion risks may be the shift of risks to other sectors. This might happen as blood becomes too expensive due to all additional safety measures. Another feared consequence, very specific to this particular sector, is loosing the confidence of the blood donors. Blood banks are unique in the medical sector as they rely entirely on disinterested volunteers to collect their goods. These volunteers are a very safe population, at low risk of infection. The history of HIV-AIDS among haemophiliacs in countries relying on paid or voluntary donors show eloquently the added safety offered by healthy volunteers. Changes to a more industrial but less voluntary approach where blood is not given free of charge by altruistic volunteers but collected from paid donors and then treated for safety by the industry will paradoxically decrease safety at increased costs.[10] To maintain the trust of the disinterested volunteers, blood has to be safe at

an acceptable cost. If costs increase over a certain threshold, volunteers may perceive this as exploitation.

The actual safety of blood transfusions is very high in Belgium. The risk is not zero, but will never be. Any increase in blood safety has to be proportional: the costs of increased safety have to be in reasonable balance with the estimated effects, given the degree of uncertainty. Leukocyte removal as a measure to increase blood safety has been known since long.[11] Leukocytes are responsible for many of the complications associated with blood transfusion.[12] They are allogeneic immunoreactive cells of other humans, without clinical benefit. The clinical benefit of leukoreduction has been well established in a number of specific patient populations, but the feeling was that costs of *universal* leukoreduction, i.e. leukoreduction on every blood concentrate, outweighed the uncertain benefits in other patient populations.[13] A new argument for universal leukoreduction has been the prevention of transfusion related transmission of variant Creutzfeldt-Jakob disease (vCJD).

Key messages:

- **The incidence of adverse events caused by blood transfusions is minimal in Belgium; most accidents are caused by administrative errors.**
- **The Belgian blood safety has been served most by volunteer donors. It is of utmost importance to keep the trust of sufficient numbers of volunteers.**
- **The investment in any further increase in blood safety has to be proportional to the expected beneficial effects.**

1.2 Transmittable spongiform encephalopathies (TSE)

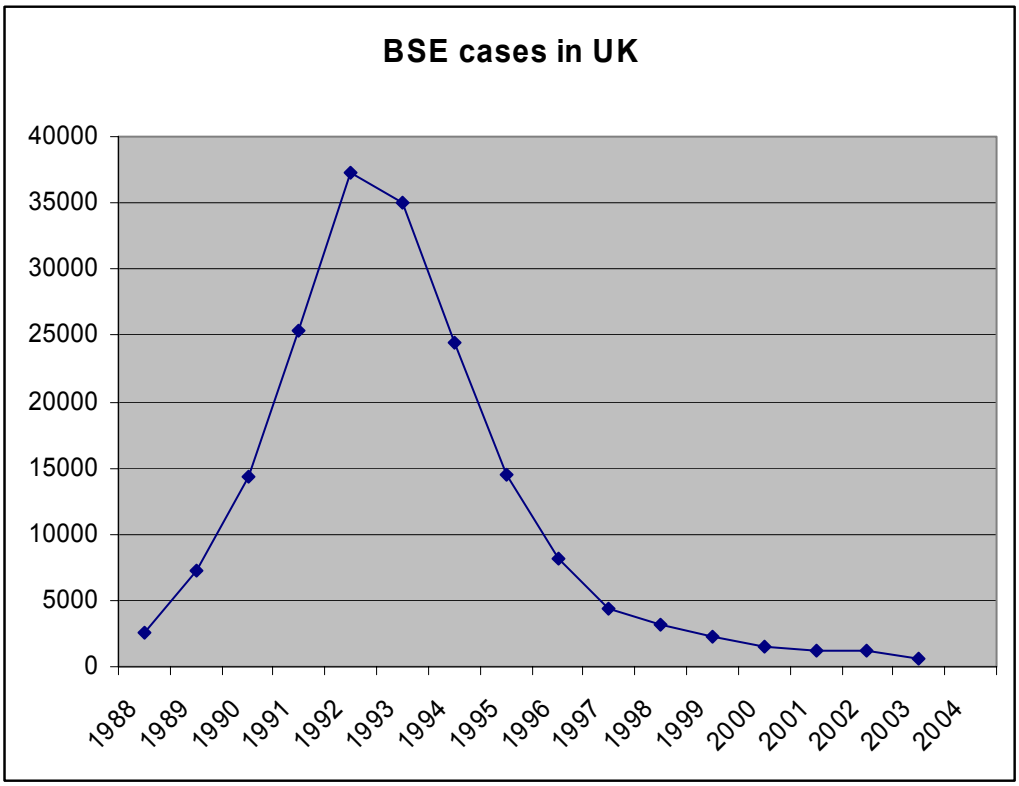
1.2.1 Bovine spongiform encephalopathie (BSE) and variant Creutzfeldt-Jakob disease (vCJD)

The pathogenesis of all Transmittable Spongiform Encephalopathies (TSE, the common name of all human and animal prion diseases), are caused by a toxic change in function of a normal host cell protein, the prion protein (PrP) (proteinaceous infectious particle). Prions are bizarre infectious particles, as they contain no DNA or RNA, only protein. Prions are infectious and cause disease by inducing the normal PrP to change in a structurally aberrant, protease resistant conformer, in vCJD PrP^{res}.[14] PrP^{res} conformers have identical primary structures as normal PrP, but differ at a higher structural level such as folding. The presence of the abnormal PrP^{res} seems to serve as a template for conversion of normal PrP to the abnormal PrP^{vCJD}.[14] The 'res' refers to the extreme resistance to denaturation, both endogeneous and exogeneous. PrP^{res} resists all normal mechanical and chemical

methods of contamination, inclusive the own body defences. The indestructible PrP^{res} accumulates in the neurons, and causes lethal encephalopathy by destroying these neurons.

The first cow with Bovine Spongiform Encephalopathy (BSE) was diagnosed in the UK in 1986. The incubation period of several years implies that the epidemic must have started years before. The theory initially favoured by most scientists was that the prion, that causes scrapie in sheep, crossed the species barrier to cows to cause BSE. In the UK, scrapie is prevalent and a large proportion of sheep carcasses was rendered for animal feed.[15] More recent evidence suggests that BSE is a completely new prion disease, emerging in cows by a sporadic mutation, that was selected for by recycling from animal to animal through the meat based cow fodder.[16] Where the prion that causes scrapie (a sheep TSE) is very species-specific, BSE can attack many species, including sheep where it causes typically BSE after experimental infection, a disease that can be distinguished from scrapie. It is beyond reasonable doubt that the prion that causes BSE in cows causes vCJD in humans.[17] The ruminant protein feed ban in 1988 slowed the further spread of BSE in the cattle. Off course, only after the incubation period the number of BSE cases could start to decrease truly. The ban was not water tight, causing 43 000 calves to contract BSE after the ban. Since august 1996 the feed ban has been water tight; 63 calves have been identified 'after the real ban' (the so-called BARB's) suggesting a third route of infection (bovine offal and transplancentary transmission being the other two). Till July 2004, 184 000 BSE cases have been identified in the UK; in 2003, still 612 BSE cases were notified in UK (seeFigure 1).[18]

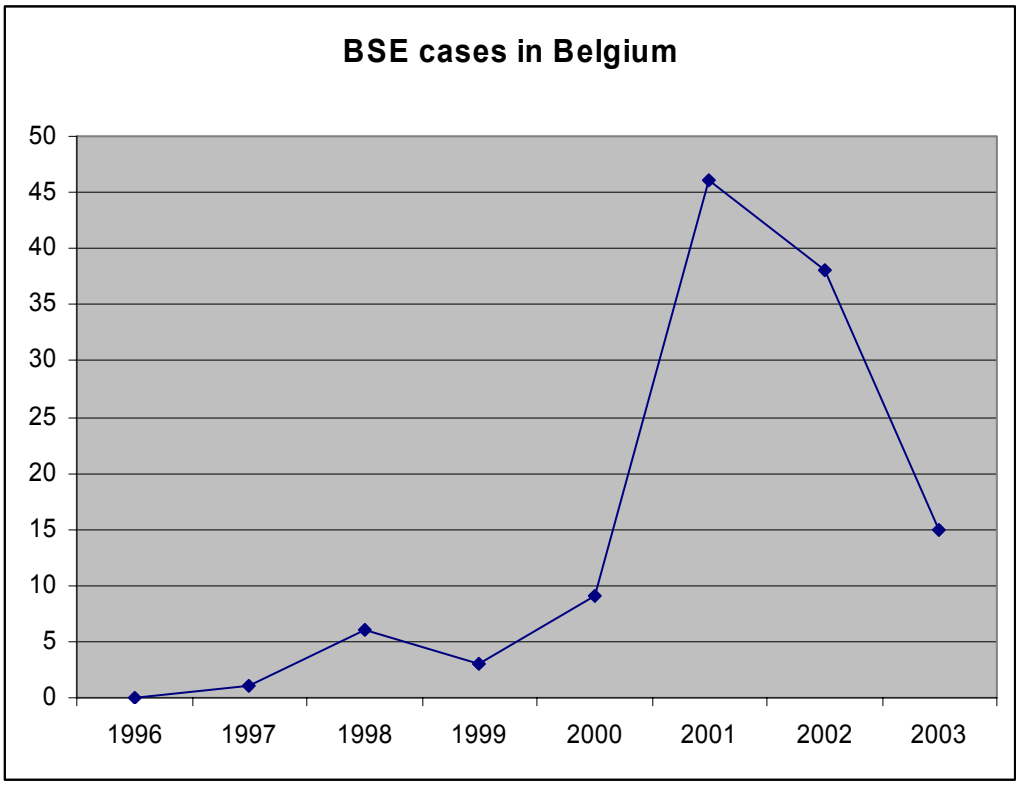
Figure 1: Number of BSE cases in the UK between 1988 and 2003



Source: World Organisation for Animal Health[18]

The BSE epidemic in Belgian cows was very limited. The sharp increase in 2001 is to be explained by the introduction of systematic screening in active surveillance from 1 January 2001 onwards, this in contrast to the UK epidemic, where most cases have been identified by passive case detection of cows with clinical disease.

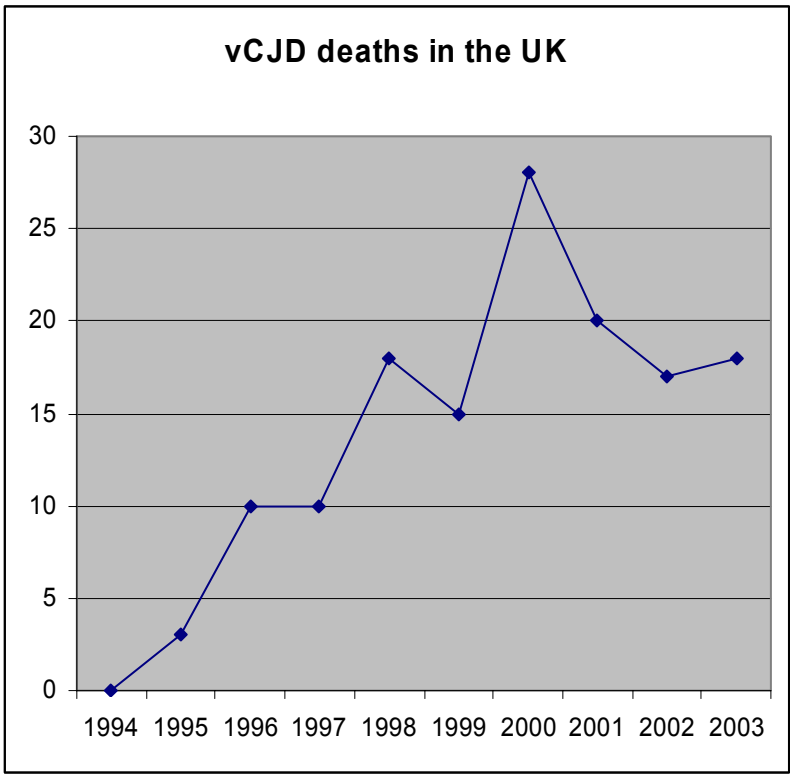
Figure 2: Number of BSE cases in Belgium between 1996 and 2003



Source: World Organisation for Animal Health[18]

The second phase was the passage of BSE to humans in the form of vCJD, an invariably fatal neurodegenerative disorder.[19] Evidence from laboratory studies strongly supports the hypothesis that vCJD is caused by the agent responsible for BSE.[17] The mechanism of transmission of the BSE agent to human beings has not been established, but is thought to be through consumption of bovine meat products contaminated with BSE. The first human deaths occurred in the UK in 1995 (Figure 3).[20] From 1994 till December 2003, a total of 145 cases and 139 deaths has been notified; the median survival is 12 months. In Belgium, no vCJD cases have been identified yet.

Figure 3: Number of vCJD deaths in the UK between 1994 and 2003



Source: Andrews et al.[20]

Human prion diseases are clinically related to Alzheimer's disease, which is also characterised by aggregating protein complexes (off course, Alzheimer's disease is not infectious). These diseases can be classified as sporadic, hereditary or acquired. The cause of sporadic Creutzfeldt-Jakob disease (sCJD) is unknown, hereditary cases are associated with mutations of the prion protein gene (PRNP) and acquired forms are caused by the transmission of infection from human to human or, as a zoonosis, from cattle to human. Experimental transmission data in mice indicate the possibility of a link of sCJD with BSE.[21 22] Switzerland has observed an unexpected increase of incidence of sCJD.[23] This increase remains unexplained; several scenarios can account for this increase in sCJD, including improved reporting or iatrogenic transmission. Transmission of a prion zoonosis is not exluded either. However, glycotype profiling, histopathology, and immunohistochemistry indicated that none of the 27 new cases fulfilled the definition of vCJD.[23] While a link between the sCJD incidence increase in Switzerland and the BSE/vCJD epidemic in the UK cannot be excluded, neither are there arguments to indicate such a link.

1.2.2 Kuru, a human TSE

Kuru came to the attention of western medicine in the 1950s. It was a fatal subacute neurodegenerative disorder limited to the Fore people of New Guinea, and transmitted via cannibalistic rituals as part of the mourning for deceased relatives. Children and women, consuming among others the central nervous system (CNS), were at higher risk of Kuru than men, consuming muscles. Kuru proved to be family of scrapie, and was successfully transmitted to chimpanzees.[14] Since cessation of cannibalism in the late 1950s, prevalence of Kuru has steadily declined, but rare cases still occur in people born before that date strongly suggesting incubation periods of at least forty years.[24] Observed polymorphism in the gene coding for prions suggests that these genes have been shaped by major epidemics of TSE-like illnesses.[24] Human vCJD cases have all been homozygous for methionine at codon 129 (MM). In the Fore people, MM is an important susceptibility determinant, increasing the risk of Kuru with resultant younger age at onset, shorter incubation period and shorter illness duration. Both in the Fore as in sporadic CJD (sCJD) in the UK, MM increases susceptibility of Kuru and sCJD but carriers of MV (V for Valine) and VV at codon 129 are not immune.[14] [24] Typically, MV and VV heterozygotes and homozygotes developed Kuru later. If Kuru is an appropriate disease model, vCJD will stay among us for many decades.

1.2.3 Potential for transmission of vCJD

Iatrogenic transmissions of sCJD have been documented, but were all due to cross-contamination with high titre tissues in or adjacent to the central nervous system; no instances of transmission through blood transfusion have been recorded.[25] However, findings suggest a greater potential for vCJD transmission than for the sporadic form. vCJD is characterised by high amounts of PrP^{vCJD} in lymphoreticular tissues such as the tonsils, the spleen and to a lesser degree lymph nodes.[26-28] This allows ante-mortem tonsil biopsy for diagnostic confirmation (but increases the risk of human-to-human transmission through medical procedures). Low amounts of PrP^{vCJD} have been detected in several organs. Data from a sheep BSE model confirmed transmission by intravenous blood transfusion, including from donor sheep in the incubation period.[29] These data were confirmed in macaques, showing short incubation periods between disease and intravenous infection, but at very high doses transfused.[26] In 2004, a first report of a likely human case of blood transmitted vCJD was reported in the UK.[30] A second likely case has been added recently.[31] There is now sufficient evidence to conclude that human to human transmission through blood transfusions is possible.

Key messages:

- **vCJD, a fatal human disease, is caused by the same agent that caused BSE in cows. There is no apparent link between vCJD and the long existing sporadic disease (sCJD), but such a link can not be excluded.**
- **The agent causing vCJD is an abnormal protein, a prion: PrPvCJD. Presence of that abnormal protein causes the normal protein to change to an abnormal, extremely denaturation resistant 'conformer'.**
- **In human TSE (Kuru), the incubation period can be at least 40 years.**
- **There is sufficient evidence available to conclude that PrPvCJD can be transmitted from (asymptomatic) human to human by transfusions of blood components.**
- **In Belgium, the BSE epidemic was soon declining, and no cases of vCJD have been identified yet.**

1.3 Leukoreduction, vCJD and a precautionary policy

It is probable that vCJD can be transmitted by whole blood, but the context has to be considered to evaluate the probability that it might happen. One definite[30] and one suspected[31] case of blood transmitted vCJD has been documented in the UK. The suspected case was a known blood transfusion recipient of a donor, dying few years later of vCJD. vCJD prions were discovered at autopsy after the patient died of a ruptured aorta aneurysm; but this case remains highly a-specific. In the UK, 184 000 cows have been identified, and back-calculation suggests almost ten times more (1.6 million) entered the human food chain.[32] This is likely several thousand times more than in Belgium. However, 5% to 10% of the meat consumed was from the UK, but prions are normally not present in the muscle meat destined for export. True BSE-exposure can therefore not be calculated for Belgium. As of April 2004, 151 vCJD cases have been notified, 141 in the UK, and 6 in France, that notified 934 cows with BSE of which 334 were clinical.[33] A seventh case is notified in France as suspect. Other cases have been notified in Ireland and in Italy. In Belgium, not a single case of vCJD has been identified yet (August 2004). The probability of vCJD outside the UK is not zero, but lower than 1 per 100 million person years in France and still lower elsewhere.

Is leukoreduction an effective tool for diminishing that very low probability even further? Leukoreduction diminishes the number of leucocytes with more than a factor 1 000, leaving less than $1x10^6$ white blood cells per unit (according to European standards).[34] It was originally 'guestimated' based on sheep models that

leukoreduction might diminish the risk with 90%, but we could not retrieve the origins of this reference, neither in the cited paper nor elsewhere.[29] Other agencies argued for a lower risk reduction of 50%, again without reference.[35] All these guestimates seemed entirely speculative. The very first article presenting plausible estimates of TSE load in (non-human) blood used scrapie (another TSE) infected hamsters as an animal model and was published in august 2004.[36] It showed poor efficacy of leukoreduction. Blood cell recovery and leukocyte removal complied with American Association of Blood Banks standards. Leukofiltration removed 42% (SD 12) of the total TSE infectivity in endogenously infected whole blood. Leukoreduction reduced the absolute transfusion risks with 17% and the relative risk with 35%: 48% of hamsters receiving buffy coat depleted infected whole blood were infected, compared to 31% of the hamsters receiving leukoreduced whole blood. The authors concluded that leukoreduction is necessary for the removal of white-cell-associated TSE infectivity from blood, but presumed that most of the TSE infectivity was plasma-associated. However, PrP proteins are very 'sticky' proteins, easily adhering to particulates, which is less an argument for leukoreduction than for filtration: the filter might catch most prions.[37] The industry is preparing now improved filters, with the aim of catching more prions.[38]

We conclude that human blood of carriers of vCJD is infective, that the infectious dose for humans is unknown, and that the clinical efficacy of filtration and/or leukoreduction is unknown, and certainly not 100%.

If health effects are unknown and uncertain, a precautionary policy is to be installed. Precaution is based on principles of reasonableness and proportionality.[39] A precautionary policy asks questions about the assumed magnitude of the health problem, the likely cost of the intervention to avoid that health problem, the amount of uncertainty of these estimates and acts on the basis of the answers. These acts have to be reasonable and proportional. The costs of protection are to be in reasonable balance with the estimated effects, taking into account a worst case scenario. As there is no scientific law that can identify what is reasonable and proportional, such decisions are to be based on a democratic debate with the stakeholders, including the public.

Outside the UK, in countries where the BSE epidemic has been contained and no or very few cases of vCJD occur, the probability of transmission of PrP^{vCJD} is low, even in worst case scenarios, compared to other transfusion risks. There is no evidence that leukoreduction will decrease risks of human to human transmission, while animal models show that the efficacy of leukoreduction is limited at best. Leukoreduction as precautionary argument for the prevention of vCJD is therefore weak. Transmission risks are low and future risk can be monitored by the evolution in the UK. The efficacy of leukoreduction is unknown, but low.

Key messages:

- In Belgium, the probability of vCJD transmission through blood transfusion should be smaller than in the UK, where it is still very small. Even in the worst case, it can be no more than a small fraction of the existing transfusion risks.

- The clinical efficacy of leukoreduction in reducing transmission of PrP^{vCJD} is unknown. Because of the sticky nature of PrP, filtration must have some effect. In an animal model, leukoreduction reduced TSE transfusion risk of whole blood with 42%.

- The opportunity costs generated by serious investments in precaution of vCJD are not proportional to the potential risk of vCJD in plausible worst case scenarios.

2 Medical advantages of leukoreduction

Patients requiring blood rarely need white blood cells.12 Leukoreduction, removing the white blood cells, has therefore several advantages that may guide policy decision making more than vCJD prevention.

2.1 Transmission of infectious agents

2.1.1 Human herpesviruses, HTLV I and II

Human herpesviruses (Cytomegalovirus, Epstein-Barr Virus, Human Herpes Virus-8) can remain present in white blood cells in latent form.[40] Cytomegalovirus (CMV) can be transmitted during the transfusion of cellular blood products and can cause significant morbidity and mortality in immunocompromised CMV-seronegative patients, such as CMV-seronegative pregnant women, premature infants (birthweight <1.2 kg) born to CMV-seronegative women, CMV-seronegative recipients of allogeneic bone marrow transplants from CMV-seronegative donors, and CMV-seronegative patients with acquired immunodeficiency syndrome (AIDS). Transfused erythrocytes, platelet concentrates, and granulocyte concentrates have all been implicated as the cause of infection by transfusion-transmitted CMV (TT-CMV), while fresh frozen plasma and cryoprecipitate have not been reported to cause CMV transmission.[41] Leukoreduction effectively reduces the probability of transmission of CMV in neonates, patients with acute leukaemia, and bone marrow transplant recipients.[42-46]

It is unknown if leukoreduction is as effective for the other herpesviruses. As seroprevalence of Epstein-Barr Virus (EBV) is very high in the adult population, clinical effectiveness of leukoreduction for removing EBV is dubious. Case reports show the possibility of severe clinical disease in EBV-seronegative immunocompromised patients.[47] In EBV seronegative high risk patients, leukoreduction may be useful. This will be done anyway, because of the lowered host-immunity.

Transfusion transmitted Human T-Lymphotropic Virus I and II (HTLV I/II) is a very rare event in Belgium, and clinical disease is even rarer. Leukoreduction likely eliminates infection, but conclusive data are lacking. For the time being, no efforts are made in Belgium to prevent HTLV I/II although transmission cannot be entirely excluded.

A correlated problem is reactivation of latent viral infection among seropositive recipients. In this case, transfusion does not transmit the infection, but makes an existing but latent infection active again. This is shown for CMV and, in vitro only, for HIV.[48 49] There is no evidence that leukoreduction might lower this risk.

2.1.2 Bacteria and parasites

Bacterial contamination of platelets is 10 to 100 times more frequent than the rates of viral contaminations, which may cause death.[3 4] Multiple studies have shown that 1:1 000 to 1:2 000 platelet units are bacterially contaminated. It is estimated that the risk of a bacterial-related death after a transfusion of a platelet unit ranges from 1:7 500 to 1:100 000.[50] Platelet products are more likely than other labile components to be associated with sepsis due to their storage at room temperature, which is permissive of bacterial growth. Surveillance studies have found rates of contamination as high as 0.4% in single donor platelets, although rates at or below 0.2% are more reported. The causes include occult bacteremia in the donor, inadequate or contaminated skin preparation at the phlebotomy site, coring of a skin plug by the phlebotomy needle, and breaches of the closed system from equipment defects or mishandling. Automated blood culture systems have been used by the Red Cross to culture components and are both highly sensitive and widely available.[51] Culturing on day 2 or 3 of storage would be expected to yield positive results concurrent with or before the bacterial concentration in the unit reaches a critical level. Leukoreduction will decrease the current risk, but the clinical efficacy of leukoreduction for bacterial removal is unknown. Platelets are already for 100% leukoreduced by the Red Cross for immunologic reasons.

Key messages:

- **Clinical evidence shows that leukoreduction reduces the probability of CMV-transmission. This is clinically useful in selected populations with poor immunity.**
- **Potential efficacy of leukoreduction reducing transmission of other Herpes-viruses, HTLVI/II and bacteria has no clinical importance.**
- **The clinical efficacy of leukoreduction in the reduction of latent viral activation is unknown.**
- **Bacterial contamination of platelets is one of the remaining more serious transfusion problems. In Belgium, 100% of platelets are leukoreduced and systematically screened for infection.**
- **The clinical efficacy of leukoreduction in the reduction of bacterial contamination of red blood cells is unknown.**
- **Experts agree that pregnant women, (premature) neonates, patients with a serious congenital or acquired immunodeficiency and transplant recipients (inclusive bone marrow transplant recipients) benefit from leukoreduced blood components, if transfusion is needed.**

2.2 Immunologic consequences

2.2.1 Human leukocyte antigen (HLA) alloimmunisation

Febrile non-haemolytic transfusion reactions (FNHTRs) have been reported to occur with an incidence of 6.8% after erythrocyte transfusion and 37.5% after platelet transfusion.[52] The major cause of severe FNHTRs is human leukocyte antigen (HLA) alloimmunisation. At repeated blood transfusions, the immunised individual attacks and destroys the allogene bloodplatelets and white blood cells, causing transfusion fever and platelet transfusion refractoriness. As there are very many human leukocyte antigens, the likelihood that two persons receive HLA compatible blood is small. If patients receive multiple transfusions, HLA alloimmunisation is a potentially serious problem. As a consequence of HLA alloimmunisation, patients become refractory to platelet transfusions. Immunised patients can only receive blood from donors that are more or less compatible.

Results of several meta-analyses,[53] [54] randomised clinical trials, prospective randomised studies[55], retrospective cohort studies,[56] and nationwide comparisons after introduction of universal leukoreduction,[57] show that leukoreduction

decreases the probability of primary HLA alloimmunisation by 70%. Results for neonates were inconclusive due to small sample sizes, but consistent with a 70% decline.[58]

It is to be noted that leukocyte reduction is less effective for patients with existing HLA-sensitisation, as the immune response is reactivated even by leukoreduced blood because of boostering of anti-HLA antibodies. That holds for FNHTRs by patients with existing anti HLA-antibodies because of previous transfusion or pregnancy. A randomised prospective study (with small sample size) did not show clinical benefit of leukoreduced blood among patients at high-risk of prior immunization induced by pregnancies.[59]

Key messages:

- **Empirical data of clinical studies shows that leukoreduction diminishes the probability of HLA alloimmunisation, platelet refractoriness and febrile non-haemolytic transfusion reactions.**
- **Experts agree that patients with haematologic and haemato-oncologic affections who require frequent transfusions, who show congenital or acquired haemotologic anemia or who have suffered from febrile non-haemolytic transfusion reactions, benefit from leukoreduced blood components.**

2.2.2 Immunodepression and improved postoperative outcome

It has been known for long that preceding blood transfusions reduce the risk of renal transplant rejection.[60] Allogeneic blood transfusions produce a variety of effects on the recipient's immunological functions, such as the decreased function of natural killer cells, macrophage migration to sites of injury, lymphocyte proliferation, and cutaneous delayed hypersensitivity. The presence of donor leukocytes in allogeneic blood may play a role in suppressing cellular immune function. This clinical syndrome is referred to in the transfusion medicine literature as transfusion-associated immunomodulation (TRIM). Possible deleterious TRIM-associated effects include increased prevalence of cancer recurrence and postoperative bacterial infections, but to a large degree the clinical consequences of transfusion induced immune effects are still a mystery.[61] Several randomised trials failed to prove an association between blood transfusion and tumour recurrence.[62 63]

In contrast to the available clinical data, studies in experimental animal models suggest that TRIM is an immunologically mediated biologic effect associated with the infusion of allogeneic leukocytes, which can be ameliorated by pre-storage leukoreduction. Four possible mechanisms have been reported to underlie the apparent association of allogeneic blood transfusion with postoperative bacterial

infection.[64] The recipient's immune system is down-regulated and predisposed for infection by

- immunologically active allogeneic white blood cells;
- soluble biologic response modifiers that are released from white blood cells during storage;
- soluble HLA peptides that circulate in allogeneic plasma or
- a related non-TRIM effect whereby postoperative organ dysfunction is caused that predisposes to infection.

The efficacy of leukoreduction to improve post-operative outcome is hotly debated. Reports suggest that allogeneic blood may increase the incidence of postoperative infection rates, and therefore increase complication rates, morbidity, antibiotic use and length of stay. However, the problem is complex, as shown before.[64]

The available clinical studies were not specifically designed for testing one of the main hypotheses. Studies are heterogeneous in patient populations, in the types of leukoreduction filters used, in the health care settings and in the outcomes studied. Thus, it is difficult to make inferences from the published data. A formal systematic review of this complex subject exceeds the aims of this short review; we limit ourselves to a qualitative discussion of the available evidence.

One way to look at the question is to profit from the actual introduction of universal leukoreduction, and to compare the situation before and after the implementation of universal leukoreduction. The results are again conflicting.[65 66] The Canadian experience suggested that the national universal leukoreduction program was potentially associated with decreased mortality, decreased fever episodes and antibiotic use but the British experience suggested no effect.[65 66] Vamvakas recently performed a systematic pooled analysis of six observational 'before and after' studies (including the previous ones).[67] He found an effect that was not upheld after adjusting for confounding.

Several randomised trials were performed that compared various types of blood transfusions (generally buffy coat poor) with leukoreduced blood transfusion (with various techniques) in selected patient populations (predominantly cardiac, colorectal and gastro-intestinal surgery).[63 68 69 70 71 72] Again the evidence was conflicting. Vamvakas updated a formal meta-analysis, comparing fourteen RCTs.[73] The outcome of interest was short term and long term mortality. In a previous version of this meta-analysis, he found an effect of leukoreduction if whole blood was used, but no effect if buffy coat poor blood was used as a comparator.[74] The updated meta-analysis concluded that an association between allogeneic blood transfusion and either short term or long term mortality was not detected across

clinical settings and transfused red blood cell components, but that an association between leukocyte-containing blood transfusions and short term mortality may exist in specific sub-groups.

In the Netherlands, using the same leukoreduction technology and comparable populations as Belgium, comparisons with buffy coat poor blood show consistently and reproducibly a beneficial effect of using leukoreduced blood on post-operative infections and mortality in specific patient populations, i.e. patients undergoing digestive tract surgery or cardiac surgery or patients who receive more than three blood transfusions.[70-72] However, negative results elsewhere remain unexplained, which makes the interpretation of these results uncertain.

Key message:

- **Evidence of the role of leukoreduced blood in improved postoperative outcome is conflicting. This is caused by both medical and methodological heterogeneity of the experimental studies.**

2.2.3 Graft versus host reactions

A rare but usually fatal complication of transfusion is transfusion-associated graft-versus-host disease (TA-GVHD). The risk associated with an individual transfusion depends on the number and viability of contaminating lymphocytes, the susceptibility of the patient's immune system to their engraftment, and the degree of the immunological (HLA) disparity between the donor and recipient. The transfused viable T lymphocytes, under certain circumstances, engraft and proliferate in the recipient. The interaction between incompatible donor T lymphocytes and recipient cells results in cellular damage. Major target tissues include skin, thymus, gastro-intestinal tract, liver, spleen, and bone marrow. The risks of TA-GVHD are highest in recipients who have an immunodeficiency or who are immunosuppressed, although TA-GVHD has not been described in patients who are infected with HIV. Current filtration technology cannot consistently produce the levels of lymphocyte removal required to avoid a TA-GVHD. The current mainstay of preventing lymphocyte proliferation continues to be gamma irradiation.[75]

Key message:

- **Current filtration technology cannot avoid a graft versus host reaction, and cannot replace gamma irradiation.**

2.2.4 Diminished clearance of bacterial contamination

Blood transfusion can be contaminated with infectious agents. Active white blood cells play a role in the elimination of these agents by phagocytosis.[76] Leukoreduction may prevent this activity and increase transfusion transmittable septic agents.

However, this is prevented by overnight storage before leukoreduction. Leukocytes are but removed after one night of storage at room temperature to benefit from the bactericidal activity of the white blood cells.

Key message

- **Overnight storage of blood before leukoreduction prevents diminished clearance of bacterial contamination.**

3 Pathogen inactivation

Next to leukoreduction and more testing, the method of pathogen inactivation is being considered. Pathogen inactivation not only inactivates all viruses but also kills bacteria, parasites, and lymphocytes. A compound based on a group of photoreactive substances known as psoralens, amotosalen, and ultraviolet light are used together to treat individual platelet concentrates in the Helinx system, which crosslinks DNA and RNA.[77] [78] Another psoralen, S-303, is in development for use in red cell concentrates. Although expensive and labour intensive, this system could inactivate all potential pathogens, except for prions. In addition, this treatment would make it unnecessary to irradiate blood components to prevent transfusion associated graft versus host disease as the donor lymphocytes responsible would be killed. A safe and affordable pathogen inactivation system would obviously the treatment of choice, as it eliminates not only known but also unknown infectious agents, except for prions (which are proteins).

However, there have been few publications to date on clinical research involving inactivation techniques. Most of the data is derived from two phase-III studies with amotosalen. Two transfusion trials in thrombocytopenic patients using pathogen inactivated compared to control platelets have now been completed; i.e. a European study (*euroSPRITE*), using buffy coat platelets, and a U.S. Trial (*SPRINT*), using Amicus collected apheresis platelets.[79] [80] In the *euroSPRITE* trial, post-transfusion platelet increments were significantly less at both 1 and 24-hours following transfusion, and also CCI's (corrected count increment, the increase in the number of platelets following correction for the patient's body surface area) at 24 hours post-transfusion for the treated compared to the control platelet transfusions.[80] In the *SPRINT* trial, all measurements (increments, CCI's, and days to next transfusion) were significantly less for the treated compared to the control platelet transfusion. However, the haemostatic efficacy of the treated platelets was comparable to the control platelets.[79] Both a loss in platelet viability as well as fewer platelets recovered for transfusions following pathogen inactivation probably accounts for the differences in transfusion responses.

Pathogen inactivation is a promising emerging technology. For the time being, it is too expensive to consider, given the paucity of published clinical research. As adverse transfusion transmitted events occur very rarely, it will be hard to prove that pathogen inactivation is safer and more cost-effective than the alternative of universal leukoreduction and additional testing. Before actual testing can be eliminated, inactivation must prove to be absolutely failsafe. This will be difficult, as adverse transfusion related events are already very rare and hence proof will be needed that such events are extremely rare.

Moreover, there is a latent danger of competing risks.[78] Most accidents are caused by clerical error. In the UK, of all serious accidents causing death or major morbidity, only 11% were caused by infections.[81] Per patient, 2.2 (35%) more platelet transfusions were needed in the larger SPRINT trial.[79] If all transfusion transmitted infections are effectively stopped, but the other risks remains unchanged, pathogen inactivation increases transfusion risks for death and major morbidity by 20%.

As new data from more trials and observational studies will accumulate, the place of pathogen inactivation in blood transfusion will be more clear. Pathogen inactivation outside carefully conducted studies has no place for the time being, and should be discouraged.

Key messages:

- **Pathogen inactivation is a promising new technology, with yet uncertain efficacy.**
- **Randomised controlled trials show an increased need for platelet transfusions after pathogen inactivation.**
- **Pathogen inactivation has as yet no place in clinical practice outside carefully conducted clinical studies.**

4 Cost-effectiveness of leukoreduction

The incremental cost-effectiveness (additional cost per additional unit of effect) of leukoreduction depends on the implementation strategy chosen. Leukoreduction for patients with specific indications only (selective leukoreduction) has other implications for costs and effects than leukoreduction of all blood products (universal leukoreduction). In this chapter, we discuss the economic advantages and disadvantages of both strategies.

4.1 Cost per unit of leukoreduction[1]

In Belgium, a unit of blood is reimbursed at € 67.85 and a unit of leukoreduced red blood cells at € 92.99. The difference with non-leukoreduced red blood cells amounts to € 25.14, which covers the cost of the filters, personnel and quality control. This € 25.14 is considered an accurate estimate of the real incremental costs of leukoreduction. In the US, the unit cost of leukoreduction lies within the range of € 21-€ 29 per blood transfusion (US$ 25-US$ 35 in 2001).[82] In the UK, the costs of the leukocyte filters for red cell concentrates was € 25.88 (UK£ 15.65 in 1998).[83] Over the last few years, the price of leukoreduction filters has decreased due to the increased competition in the industry. After the introduction of universal leukoreduction in many European countries new and cheaper systems became available.

The unit costs of leukoreduction are obviously higher than the mere cost of the filters. Costs are incurred at several stages in the blood donation process. Filtration is time consuming: it takes approximately 45 minutes to prepare a unit of filtered blood, compared to 20 minutes for unfiltered blood. The workload and the administrative load at the component-processing laboratory of the blood transfusion centres increases. The use of filtration sets is more complex, especially if blood is not collected centrally but during ambulatory campaigns in the community (logistical problems). Leukoreduction generates high volumes of medical waste, and approximately 10% of blood cells is lost, although this does not jeopardize the dose requirements defined by the European regulation.[82] [84] Finally, additional quality control is needed in case of leukoreduction to monitor the remaining number leukocytes in the red blood cell concentrate by flow cytometry.

A Dutch study estimated the additional cost of leukoreduction at € 23.28 if universal leukoreduction would be applied and at € 41.90 if selective leukoreduction would be applied (figures derived from the accounting system of Sanquin, Netherlands, € 20.60,

[1] All cost figures are expressed in € for price year 2003. Conversion from the original currency unit and price year in the publications is done by first inflating the figures to the year 2003 and then multiplying by the exchange rate.

resp. 37.08 at price level 1999)[85]. These costs include the costs of filters, excess costs in processing and salaries of additional personnel. The lower unit cost of universal leukoreduction is due to economies of scale: higher output volumes are associated with lower average costs because the equipment can be used more efficiently. It can be argued that with increasing experience in leukoreduction, also the additional personnel time will decrease due to learning.

A comparison of the unit costs of leukoreduced red blood cells between a number of European countries and Belgium for the years 2000 until 2003 is made in Table 2.

Table 2: Comparison of unit costs of leukoreduced red blood cells between European countries and Belgium[86]

		% difference with Belgium	2002	*% difference with Belgium*	2003	*% difference with Belgium*
Belgium	92		92		92	
Netherlands	208	*126*	163	*77*	178	*93*
France	149	*62*	166	*80*	169	*84*
Luxembourg	142	*55*	143	*55*	143	*55*
Ireland	122	*33*	154	*67*		
Finland	97	*6*	100	*9*		
Austria	103	*12*	113	*23*		
Average	***137***	***+ 49***	***140***	***+ 52***	***163***	***+ 78***

Two things appear from the table. First, the reimbursement for a unit of leukoreduced red blood cells (RBCs) has not changed over the past four years in Belgium, while it has increased in most other countries. Second, the reimbursement of RBCs is relatively low in Belgium compared to other countries.

Key messages:

- **The current reimbursement for a unit of leukoreduced erythrocytes is € 92.99, which is € 25.14 higher than the reimbursement for a unit of non-leukoreduced erythrocytes (for adults). The difference of € 25.14 covers the costs of the filters, personnel and quality control.**
- **In the Netherlands, the additional production cost associated with leukoreduction has been estimated between € 23.28 in case of universal leukoreduction and € 41.90 per unit in case of selective leukoreduction.**
- **Whereas the incremental costs of leukoreduction per unit is similar between Belgium and other countries, the reimbursement for one unit of red blood cells shows important differences. Belgium has a low reimbursement price compared to other European countries.**

4.2 Selective leukoreduction

4.2.1 Gross budget impact

Belgium currently has a policy of selective leukoreduction. About 35% of the red blood cell concentrates and 100% of the platelets are leukoreduced in Belgium. The current expenditures amount to € 15.75 million for leukoreduced red blood cell concentrates (RBC) and to € 20.80 million for non-leukoreduced red blood cells. Including the expenditures for CMV negative RBC and autologous RBC, the total expenditures amount to €36.69 million per year. With the difference of € 25.14 in the reimbursement of leukoreduced and non-leukoreduced RBC, selective leukoreduction took up € 4.25 million (11%) of the total RBC budget in 2003 (for a detailed calculation, see appendix 1).

4.2.2 Cost-effectiveness of selective leukoreduction

Selective leukoreduction implies that only patients for whom the (cost-)effectiveness of leukoreduced blood has been proven, receive leukoreduced blood. The economic arguments in favour of selective leukoreduction are strong.

The indications for leukoreduced blood are defined by the Belgian law (Royal Decree, March 12, 1998[87]):

- Immunocompromised patients, including
  - Children in centres for neonatology
  - Patients with heavy burn lesions
  - Patients on an intensive care unit
  - Patients at risk for developing CMV
  - Haematology patients
- Transplantation candidates or transplant recipients
- Patients requiring multiple transfusions
- Patients with recurrent non-haemolytic transfusion reactions

These indications were intended to limit the use of leukoreduced blood, by limiting the patients in which leukoreduced blood *could* be used. Instead, however, it actually increased the leukoreduced blood use as physicians started to use leukoreduced blood precautionary in all these patients.

For patients at risk for HLA alloimmunisation and transfusion-transmitted CMV infection, there is consensus that leukoreduction is cost-effective relative to no leukoreduction.[88] [89] These patient groups include patients with recurrent febrile non-haemolytic transfusion reactions (FNHTR), patients with long-term or chronic need for transfusion (e.g. haematology patients), patients with a compromised or immature immune system (e.g. cancer patients receiving chemotherapy) and organ

donors or transplantation candidates. It can be questioned whether leukoreduction should be generalised to all surgery patients receiving blood, for whom the effectiveness of leukoreduction has not been substantiated yet.

A number of studies on the cost-benefit or cost-effectiveness of selective leukoreduction for specific patient groups have been performed. Most agree that leukoreduction is efficient for certain groups of surgical patients, such as patients undergoing cardiac surgery, aneurysm repair, gastrointestinal surgery and colorectal surgery.[72 82 83 90 91] Because there was no strong evidence of the clinical effectiveness of leukoreduction for other surgical patients, cost analyses showed high additional costs and no savings of leukoreduction in these patient groups.[83 90] However, as the evidence on the effectiveness in these patients is still contradictory, no clear conclusions can be drawn.

Key messages:

- **The current budget devoted to leukoreduction amounts to € 4.25 million per year.**
- **Leukoreduction is cost-effective for patients requiring frequent transfusions, patients with a compromised immune system or recurrent febrile non-haemolytic transfusion reactions, organ donors and transplant recipients.**
- **There are strong indications that leukoreduction is also cost-effective for patients undergoing cardiac surgery, aneurysm repair, gastrointestinal surgery and colorectal surgery.**
- **Evidence on the cost-effectiveness for other patient groups is limited.**

4.3 Universal leukoreduction

4.3.1 Gross budget impact

The budgetary impact of universal leukoreduction for Belgium (10 million inhabitants), compared to the current practice of selective leukoreduction, is estimated at an additional € 7.71 million per year (for a detailed calculation see appendix 2). In the UK (48 million inhabitants), the additional cost of universal leukoreduction has been estimated at € 64.67 million/year (UK£ 40 million in 1999).[92] The cost of universal leukoreduction per inhabitant per year is thus € 0.771 for Belgium and € 1.35 for the UK. The Dutch Health Council estimated that the costs of universal leukoreduction would be around € 26.17 million per year (fl. 40 million, price year 2000), an added cost of € 1.63 per inhabitant per year. This estimate includes the cost of filters, additional procedures, personnel, equipment, quality control, maintenance and accommodation.[93] Belgium has a significantly lower

cost of universal leukoreduction per inhabitant than the Netherlands and the UK, partly because of the lower prices of more recent filters.

4.3.2 Potential savings

None of the above cost estimates takes the potential savings from leukoreduction into account. Leukoreduction can reduce the costs associated with HLA alloimmunisation, FNHTRs and transfusion-transmitted CMV (and other) infections (see chapter 2, the medical advantages of leukoreduction). The alleged beneficial effect of leukocyte reduction on the rate of postoperative infections could moreover result in shorter length of stay in hospital after blood transfusion. The largest prospective randomised study of universal leukoreduction (n=2 780) found no differences in in-hospital mortality, hospital length of stay, intensive care unit length of stay, postoperative length of stay, antibiotic usage and readmission rates between patients receiving leukoreduced blood and patients receiving non-leukoreduced blood.[95] The study did not find a beneficial clinical effect from leukocyte reduction, except in terms of incidence of febrile reactions.

It is difficult to generalise these results to a Belgian setting, however, as the buffy coat was not removed in the group receiving non-leukoreduced blood in this study. In Belgium about 30% of the RBC are already buffy coat depleted. The problem of generalisability applies to most of the literature in this field. Individual clinical trials often use different study settings, different technologies and different comparators (e.g. buffy-coat depleted versus non-buffy-coat depleted, bed-side versus pre-storage filtration). To put the results into perspective, it is therefore important to compare studies with similar conditions.

The conflicting evidence of benefits of leukoreduction has led to intense debate over the wisdom of universal leukocyte reduction of all transfusions. Both pro[94] and con[96] views can be given, depending on which setting and technology is considered.

4.3.3 General impact of universal leukoreduction

It is sometimes argued that the savings associated with universal leukoreduction offset the costs, in which case universal leukoreduction is obviously the choice of preference. However, the evidence is conflicting. The Canadian Coordinating Office for Health Technology Assessment concluded that universal leukoreduction was not net cost-saving but that selective leukoreduction can be cost-saving.[97] The Australasian Society of Blood Transfusion (ASBT) concluded that the additional cost of universal leukoreduction would be offset by reduced cost in clinical management of the adverse effects of non-leukoreduced product in the hospitals. The ASBT therefore recommended universal leukoreduction for all red blood cell concentrates.[98] In 2001, the University Healthsystem Consortium (UHC) concluded that there was insufficient evidence to justify universal leukoreduction for the

prevention of bacterial and viral transmission, decreasing the incidence of cancer recurrence, preventing postoperative mortality and infection, and safeguard against vCJD transmission.[88 89]

Table 3 summarizes the advantages and disadvantages of universal leukoreduction, according to their strengths of evidence.

Table 3: Advantages and disadvantages of universal leukoreduction

	Advantages	Disadvantages
Strong evidence	• reduction in non-hemolytic febrile transfusion reactions • reduction in HLA immunisation • reduction of transfusion transmitted CMV • simplified stock control	• decrease in quantity of red blood cells[82 84] (note: the operational consequences of this quantity loss are minimal) • increased costs in the short run (time, manpower, materials) • increased volume of medical waste • logistics (more space needed)
Weak evidence	• reduction in allergic reactions • reduction in transfusion-related post-operative morbidity or mortality • reduction in vCJD transmission • reduced legal charges	

The two main disadvantages are a decrease in the quantity of red blood cells, though within acceptable limits, and increased costs. These disadvantages may be limited to the short run. Increased competition between the manufacturers of filters may lower prizes, increase potential capture of prions and lower waste of red blood cells. The personnel of the blood transfusion centres will become more experienced with the leukoreduction techniques. The process of innovation is demonstrated by the fact that modern filtration systems retain more leukocytes, generating a residual leukocyte count of $<1x10^6$, whilst the Belgian law still demands a residual leukocyte count of $<5X10^6$ (Royal Decree April 4, 1996[87]).

From the perspective of the blood donor centres, there are two important sources of savings associated with universal leukoreduction: simplification of the stock management and reduction in the costs of legal charges. Simplification of the stock management will reduce the administrative workload and the amount of wasted blood units due to passed of shelf-life. The same advantage is experienced by the hospitals. Universal leukoreduction will reduce the costs of blood stock management

in hospitals. Currently, the blood donor centres are confronted with costly litigations whenever a patient experiences a transfusion-related complication (see chapter 6). By reducing the risk of transfusion-related complications, it is hoped that the insurance premium can be maintained at the same level or even reduced as the number of legal charges is reduced. These costs currently impose a heavy burden on the budget of the blood bank.

From the point of view of the existing evidence, we can conclude that the economic basis for universal leukoreduction is rather limited. From a legal point of view, we must comply with the European Directive 2002/98/EC. This directive sets the standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and says:

> *"… In order to safeguard public health and to prevent the transmission of infectious diseases, all precautionary measures during their (blood and blood components) collection, processing, distribution and use need to be taken making appropriate use of scientific progress in the detection and inactivation and elimination of transfusion transmissible pathogenic agents."*

No concrete interpretation of what constitutes these precautionary measures is provided in the European Directive but it is clear that it is in favour of universal leukoreduction. However, a precautionary policy is no license to increase inefficiency at will, as inefficiency decreases resources elsewhere.

Despite the contradicting evidence, many European countries decided to implement universal leukoreduction. The motive was not primarily to avoid HLA alloimmunisation, virus transmission or other well-established risks of transfusion, nor to improve cost-effectiveness in transfusion medicine, nor to avoid to donate useless immune-active allogeneic white blood cells, but to avoid the risk of vCJD transmission through blood transfusion. A precautionary policy does not mean that anything goes: the intervention has to be proportional to the alleged risk. In a modern context of defensive acting, optimal blood safety conflicts with maximal blood safety. By competing risks with other sectors and opportunity costs generated by inefficient technology, maximal blood safety may paradoxically lower the quality of health care.

Universal leukoreduction is somewhere in between optimal and maximal. It is clearly not optimal, but the evidence of its advantages, although conflicting, and the justified expectation of future lowering costs make it an intervention worthwhile to consider. The core-argument of a precautionary policy against vCJD (outside the UK) is a testimony of defective risk communication with the general public and its' elected politicians. Public opinion is a very important fact to weigh in any decision, certainly in this decision directly relevant to the trust of unpaid volunteers. But the poor public understanding of risk will not go away by introducing increasingly inefficient

technology. It is unfair to burden the blood bank operators such as the Red Cross with all foreseeable and unforeseeable consequences of all transfusions. The problem of poor understanding of risks should be stated as such, and presented to European policy makers. Laws should be changed, to make blood safety policy makers 'accountable for reasonableness', not for anything that conceivably and inconceivably can go wrong during a blood transfusion.[99]

Key messages:

- **With the current difference in charges between leukoreduced and non-leukoreduced red blood cells in Belgium, the additional budget required to implement a strategy of universal leukoreduction is estimated at approximately € 7.71 million per year.**
- **Universal leukoreduction reduces the costs of transfusion related clinical complications. These savings cannot be estimated due to conflicting evidence on the clinical effectiveness of universal leukoreduction.**
- **The economic arguments for universal leukoreduction are limited. The European law is clearly in favour.**
- **The blood banks hope that universal leukoreduction would seriously reduce their outlays for legal charges. There is no evidence that this hope will materialise.**
- **The rational arguments for universal leukoreduction are old. The present introduction, based on the hypothetical risk of vCJD has - outside the UK - no rational basis.**
- **In a precautionary policy, involvement of the informed public is crucial. This holds even more for blood safety policy in Belgium, founded on the trust of volunteer donors. Maintaining the trust of the public is a strong pragmatic argument for introducing universal leukoreduction.**
- **Defective risk communication with the general public and its elected politicians will not go away by introducing more and more inefficient technology. The problem has to be framed and tackled as such.**
- **Blood operators need improved legal coverage, to be held 'accountable for reasonableness', not for the unreasonable.**

5 Organisation and logistics

For the organisation of leukoreduction, two options exist: pre-storage leukoreduction or bed-side leukoreduction. In pre-storage leukoreduction, leukocytes are re-moved in the component-processing laboratory before storage, within 18 hours after collection of the blood, to allow phagocytosis of any bacteria present in the red cell or platelet concentrate.[100 101] Bed-side leukoreduction was performed during transfusion, but is now obsolete as pre-storage leukoreduction has obvious advantages.[102-104]

In Belgium, leukoreduction is currently organised centrally at each blood transfusion centre. The advantage of a centrally organised system is that it guarantees quality control and that manipulation of blood products is done by experienced people. Larger centres can also guarantee 24 hours permanence, which is useful for urgent demands from hospitals.

The benefits of universal leukoreduction for the blood transfusion centres and hospitals would be a simplified stock control and administration, as there is no longer a need for double stocks (leukoreduced versus non-leukoreduced blood components). In addition, the blood banks hope for reduced litigation costs when less transfusion-related complications occur.

Key messages:

- **Pre-storage leukoreduction is to be preferred over bed-side leukoreduction, as it leads to a clinically superior product.**
- **Centrally organised leukoreduction has a number of obvious economic advantages, including economies of scale, improved quality control and experienced staff.**

5.1 Quality assurance

Leukoreduction should be subject to quality assurance. This includes control of standardized procedures and adequate training of staff.[103] The following procedures for quality assurance should at least be performed:

- controlling the temperature
- controlling the duration of filtration
- controlling the age of the blood component
- measuring the leukocyte counts

It is generally accepted that leukoreduction should be carried out <48 hours after blood collection.[102 103]

According to the "Guidelines on the clinical use of leukocyte-depleted blood components" of the British Committee for Standards in Haematology, it is not necessary to measure leukocyte counts on every concentrate prior to release for transfusion. A statistical process control to ensure that the leukocyte-depletion procedure remains within predetermined limits is considered equally acceptable.[103] Residual leukocyte counts should be less than $5X10^6$ (according to the Belgian Law; Royal Decree April 4, 1996[87]). In practice, however, Belgian transfusion centres guarantee a leukocyte count below $1X10^6$, as defined in the European law (Directive 2004/33/EC[34]).

Residual leukocytes can be counted by means of flow cytometry or large-volume microscopic chambers (e.g. Nageotte chamber). Automated blood cell counters are inadequate for estimation of the low levels of leukocytes present in leukoreduced blood components. Automated blood cell counters can be useful, however, for quality control of buffy coat depleted RBC concentrates. Every month, each blood transfusion centre sends a sample of 20 units per type of blood concentrate to the central laboratory for quality control. Testing of the blood products for HIV, HCV, Syphilis and ALT is done at the central laboratory in Leuven or Namen. Universal leukoreduction would not require additional flow cytometries, as the actual capacity is not yet exhausted.

After a process of successful leukoreduction (i.e. residual leukocyte count $<1X10^6$), the leukoreduced blood components need to be stored. The requirements for storage are not different from non-leukoreduced blood components.

Key messages:

- **Quality assurance is a crucial step in the leukoreduction process. It should be organised centrally to benefit from economies of scale.**
- **Quality assurance is already organised in central laboratories in Belgium.**

6 Legal issues

6.1 Product liability

According to the Belgian law, the Red Cross is held liable, as the producer of blood and blood products, for any possible defaults of the products. An exception is made when the producer can prove that it was, at the moment diffusion of the product, not possible to detect the default on the basis of the state-of-the art scientific evidence. Such exceptions need to be defended before the court of law. The impossibility to detect a default due to a lack of resources is not accepted. This legal state of affairs may cause that an increasingly illegitimate and unfair share of the health care budget is spent to increasingly inefficient blood safety procedures.

Further, Belgium must comply with the European Directive 2002/98/EC. This directive sets the standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and says:

> *"… In order to safeguard public health and to prevent the transmission of infectious diseases, all precautionary measures during their (blood and blood components) collection, processing, distribution and use need to be taken making appropriate use of scientific progress in the detection and inactivation and elimination of transfusion transmissible pathogenic agents."*

No concrete interpretation of what constitutes these precautionary measures is provided in the European Directive, and when measures stop to be reasonable and proportional to the public health threat.

The regulation implies that the Red Cross will also be liable for the transmission of vCJD through blood transfusion. The fact that all neighboring countries implemented a universal leukoreduction policy will be used to demonstrate that the Red Cross has not taken all precautionary measures to avoid a vCJD transmission.

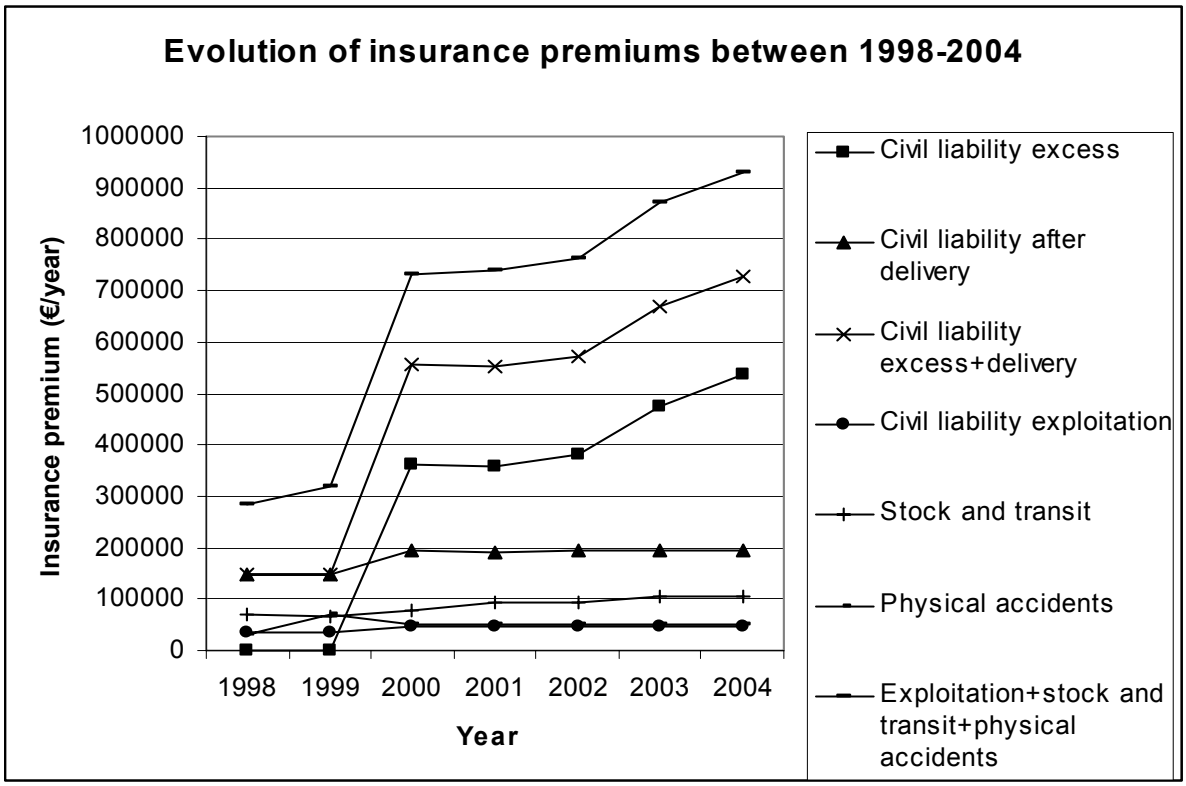
Key messages:

- **In Belgium, the Red Cross is held liable for all blood products it delivers. If damage is caused to a patient due to a default of a transfused blood product, the Red Cross has to defend itself before the court of law.**
- **The present Belgian and European laws fail to define a precautionary policy in terms of reasonability and proportionality. This causes a safety policy that is driven by available technology, not by actual need.**
- **The fact that all neighbouring countries introduced universal leukoreduction makes the Belgian Red Cross very vulnerable to litigation, even for a single case of transmission.**

6.2 Insurance

Given the product liability, the Red Cross will take an insurance to protect the organisation from huge monetary losses. Insurance premiums currently impose a heavy burden on the budget of the Red Cross and are likely to continue to do so. Over the past 6 years, the total health insurance fees for the Belgian Blood Services have risen with 228% (Figure 4).

Figure 4: Insurance premiums paid by the Red Cross in Belgium



This rapid increase in insurance premiums was mainly due to increased coverage for civil liability after delivery. Between 1998 and 2004, the insurance premiums for civil liability for blood and excess civil liability increased with 395%. According to the Red Cross, these higher premiums are mainly due, first, to the high hopes of the general public with respect to health care safety management in general and blood safety in particular and, second, to the product liability of the Red Cross.

The danger of the continually increasing premiums is that blood transfusion will eventually become un-insurable and subsequently economically unsustainable for the Red Cross. It is to be expected that the insurance premiums will further increase if Belgium decides not to implement a universal leukoreduction programme. In the worst case, insurance companies will no longer be prepared to insure this risk. In this particular case, the government will need to take up this responsibility.

The current situation is moreover undesirable as it implies a shift of financial resources to foreign private health insurance companies. The budget of the Red Cross is obtained from the reimbursement of blood products. As part of this budget flows away to private insurers, this is a loss for the health care sector. Only a fraction of these resources will flow back to the health care system for the treatment of unfortunate blood transfusion patients, but the bulk of the premiums will be used to cover huge compensation claims. Consequently, the resources do not flow back to the health care system for health improvement may be considered as inefficient use of the health care budget.

Key messages:

- **Insurance premiums for the Red Cross are rising rapidly and impose a heavy burden on the Red Cross budget. As this budget eventually comes from the health care payer, these insurance premiums are an inefficient use of scarce health care resources.**

- **Unfounded fears of the badly informed general public and product liability makes the Red Cross easy prey for the international insurance companies.**

7 Conclusions and recommendations

Leukoreduction and haemofiltration have obvious advantages. Patients but very rarely need the immuno-active white blood cells. Leukoreduced blood is of better quality than buffy coat depleted blood, even regardless of the risks of BSE/vCJD transmission, but the clinical benefits are only shown in specific patient populations. Quality may have its' price, considerable but affordable. With increasing experience and industrial competition, costs will decrease further. Still, selective leukoreduction avoids the costs of leukoreduction in 65-75% of blood donations, probably at very little extra risks in the rest of the patient population receiving blood.

Are the costs of universal leukoreduction worthwhile? The estimated incremental cost for the health care payer of universal above selective leukoreduction in Belgium is € 7.71 million per year, around € 25 per unit of treated blood. Universal leukoreduction will generate additional savings, but these savings are difficult to estimate, as the state of the art evidence on the clinical benefits of leukoreduction is both debated and debatable. Savings may also be induced by simplified logistics, both at the blood transfusion centres and the hospitals. The existing evidence on savings generated by universal leukoreduction is contradictory, not only due to diverging study settings, methodologies, technology, study populations and changes over time. Nevertheless, there will be at least some savings, and the net budgetary impact of universal leukoreduction will be less than € 7.71 million per year.

7.1 Arguments against universal leukoreduction

Avoidance of transfusion-related complications, such as CMV infection, HLA immunisation and non-haemolytic transfusion reactions, is not sufficient to justify universal leukoreduction. The patient groups who might benefit from leukoreduction in terms of reduced CMV infections, HLA immunisation and non-haemolytic transfusion reactions, are relatively well defined (e.g. haematology patients, major surgery patients). Therefore, selective leukoreduction is cost-effective. The additional costs of universal leukoreduction must be justified by the additional benefits and must be in favourable balance with other possible uses of the invested resources before we can draw firm conclusions about the efficiency of universal leukoreduction relative to other health interventions.[105]

The introduction of universal leukoreduction in the UK and many European countries was mainly inspired by the suspected transmissibility of vCJD via blood transfusions. Although the evidence of vCJD transmission through blood transfusion is limited to a single clinical case, we can conclude that the risk is real. However, this is still a very small risk, in the UK, but even more elsewhere. Further, there is no evidence that leukoreduction will decrease that risk of transmission tangibly. If the hamster model holds – for the time being the only available empirical data on the

effect of leukoreduction on TSE transmission by blood transfusion – leukoreduction causes but a limited reduction of that risk.

Universal leukoreduction is advocated as a precautionary policy. However, claims for a precautionary policy are often not well founded. A precautionary policy does not mean that anything goes in the face of any risk. Resources used up for precaution are not available elsewhere, where they could be of better use. To be legitimate and fair, the resources used up are to be proportional to a reasonable assessment of the potential risk. What is proportional and what is reasonable exceeds empirical evidence: that can only be decided by democratic deliberation with the stakeholders.

7.2 Arguments for universal leukoreduction

Universal leukoreduction offers undoubtedly a better blood quality than buffy coat removed red blood cells, removing most of an essentially undesirable component, white blood cells. This goes at a limited cost per unit: € 25 per unit of blood is a relatively small marginal cost, compared to the whole of costs made for the care of a transfused patient. These costs will decrease, as the experience of blood operating teams increases and the high demands in universal leukoreduction drives industrial competition to search for cheaper filtration systems.

The public system of blood transfusion in Belgium is based on voluntary, unpaid donors. These donors have guaranteed the very safe blood supply Belgium has, avoiding most of the catastrophes based on paid donorship. Maintaining the trust of the public is therefore of utmost importance. If many countries are introducing universal leukoreduction, it is hard to explain to the public that such choice is irrational. It is even harder if that choice costs around € 25 per unit of donated blood by an unpaid volunteer donor, and increases its quality. If such seemingly rational policy would undermine public trust, the results might be very irrational indeed, costing a multiple.

While the medical and economic justification of universal leukoreduction is rather poor, the societal consequences of abstaining from universal leukoreduction may be large. It takes the precautionary argument upside down: spending resources to lighten the fear of the public, even if that fear is irrational, may well be proportional and reasonable to the considerable risk of losing its trust.

7.3 Research questions improving optimal blood safety

The history of leukoreduction is an interesting example of how priority setting for optimal blood safety is now impeded by legal and societal obstacles. What was rational in 1999 in the UK, facing a looming epidemic of vCJD and absolute uncertainty, was not rational later and elsewhere. However, there are many sensible

arguments to support a policy of universal leukoreduction. In contrast, nucleic acid testing (NAT) of all blood donations to reduce the risk of HIV transmission during the pre-seroconversion period (before there are conventional tests HIV antibodies) is a testimony to how HIV-AIDS captures the fear of the public, but is not to a wise use of scarce resources. The public seems to have exaggerated expectations of blood safety, which, if it leads to exaggerated costs, may endanger good blood transfusion policy and efficient use of scarce resources in health care.

First, the public needs to be better educated about the prevailing risks of blood transfusion.[98] We need research to discover how to inform the public about risk management and the inevitable trade-offs between accepting certain risks and investing to ward off others. Public perception of risk may be distorted by exaggerating the risk and harms of rare events and underestimating the (opportunity) costs of preventing these. This leads to political overregulation and inefficient use of resources. Better risk perception allows the public to see a certain risk in a general perspective and to deal with this risk on a realistic basis of accepting some risks and rejecting others. The ultimate aim is better policy making, with better use of the available resources. Efforts to persuade the public by hard scientific facts are rarely effective, while the best results are obtained by interaction with the public and communication about the risks.[106] Such communication and interaction strategies have to be studied and deployed in action research, to make the public (and hence its' elected representatives) accept a realistic low risk and not expect an unattainable no risk. In the management of blood transfusion safety, decisions should be based on a balance between maintaining safety and ensuring the ability to provide blood and blood products to the users in sufficient quantity and at affordable costs.[98] If blood transfusions become expensive, they risk endangering the cost-effectiveness of other interventions relying on readily available and affordable blood, and they risk leading to underuse: maximising blood safety at all costs minimises health elsewhere.

Second, in an ageing society with rapidly increasing technology, priority setting in health care is unavoidable. Such priority setting includes blood transfusion safety. For the time being, the law suggests that a precautionary policy equals maximal safety. However, precaution is never absolute: precaution needs to be proportional to the costs and risk avoided. The impact of European and Belgian laws on the use of public resources for blood transfusion safety should be reassessed: the present laws drive at introducing technology because she is available, not because she is useful. Juridical analysis should lead to improved legislation, balancing the duty of the society to use resources wisely and efficiently and the right of the individual to blood transfusions which are as safe as possible. The risk of harm should be reduced within the limits of available resources, not at all costs. The aim of legislation adapted to the need of priority setting in health care is blood transfusions which are as safe as

reasonably achievable, and blood transfusion patients who are well compensated for the (very low) risks that cannot be reasonably avoided.

Third, blood bank operators should not be held accountable for all risks, conceivable and inconceivable. This leads to defensive medicine, increasing the costs of blood at little benefit. The present legal situation leads to increasingly large outlays for insurance costs, which are scarce health care resources that are lost and no longer available for the improvement of health. Blood bank operators should be held accountable for reasonableness, not for anything. Improved insurance policies should reward good blood transfusion practice, cover unforeseeable risks and avoid litigation for greed.

At the end, any report on blood safety has to thank the many volunteer blood donors. They are our best guarantee for safe and sufficiently available blood. It is important that we maintain their trust, guaranteeing an optimal quality and safety, at an affordable cost.

Key messages:

- **The medical and economic basis for universal leukoreduction is weak. Selective leukoreduction is more cost-effective.**
- **Universal leukoreduction delivers a better quality of blood product to everybody, at uncertain health effects and at increased, but affordable costs.**
- **Maintaining the trust of the public and its blood-donors is of utmost importance.**
- **Further research needs to address:**
  - improved information and education of the public of optimal risk management;
  - improved legislation, supporting optimal more than maximal blood safety;
  - an improved insurance policy, supporting good blood transfusion practice and covering for unforeseeable risks.

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Appendix 1: Calculation of the total costs associated with selective leukoreduction in Belgium

Table 4 presents the volumes and unit charges of red blood cell concentrates (RBC) in 2003 in Belgium and the total budget impact associated with selective leukoreduction.

Table 4: Volume and unit charges of diverse red blood cell concentrates (RBC) and total budget impact of selective leukoreduction

Type	Number	Price/unit	Incremental cost leukoreduction/unit compared to non-leukoreduced RBC	Total incremental cost selective leukoreduction (compared to no leukoreduction at all)
Non-leukoreduced RBC adults	306,605	€ 67.85	-	-
Non-leukoreduced RBC infants	4	€ 27.65	-	-
Leukoreduced RBC adult	168,112	€ 92.99	€ 25.14	€ 4.23 million
Leukoreduced RBC infant	3,472	€ 35.19	€ 7.54	€ 26,179
CMV negative RBC	208	€ 72.88	-	-
Autologous RBC	1,606	€ 71.62	-	-
TOTAL	480,007			€ 4.25 million

The budget impact of selective leukoreduction, compared to no leukoreduction at all, is € 4.25 million.

Appendix 2: Calculation of the additional costs associated with universal leukoreduction in Belgium

Table 5 presents the volumes and unit prices of red blood cell concentrates (RBC) in 2003 in Belgium and the incremental cost associated with leukoreduction of the diverse concentrates.

Table 5: Volume and unit prices of diverse red blood cell concentrates (RBC) and incremental costs of universal leukoreduction

Type		Number	Price/unit	Incremental cost leukoreduction/unit	Total Incremental cost universal leukoreduction compared to selective leukoreduction
Non-leukoreduced adults	RBC	306,605	€ 67.85	€ 25.14	€ 7.71 million
Non-leukoreduced infants	RBC	4	€ 27.65	€ 7.54	€ 30.16
Leukoreduced RBC adult		168,112	€ 92.99	-	-
Leukoreduced RBC infant		3,472	€ 35.19	-	-
CMV negative RBC		208	€ 72.88	€ 20.11	€ 4,182.88
Autologous RBC		1,606	€ 71.62	-	-
TOTAL		480,007			€ 7.71 million

In case of a universal leukoreduction policy, all currently non-leukoreduced RBC (for adults or for infants and CMV negative RBC) will be leukoreduced. Under the assumption that the number of RBC remains the same in the coming years, it can be estimated that an additional 306 817 RBC will be leukoreduced. The additional cost for leukoreduction of adult RBC is € 25.14.

The total additional cost per year associated with universal leukoreduction compared to selective leukoreduction (current practice) will be around € 7.71 million. Compared to no leukoreduction at all, the incremental cost of universal leukoreduction will be much higher. The incremental cost of selective leukoreduction (i.e. 35% of the total RBC leukoreduced, as in the current practice) is € 4.25 million (see appendix 1, table 4).

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Dépôt légal : D/2004/10.273/8

KCE reports

1. Efficacité et rentabilité des thérapies de sevrage tabagique. D/2004/10.273/2.
2. Etude relative aux coûts potentiels liés à une éventuelle modification des règles du droit de la responsabilité médicale (Phase 1). D/2004/10.273/4.
3. Utilisation des antibiotiques en milieu hospitalier dans le cas de la pyélonéphrite aiguë. D/2004/10.273/6.
4. Leucoréduction. Une mesure envisageable dans le cadre de la politique nationale de sécurité des transfusions sanguines. D/2004/10.273/8.
5. Evaluation des risques préopératoires. D/2004/10.273/10.

Renseignements

KCE -Federaal Kenniscentrum voor de Gezondheidszorg - Centre Fédéral d'Expertise des Soins de Santé.
Résidence Palace (10de verdieping-10ème étage)
Wetstraat 155 Rue de la Loi
B-1040 Brussel-Bruxelles
Belgium
Tel: +32 [0]2 287 33 88
Fax: +32 [0]2 287 33 85
Email : info@kenniscentrum.fgov.be , info@centredexpertise.fgov.be
Web : http://www.kenniscentrum.fgov.be , http://www.centredexpertise.fgov.be