



LEUKOREDUCTIE. EEN MOGELIJKE MAATREGEL IN HET KADER VAN EEN NATIONAAL BELEID VOOR BLOEDTRANSFUSIEVEILIGHEID.

KCE reports vol.4A

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

Een mogelijke maatregel
in het kader van een
nationaal beleid voor
bloedtransfusieveiligheid

KCE REPORTS VOL.4A

IRINA CLEEMPUT
DIRK RAMAEKERS
MARK LEYS
LUC BONNEUX

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Auteurs : Cleemput, Irina
Ramaekers, Dirk
Leys, Mark
Bonneux, Luc

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

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

Résidence Palace (10^{de} verdieping-10^{ème} 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>

Inleiding

Leukoreductie verwijdert 99.99% van de witte bloedcellen uit het bloed door filtering. De baten van leukoreductie zijn reeds lang bekend, maar werden totnogtoe te beperkt geacht om de bijkomende kosten van een filtering van al het bloed (universele leukoreductie) te verantwoorden. Het Belgische Rode Kruis verwijdert momenteel enkel de witte bloedcellen uit het bloed dat bestemd is voor transfusie in patiënten met een hoog risico op leukocyten-gerelateerde negatieve reacties (selectieve leukoreductie). In 2004 hebben de meeste Europese landen universele leukoreductie ingevoerd. De voornaamste reden was de overdracht van de gevreesde variant Creutzfeldt-Jakob Disease (vCJD) via bloedtransfusie; vCJD wordt veroorzaakt door dezelfde agens die de dolle koeienziekte (BSE) veroorzaakt. Het Belgische Rode Kruis wordt geconfronteerd met enerzijds de aanzienlijke kosten van universele leukoreductie of anderzijds de kosten van hoge verzekeringspremies en het minimale maar reële risico op lange, dure en traumatiserende rechtszaken. Het Rode Kruis heeft daarom de Minister van Volksgezondheid verzocht om een oplossing te bieden voor dit probleem.

De Minister van Volksgezondheid, Mr. Rudy Demotte, heeft aan het Federaal Kenniscentrum voor de Gezondheidszorg gevraagd om de wetenschappelijke stand van zaken omtrent universele leukoreductie kritisch samen te vatten, ter ondersteuning van beslissingen in verband met de keuze tussen universele of selectieve leukoreductie.

Dit rapport is het resultaat van een multidisciplinaire samenwerking tussen interne en externe experten. In de eerste plaats willen wij de externe experten en validators, Prof. Dr Sondag (Croix Rouge), Prof Dr Vandekerckhove (Rode Kruis)), Dr Vanopdenbosch (CODA, BSE-expert) and Dr van der Poel (Sanquin, het Nederlandse bloedtransfusiecentrum), van harte bedanken. Hun hulp was van onschabare waarde bij het schrijven van dit rapport.

Vervolgens willen wij onze dank uitdrukken aan Dr Crott van het KCE voor zijn hulp alsook aan Dr Baeten en haar collega's van het Antwerpse bloedtransfusiecentrum voor de stimulerende en informatieve rondleiding aan de KCE-experten in hun Centrum.

Een speciaal woordje van dank willen wij richten tot de vrijwillige bloeddonoren. Niemand mag vergeten dat het bloed dat zij afstaan als een onbaatzuchtige dienst aan de maatschappij de hoeksteen is van de hoge bloedveiligheid die wij kennen in België.

Jean-Pierre Closon
Adjunct General Director

Dirk Ramaekers
General Director

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

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

Rue de la loi, 155
1040 - BRUXELLES

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

Samenvatting van het rapport

Universele leukoreductie: de achtergrond

Het garanderen van bloedveiligheid is één van de primaire doelstellingen in het bloedtransfusiebeleid. Het risico op overdracht van virale infecties via bloedtransfusie, zoals Hepatitis B, Hepatitis C en HIV, is zeer laag in België; het varieert van 1 op 200 000 voor Hepatitis B tot 1 op enkele miljoenen voor HIV. De sterfte door transfusie-overgedragen infecties is nog veel geringer. Ook relatief is ziekte en sterfte door transfusie-overgedragen infecties veel kleiner dan door andere oorzaken (administratieve vergissingen waardoor verkeerd bloed wordt gegeven blijven – zoals overal elders - het grootste probleem...). Naast het risico op overdracht van virale infecties, bestaat er een risico op bacteriële besmetting, vooral van bloedplaatjes (deze dienen op kamertemperatuur bewaard te worden, wat bacteriële overgroei bevordert). Dit risico wordt in België geminimaliseerd door een systematische screening van alle bloedplaatjesconcentraten. De belangrijkste preventieve factor is nog de vrijwillige, onbetaalde donor, die doorgaans zeer zuiver bloed levert. Hierdoor is het risico op ernstige ziekte door bloedtransfusies uiterst gering.

Leukoreductie, deleukocytering of leukodepletie betekent vermindering van het aantal leukocyten (witte bloedcellen) met een factor >1000 in het te transfunderen bloed door ondermeerfiltratie. Leukocyten zijn voor de ontvanger immuun actieve lichaamsvreemde cellen, verantwoordelijk voor een aantal complicaties na bloedtransfusie, die geen klinisch voordeel bieden aan de patiënt. Leukoreductie heeft aangetoonde positieve klinische effecten voor specifieke patiënten, met name patiënten die vaak bloedtransfusies moeten ondergaan, patiënten met een verminderde weerstand (inclusief pasgeborenen), transplantkandidaten en organdonoren. Deze patiënten krijgen nu reeds gedeleukocyteerd bloed in België. De huidige beleidskeuze betreft dus de keuze tussen het bestaande beleid van selectieve leukoreductie voor bepaalde patiëntengroepen of het voorgestelde beleid van universele leukoreductie voor alle transfusies.

De aanleiding tot dit onderzoek was de vraag van de Minister van Volksgezondheid Rudy Demotte om de wetenschappelijke kennis omtrent medische en economische voor- en nadelen van leukoreductie te evalueren. Verschillende van de ons omringende landen hebben een beleid van universele leukoreductie geïntroduceerd. De medische voordelen van leukoreductie zijn echter reeds lang bekend, of even lang omstreden. De invoering gebeurde doorgaans als reactie op het toen nog hypothetische gevaar van overdracht van variant Creutzfeldt-Jakob Disease (vCJD, de humane variant van de dolle koeienziekte) via bloedtransfusie.

Variant Creutzfeldt-Jakob Disease (vCJD)

Variant Creutzfeldt-Jakob Disease (vCJD) is de menselijke variant van Bovine Spongiform Encephalopathy (BSE), de beruchte dolle koeienziekte. De groep prion-aandoeningen bij mens en dier staat bekend onder de naam TSE (Transmissible Spongiform Encephalopathy) omdat ze allen gekenmerkt worden door vernieling van de hersenen. Het is boven alle redelijke twijfel verheven dat vCJD en BSE dezelfde aandoening betreft, overgedragen door eenzelfde abnormaal prion, een 'conformer'. Daarnaast bestaan er experimentele aanwijzingen dat er ook een verband zou kunnen bestaan tussen de klassieke, sporadische vorm van deze aandoening (sCJD) en BSE. Prionen zijn normale eiwitten, product van het menselijk genoom. Abnormale prionen zijn eiwitten met dezelfde eiwitketens, maar die zich anders opvouwen. Deze anders gevouwen prionen veroorzaken dat ook de normale prionen zich anders vouwen. Deze abnormaal gevouwen eiwitten zijn buitengewoon resistent aan alle vormen van afbraak, denaturatie of degeneratie. Daardoor stapelen ze zich op, vooral in het zenuwstelsel, dat daardoor vernield wordt.

Hoe BSE overgedragen wordt van koe op mens is voorlopig nog onbekend, al gebeurt het vermoedelijk door het eten van met prionen besmet vlees. In het Verenigde Koninkrijk (en elders, door vleesexport uit Engeland) kwamen letterlijk miljoenen besmette koeien in de voedingsketen. Er zijn in april 2004 151 gevallen van vCJD gesignalerd, waarvan 141 in het Verenigd Koninkrijk. Buiten het Verenigd Koninkrijk telt Frankrijk 6 erkende gevallen (er is een zevende dat sterk verdacht is), of 1 per 10 miljoen inwoners over de laatste tien jaar. In België werd tot op heden (6 september 2004) geen geval van vCJD geïdentificeerd.

Diermodellen tonen dat BSE overdraagbaar is door bloedtransfusie, ook als het besmet dier nog geen symptomen vertoont. In het Verenigd Koninkrijk is er recent één klinisch geval van een patiënt die getransfundeerd is met bloed van een laterelijder aan vCJD. Een tweede (subklinisch) geval werd ontdekt bij autopsie na overlijden aan een andere doodsoorzaak. Het risico van overdracht van vCJD via bloedtransfusie staat daarmee vast, al moet hier aan toegevoegd worden dat één klinisch geval van transmissie over miljoenen bloedtransfusies nog steeds een uiterst klein risico vormt. Het valt moeilijk te bedenken hoe het transfusierisico buiten het Verenigd Koninkrijk meer dan uiterst laag kan zijn.

Het is onbekend of leukoreductie ter preventie van overdracht van vCJD via bloedtransfusie een effectieve maatregel is. Het veel geciteerde cijfer van 90% risicoreductie is speculatief en niet gefundeerd op enig proefondervindelijk onderzoek, bij mens of bij dier. Zeer recent onderzoek bij hamsters toonde aan dat bij met schapen-TSE (scrapie) geïnfecteerde dieren het effect door leukoreductie beperkt bleef tot 42% reductie van de 'TSE load' en 35% van de infectiekans.

Vermoedelijk is daarbij de handeling van de filtering belangrijker dan de reductie van het aantal witte bloedcellen: prionen zijn plakkerig, en adsorberen gemakkelijk aan oppervlakten. Dat maakt de zoektocht naar betere filters een wenselijke optie.

Een voorkomingsbeleid is gebaseerd op principes van redelijkheid en proportionaliteit bij onzekerheid over risico's. De schrikaanjagende toestand in het Engeland van het einde van de jaren '90 werd niet bevestigd, maar universele leukoreductie in die toestand was zeker redelijk en proportioneel in verhouding tot een potentieel afschuwelijk risico. Vijf jaar later lijkt universele leukoreductie buiten Engeland medisch-wetenschappelijk moeilijk te verdedigen. Universele leukoreductie heeft een matig effect op een louter hypothetisch risico bij gezonde bloeddonors, dat zich tien jaar na het begin van de epidemie in het Verenigd Koninkrijk (nog) niet gematerialiseerd heeft in België.

Bewezen medische voordelen van leukoreductie

Leukoreductie vermindert de overdracht van infectieuze ziekten, HLA allo-immunisatie en mogelijke immunologische gevolgen van bloedtransfusie.

De klinisch relevante infectieziekte die met grote zekerheid door leukoreductie wordt voorkomen is cytomegalievirus (CMV). Ongeveer 1% van de bloedgevers is drager van het CMV virus en kan dit ook aan de ontvanger van zijn bloed overdragen. CMV veroorzaakt ernstige morbiditeit en mortaliteit bij CMV-seronegatieve patiënten met verzwakte weerstand. Preventie van andere infectieziekten, zoals HTLV I/II en EBV, is klinisch weinig relevant.

Witte bloedcellen bevatten weefsel-antigenen (het zogenaamde HLA-systeem), die immuniserend kunnen werken. Dit kan zeer ernstige klinische gevolgen hebben voor de patiënt, vooral voor mensen die blootstaan aan meerdere transfusies: polytransfusiepatiënten. Leukoreductie vermindert het risico op de ontwikkeling van HLA immunisatie met 70% en is dus zeer effectief in het voorkomen van deze ernstige transfusiereacties. Leukoreductie speelt bovendien een belangrijke rol in het voorkomen van inefficiënte bloedplaatjestransfusies veroorzaakt door bij de patiënt ontwikkelde HLA-antistoffen.

Het is onduidelijk of leukoreductie andere immunologische gevolgen van transfusie met leukocyten kan voorkomen. Er bestaan aanduidingen dat leukoreductie betere resultaten biedt bij operatiepatiënten, zowel in termen van kortere ligduren als minder operatie-effecten, maar deze resultaten zijn niet éénduidig. Dit heeft te maken met grote heterogeniteit tussen studies, gezondheidszorgsystemen, gebruikte technieken en kleine kansen in diverse patiëntengroepen. De uitspraak die met voldoende zekerheid kan gedaan worden is dat de kwaliteit van gefilterd bloed met duizend maal minder witte bloedcellen beter is dan van ongefilterd bloed. Wat de juiste klinische relevantie van deze verbeterde kwaliteit is, blijft onzeker.

Pathogeeninactivatie

Een mogelijk alternatief voor leukoreductie is pathogeeninactivatie. Deze zich nog ontwikkelende technologie is veelbelovend en is ondertussen beschikbaar voor routine toepassing op plasma en bloedplaatjesconcentraten. Het is nog onzeker wanneer pathogeeninactivatie ter beschikking zal komen voor erythrocytenconcentraten. Zij baseert zich op het principe van de specifieke denaturatie van nucleïnezuren (DNA en RNA). Rode bloedcellen en bloedpaatjes bevatten geen DNA of RNA, en blijven dus in principe gespaard. Pathogeeninactivatie kan geen prionen onschadelijk maken, gezien dit (bovendien buitengewoon resistente) eiwitten zijn en geen nucleïnezuren, maar kan in principe alle bekende en onbekende virussen, bacteriën en witte bloedcellen inactiveren. De ervaring met deze techniek is echter nog erg beperkt. De eerste klinische studies toonden verminderde leefbaarheid van behandelde bloedplaatjes aan, wat de nood aan transfusies doet toenemen. Gezien infectierisico's maar een beperkt aandeel vormen in alle transfusierisico's, verhoogt dit de onveiligheid. In afwachting van meer en betere resultaten van klinische studies, blijft pathogeeninactivatie veelbelovend maar onzeker. Gezien reële transfusie-risico's zeer klein zijn, mag de kostprijs bovendien niet te hoog zijn, om in een redelijke verhouding te staan tot de baten.

Economische aspecten van leukoreductie

Kosten van leukoreductie

Een eenheid rode bloedcellen wordt in België terugbetaald aan € 67.85; de terugbetaling van een eenheid gedeleukocyteerde rode bloedcellen ligt € 25.14 hoger. Dit bedrag is vermoedelijk een vrij goede weergave van de werkelijke bijkomende kost van leukoreductie, en is goed vergelijkbaar met de kost in andere landen.

In België wordt momenteel selectieve leukoreductie toegepast: 35% van de rode bloedcellenconcentraten wordt gedeleukocyteerd. Selectieve leukoreductie beperkt het gebruik van gefilterd bloed voor indicaties waarvoor de klinische effectiviteit redelijk vaststaat, vastgelegd bij Koninklijk Besluit (12 maart 1998). Er bestaat voldoende bewijs dat leukoreductie kosten-effectief is bij gebruik in deze specifieke indicaties.

Universele leukoreductie

Universele leukoreductie breidt leukoreductie uit tot alle bloedgaven. De budgettaire impact van universele leukoreductie in België wordt geschat op € 7.71 miljoen extra per jaar, bovenop de € 4.25 miljoen momenteel besteed aan selectieve leukoreductie. Het wordt verwacht dat deze extra kosten zullen blijven dalen, door toenemende ervaring van de bloedoperatoren en door industriële competitie om

goedkopere filters. Deze berekening houdt bovendien geen rekening met mogelijke besparingen door het vermijden van met witte bloedcellen geassocieerde complicaties na bloedtransfusies. Gezien de onzekerheid over de klinische relevantie in patiëntengroepen die buiten de bekende indicaties van selectieve leukoreductie vallen, zijn deze besparingen niet te becijferen.

Vanuit het perspectief van de bloedtransfusiecentra heeft universele leukoreductie onmiskenbare voordelen die eveneens kosten besparen: vereenvoudiging van het stockbeheer, standaardisatie van procedures, vermindering van het aantal rechtklagen en verhoopte vermindering of stabilisatie van de verzekeringspremies voor burgerlijke aansprakelijkheid. De immense verzekeringspremies die het Rode Kruis momenteel betaalt voor burgerlijke aansprakelijkheid zijn een belangrijk verlies voor de Belgische gezondheidszorg. Er bestaat een wanverhouding tussen de premies en de uitbetalingen. Hierdoor vermindert de efficiëntie van de gezondheidszorg in het algemeen en van bloedtransfusies in het bijzonder.

Het staat vast dat de kwaliteit van gefilterd bloed beter is dan van ongefilterd bloed. Het is onzeker of dit opweegt tegen de gemaakte investering om ieder deze verbeterde kwaliteit te bieden.

Legale aspecten

Als producent van de bloedproducten is het Rode Kruis aansprakelijk voor de afgeleverde producten. Deze aansprakelijkheid heeft geleid tot een enorme stijging in het niveau van de verzekeringspremies voor burgerlijke aansprakelijkheid over de laatste 5 jaar. Deze kostenexplosie staat in geen enkele verhouding tot de werkelijke risico's van bloedtransfusies, die enkel blijven afnemen. Universele leukoreductie zou de kans op rechtsvervolging kunnen verminderen – aangezien dan de argumentatie van niet alles gedaan te hebben om de schade te voorkomen vervalt - en bijgevolg de omvang van de verzekeringspremies. Dit lijkt onzeker, gezien er geen enkele relatie bestaat tussen de verzekeringspremies en de objectieve bloedveiligheid.

De Europese wetgeving is niet aangepast aan moderne inzichten inzake de medische-ethische noodzaak tot het stellen van prioriteiten in investeringen in nieuwe medische technologie. De moderne inzichten worden samengevat in het begrip "accountability for reasonableness". Bloedbankoperatoren horen rekenschap af te leggen over de bloedveiligheid binnen redelijke grenzen, niet over ieder denkbaar risico. Wat redelijk is, hoort vastgelegd te worden na democratisch geïnformeerd debat met de verschillende actoren door de verkozen vertegenwoordiging van het volk.

Adequate communicatie over de relatieve omvang van de risico's van bloedtransfusies, zowel over de onvermijdelijkheid van enig residuueel risico als over het minimale huidige risico, is noodzakelijk om het publiek te betrekken bij het

beleid. Dit is hier des te belangrijker, gezien de veiligheid van het bloed best gediend is met onbaatzuchtige bloeddonors.

De huidige wetgeving bevordert het het invoeren van bloedveiligheidsmaatregelen door beschikbare technologie, niet door objectieve behoeften. Hierdoor gaan middelen, bestemd voor het verbeteren van de gezondheidszorg, verloren in verzekeringspremies, rechtzaken en inefficiënte technologie.

Bij onveranderde wetgeving blijven de bloedbanken afhankelijk van een willekeurige interpretatie van het begrip “precaution” door de rechtbank. Het zal daarbij lastig zijn om uit te leggen waarom de ons omringende landen dit wel hebben ingevoerd. De kans dat zij veroordeeld worden, vinden de bloedbankoperatoren ondraaglijk hoog.

Conclusies

Door het gebruik van vrijwillige, onbetaalde bloeddonoren en de strenge kwaliteitscontrole is het bloed geleverd door het Belgische Rode Kruis kwalitatief hoogstaand en uiterst veilig. Witte bloedcellen in een bloedtransfusie zijn echter lichaamsvreemde en overbodige cellen, die ongewenste activiteiten kunnen uitvoeren. Ongefilterd bloed kost € 68; het verwijderen van witte bloedcellen door filtering kost per eenheid in België € 25. Het nut van het verwijderen van deze witte bloedcellen is lang bekend, en bewezen voor specifieke indicaties. Het huidige beleid in België, selectieve leukoreductie voor bloedtransfusies in specifieke patiëntenpopulaties, is daarom effectief en kosten-effectief.

De effectiviteit en kosten-effectiviteit van het uitbreiden van leukoreductie tot alle bloedtransfusies is onbekend. Behandeld bloed is kwalitatief beter dan onbehandeld bloed, maar het is onduidelijk of deze toegenomen kwaliteit kan opwegen tegen de toegenomen kosten. Het is redelijk om te verwachten dat in de toekomst de kosten van leukoreductie verder zullen afnemen. De overheid dient de kostprijs van de filtersystemen zo laag mogelijk te houden, door efficiënte onderhandeling met de industrie.

Het vermijden van onnodige bloedtransfusies is belangrijk in de preventie van ongewenste gevolgen van bloedtransfusies. Het huidige beleid dat streeft naar zuiniger gebruik van bloedtransfusies moet verder gezet worden. De ingestelde bloedtransfusiecomités in de Belgische ziekenhuizen moeten het optimaal gebruik van bloed en bloedproducten actief bewaken. Daartoe dienen door de beroepsgroepen ondersteunde richtlijnen voor optimaal gebruik van bloed en bloedproducten verder ontwikkeld en toegepast te worden.

De basis van de beslissing tot universele leukoreductie in verschillende landen was de preventie van variant Creutzfeldt-Jakob (vCJD), de menselijke variant van de dolle

koeienziekte (BSE). Universele leukoreductie in het Verenigde Koninkrijk van het einde van de jaren 90 was redelijk en proportioneel tot de bedreiging. De invoering van universele leukoreductie in andere landen buiten het Verenigd Koninkrijk kan echter niet gemotiveerd worden op basis van deze dreiging van vCJD. Tien jaar na zijn begin blijft de epidemie van vCJD beperkt tot het Verenigd Koninkrijk en tot 1 per tien miljoen inwoners in Frankrijk. De effectiviteit van leukoreductie in het voorkomen van overdracht door bloed van prionen was speculatief. Recent onderzoek bevestigt dat leukoreductie met de bestaande filters maar matig prionen afvangt. Dit zou kunnen veranderen met betere filters.

Het onderliggend maatschappelijk probleem wordt beter aangegeven door de grote stijging van de kosten van verzekering van de bloedbanken. Deze kosten staan in geen enkele verhouding tot de steeds toenemende veiligheid van bloedtransfusies. Voor de bloedbanken zijn deze verzekeringsuitgaven essentieel voor hun voortbestaan, maar voor de Belgische gezondheidszorg zijn zij een inefficiënte aanwending van middelen. De wetgeving in Europa is momenteel niet aangepast aan de nood tot het stellen van prioriteiten in investeringen in kwaliteitsverbetering. Hierdoor worden investeringen beheerst door het toenemend technologisch aanbod, niet door de objectieve behoefte.

Wij concluderen dat er geen wetenschappelijke argumenten bestaan om een duidelijke voorkeur uit te spreken tussen het bestaande beleid in België - selectieve leukoreductie - en het door de meeste andere landen van het Verenigd Koninkrijk overgenomen beleid, universele leukoreductie. Bij universele leukoreductie worden meer kosten gemaakt, om een kwalitatief beter product af te leveren aan alle patiënten. Universele leukoreductie biedt daarnaast het theoretisch voordeel dat het de overdracht van nieuwe of gekende celgebonden virussen waarvoor niet wordt getest voorkomt. De klinische relevantie van deze verbetering blijft beperkt en is discutabel. Dat argument geldt evengoed voor de gemaakte kosten.

De onduidelijke invulling van het begrip 'precautionary policy' in de Europese regelgeving riskeert een medisch investeringsbeleid te bevorderen dat gedreven wordt door de beschikbare technologie, niet door de objectieve behoefte. Wij bevelen verder juridisch onderzoek aan, met als doel de nationale en Europese wetgeving aan te passen aan de moderne principes van de medische ethiek, gebaseerd op 'accountability for reasonableness'. Investeringen in meer veiligheid dienen redelijk en proportioneel te zijn tot de bedreiging. Zolang de huidige wettelijke onzekerheid blijft bestaan, is het invoeren van steeds meer veiligheidsmaatregelen zonder medisch-wetenschappelijke zingeving onvermijdelijk. Universele leukoreductie is hiermee vergeleken zinvol, omdat er minstens enige goede motieven bestaan.

Een rapport over bloedveiligheid is niet af, zonder de talloze belangeloze bloeddonors te bedanken. Zij vormen de grootste garantie op veilig bloed. Daarom is het belangrijk dat zij betrokken worden in het transfusiebeleid: zij hebben het recht op een optimaal gebruik van hun vrijwillig afgestaan bloed aan de beste kwaliteit en een betaalbare prijs. Adequate risico-communicatie is daarom essentieel.

Kort overzicht

Over bloedveiligheid in België

De veiligheid van bloedtransfusies in België is zeer hoog, door een strenge kwaliteitscontrole en door het gebruik van bloed van vrijwillige en onbetaalde donors.

De investeringen voor een verdere verbetering van de bloedveiligheid moeten proportioneel blijven met de verwachte, noodzakelijkerwijze geringe, baten.

Over BSE (dolle koeienziekte) en vCJD

Het infectieuze agens dat de dolle koeienziekte veroorzaakt en variant Creutzfeldt-Jakob ziekte (vCJD), is identiek. Het is een prion, een eiwit met zeer grote weerstand tegen alle vormen van denaturatie, dat de hersenen vernielt door stapeling.

Het prion dat BSE/vCJD veroorzaakt is overdraagbaar door bloedtransfusies; er zijn twee gevallen van vermoedelijke overdracht van vCJD via besmette bloedtransfusie gekend in Engeland. Het juiste bloedtransfusierisico in Engeland is niet te voorspellen, maar lijkt momenteel nog erg klein.

Tien jaar na het begin van de vCJD epidemie in Engeland, blijft deze nagenoeg beperkt tot Engeland. Het risico in Frankrijk, het enige land met meer dan enige gevallen, betrof 1 per 10 miljoen inwoners over 10 jaar.

Het verwijderen van witte bloedcellen uit het te transfunderen bloed is maar matig effectief in het voorkomen van infectie. Betere filters zouden in theorie meer prionen kunnen afvangen.

Het verwijderen van witte bloedcellen uit het te transfunderen bloed in Engeland was een goed te verdedigen maatregel, in het licht van grote onzekerheid over de omvang van de epidemie. Vijf jaar later, en tien jaar na het begin van de epidemie, is deze maatregel buiten Engeland een reactie met een waarschijnlijk beperkt nut.

Over medische voordelen van leukoreductie

Witte bloedcellen in te transfunderen bloed zijn immuun actieve lichaamsvreemde cellen. Het is lang bekend dat zij ongewenste effecten kunnen uitoefenen bij de ontvanger.

Patiënten met gedaalde immuniteit, of die anderszins risico lopen om meerdere bloedtransfusies te ontvangen, hebben baat bij rode bloedcellen met een minimum aan witte bloedcellen.

In België geldt daarom een beleid van selectieve leukoreductie. Patiënten met gedaalde immunitaire afweer, zwangere vrouwen, transplantatie patiënten, pasgeborenen, polytransfusiepatiënten en patiënten met hoog risico op transfusiereacties, of die voordien dergelijke reacties hebben gedaan, krijgen bloed zonder witte bloedcellen.

Er zijn tegenstrijdige berichten dat leukodepletie ook voordelen biedt bij andere patiëntengroepen, meer bepaald door verbeterde resultaten na heelkunde.

Over pathogeeninactivatie

Pathogeeninactivatie is gebaseerd op het principe van de selectieve denaturatie van DNA en RNA. Dat inactiveert virussen, bacteriën en protozoën. Het heeft geen effect op prionen (dit zijn eiwitten).

Ongevallen door transmissie van infectieuze agentia via een bloedtransfusie zijn momenteel uiterst zeldzaam: dat beperkt het nut van dergelijke technologie, die daarom ook uiterst veilig moet zijn.

Pathogeeninactivatie is een veelbelovende, maar nog experimentele technologie. Er blijven nog veel vragen over de kwaliteit van de met pathogeeninactivatie behandelde bloedplaatjes en rode bloedcellen.

Het gebruik van pathogeeninactivatie buiten zorgvuldig uitgevoerde klinische studies is af te raden.

Over kosten-effectiviteit van leukoreductie

Onbehandeld bloed (dit is ongefilterd) wordt in België terugbetaald aan € 68 per eenheid. Bij leukoreductie, momenteel voorbehouden voor bepaalde patiënten, wordt 99.99% van de witte bloedcellen verwijderd door filtering. Dit kost € 25 per eenheid extra. De terugbetaling van bloed in België is opmerkelijk laag vergeleken met het buitenland. De kosten van leukoreductie zijn goed vergelijkbaar met schattingen uit het buitenland.

Selectieve leukoreductie, het huidige beleid in België, levert een betere kwaliteit van bloed aan die patiënten die er het meest baat bij hebben. Dit is kosten-effectief. Universele leukoreductie, het voorgestelde beleid, levert deze betere kwaliteit aan iedereen. De klinische baten, en de daarmee gepaard gaande besparingen, van universele leukoreductie zijn onzeker.

Op wetenschappelijke basis valt er daarom geen voorkeur uit te spreken voor universele of selectieve leukoreductie. Universele leukoreductie levert ontegenzeggelijk een verbeterde kwaliteit van bloed en voorkomt transmissie van nieuwe en gekende (maar waarvoor nu nog niet getest wordt) celgebonden virussen. Het is onduidelijk of de klinische baten opwegen tegen de procedurele meerkost.

Vanuit het standpunt van de bloedbanken is de additionele verzekerkost verbonden aan selectieve leukoreductie ten opzichte van universele leukoreductie echter niet gering. Doordat de verzekeringspremies niet proportioneel zijn aan het beperkte risico van bloedtransfusies, is de werkelijke kost van selectieve leukoreductie voor het gezondheidszorgsysteem vermoedelijk hoger dan algemeen wordt aangenomen.

Over sociale en maatschappelijke aspecten

Over de laatste zes jaren stegen de kosten van de verzekeringen voor het Rode Kruis van minder dan € 300 000 per jaar tot meer dan € 900 000 per jaar. Deze kostenstijging staat in geen enkele verhouding tot de zeer hoge en toenemende bloedveiligheid van het door het Belgische Rode Kruis geleverde bloed.

De Europese wetgevende praktijk is onduidelijk en voor teveel interpretatie vatbaar. De jurisprudentie suggereert dat bloedveiligheid maximaal moet zijn. Dat leidt tot investeringen in technologie omdat ze beschikbaar is, maar waarvan het nut niet altijd even duidelijk aangetoond kan worden.

De onduidelijkheid in de wetgeving en de daaruit voortvloeiende mogelijkheid voor juridische willekeur leidt ertoe dat de bloedbanken zich financieel en strafrechtelijk aansprakelijk weten. Overwegingen over medische zingeving worden dan bijkomstig. Als deze aansprakelijkheid niet van de bloedbanken wordt overgenomen, moeten zij alle maatregelen overwegen om de kans op een menselijk en financieel kostbare veroordeling zo klein mogelijk te houden.

Een voorkomingsbeleid in medisch-ethisch perspectief betekent dat de veiligheid optimaal moet zijn. Dat wil zeggen dat de in te voeren veiligheidsmaatregelen redelijk en proportioneel tot de bedreiging moeten zijn.

Wat redelijk en wat proportioneel is, wordt vastgelegd in geïnformeerd democratisch debat met de relevante actoren.

Aangezien de bloedveiligheid het best gediend is met bloed van vrijwillige en onbetaalde donors, is het bewaren van hun vertrouwen uitermate belangrijk. Uiteraard is vertrouwen in de kwaliteit en veiligheid van het bloed ook van belang voor de patiënten en hun behandelende artsen. Dit geldt zowel voor het garanderen van optimale bloedveiligheid, als voor het garanderen van acceptabele kosten van transfusiebloed.

Kernboodschappen en beleidsaanbevelingen

- **Medisch-wetenschappelijk**

Op medisch-wetenschappelijk vlak is er geen voorkeur uit te spreken voor een beleid van selectieve of universele leukoreductie: Universele leukoreductie levert een betere bloedkwaliteit maar de klinische baten zijn enkel aangetoond in bepaalde risicopopulaties. Gezien de oorsprong van het bloed en de uiterst lage prevalentie van vCJD in België zijn de risico's van trans fusie in ons land uiterst laag.

- **Economisch**

Op economisch vlak zijn de met een universele leukoreductie gepaard gaande besparingen door het verminderen van complicaties niet gekend. Wel is er een significante vereenvoudiging van de distributieketen, zowel langs de kant van de trans fusiecentra als van de ziekenhuizen. Leukoreductie genereert een toegenomen bruto kost van € 25 per eenheid.

- **Juridische context**

De huidige Europese wetgeving bevordert geen verantwoord gebruik van middelen. Er is meer onderzoek nodig naar een verbeterde (Europese) wetgevende praktijk, die een voorkomingsbeleid bevordert. Een voorkomingsbeleid in medisch-ethisch perspectief bevordert een optimale veiligheid, maar het is moeilijk in te schatten welke additionele investeringen in veiligheidsmaatregelen redelijk en proportioneel zijn tot de bedreiging.

De bloedbanken en hun operatoren staan bloot aan toenemende juridische onzekerheid. Dit veroorzaakt sterk stijgende kosten voor verzekeringen die in geen verhouding staan tot de geleverde inspanningen om de hoogste kwaliteit en veiligheid van bloed te garanderen. Er is meer onderzoek nodig naar een verbeterde juridische veiligheid van bloedbanken en hun operatoren.

- **Beleidsaanbevelingen**

De kern van het probleem betreft de juridische en financiële aansprakelijkheid voor ieder voorkombaar risico, ongeacht de kosten. Als het beleid kiest om geen universele leukoreductie door te voeren, stelt zich de vraag of de uitvoerende macht dit financiële en juridische risico van de bloedbanken niet moet overnemen.

Een voorkomingsbeleid is gebaseerd op deelname aan de beslissingen van de relevante actoren. Dit betekent de vrijwillige en belangeloze bloeddonor, de patiënt en de behandelende arts. Hoe dit best dient te gebeuren is vooralsnog onduidelijk.

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I Introduction

I.I 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 I).^{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 I: 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)

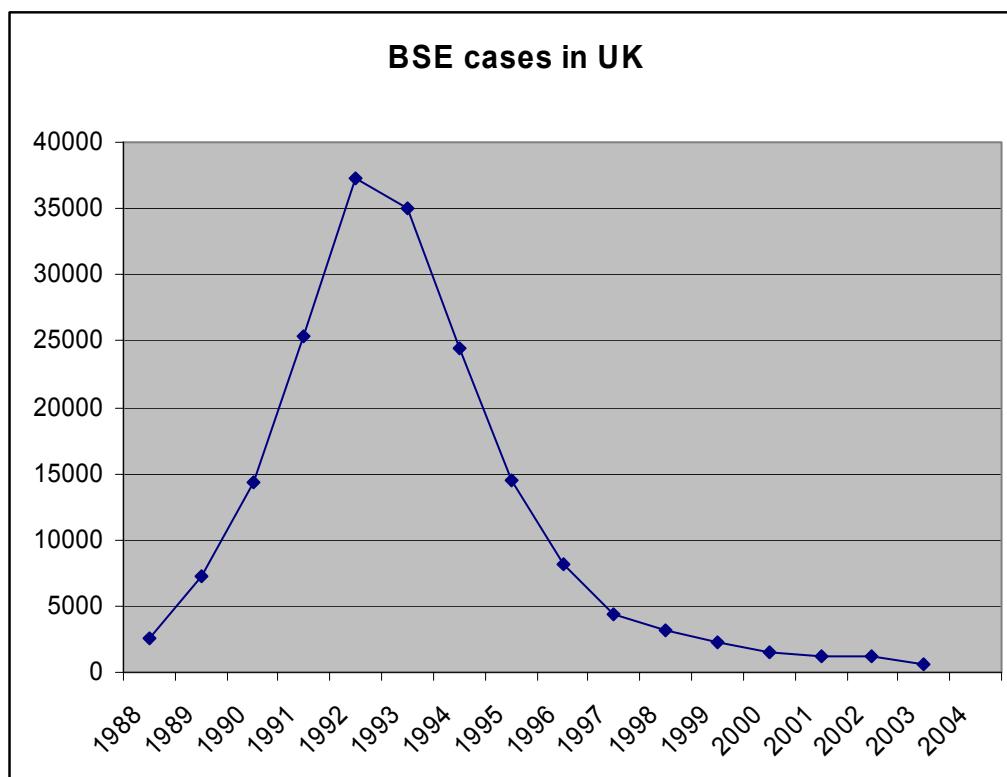
1.2.1 Bovine spongiform encephalopathy (BSE) and variant Creutzfeldt-Jakob disease (vCJD)

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 Pr^{Pres}.¹⁴ Pr^{Pres} conformers have identical primary structures as normal PrP, but differ at a higher structural level such as folding. The presence of the abnormal Pr^{Pres} 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 endogenous and exogenous. Pr^{Pres} resists all normal mechanical and chemical methods of contamination, inclusive the own body defences. The indestructible Pr^{Pres} 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

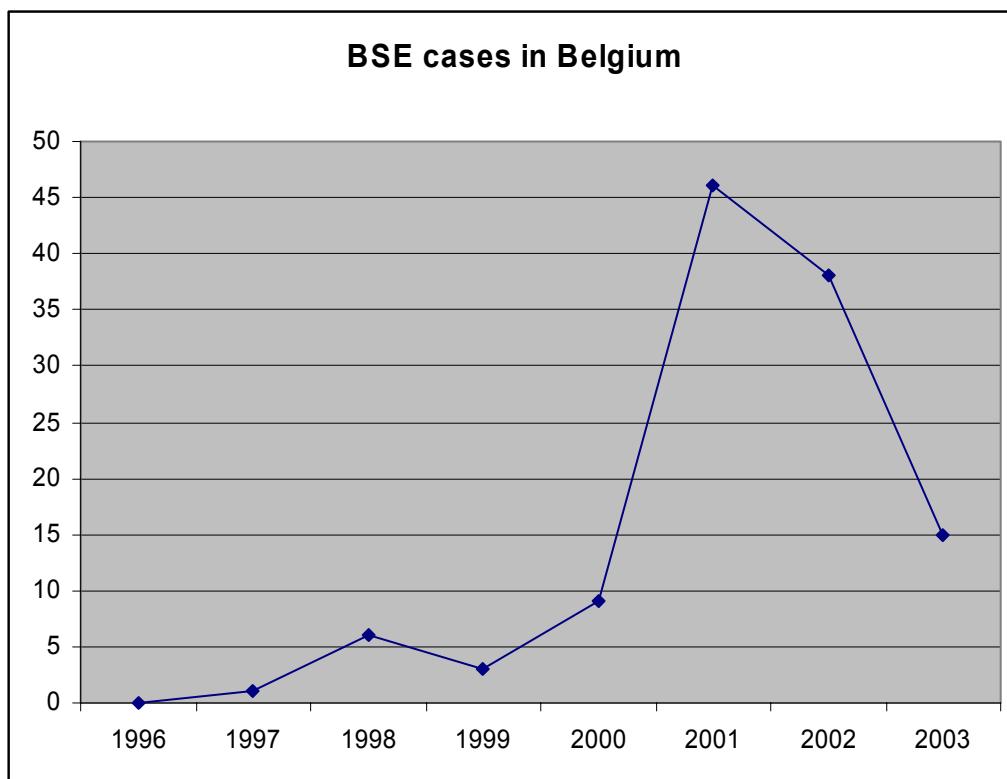
doubt that the prion that causes BSE in cows causes vCJD in humans.¹⁷ The ruminant protein feed ban in 1988 slowed the further spread of BSE in the cattle. Of course, only after the incubation period the number of BSE cases could start to decrease truly. The ban was not water tight, causing 43 000 calves 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 transplacental 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 (see Figure 1).¹⁸

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



Source: World Organisation for Animal Health¹⁸

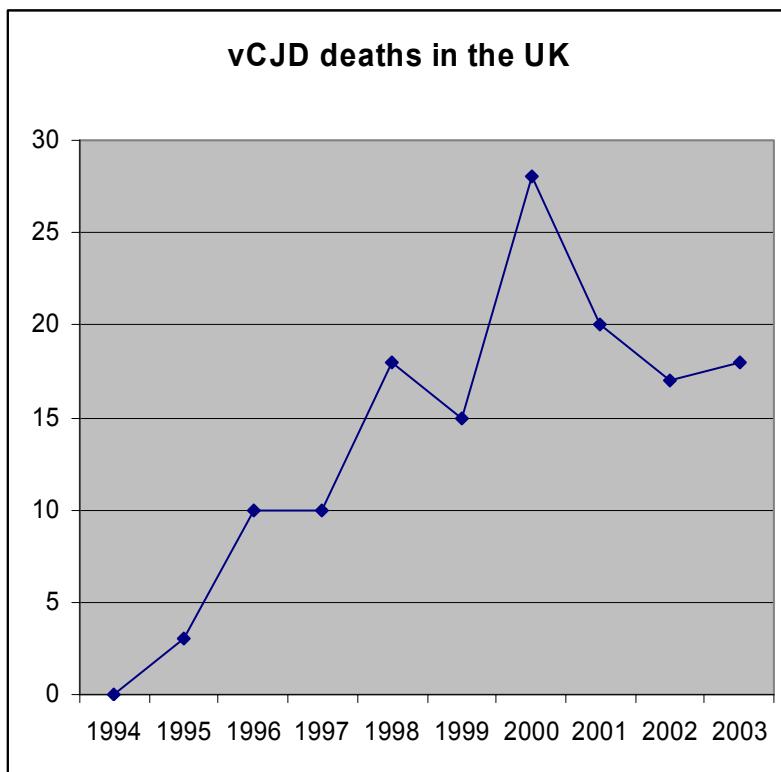
The BSE epidemic in Belgian cows was very limited. The sharp increase in 2001 is to be explained by the introduction of systematic screening in active surveillance from 1 January 2001 onwards, this in contrast to the UK epidemic, where most cases have been identified by passive case detection of cows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

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

Source: World Organisation for Animal Health¹⁸

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 (of 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 excluded either. However, glycoprotein 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: PrP^{vCJD}. 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 PrP^{vCJD} 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 definite³⁰ and one suspected³¹ 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 1×10^6 white blood cells per unit (according to European standards).³⁴ It was originally ‘guesimated’ 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, HTLV/I/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 studies⁵⁵, retrospective cohort studies,⁵⁶ and nationwide comparisons after introduction of universal leukoreduction⁵⁷ 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 boosting 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 haematologic 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, gastrointestinal 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 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 be 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 leukoreduction¹

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 Belgium⁸⁶

	2000	% 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 I).

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, 1998⁸⁷):

- 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 pro⁹⁴ and con⁹⁶ 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	<ul style="list-style-type: none"> reduction in non-hemolytic febrile transfusion reactions reduction in HLA immunisation reduction of transfusion transmitted CMV simplified stock control 	<ul style="list-style-type: none"> decrease in quantity of red blood cells⁸² 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	<ul style="list-style-type: none"> 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 $<1 \times 10^6$, whilst the Belgian law still demands a residual leukocyte count of $<5 \times 10^6$ (Royal Decree April 4, 1996⁸⁷).

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 removed 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 5×10^6 (according to the Belgian Law; Royal Decree April 4, 1996⁸⁷). In practice, however, Belgian transfusion centres guarantee a leukocyte count below 1×10^6 , as defined in the European law (Directive 2004/33/EC³⁴).

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 $< 1 \times 10^6$), 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.

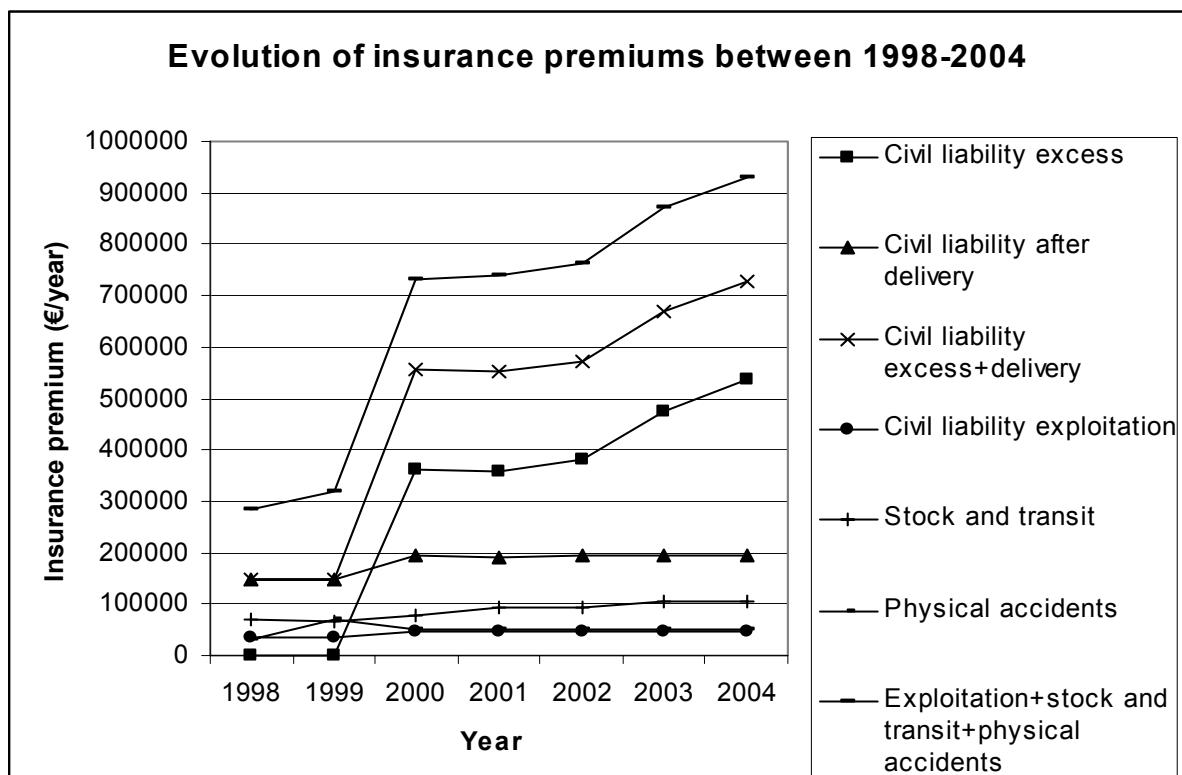
Key messages:

- **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 I: 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 RBC adults	306,605	€ 67.85	€ 25.14	€ 7.71 million
Non-leukoreduced RBC infants	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 I, table 4).

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Wettelijk depot : D/2004/10.273/7

KCE reports

1. Effectiviteit en kosten-effectiviteit van behandelingen voor rookstop. D/2004/10.273/1.
2. Studie naar de mogelijkekosten van een eventuele wijziging van de rechtsregelsinzake medische aansprakelijkheid (Fase 1). D/2004/10.273/3.
3. Antibioticagebruik in ziekenhuizen bij acute pyelonefritis. D/2004/10.273/5.
4. Leukoreductie. Een mogelijke maatregel in het kader van een national beleid voor bloedtransfusieveiligheid. D/2004/10.273/7.
5. Het preoperatief onderzoek. D/2004/10.273/9.

Inlichtingen

KCE - Federaal Kenniscentrum voor de Gezondheidszorg - Centre Fédéral d'Expertise des Soins de Santé.

Résidence Palace (10^{de} verdieping-10^{ème} 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>

