資料2

感染症定期報告に関する今後の対応について

平成１６年度第５回
運営委員会確認事項
（平成１６年９月１７日）

1 基本的な方針

運営委員会に報告する資料においては、

(1) 文献報告は、同一報告に由来するものの重複を廃した一覧表を作成すること。

(2) 8月の運営委員会において、国内の輸血及び血漿分画製剤の使用した個別症例の感染症発生報告は、定期的にまとめた「感染症報告事例のまとめ」を運営委員会に提出する取り扱いとされた。これにより、感染症定期報告に添付される過去の感染症発生症例報告よりも、直近の「感染症報告事例のまとめ」を主として利用することとすること。

2 具体的な方法

(1) 感染症定期報告の内容は、原則、すべて運営委員会委員に送付することとするが、次の資料概要を作成し、委員の資料の確認を効率的かつ効果的に行うことができるようにする。

① 研究報告は、同一文献による重複を廃した別紙のような形式の一覧表を作成し、当該一覧表に代表的なものの報告様式（別紙様式第2）及び該当文献を添付した**「資料概要A」**を事務局が作成し、送付する。

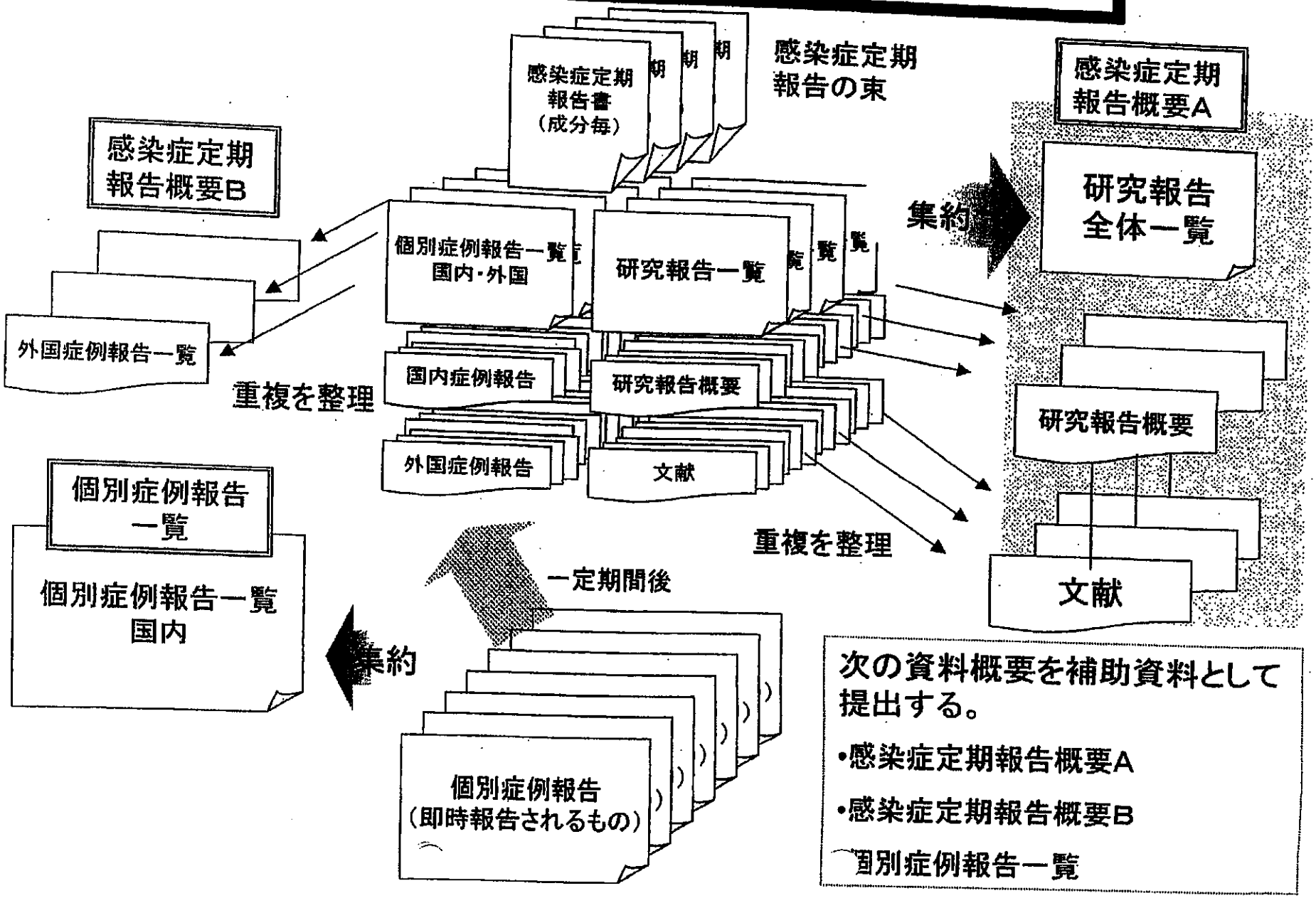
② 感染症発生症例報告のうち、発現国が「外国」の血漿分画製剤の使用による症例は、同一製品毎に報告期間を代表する感染症発生症例一覧（別紙様式第4）をまとめた**「資料概要B」**を事務局が作成し、送付する。

③ 感染症発生症例報告のうち、発現国が「国内」の輸血による症例及び血漿分画製剤の使用による感染症症例については、「感染症報告事例のまとめ」を提出することから、当該症例にかかる「資料概要」は作成しないこととする。ただし、運営委員会委員から特段の議論が必要との指摘がなされたものについては、別途事務局が資料を作成する。

(2) 発現国が「外国」の感染症発生症例報告については、国内で使用しているロットと関係がないもの、使用時期が相当程度古いもの、因果関係についての詳細情報の入手が困難であるものが多く、必ずしも緊急性が高くないと考えられるものも少なくない。また、国内症例に比べて個別症例を分析・評価することが難しいものが多いため、緊急性があると考えられるものを除き、その安全対策への利用については、引き続き、検討を行う。

(3) 資料概要A及びBについては、平成16年9月の運営委員会から試験的に作成し、以後「感染症的報告について（目次）」資料は廃止することとする。

感染症定期報告・感染症個別症例報告の取り扱い



感染症定期報告概要

（平成２３年１２月１３日）

平成２３年７月１日受理分以降

Ａ　研究報告概要
Ｂ　個別症例報告概要

Ａ　研究報告概要

○　一覧表（感染症種類毎）
○　感染症毎の主要研究報告概要
○　研究報告写

研究報告のまとめ方について

１　平成２３年７月１日以降に報告された感染症定期報告に含まれる研究報告（論文等）について、重複している分を除いた報告概要一覧表を作成した。

２　一覧表においては、前回の運営委員会において報告したもの以降の研究報告について、一覧表の後に当該感染症の主要研究報告の内容を添付した。

感染症定期報告の報告状況(2011/7/1～2011/9/30)

血対ID	受理日	番号	感染症(PT)	出典	概要	新出文献No
100392	2011/7/26	110321	インフルエンザ	MMWR. 60(2011)705-706	ブタインフルエンザウイルス(A/H3N2)のヒトーヒト感染に関する報告。米国において、2010-2011年シーズンに新規インフルエンザAウイルスとしてブタインフルエンザウイルス(A/H3N2)感染症例が5例報告された。2例は入院したが、5例全てが回復した。このうち2例は親子の症例であり、父親は発症前にブタと接触していたが、子にはブタとの直接接触はなく父親との接触により感染した可能性が高かった。	1
100409	2011/9/28	110527	ウイルス感染	ProMED-mail 20110701.2003	米国におけるポワッサンウイルス脳炎の報告。2011年5月、ミネソタ州においてポワッサンウイルス脳炎が2例報告された。1例は60代女性であり、ミネソタ州で初めての死亡例となった。もう1例は60代男性で、回復している。2例とも屋外にてダニに噛まれていたことが分かった。	2
100388	2011/7/25	110317	大腸菌性胃腸炎	http://www.47news.jp/CN/201106/CN20110613010000034.html	欧州におけるO104感染に関する報告。欧州で腸管出血性大腸菌O104の感染が拡大している問題で、ドイツ保険当局は死者が4人増えて35人になったと発表した。ドイツ当局は同国ニーダーザクセン州の農場で生産されたモヤシ等の発芽野菜から同じタイプの菌を検出し、感染源であると特定した。	3
100388	2011/7/25	110317	大腸菌性胃腸炎	http://www.cnn.co.jp/world/30003049.html	欧州におけるO104感染に関する報告。欧州で腸管出血性大腸菌O104の感染が拡大している問題で、ドイツ保険当局は死者が4人増えて35人になったと発表した。ドイツ当局は同国ニーダーザクセン州の農場で生産されたモヤシ等の発芽野菜から同じタイプの菌を検出し、感染源である可能性が高いとして回収を指示した。ただ、農場が汚染された経路は明らかとなっていないとした。	4
100388	2011/7/25	110317	大腸菌性胃腸炎	m3.com「医療ニュース」2011年7月6日付	欧州におけるO104感染に関する報告。欧州で腸管出血性大腸菌O104の感染が拡大している問題で、EU食品安全管理当局はドイツ産発芽野菜にO104が混入した経路としてエジプトから輸入されたフェヌグリークという植物の種子の可能性が高いとした。	5
100405	2011/9/26	110520	大腸菌性胃腸炎	読売新聞電子版. 2011 Jun. 3	欧州における腸管出血性大腸菌O104に関するニュース。ドイツで発生したO104について、WHO報道官は新種である可能性を示唆するコメントをした。複数の専門家も同様に述べている。感染は少なくても10カ国に及び、2011/6/2までに17人が死亡、感染者は1500人以上に達した。	6
100405	2011/9/26	110520	バベシア症	Emarging Infectious Diseases. 17(2011)843-847	米国におけるバベシア症増加に関する報告。ニューヨーク州ハドソン渓谷において、2001年以来バベシア症が増加している。2001年から2008年にかけて、ニューヨーク州の他の地域が1.6倍の患者数増加であるのに対し、ハドソン渓谷住民では6例から119例と20倍に増加した。2002年から2009年の間、計19人が地域3次医療センターへ入院し、1人が死亡している。	7
100409	2011/9/28	110527	異型クロイツフェルト・ヤコブ病	ProMED-mail 20110419.1218	日本におけるスクレイピー発生の報告。福岡県にて2011/3/30、ヒツジ1匹にスクレイピーが発症し死亡したと国際獣疫事務所(OIE)に報告された。屍体は焼却された。スクレイピーの報告は2004年以来であったが、今回のアウトブレイクは以前の報告と同じ古典的スクレイピーであった。	8
100410	2011/9/29	110534	異型クロイツフェルト・ヤコブ病	Transfusion medicine reviews. 25(2011)133-144	異型クロイツフェルト・ヤコブ病(vCJD)感染阻止に対して、輸血製剤の白血球除去の有効性に関するレビュー。輸血時のvCJD感染阻止の観点から、欧州では全製剤に対し白血球除去処理が導入されている。しかし、齧歯類モデルからは残存血漿にも感染性があり、白血球除去処理により感染は阻止できないことが示唆されている。一方、ヒツジモデルでは白血球除去処理後の輸血による感染は認められておらず、ヒトでも処理後の赤血球輸血においてvCJD感染の報告はない。従って、現在行われている全例処理は今後も継続されるべきである。	9

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日	第一報入手日 2011年6月3日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称	別紙のとおり		研究報告の公表状況	MMWR. 2011;60:705-706	公表国 米国	
販売名（企業名）	別紙のとおり					

研究報告の概要

問題点：ブタインフルエンザA（H3N2）のヒト-ヒト感染の可能性を示唆する初めて報告である。

米国で2010年11年シーズンに人のブタインフルエンザA（H3N2）感染例が5例報告された。この内2例は成人、3例は小児であり、2例は入院したが、5例全てが回復した。また、この内の2例は父と子の症例であり、父親は発症の6日前にブタと直接接触していた。子は数週間後に血清学的検査でH3N2株感染が確認されたが、豚との直接接触は無く、父親との接触で感染した可能性が高い。なお、同時期に他の家族もインフルエンザ様症状を呈したが、血清学的検査は陰性または不確定であった。

報告企業の意見	今後の対応
別紙のとおり	今後とも関連情報の収集に努め、本剤の安全性の確保を図っていきたい。

使用上の注意記載状況・その他参考事項等

記載なし

Morbidity and Mortality Weekly Report

Update: Influenza Activity — United States, 2010–11 Season, and Composition of the 2011–12 Influenza Vaccine

During the 2010–11 influenza season, influenza activity* first began to increase in the southeastern United States, and peaked nationally in early February. Compared with the previous pandemic year (2009–10), higher rates of hospitalization were observed for persons aged ≥65 years during the 2010–11 season, whereas lower hospitalization rates were observed in younger populations than during the pandemic year. Overall, the percentages of outpatient visits for influenza-like illness (ILI) were lower during the 2010–11 season than the 2009–10 pandemic influenza season. In the United States, influenza A (H3N2) remained the predominant virus throughout the season; however, 2009 influenza A (H1N1) and influenza B viruses also circulated, and the predominant virus varied by U.S. Department of Health and Human Service (HHS) region and week. This report summarizes influenza activity in the United States during the 2010–11 influenza season (October 3, 2010–May 21, 2011) and describes the components of the 2011–12 Northern Hemisphere influenza vaccine.

Viral Surveillance

During October 3, 2010–May 21, 2011, World Health Organization (WHO) and National Respiratory and Enteric Virus Surveillance System (NREVSS) collaborating laboratories in the United States tested 246,128 specimens for influenza viruses; 54,226 (22%) were positive (Figure 1). Of the positive specimens, 40,282 (74%) were influenza A viruses, and 13,944 (26%) were influenza B viruses. Among the influenza A viruses, 28,545 (71%) were subtyped; 17,599(62%) were influenza A (H3N2) viruses, and 10,946 (38%) were 2009 influenza A (H1N1) viruses.

The proportion of specimens testing positive for influenza during the 2010–11 season first exceeded 10%, indicating higher levels of virus circulation, during the week ending November 27, 2010. The proportion peaked at 36% during the week ending February 5, 2011, and declined to <10% during the week ending April 16, 2011.

Although influenza A (H3N2) viruses predominated, 2009 influenza A (H1N1) and influenza B viruses also circulated widely. The relative proportion of each type and subtype of influenza virus varied by region and week. From early November though early December, influenza B viruses accounted for 40%–49% of influenza viruses reported nationally, with the largest numbers reported from the southeastern states (HHS Region 4).† Influenza B viruses were predominant in Region 4 from early November through late December. The proportion of 2009 influenza A (H1N1) viruses increased nationally, beginning in January, and peaked during the week ending February 20, 2011, when 49% of all subtyped influenza A viruses were 2009 influenza A (H1N1) viruses. Although during this time influenza A (H3N2) viruses still predominated nationally, 2009 influenza A (H1N1) predominated in five of the 10 regions (Regions 3, 4, 5, 8, and 9) for 5–7 consecutive weeks, ranging from the week ending January 15 to the week ending April 2, 2011.

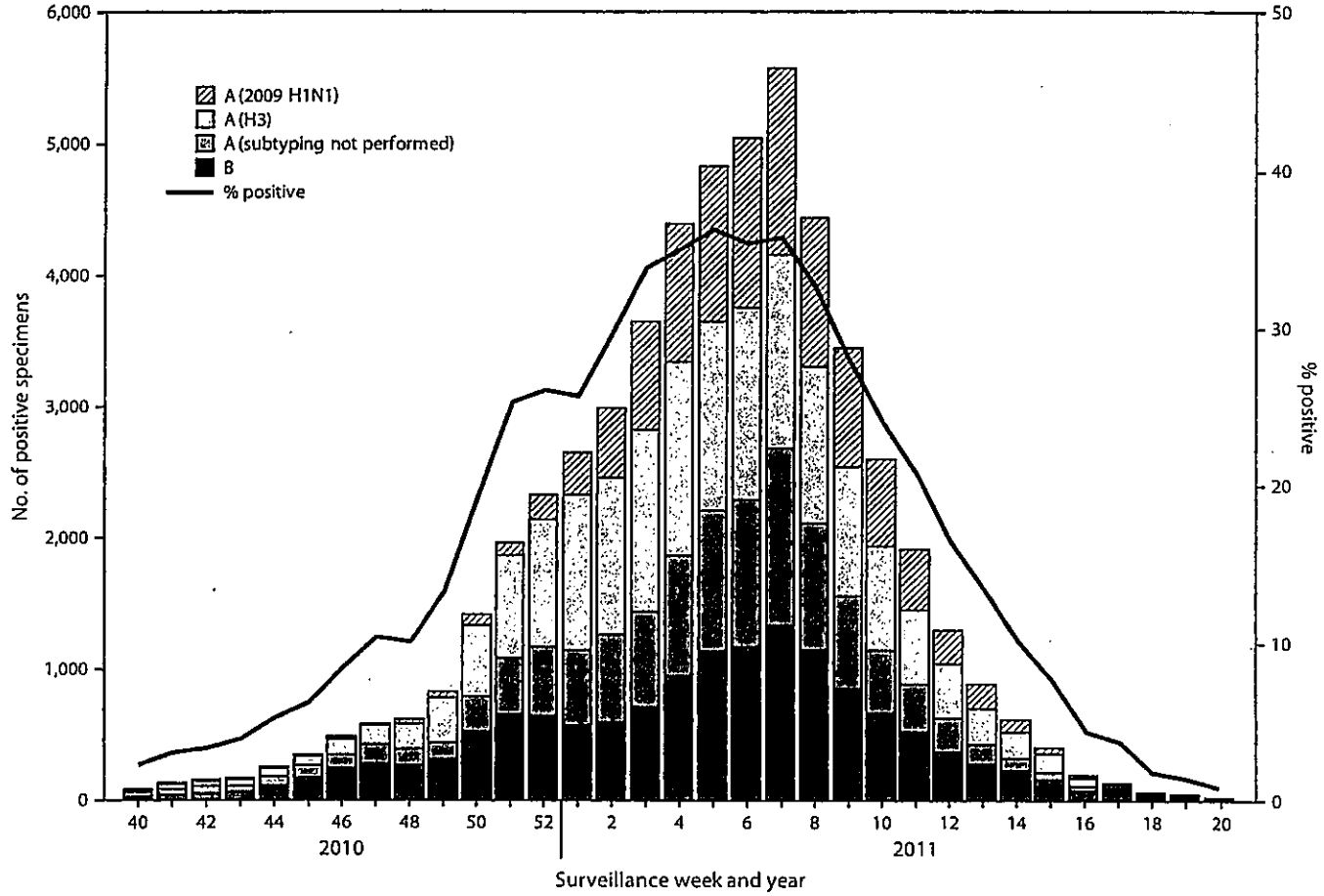
Novel Influenza A Viruses

Five cases of human infection with a novel influenza A virus were reported during the 2010–11 influenza season from three states. All five cases were infected with swine-origin influenza A (H3N2) viruses. Two cases occurred in September (Pennsylvania and Wisconsin), one case in October (Pennsylvania), and two cases in November (Minnesota). Two of the five cases occurred in adults, and three occurred in children. Two of the five cases were hospitalized; all five have recovered fully from their illness. The two cases in Pennsylvania were not related. The cases in Wisconsin and Pennsylvania had direct contact with swine or lived in areas close to swine farms. The two cases from Minnesota occurred in a father (index case) and child. The father had a nasopharyngeal swab positive for swine-origin influenza A (H3N2) virus and had direct swine

*The CDC influenza surveillance system collects five categories of information from 10 data sources: 1) viral surveillance (World Health Organization collaborating laboratories, the National Respiratory and Enteric Virus Surveillance System, and novel influenza A virus case reporting); 2) outpatient illness surveillance (U.S. Outpatient Influenza-like Illness Surveillance Network); 3) mortality (122 Cities Mortality Reporting System, Aggregate Hospitalization and Death Reporting Activity, and influenza-associated pediatric mortality reports); 4) hospitalizations (FluSurv-NET, which includes the Emerging Infections Program and surveillance in six additional states, and Aggregate Hospitalization and Death Reporting Activity); and 5) summary of the geographic spread of influenza (state and territorial epidemiologist reports).

†The 10 HHS regions include the following states and territories: Region 1: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont; Region 2: New Jersey, New York, Puerto Rico, and the U.S. Virgin Islands; Region 3: Delaware, District of Columbia, Maryland, Pennsylvania, Virginia, and West Virginia; Region 4: Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, and Tennessee; Region 5: Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin; Region 6: Arkansas, Louisiana, New Mexico, Oklahoma, and Texas; Region 7: Iowa, Kansas, Missouri, and Nebraska; Region 8: Colorado, Montana, North Dakota, South Dakota, Utah, and Wyoming; Region 9: Arizona, California, Hawaii, Nevada, American Samoa, Commonwealth of the Northern Mariana Islands, Federated States of Micronesia, Guam, Marshall Islands, and Republic of Palau; Region 10: Alaska, Idaho, Oregon, and Washington.

FIGURE 1. Number* and percentage of respiratory specimens testing positive for influenza, by type, surveillance week, and year — World Health Organization and National Respiratory and Enteric Virus Surveillance System collaborating laboratories, United States, October 3, 2010–May 21, 2011†



* N = 54,226.
† As of May 25, 2011.

exposure 6 days before illness onset. The child, whose infection with influenza A (H3N2) virus was confirmed several weeks later by serologic testing, did not have direct swine exposure, and most likely acquired infection from close contact with her father. Other persons in the same household also had ILI during the same period, but serologic results were either negative or inconclusive.

Antigenic Characterization

Since October 1, 2010, CDC has antigenically characterized 2,494 influenza viruses submitted by U.S. laboratories. Those have included 613 2009 influenza A (H1N1) viruses, 1,139 influenza A (H3N2) viruses, and 742 influenza B viruses. Of the 613 2009 influenza H1N1 viruses tested, 612 (99.8%) were characterized as A/California/7/2009-like, the 2009 influenza A (H1N1) component of the 2010–11 influenza vaccine. One virus (0.2%) of the 613 tested showed reduced titers with antiserum produced against A/California/7/2009. Of the 1,139 influenza A (H3N2) viruses, 1,103 (96.8%) were characterized as A/Perth/16/2009-like, the influenza A (H3N2) component of the 2010–11 influenza vaccine for the Northern Hemisphere. Of the 1,139 tested, 36 (3.2%) showed reduced titers with antiserum produced against A/Perth/16/2009.

Of the 742 influenza B viruses tested, 699 (94%) belonged to the B/Victoria lineage and 698 (99.9%) of these were characterized to be B/Brisbane/60/2008-like, the influenza B vaccine component for the 2010–11 Northern Hemisphere influenza vaccine. One (0.1%) of the 699 viruses belonging to the B/Victoria lineage showed reduced titers with antisera produced against B/Brisbane/60/2008. Of the 742 viruses tested, 43 (5.8%) belonged to the B/Yamagata lineage.

別紙様式第2-1

No. 15

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2011. 7. 11	該当なし	

一般的名称	人血清アルブミン	研究報告の公表状況		公表国
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 赤十字アルブミン5%静注12.5g/250mL(日本赤十字社) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)		ProMED 20110701.2003, 01-JUL-2011	米国

研究報告の概要

○Powassan ウイルス脳炎－米国ミネソタ
ミネソタ州北部の60歳代女性がPowassan(POW)ウイルスによる脳炎で死亡した。この感染症による死亡例はミネソタ州では初めてである。またミネソタ州でもう一人のPOWウイルス感染症例が確認された。この60歳代の男性は現在回復している。二人は2011年5月に発症した。二人とも屋外でダニに噛まれた。
POWウイルスはシカダニにより感染する。1958年にオンタリオ州ポワッサン地域で最初に記録されて以来、北米で約60人の感染が確認されている。POWウイルスは中枢神経系の重症疾患を起こし、脳炎や髄膜炎を起こす。

報告企業の意見

ミネソタ州で二人がシカダニによって媒介されるPowassanウイルスに感染し、そのうち一人は脳炎によって死亡したとの報告である。
Powassanウイルスは脂質膜を持つRNAウイルスである。これまで本製剤によるPowassanウイルス感染の報告はない。製剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれていることから、本製剤の安全性は確保されていると考える。

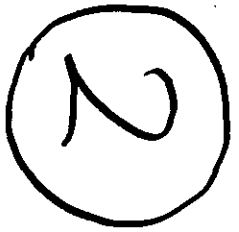
今後の対応

日本赤十字社では、輸血感染症対策として受付時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、発熱などの体調不良者を献血不適としている。今後も引き続き、新興・再興感染症の発生状況等に関する情報の収集に努める。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25
赤十字アルブミン5%静注12.5g/250mL
赤十字アルブミン20%静注4g/20mL
赤十字アルブミン20%静注10g/50mL
赤十字アルブミン25%静注12.5g/20mL

血液を原料とすることに由来する感染症伝播等



Archive Number 20110701.2003
Published Date 01-JUL-2011
Subject PRO/AH/EDR> Powassan virus, encephalitis - USA: (MN) fatal

POWASSAN VIRUS, ENCEPHALITIS - USA: (MINNESOTA) FATAL
****
A ProMED-mail post
<http://www.promedmail.org>
ProMED-mail is a program of the
International Society for Infectious Diseases
<http://www.isid.org>

Date: Wed 29 Jun 2011
Source: Shakopee Valley News [edited]
<http://www.shakopeenews.com/view/full_story/14512744/article-Minnesota-records

A woman in her 60s from northern Minnesota has died from a brain infection [presumed to be encephalitis] due to Powassan (POW) virus infection. This is the 1st death in the state attributed to the disease.

One other likely POW virus infection case has been identified this year [2011] in Minnesota, in an Anoka County man in his 60s who was hospitalized with a brain infection and is now recovering at home. POW virus is transmitted through the bite of an infected tick.

Both 2011 cases became ill in May after spending time outdoors and noticing tick bites. The fatal case was likely exposed to ticks near her home. The case from Anoka County might have been exposed near his home or at a cabin in northern Minnesota.

Health officials say this death serves as a reminder of the vital importance of preventing tick bites.

"Although Powassan cases are rarely identified, it is a severe disease which is fatal in about 10 percent of cases nationwide, and survivors may have long-term neurological problems" said Dr Ruth Lynfield, state epidemiologist with the Minnesota Department of Health (MDH).

"Powassan disease is caused by a virus and is not treatable with antibiotics, so preventing tick bites is crucial."

In Minnesota, POW virus can be transmitted by the blacklegged tick (also called the deer tick), which can also carry Lyme disease, anaplasmosis, and babesiosis. The blacklegged tick is abundant during our warm weather months in hardwood and mixed-hardwood forests of Minnesota. When a tick infected with POW virus attaches to a person, it might take only minutes of tick attachment for the virus to be transmitted.

POW virus infection was first detected in Minnesota in 2008, in a Cass County child who was exposed near home. In 2009-2010, 5 additional POW cases were identified in Minnesota. These cases were likely exposed to infected ticks in north-central or east-central counties (Cass, Carlton, Hubbard, Itasca, or Kanabec). In addition to these human cases, MDH has found POW-infected ticks in northern counties (Cass, Clearwater, and Pine) and in southeastern Minnesota (Houston County).

POW virus was first described in 1958 in Powassan, Ontario. Since then, about 60 cases have been identified in North America. Most of

these cases were from eastern Canada and the northeastern USA until the last decade, when cases began to be reported from Michigan, Wisconsin, and now Minnesota.

POW virus is related to West Nile virus (WNV). Like WNV, POW virus can cause severe disease of the central nervous system, involving inflammation of the brain (encephalitis) or the lining of the brain and spinal cord (meningitis). People with POW may have fever, headache, vomiting, weakness, confusion, loss of coordination, speech difficulties, and memory loss. Signs and symptoms occur within 1 to 5 weeks of an infectious tick bite.

To prevent tick-borne diseases, always use tick repellents containing DEET (up to 30 percent concentration) or permethrin when spending time in tick habitat. Products with DEET can be used on the skin or clothing. Permethrin-based products, which are only applied to clothing, are highly effective and can last through several washings and wearings. Also, wear long pants and light-colored clothing to help detect and remove ticks before they've had time to bite. People with homes or cabins near the woods can also use landscape management and targeted pesticide applications to reduce exposure to disease-carrying ticks.

After returning from outdoors, check your body carefully for ticks and promptly remove any you find. The process of bathing or showering shortly after returning indoors can help remove ticks before they bite or before they've been attached for long.

The back end of the adult female blacklegged tick is reddish-orange in appearance and teardrop-shaped. The nymph, or immature, stage of the blacklegged tick is about the size of a poppy seed and dark-colored. It is so small that it often goes unnoticed. When the nymph is noticed, it is easily mistaken for a speck of dirt or small freckle on people's skin. Blacklegged ticks are smaller and darker in color than American dog ticks (also known as wood ticks). They also lack the dog tick's characteristic white markings. To remove a tick, use tweezers to grasp it by its head close to the skin and pull it out gently and steadily.

More information about Minnesota's tickborne diseases, including details on tickborne disease prevention and pictures of ticks, is available on the MDH Web site at <http://www.health.state.mn.us/divs/idepc/dtopics/tickborne/index.html> or by calling MDH at 651-201-5414>.

--
Communicated by:
ProMED-mail
<promed@promedmail.org>

[According to the Minnesota Department of Health website one type of POW virus is carried by _Ixodes scapularis_ (known as the blacklegged tick or deer tick), the same tick that transmits Lyme disease, human anaplasmosis, and babesiosis. The blacklegged tick is common in many wooded areas of north central, east central, and southeast Minnesota.

Another type of POW virus is carried by _Ixodes cookei_, a related tick species that usually feeds on woodchucks or other medium-sized mammals instead of humans. _I. cookei_ has also been found in wooded areas in Minnesota.

A tick needs to be attached to a person for a certain length of time before it can cause disease. Contrary to the information in the press report above, this time interval is not known for POW virus, but it may be shorter than the attachment time needed for Lyme disease (24-48 hours) or anaplasmosis (12-24 hours).

The website includes a scaled illustration of adults and a nymph of the blacklegged tick vector of Powassan virus.

The HealthMap/ProMED-mail interactive map of the state of Minnesota can be accessed at <http://healthmap.org/r/00DI>. A Minnesota county map can be seen at <http://www.digital-topo-maps.com/county-map/minnesota.shtml>. - Mod.CP]

[see also:
2009

Powassan virus, encephalitis - USA: (MN) 20090731.2684
2001

Encephalitis, Powassan virus - USA (Maine & Vermont) (02) 20010910.2174
Encephalitis, Powassan virus - USA (Maine & Vermont) 20010907.2146]
.....sb/cp/mj/jw
##
****

****

****

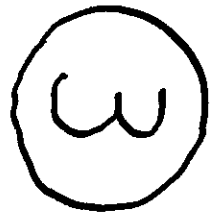
##
##

別紙3

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日： 平成23年7月25日	第一報入手日： 平成23年6月13日	新医薬品等の区分： 該当なし	総合機構処理欄
一般的名称	－		研究報告の公表状況	－	公表国： 日本	
販売名（企業名）	－					
研究報告の概要	問題点（　欧州における腸管出血性大腸菌O-104の大規模感染　） 欧州で腸管出血菌「O-104」の感染が拡大している問題で、ドイツ保健当局は6月12日までに、同国の死者が4人増えて35人になったと発表した。スウェーデンの死者も含めると計35人。 感染源については、ドイツ当局は同日までに、同国北部ニーダーザクセン州の農場で生産されたモヤシなどの発芽野菜から今回問題となったO-104と同じタイプの菌を検出し、感染源と特定した。					使用上の注意記載状況・その他の参考事項等

報告企業の意見	今後の対応
本報告は，当該生物由来製品による感染症情報ではない。腸管出血性大腸菌は既知感染症であるが、欧州や北米での大規模感染を“発生動向の変化”と考え、35人もの死者が発生したことを“重大な感染症”と考え、報告することにした。	今後も感染症情報の収集に努め，当該生物由来製品に係る情報を入手した場合には速やかに調査・報告を行い安全性の確保に努める．



NMP 2011-0001

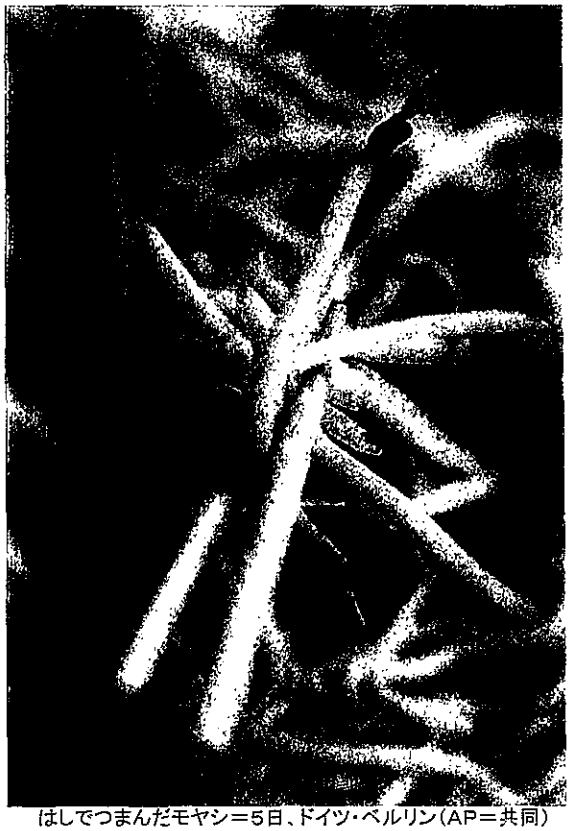
欧州大腸菌、死者35人に 感染源、独産モヤシと特定

【ベルリン共同】欧州で腸管出血性大腸菌「O104」の感染が拡大している問題で、ドイツ保健当局は12日、同国の死者が4人増えて34人になったと発表した。スウェーデンの死者も含めると計35人。

感染源については、ドイツ当局は同日までに、同国北部ニーダーザクセン州の農場で生産されたモヤシなどの発芽野菜から、今回問題となったO104と同じタイプの菌を検出し、感染源であると特定した。

欧州連合(EU)のダリ欧州委員(保健・消費者保護担当)は「極めて重要な進展だ」と指摘。ロシアがEU全域からの生野菜の輸入を停止していることを踏まえ、この解除に期待を表明した。

2011/06/13 05:39 【共同通信】



はしでつまんだモヤシ＝5日、ドイツ・ベルリン(AP＝共同)

番号２

別紙３

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日： 平成 23 年 7 月 25 日	第一報入手日： 平成 23 年 6 月 13 日	新医薬品等の区分： 該当なし	総合機構処理欄
一般的名称	－		研究報告の公表状況	－	公表国： 日本	
販売名（企業名）	－					

研究報告の概要

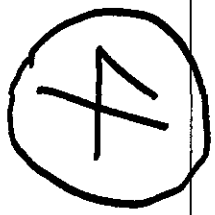
問題点（　欧州における腸管出血性大腸菌O-104 の大規模感染　）

欧州で腸管出血菌O-104 の感染が拡がっている問題で、ドイツ保健当局は 6 月 12 日までに、新たに 4 人の死亡が確認され。大腸菌による死者は 35 人になったと発表した。

欧州疾病対策センター（ＥＣＤＣ）による 12 日時点のまとめでは、感染者は 3256 人に上り、このうち 812 人が重度の腸疾患を発症した。感染源については、ドイツ当局は、同国北部のニーダーザクセン州の農場で生産されたモヤシなどのスプラウト（新芽野菜）が感染源となった可能性が高いとして、この農場から出荷された食品すべての回収を指示した。ただ、菌は従業員が持ち込んだのか種子に付着していたのかなど、農場が汚染された経路は依然として明らかになっていないと述べた。

報告企業の意見	今後の対応
本報告は，当該生物由来製品による感染症情報ではない。腸管出血性大腸菌は既知感染症であるが、欧州や北米での大規模感染を“発生動向の変化”と考え、35 人もの死者が発生したことを“重大な感染症”と考え、報告することにした。	今後も感染症情報の収集に努め，当該生物由来製品に係る情報を入手した場合には速やかに調査・報告を行い安全性の確保に努める．

使用上の注意記載状況・その他の参考事項等



MedDRA/J Ver. 14.0J

欧州でO104感染拡大、死者35人に　汚染経路は依然不明

関連記事を検索してみますか？　ドイツ O-104

2011.06.13 Mon posted at: 11:17 JST

（CNN） 欧州で腸管出血性大腸菌O（オー）104の感染が広がっている問題で、ドイツ保健当局は12日、新たに4人の死亡が確認され、大腸菌による死者が35人となったと発表した。

世界保健機関（WHO）などによると、これまでの死者はスウェーデンの1人を除き、すべてドイツ国内で報告された。欧州疾病対策センター（ECDC）による12日時点のまとめでは、感染者は3256人に上り、このうち812人が重度の腸疾患を発症。WHOは、感染者は5人を除く全員がドイツ在住か、3～4日とされる潜伏期間内にドイツを訪れていたとしている。

ドイツ当局は、同国北部ニーダーザクセン州の農場で生産されたモヤシなどのスプラウト（新芽野菜）が感染源となった可能性が高いとして、この農場から出荷された食品すべての回収を指示した。ただ、同州農業当局は12日、菌は従業員が持ち込んだのか種子に付着していたのかなど、農場が汚染された経路は依然として明らかになっていないと述べた。

初感染源とされたスペインをはじめ、フランス、オランダ、ベルギーの農家が補償を求めている問題では、欧州委員会が、欧州連合（EU）から約3億ドル支出する案を提示した。ただ、請求額はスペインだけで約6億ドルに上っている。

こんな話題も

- オーストラリアとNZで数千人足止め、チリ火山灰の影響 06/13
- 料理店テーブルで食塩追放、高血圧対策　アルゼンチン 06/17
- バフェット氏との昼食参加権、競売で2億1000万円 06/15
- 2億円超える「戦う恐竜」の化石が競売に　珍しい隕石も 06/16
- 家庭ゴミからO104検出、死者は31人に　ドイツ 06/17

別紙3

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日： 平成23年7月25日	第一報入手日： 平成23年7月6日	新医薬品等の区分： 該当なし	総合機構処理欄
一般的名称	－		研究報告の公表状況	－	公表国： 日本	
販売名（企業名）	－					
研究報告の概要	問題点（　欧州における腸管出血性大腸菌O-104の大規模感染　） 欧州連合（EU）は5日、ドイツなどで40人を超える死者を出した腸管出血性大腸菌「O-104」の感染源は、エジプト産植物の種子の可能性が高いとした。EUの食品安全管理当局が、感染源は2009年以降にエジプトから輸入されたフェヌグリークと呼ばれる植物の種子との見方を強めている。					使用上の注意記載状況・その他の参考事項等

報告企業の意見	今後の対応
本報告は，当該生物由来製品による感染症情報ではない。腸管出血性大腸菌は既知感染症であるが、欧州や北米での大規模感染を“発生動向の変化”と考え、35人もの死者が発生したことを“重大な感染症”と考え、報告することにした。	今後も感染症情報の収集に努め，当該生物由来製品に係る情報を入手した場合には速やかに調査・報告を行い安全性の確保に努める．

感染源はエジプト産種子か　大腸菌感染でEU輸入禁止

2011年7月6日　提供：共同通信社

【ブリュッセル共同】欧州連合（EU）は5日、ドイツなどで40人を超える死者を出した腸管出血性大腸菌「O104」の感染源は、エジプト産植物の種子の可能性が高いとして、同国産のマメ科の種子の輸入とEU域内での流通を禁止した。

EUの食品安全管理当局が、感染源は2009年以降にエジプトから輸入されたフェヌグリークと呼ばれる植物の種子との見方を強めているという。発芽したフェヌグリークは食用に用いられている。

ドイツ当局は6月中旬、北部ニーダーザクセン州の農場で生産されたモヤシなどの発芽野菜を感染源と特定。EUと協力し、この農場の発芽野菜にO104が混入した経路を追跡調査していた。

この記事を知り合いに転送　前の記事　次の記事

医療ニュース一覧

前週　7/4(月)　7/5(火)　7/6(水)　7/7(木)　7/8(金)　次週

一般医療ニュース

臨床

乳がん、早期発見も　スイスの大学、仕組み解明（共同）

行政

熱中症搬送が前年比3倍に　6月、下旬の猛暑が原因　消防庁速報、死者15人（共同）

感染の妊婦3千人調査へ　T細胞白血病ウイルスで授乳法による影響検証（共同）

「レバ刺し」提供自粛を 法的禁止も本格検討へ 食中毒防止で厚労省（共同）

地域

栃木・3病院再編　下都賀総合病院の存続求め要望書　地域医療考える会（毎日）

救急隊のAED故障、搬送中の男性死亡　東京・目黒署（毎日）

救急隊のAEDに不具合　東京消防庁、患者は死亡（共同）

四国初、肝炎「出前検診」導入　徳島県、受診者掘り起こし（毎日）

その他

別紙様式第 2-1
番号 5

医薬品
医薬部外品　　研究報告　調査報告書
化粧品

識別番号・報告回数			報告日	第一報入手日 2011 年 6 月 3 日	新医薬品等の区分	厚生労働省処理欄
一般的名称	①②③④⑤ポリエチレングリコール処理 人免疫グロブリン ⑥⑦人免疫グロブリン					
販売名 （企業名）	①献血ヴェノグロブリン IH5%静注 0.5g/10mL　（ベネシス） ②献血ヴェノグロブリン IH5%静注 1g/20mL　（ベネシス） ③献血ヴェノグロブリン IH5%静注 2.5g/50mL　（ベネシス） ④献血ヴェノグロブリン IH5%静注 5g/100mL　（ベネシス） ⑤献血ヴェノグロブリン-IH ヨシトミ　（ベネシス） ⑥グロブリン筋注 450mg/3mL「ベネシス」　（ベネシス） ⑦グロブリン筋注 1500mg/10mL「ベネシス」　（ベネシス）		研究報告の公表状況	読売新聞電子版 /2011/06/03	公表国 ドイツ	

研究報告の概要

ドイツで発生した腸管出血性大腸菌 O104 について、WHO 報道官が「これまでの感染例で確認されたことがない菌だ」と述べ、新種である可能性を示唆した。

（なお、その後、eurosurveillanceに「2011年5月から6月にドイツで溶血性尿毒症症候群流行を引き起こした腸管凝集性志賀毒素/ベロ毒素産生大腸菌O104:H4株の特性」が6月16日付で掲載され、食品における検出のための臨床検体および新たなリアルタイムPCRに集団発生株を検出する簡単な診断スクリーニングツールを説明している。また、7月5日ロータ一伝として「欧州食品安全庁(EFSA)は5日、エジプトから輸入した「フェヌグリーク（コロハ）」という植物の種子が感染源である可能性が高いと発表。これを受け、欧州連合(EU)は、エジプト産の一部種子と豆の輸入を10月31日まで禁止する措置を明らかにした。」との情報が入っているが、未だ結論は出ていない。）

報告企業の意見	今後の対応
大腸菌の大きさは長さ1～3μm、幅0.4～0.7μmで、多くの場合長さ5～10μm、幅20nmの周毛性鞭毛を持ち、活発な運動性を示す。滅菌・消毒に比較的弱く、加熱（湿熱）の場合には75℃以上1分間で死滅すると言われている。万一、大腸菌が原料血漿に混入したとしても、除菌ろ過等の製造工程にて除去されるものと考えている。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

使用上の注意記載状況・その他参考事項等

代表として献血ヴェノグロブリン IH5%静注 0.5g/10mL の記載を示す。

2. 重要な基本的注意

1) 本剤の原材料となる献血者の血液については、HBs 抗原、抗 HCV 抗体、抗 HIV-1 抗体、抗 HIV-2 抗体及び抗 HTLV-I 抗体陰性で、かつ ALT（GPT）値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV 及び HCV について核酸増幅検査（NAT）を実施し、適合した血漿を本剤の製造に使用しているが、当該 NAT の検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した血漿を原料として、Cohn の低温エタノール分画で得た画分からポリエチレングリコール 4000 処理、DEAE セファデックス処理等により人免疫グロブリンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において 60℃、10 時間の液状加熱処理、ウイルス除去膜によるろ過処理及び pH3.9～4.4 の条件下での液状インキュベーション処理を施しているが、投与に際しては、次の点に十分注意すること。

欧州で広がるO104、新種の可能性…WHO

【ジュネーブ＝佐藤昌宏】ドイツを中心に欧州で感染が広がる腸管出血性大腸菌O104について、世界保健機関（WHO）報道官は2日、ロイター通信に「これまでの感染例で確認されたことがない菌だ」と述べ、新種である可能性を示唆した。

複数の専門家は「感染力も毒性も強い新種だ」と述べている。感染はドイツ、フランスなど少なくとも10か国に及び、2日午後（日本時間3日未明）までに17人が死亡、感染者は1500人以上に達した。

（2011年6月3日 読売新聞）

yomiDr. トップページへ

別紙様式第 2-1
番号 6

医薬品
医薬部外品　　研究報告　調査報告書
化粧品

識別番号・報告回数			報告日	第一報入手日 2011 年 6 月 16 日	新医薬品等の区分	厚生労働省処理欄

一般的名称	①②③④⑤ポリエチレングリコール処理　人免疫グロブリン ⑥⑦人免疫グロブリン	研究報告の公表状況	Emerging Infectious Diseases 2011; 17(5): 843-847	公表国 アメリカ
販売名（企業名）	①献血ヴェノグロブリン IH5%静注 0.5g/10mL　(ベネシス) ②献血ヴェノグロブリン IH5%静注 1g/20mL　(ベネシス) ③献血ヴェノグロブリン IH5%静注 2.5g/50mL　(ベネシス) ④献血ヴェノグロブリン IH5%静注 5g/100mL　(ベネシス) ⑤献血ヴェノグロブリン-IH ヨシトミ　(ベネシス) ⑥グロブリン筋注 450mg/3mL「ベネシス」　(ベネシス) ⑦グロブリン筋注 1500mg/10mL「ベネシス」　(ベネシス)			

研究報告の概要

ライム病は 20 年以上、米国ニューヨーク州の低地ハドソン渓谷(LHV)地域に特有であったが、バベシア症は 2001 年以来、そこでだけ発生している。バベシア症と診断された低地ハドソン渓谷住人の数は、ニューヨーク州の他の地域の約 1.6 倍の増加と比較して、2001 年から 2008 年の間、6 症例/年から 119 症例/年へと 20 倍に増加した。2002 年から 2009 年の間、バベシア症の合計 19 人の患者は地域の三次医療センターへ 22 回入院し、併用病状は高齢、悪性腫瘍、脾臓摘出術と AIDS が含まれた。二人の患者が輸血から感染した。一人はダニに噛まれたよりも周産期の暴露で感染、一人の患者は死亡した。
臨床医はダニの被害があった、或いは血液製剤を受けた発熱と溶血性貧血の人のバベシア症を考慮すべきである。

報告企業の意見	今後の対応
ボレリアは、マダニ科マダニ（Ixodes ricinus）属群のマダニ刺咬により媒介される全長 3～25μm、直径 0.2～0.5μm の螺旋状のスピロヘータの一種である。万一、ボレリアが原料血漿に混入したとしても、除菌ろ過等の製造工程にて除去されるものと考えている。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

使用上の注意記載状況・その他参考事項等

代表として献血ヴェノグロブリン IH5%静注 0.5g/10mL の記載を示す。
2. 重要な基本的注意
1) 本剤の原材料となる献血者の血液については、HBs 抗原、抗 HCV 抗体、抗 HIV-1 抗体、抗 HIV-2 抗体及び抗 HTLV-I 抗体陰性で、かつ ALT（GPT）値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV 及び HCV について核酸増幅検査（NAT）を実施し、適合した血漿を本剤の製造に使用しているが、当該 NAT の検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した血漿を原料として、Cohn の低温エタノール分画で得た画分からポリエチレングリコール 4000 処理、DEAE セファデックス処理等により人免疫グロブリンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において 60℃、10 時間の液状加熱処理、ウイルス除去膜によるろ過処理及び pH3.9～4.4 の条件下での液状インキュベーション処理を施しているが、投与に際しては、次の点に十分注意すること。

DOI: 10.3201/eid1705.101334

Suggested citation for this article: Joseph JT, Roy SS, Shams N, Visintainer P, Nadelman RB, Hosur S, et al. Babesiosis, in Lower Hudson Valley, New York, USA. Emerg Infect Dis. 2011 May; [Epub ahead of print]

Babesiosis in Lower Hudson Valley, New York, USA

Julie T. Joseph, Sumith S. Roy, Navid Shams, Paul Visintainer, Robert B. Nadelman, Srilatha Hosur, John Nelson, and Gary P. Wormser

Author affiliations: New York Medical College, Valhalla, New York, USA (J.T. Joseph, S.S. Roy, N. Shams, R.B. Nadelman, S. Hosur, J. Nelson, G.P. Wormser); and Baystate Health System, Springfield, Massachusetts, USA (P. Visintainer)

Although Lyme disease has been endemic to parts of the Lower Hudson Valley of New York, United States, for >2 decades, babesiosis has emerged there only since 2001. The number of Lower Hudson Valley residents in whom babesiosis was diagnosed increased 20-fold, from 6 to 119 cases per year during 2001–2008, compared with an ≈1.6-fold increase for the rest of New York. During 2002–2009, a total of 19 patients with babesiosis were hospitalized on 22 occasions at the regional tertiary care center. Concurrent conditions included advanced age, malignancies, splenectomy, and AIDS. Two patients acquired the infection from blood transfusions and 1 from perinatal exposure, rather than from a tick bite. One patient died. Clinicians should consider babesiosis in persons with fever and hemolytic anemia who have had tick exposure or have received blood products.

Babesiosis is a tick-borne infection of erythrocytes. *Babesia microti*, the most common cause of babesiosis in North America, is transmitted by *Ixodes scapularis* ticks, which also transmits *Borrelia burgdorferi*, the cause of Lyme disease, and *Anaplasma phagocytophilum*, the cause of human granulocytic anaplasmosis (HGA) (*1*,*2*). Babesiosis, however, does not occur in all Lyme disease–endemic areas (*1*). Although Lyme disease has been highly endemic to parts of the Lower Hudson Valley (LHV) of New York in the United States since the mid-1980s, the first indigenous case of babesiosis did not occur there until 2001 (*3*).

To better characterize the recent emergence of babesiosis in this region, we reviewed data for 2001–2008 on *I. scapularis* tick–transmitted infections in the 7 counties that make up the LHV. These counties are located immediately north of New York City. In addition, we reviewed the medical records of patients with babesiosis who were hospitalized during January 1, 2002–December 31, 2009, at the Westchester Medical Center (WMC), the sole tertiary care medical center in the LHV.

Methods

Reported Babesiosis Cases in the LHV

For this report, we defined the LHV as Westchester, Putnam, Dutchess, Orange, Rockland, Ulster, and Sullivan counties (*4*). Cases of babesiosis, Lyme disease, and HGA in this region were tabulated on the basis of statistics on reportable diseases available on the New York State Department of Health (NYSDOH) website (*5*). Cases listed as ehrlichiosis were assumed to be a surrogate for HGA in this region. For purposes of surveillance by the NYSDOH during the period reviewed, a diagnosis of babesiosis was considered confirmed when 1) a clinically compatible illness occurred in conjunction with identification of *Babesia* spp. parasites on blood smear or a positive immunoglobulin G (or total antibody) *Babesia* spp. serologic titer of $\geq$256 (with testing confirmed by NYSDOH), or 2) in the absence of a clinically compatible illness, *Babesia* spp. parasites were present on blood smear (*5*).

Patients Hospitalized with Babesiosis at WMC

WMC is located in Valhalla, Westchester County, New York. We retrospectively reviewed medical records of patients with babesiosis documented by peripheral blood smear who were hospitalized at WMC during January 1, 2002–December 31, 2009. Case ascertainment was based on review of microbiology and infectious diseases records. For the 2 patients who had >1 hospitalization for babesiosis, we included data for only the first hospitalization. Complete records were available for all but 1 patient; partial records were available for that patient. The Institutional Review Board at New York Medical College approved the medical records review.

Statistical Methods

Continuous variables were described with means and standard deviations. Categorical variables were described with frequencies and percentages, and differences were compared with

the Fisher exact test (2-tailed). Relative risk estimates over time and among counties were computed by using Poisson regression adjusting for population size. A p value <0.05 was considered significant.

Results

The LHV comprises 4 counties west of the Hudson River (Rockland, Orange, Sullivan, and Ulster) and 3 counties east of the Hudson River (Westchester, Putnam, and Dutchess) (Figure 1). Westchester County is located immediately north of the Bronx, New York.

Babesiosis has been a reportable disease in New York since 1986. According to statistics compiled by NYSDOH (*5*), the number of cases of babesiosis diagnosed in residents of the 7-county LHV increased nearly 20-fold from 6 per year to 119 per year during 2001–2008 (Figure 2), with an average increase in incidence of 48.7% per year (95% confidence interval [CI] 40.6%–57.2%) (Table 1) (*5,6*). In the rest of the state, the number of cases increased only ≈1.6-fold during the same period (from 89 cases in 2001 to 142 cases in 2008) (*5*).

Although the number of babesiosis cases increased on both sides of the river, 104 (87.4%) of 119 reported cases in 2008 occurred in residents of counties east of the Hudson River (Table 1). The 104 cases in the 3 counties east of the Hudson River, with a total population of 1,346,065 (*6*), corresponds to 7.7 cases per 100,000 residents, compared with 15 cases among a total population of 936,051 or 1.6 cases per 100,000 for the 4 counties west of the Hudson River (relative risk [RR] 4.82, 95% CI 2.79–8.92; p<0.001). In the 3 counties east of the river, Dutchess County accounted for 62 of the babesiosis cases in 2008 (21.2/100,000), Westchester County for 36 cases (3.8/100,000), and Putnam County for 6 cases (6.0/100,000); thus, the prevalence of babesiosis in 2008 was significantly greater for Dutchess County than for Westchester County (RR 5.61, 95% CI 3.72–8.46; p<0.001) or for Dutchess than for Putnam County (RR 3.53, 95% CI 1.51–8.09; p = 0.003). No significant difference was detected between Putnam and Westchester Counties (RR 1.60, 95% CI 0.68–3.81; p = 0.28) (*5,6*).

For purposes of comparison, in 2001, a total of 2,584 Lyme disease cases were reported from the LHV, compared with 4,609 in 2008, representing a <2-fold increase; 78 ehrlichiosis (HGA) cases were reported in 2001, compared with 213 in 2008, a <3-fold increase (*5*). In 2008,

2,369 (51.4%) of the 4,609 reported Lyme disease cases occurred in residents of counties east of the Hudson River, compared with 186 (87.3%) of 213 reported ehrlichiosis (HGA) cases.

Hospitalized Patients with Babesiosis

Coincident with the emergence of babesiosis in the LHV, the number of patients hospitalized at WMC with this infection also markedly increased. Nineteen patients (18 adults) were hospitalized with babesiosis at WMC on 22 occasions from 2002 through 2009. All 19 patients were residents of LHV; 15 (79%) resided in Westchester County, 2 in Dutchess County, and 1 each in Orange and Putnam Counties.

The only child affected was a 6-week-old infant who acquired *B. microti* infection perinatally; a detailed case history for this patient will be reported elsewhere. For 2 of the 18 cases in adults, transfusion of infected blood products was believed to have been the route of infection; 1 of these cases is described in more detail elsewhere (*7*). Fifteen (94%) of the 16 other adult patients had potential tick exposure in the LHV (tick exposure is defined as exposure to outdoor environments where ticks are likely to reside); for 10 (67%) of these patients, this was the only known tick exposure within 30 days before onset of symptoms. Of the 16, however, only 3 (19%) actually recalled a tick bite within this 30-day period.

All 18 adult patients had a positive peripheral blood smear for *Babesia* spp. parasites (Table 2). Of the 8 patients who were tested for *B. microti* DNA by PCR, all had positive results. All but 2 of the patients were admitted during May–October. One patient was admitted in December, and the other was admitted in January. The patient who sought care in December had a tick bite 1 month before admission. Thirteen (72%) patients were men; the mean age was 54.1 years (range 21–95 years). Mean time from onset of symptoms to diagnosis was 13.6 days (median 11 days, range 3–33 days).

Five (28%) patients had had a splenectomy before the babesiosis diagnosis, 2 (11%) had AIDS, and 5 (28%) had malignancies (2 of whom were among the 5 patients who had splenectomies). Of the 5 patients with malignancies, 1 had acute myelogenous leukemia and had received a stem cell bone marrow transplant, 2 patients had B-cell follicular lymphoma (and had been treated with rituximab), 1 had a teratoma, and 1 had renal cell carcinoma. Of the 8 patients <50 years of age, 5 (63%) were potentially immunocompromised because of malignancy, splenectomy, or AIDS.

Common symptoms or signs were fever (temperature ≥38°C) (83%), headache (39%), malaise (33%), and chills (28%); splenomegaly was present in 2 (15%) of the 13 patients with an intact spleen. Frequent laboratory findings included anemia, thrombocytopenia, and abnormal liver function tests (Table 2). All 15 patients for whom a lactate dehydrogenase level was available had a value above the upper reference limit (221 U/L). Reticulocytes varied from 1.1% to 19.9% in 12 patients (median 3.1%; reference 0.5%–1.5%). Haptoglobin level was <20 mg/dL in all 10 patients who were tested (reference 26–85 mg/dL).

Eleven patients were treated with azithromycin and atovaquone; a rash to azithromycin developed in 1 patient, and the drug regimen was changed to clindamycin and atovaquone. In another patient, a rash to atovaquone developed, and clindamycin and quinine was prescribed. Six patients were initially treated with clindamycin and quinine; adverse reactions to quinine developed in 3. In 1 patient, QT prolongation developed, and in 2 patients, hearing loss developed. One patient was initially treated with clindamycin and atovaquone. Eight (44%) patients required blood transfusion for anemia, and 3 (17%) received erythrocyte exchange as adjunctive therapy.

Length of hospital stay ranged from 3 to 73 days (median 8 days). One patient had left upper quadrant pain and splenic rupture and was treated conservatively without surgery. The 1 death occurred in a 95-year-old patient in whom shock and respiratory failure developed and who required admission to the intensive care unit. Another patient required ventilator support. In 15 (83%) patients, infection resolved with a single course of antimicrobial drugs. Illness recurred in 2 patients but resolved after a subsequent and more prolonged course of antimicrobial drug treatment (the 2 latter patients have been included in previous reports [*7–9*]).

Discussion

As of 2008, babesiosis cases in residents of the LHV accounted for 45.6% of the 261 cases reported in New York (*5*). Testing of selected *I. scapularis* ticks by PCR in 2002 showed positive results for *B. microti* in tick pools collected in Dutchess and Westchester Counties (*5*). A more recent study of 154 adult *I. scapularis* ticks collected in 2008 from 2 locations in Westchester County identified 24 (15.6%) ticks that were infected with *B. microti* according to PCR, compared with 34 (25.8%) of 132 adult ticks collected from 3 locations in Suffolk County,

in Long Island, New York ($p<0.04$) (*10*); babesiosis has been indigenous to Suffolk County since 1975, with 95 cases reported there in 2008 alone (*5*). These infection rates, however, should be interpreted cautiously because an unknown proportion of positive findings may have resulted from detection of *B. odocoilei* in the ticks evaluated, rather than *B. microti*. *B. odocoilei*, which is not regarded as a human pathogen, infects deer ticks more frequently than does *B. microti* in sites where these piroplasms coexist (*11*).

There are 2 prior reports of hospitalized patients in New York with babesiosis. One report published in 1998 described 139 adults with babesiosis hospitalized during 1982–1993 (*12*). More than 90% of these patients resided in Suffolk County; only 2 resided in Westchester County. The other report, published in 2001, described 34 adults and children with babesiosis hospitalized at 2 tertiary care centers in Suffolk County (*13*). The latter patients were hospitalized over 13 consecutive years, but the exact years were not specified. The general clinical and laboratory features of babesiosis in these 2 case series were similar to those observed in the patients in our study. Most patients had a nonspecific febrile illness associated with hemolytic anemia, thrombocytopenia, and abnormal liver function test results. Of the 139 patients in the 1998 series, 16 (11.7%) had had a splenectomy (*12*), as did 8 (27%) of the 30 adults in the 2001 report (*13*), but in neither of the 2 earlier reports were any patients identified as having lymphoma and receiving treatment with rituximab (*9*), receiving a transplantation, or having AIDS. Thus, our case series presumably included more patients now recognized to be at high risk for relapse of infection (*9*). The 5.6% case-fatality rate in our study, however, is slightly lower than the 6.5% in the 1998 report (*12*) and the 8.8% in the 2001 report (*13*). Unlike the 2 prior case series, 2 (11%) of the patients in our study were believed to have been infected through receipt of an infected blood product (*7*), which provides further evidence of the growing importance of this route of transmission (*14–18*).

Six (33%) of the patients reported here had serologic evidence of Lyme disease, but this finding may overestimate the frequency of coinfection because only 1 had an objective clinical manifestation of Lyme disease (erythema migrans). Among the adult ticks collected in Westchester County in 2008 (*10*), 79.2% of those infected with *Babesia* spp. were also infected with *B. burgdorferi*, which reinforces the need to consider the possibility of concomitant Lyme disease in patients from the LHV in whom babesiosis is diagnosed.

How *B. microti* found its way from areas to which this microorganism is endemic into the *I. scapularis* tick population of the LHV is unclear. Evidence suggests that babesiosis is also emerging as a human pathogen in contiguous geographic areas of western Connecticut (*19,20*). The principal animal reservoir for *B. microti* is the white-footed mouse, *Peromyscus leucopus* (*1*). Other reservoirs include voles and shrews. These animals are not likely to travel great distances, which suggests that movement of these animals is an unlikely explanation for the emergence of babesiosis in the LHV.

Babesiosis is an emerging infectious disease in the LHV of New York with the potential to cause serious illness and death, especially in highly immunocompromised patients. Clinicians should consider this diagnosis in persons with fever and hemolytic anemia who have been exposed to ticks or have received blood products.

Acknowledgments

We thank Lisa Giarratano, Lenise Banwarie, Richard C. Falco, Maria Aguero-Rosenfeld, Guiqing Wang, and Albert Lowenfels for their assistance.

Dr Joseph is an assistant professor of medicine in the Division of Infectious Diseases at New York Medical College, Valhalla, New York, USA. Her main research interests are tick-borne infections, specifically babesiosis.

References

1. Vannier E, Gewurz BE, Krause PJ. Human babesiosis. Infect Dis Clin North Am. 2008;22:469–88. PubMed doi:10.1016/j.idc.2008.03.010

2. Swanson SJ, Neitzel D, Reed KD, Belongia EA. Coinfections acquired from *Ixodes* ticks. Clin Microbiol Rev. 2006;19:708–27. PubMed doi:10.1128/CMR.00011-06

3. Kogut SJ, Thill CD, Prusinski MA, Lee JH, Backerson PB, Coleman JL, et al. *Babesia microti*, upstate New York. Emerg Infect Dis. 2005;11:476–8. PubMed

4. New York State Department of Environmental Conservation. Lower Hudson Valley—Region 3 [cited 2011 Mar 4]. http://www.dec.ny.gov/outdoor/7804.html

5. New York State Department of Health. Statistics and data [cited 2011 Mar 4]. http://www.health.state.ny.us/statistics

6. U.S. Census Bureau. State & county quick facts [cited 2011 Mar 4]. http://quickfacts.census.gov/qfd/states/36000.html

7. Wormser GP, Lombardo G, Silverblatt F, El Khoury MY, Prasad A, Yelon JA, et al. Babesiosis as a cause of fever in patients undergoing a splenectomy. Am Surg. 2011;77:345–7. PubMed

8. Wormser GP, Prasad A, Neuhaus E, Joshi S, Nowakowski J, Nelson J, et al. Emergence of resistance to azithromycin-atovaquone in immunocompromised patients with *Babesia microti* infection. Clin Infect Dis. 2010;50:381–6. PubMed doi:10.1086/649859

9. Krause PJ, Gewurz BE, Hill D, Marty FM, Vannier E, Foppa IM, et al. Persistent and relapsing babesiosis in immunocompromised patients. Clin Infect Dis. 2008;46:370–6. PubMed doi:10.1086/525852

10. Tokarz R, Jain K, Bennett A, Briese T, Lipkin WI. Assessment of polymicobial infections in ticks in New York state. Vector Borne Zoonotic Dis. 2010;10:217–21. PubMed doi:10.1089/vbz.2009.0036

11. Armstrong PM, Katavolos P, Caporale DA, Smith RP, Spielman A, Telford SR III. Diversity of *Babesia* infecting deer ticks (*Ixodes dammini*). Am J Trop Med Hyg. 1998;58:739–42. PubMed

12. White DJ, Talerico J, Chang H-G, Birkhead GS, Heimberger T, Morse DL. Human babesiosis in New York state. Review of 139 hospitalized cases and analysis of prognostic factors. Arch Intern Med. 1998;158:2149–54. PubMed doi:10.1001/archinte.158.19.2149

13. Hatcher JC, Greenberg PD, Antique J, Jimenez-Lucho VE. Severe babesiosis in Long Island: review of 34 cases and their complications. Clin Infect Dis. 2001;32:1117–25. PubMed doi:10.1086/319742

14. Gerber MA, Shapiro ED, Krause PJ, Cable RG, Badon SJ, Ryan RW. The risk of acquiring Lyme disease or babesiosis from a blood transfusion. J Infect Dis. 1994;170:231–4. PubMed

15. Gubernot DM, Lucey CT, Lee KC, Conley GB, Holness LG, Wise RP. *Babesia* infection through blood transfusions: reports received by the U.S. Food and Drug Administration, 1977–2007. Clin Infect Dis. 2009;48:25–30. PubMed doi:10.1086/595010

16. Lux JZ, Weiss D, Linden JV, Kessler D, Herwaldt BL, Wong SJ, et al. Transfusion-associated babesiosis after heart transplant. Emerg Infect Dis. 2003;9:116–9. PubMed

17. Leiby DA, Chung APS, Gill JE, Houghton RL, Persing DH, Badon S, et al. Demonstrable parasitemia among Connecticut blood donors with antibodies to *Babesia microti*. Transfusion. 2005;45:1804–10. PubMed doi:10.1111/j.1537-2995.2005.00609.x

18. Gubernot DM, Nakhasi HL, Mied PA, Asher DM, Epstein JS, Kumar S. Transfusion-transmitted babesiosis in the United States: summary of a workshop. Transfusion. 2009;49:2759–71. PubMed doi:10.1111/j.1537-2995.2009.02429.x

19. Anderson JF, Magnarelli LA. Babesiosis in Fairfield County, Connecticut. Emerg Infect Dis. 2004;10:545–6. PubMed

20. Johnson ST, Cable RG, Tonnetti L, Spencer B, Rios J, Leiby DA. Seroprevalence of *Babesia microti* in blood donors from *Babesia*-endemic areas of the northeastern United States 2000 through 2007. Transfusion. 2009;49:2574–82. PubMed doi:10.1111/j.1537-2995.2009.02430.x

Address for correspondence: Julie T. Joseph, Division of Infectious Diseases, New York Medical College, Munger Pavilion, Rm 245, Valhalla, NY 10595, USA; email: julie_joseph@nymc.edu

Table 1. Babesiosis cases reported to the New York State Department of Health, Lower Hudson Valley, New York, USA, 2001–2008

Area (2008 population)	2001	2002	2003	2004	2005	2006	2007	2008
West of Hudson River (936,051)	0	0	1	2	5	7	5	15
Rockland County (298,545)	0	0	0	1	0	2	0	3
Orange County (379,647)	0	0	1	1	1	5	5	7
Sullivan County (76,189)	0	0	0	0	1	0	0	1
Ulster County (181,670)	0	0	0	0	3	0	0	4
East of Hudson River (1,346,065)	6	8	20	16	38	70	74	104
Dutchess County (292,878)	2	4	6	7	23	42	44	62
Putnam County (99,244)	1	0	1	0	2	3	1	6
Westchester County (953,943)	3	4	13	9	13	25	29	36

Table 2. Selected demographic and clinical features and laboratory test results for 18 adults with babesiosis hospitalized at Westchester Medical Center, Valhalla, New York, USA, 2001–2008*

Characteristic	Value
Mean age, y, ± SD (range)	54.1 ± 20.1 (21–95)
Male, no. (%)	13 (72.2)
Mean time from symptom onset to diagnosis, d, ± SD (range)	13.6 ± 9.28 (3–33)
Recollection of tick bite within 30 d, no. (%)	3 (18.8)
Temperature >38°C, no. (%)	15 (83.3)
Splenomegaly, no. (%), n = 13	2 (15.4)
Mean initial parasitemia, %, ± SD (range), n = 17†	4.49 ± 4.57 (0.01–14)
Mean highest level of parasitemia, %, ± SD (range), n = 17†	5.34 ± 5.79 (0.05–18)
Mean initial lymphocyte count × 10^9/L,± SD (range), n = 17	7.2 ± 3.38 (3.2–15.4)
Lymphocyte count <1,000 ×10^6/L, no. (%), n = 12	5 (41.6)
Mean hemoglobin minimum, g/dL,± SD (range)	8.2 ± 1.98 (3.5–11.1)
Mean platelets minimum, × 10^9/L, ± SD (range)	110.8 ± 139.2 (19–615)
Platelets minimum <150 × 10^9/L, no. (%)	16 (88.9)
Mean initial erythrocyte sedimentation rate, mm/h,± SD (range), n = 9	76.7 ± 33.3 (32–138)
Mean initial lactate dehydrogenase, U/L, ± SD (range), n = 15	931.5 ± 562 (229–2074)
Mean initial aspartate aminotransferase, U/L, ± SD (range)	237.7 ± 366.9 (19–1450)
Initial aspartate aminotransferase >30 U/L, no. (%)	14 (77.8)
Mean initial alanine aminotransferase, U/L, ± SD (range)	110.2 ± 111 (16–433)
Initial alanine aminotransferase >40 U/L, no. (%)	13 (72.2)
Mean initial total bilirubin, mg/dL, ± SD (range)	3.4 ± 5.59 (0.4–24.6)
Initial total bilirubin >1.2 mg/dL, no. (%)	10 (55.6)
Mean serum sodium minimum, meq/L, ± SD (range), n = 17	127.6 ± 10.1 (94–139)
Mean creatinine maximum , ng/mL, ± SD (range), n = 17	1.3 ± 0.59 (0.7–2.7)

*Data were obtained from all 18 patients unless otherwise indicated.
†For 1 patient with a positive smear, the level of parasitemia is unknown.

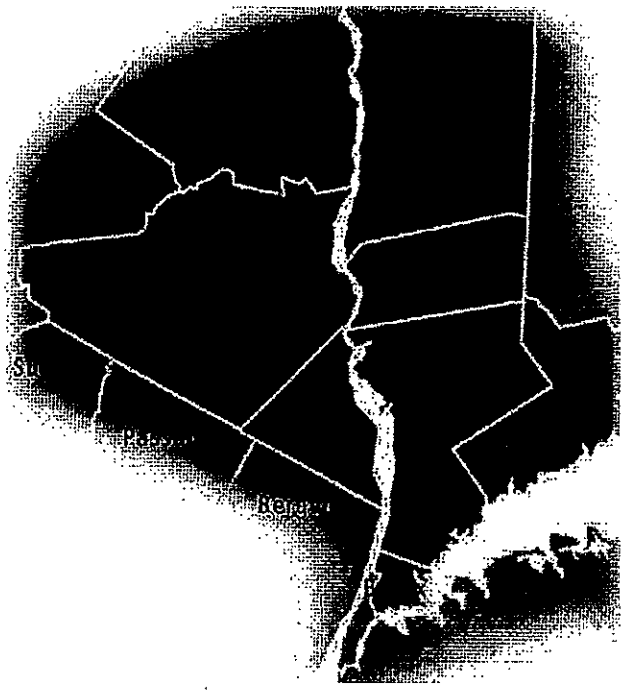


Figure 1. Map of the Lower Hudson Valley of New York, USA. Westchester, Putnam, and Dutchess Counties are east of the Hudson River, and Orange, Rockland, Ulster and Sullivan Counties are west of the Hudson River. The star indicates the site of the Westchester Medical Center. Permission for use of this image granted from the Westchester Institute for Human Development on July 23, 2010.

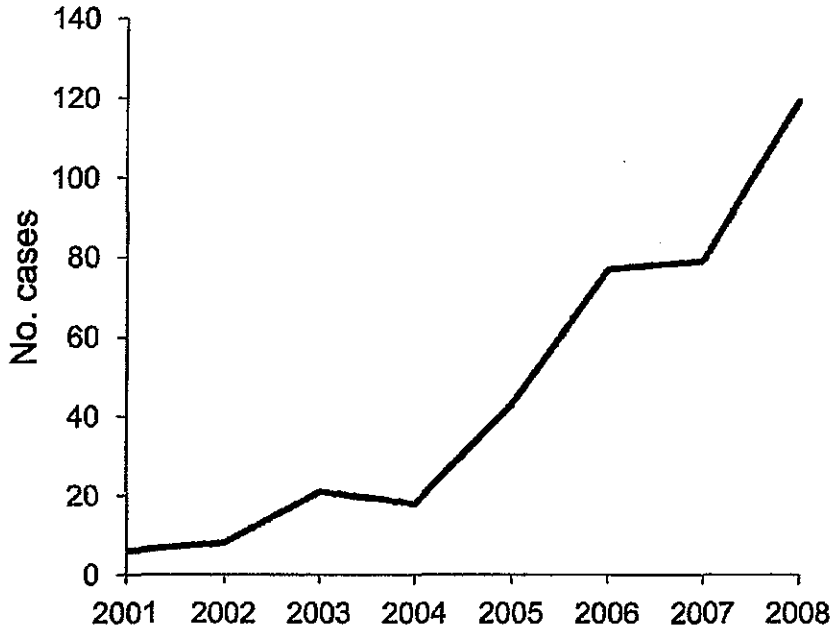


Figure 2. Annual number of reported babesiosis cases, Lower Hudson Valley, New York, USA, 2001–2008.

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2011. 4. 23	該当なし	

一般的名称	人血清アルブミン	研究報告の公表状況		公表国
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 赤十字アルブミン5%静注12.5g/250mL(日本赤十字社) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)		ProMED 20110419.1218, 19-APR-2011	OIE

研究報告の概要

○[1]日本のスクレイピー
2011年4月15日国際獣疫事務所(OIE)は農林水産省の家畜衛生部からのスクレイピー発生の報告を受理した。
新しいアウトブレイクは2011年3月30日に福岡県福岡市で発生し、ヒツジ1匹が発症し死亡した。屍体はサンプリング後焼却した。
アウトブレイクの原因は不明または未定。現在の状況は既に解決済みである。2005年以降、日本でのスクレイピー発生報告はなかった。今回のアウトブレイクは、日本での以前の報告と同じく古典的スクレイピーである。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25
赤十字アルブミン5%静注
12.5g/250mL
赤十字アルブミン20%静注
4g/20mL
赤十字アルブミン20%静注
10g/50mL
赤十字アルブミン25%静注
12.5g/20mL

血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
福岡県でスクレイピーがヒツジ1匹に発生し、国際獣疫事務所に報告されたとの報告である。 プリオン病の原因とされる異常プリオンがコーン分画工程で効果的に除去されるとの成績と併せて、これまでの疫学研究ではいかなるプリオン病も、アルブミンを介して伝播するという証拠は無い。また本製剤の使用は一時的かつ限定的であることから伝播のリスクは非常に低いものと考える。	本剤の安全性は確保されていると考えるが、念のため今後も情報収集に努め、今後とも血漿分画製剤の安全性向上のために努力する。

Archive Number 20110419.1218
Published Date 19-APR-2011
Subject PRO/AH/EDR> Scrapie - Japan, Norway: OIE, ovine, review

SCRAPIE - JAPAN, NORWAY: OIE, OVINE, REVIEW
****
A ProMED-mail post
<http://www.promedmail.org>
ProMED-mail is a program of the
International Society for Infectious Diseases
<http://www.isid.org>

This posting replaces: Scrapie - Japan, Norway: OIE, ovine, review
20110416.1199
which, for technical reasons, was incomplete. - Mod.SH

In this posting:
[1] Japan: OIE
[2] Norway: NFSA, scrapie control programme

******
[1] Japan: OIE
Date: Fri 15 Apr 2011
Source: OIE, WAHID (World Animal Health Information Database), weekly disease information 2011; 24(16) [edited]
<http://web.oie.int/wahis/public.php?page=single_report&pro=14&reportid=10482>

Scrapie, Japan

Information received on (and dated) 15 Apr 2011 from Dr Toshiro Kawashima, CVO, Animal Health Division, Ministry of Agriculture, Forestry and Fisheries, Tokyo, Japan
Summary
Report type: immediate notification
Start date: 30 Mar 2011
Date of 1st confirmation of the event: 14 Apr 2011
Date submitted to OIE: 15 Apr 2011
Reason for notification: reoccurrence of a listed disease
Date of previous occurrence: April 2005
Manifestation of disease: clinical disease
Causal agent: Prion protein
Nature of diagnosis: laboratory (advanced)
This event pertains to the whole country

New outbreaks
Outbreak 1: Minami-ku, Fukuoka city, Fukuoka
Date of start of the outbreak: 30 Mar 2011
Outbreak status: resolved (14 Apr 2011)
Epidemiological unit: farm
Affected animals
Species / Susceptible / Cases / Deaths / Destroyed / Slaughtered
Goats / 14 / 0 / 0 / 0 / 0
Sheep / 43 / 1 / 1 / 0 / 0

Epidemiology
Source of the outbreak(s) or origin of infection: unknown or inconclusive
Epidemiological comments: one scrapie-positive sheep was detected as a result of the regular surveillance conducted by Fukuoka prefecture on 14 Apr 2011.
The sheep was dead on 30 Mar 2011 and the carcass has been incinerated after the sampling.
An epidemiological survey is being conducted.

Control measures

Measures applied: quarantine, disinfection of infected premises/establishment(s).
Measures to be applied: no other measures

Diagnostic test results
Laboratory name and type: National Institute of Animal Health (national laboratory)
Tests and results
Species / Test / Test date / Result
Sheep / histopathological examination / 14 Apr 2011 / positive
Sheep / immunohistochemical test / 14 Apr 2011 / positive
Sheep / western blotting / 14 Apr 2011 / positive [see item 2 re- this test differentiating between classical and atypical scrapie].

--
communicated by:
ProMED-mail
<promed@promedmail.org>

[It may be assumed that the sheep's tissues/organs were forwarded to the laboratory within the framework of Japan's TSE (transmissible spongiform encephalopathies) surveillance, requiring the testing of fallen stock. No information on clinical signs or further details, such as the age of the animal, are included. The case seems to be defined as "classical scrapie", similar to all previous scrapie cases reported from Japan since the disease was introduced, allegedly with imported sheep in the 1970s. The 1st clinical case was recognised in Japan in the early 1980s; until 2002, about 60 scrapie cases were officially reported. Since then, 3 additional cases have been reported to the OIE (one each in 2003, 2005, and the current one). All cases, so far, involved sheep.

Scrapie (sometimes termed "classical scrapie") is considered not to pose a risk to human health. This is in contrast to so-called "atypical scrapie", whose potential risk to public health is under study. Atypical scrapie is clinically, pathologically, biochemically, and epidemiologically unrelated to classical scrapie, may not be contagious and may, in fact, be a spontaneous degenerative condition of older sheep. So far, no case of atypical scrapie has been diagnosed in Japan. OIE's Terrestrial Animal Health Code chapter 14.9, "scrapie", does not cover atypical scrapie; see the introduction to the chapter at <http://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_1.14.9.htm>.

Reference

M Horiuchi, T Nemoto, N Ishiguro, et al. Biological and Biochemical Characterization of Sheep Scrapie in Japan. J Clin Microbiol. 2002; 40(9): 3421-6; available at <http://jcm.asm.org/cgi/content/full/40/9/3421>. - Mod.AS

The location of the outbreak can be seen on the map included in the OIE report at the source URL above. The HealthMap/ProMED-mail interactive map of Japan is available at <http://healthmap.org/r/0I73>. - Sr.Tech.Ed.MJ]

******
[2] Norway: NFSA, scrapie control programme
Date: Sat 16 Apr 2011
Source: Norwegian Food Safety Authority (NFSA) [edited]
<http://www.mattilsynet.no/english/animal_disease_control/scrapie>

[The differentiation between scrapie and atypical scrapie (initially discovered in Norway), is important from epidemiological, disease control, international trade, and public health considerations. Wishing to provide our subscribers with the most up-to-date experience, we have applied to the Norwegian Food Safety Authority requesting a description of their current policy on both disease entities. We are very grateful to Norway's CVO for kindly referring us to the following updated control programme. - Mod.AS]

The Norwegian scrapie control programme small ruminants [January 2011]
---

1. Distribution of the disease in Norway

Currently (2010) the Norwegian sheep population is about 1 050 000 breeding sheep distributed on about 15 000 flocks based upon the Register of production subsidies. Corresponding figures for goat are about 45 000 and 1000 flocks, respectively.

Scrapie has been a notifiable disease in Norway since 1965.

Scrapie was first diagnosed in indigenous Norwegian sheep in 1981. Increasing numbers of scrapie-infected flocks were identified in the 1990s, culminating with 31 detected flocks in 1996. Including 2010, scrapie had been diagnosed in a total of 148 sheep flocks. Regarding goat, the 1st and only case of scrapie (classical) was diagnosed in 2006.

In 1998 a new scrapie strain, scrapie Nor98 (an atypical scrapie), was detected in Norway and thereafter the scrapie cases have been categorized as either classical scrapie or scrapie Nor98. Due to lack of proper material, it has not been possible to classify the cases before 1998 to scrapie strain, but the pathological findings and genotypes affected indicates that the majority of the cases have been classical scrapie.

Since 1998, a total of 11 sheep flocks (corresponding to 0.07 per cent of all the sheep flocks) with classical scrapie have been detected. The classical scrapie flocks have been located in a limited geographical area of Norway, with the majority found at the western coast with and some additional cases in Nordland County.

During the same period scrapie Nor98 has been detected in 86 sheep flocks (corresponding to 0.6 per cent of all the sheep flocks). The scrapie Nor98 flocks have been geographically widely spread [For maps and figures, please refer to the original text at the source URL above. - Mod.AS]

2. The reasons for the programme

Classical scrapie is a serious disease which causes considerable economic loss to the farmers and reduced animal welfare. Norwegian authorities have always regarded classical scrapie as one of the most important contagious small ruminant diseases in Norway. The emerging BSE crises in Europe during the 1990s contributed to increased public attention towards prion diseases in general. As a consequence of the sudden increase in classical scrapie cases in 1995 and 1996, Norway implemented a national scrapie control programme in 1997.

The Norwegian scrapie control programme aims at eradication of the infective agent in affected flocks and contact flocks. The scrapie control programme consists of several elements:
a. Surveillance of the small ruminant population
b. Stamping out of infected flocks and contact flocks, washing and disinfection, followed by an empty period of the premises for at least 2 years
c. Strict administrative provisions concerning movements of small ruminants in Norway

A high level of education and awareness towards the disease among the farmers and veterinarians is considered to be important for the programme.

Since the strict control measures in positive flocks were introduced in the 1st part of the 1990s, there have been no recurrent cases in eradicated flocks, indicating that the applied control measures are sufficient to eradicate classical scrapie at the premises. The low prevalence of classical scrapie flocks detected since 1998 (0-2 cases each year, corresponding to an annual prevalence less than 0.05 per cent) is taken as an indication that the extensive slaughtering of scrapie flocks and their contacts (approximately 600 flocks) was effective in reducing the prevalence of classical scrapie.

The government offers full compensation to owners who lose animals and income because of the programme eradication measures. Thus, considerable economic and social resources have been invested in the programme. The results of the programme are achieved by a collective effort among Norwegian farmers, livestock industry, and animal health authorities.

Norwegian authorities and stakeholders want to continue the strategy laid down in the national scrapie control programme. An alternative to the current programme is selective breeding for certain genotypes. However, based upon the low prevalence of classical scrapie in the country, a breeding programme is considered not to be cost effective. As regards scrapie Nor98, the wide range of genotypes found in scrapie Nor98 cases, implies that the breeding programme is not suitable for controlling atypical scrapie either. Besides, several cases of atypical scrapie have occurred in animals with the ARR/ARR genotype.

Therefore, in 2006 Norway applied for derogation from the requirement of introducing breeding programmes to select for resistance to TSEs, which was subsequently granted by the EFTA [European Free Trade Association between Iceland, Norway, Switzerland, and Liechtenstein] Surveillance Authority (2007).

3. Categories of holdings

The nationwide programme is mandatory and includes all small ruminants. According to the number of years a holding has been under surveillance, it is classified in one of 5 different classes [for their details, go to the source URL above].

Movements of flocks are restricted. Basically, it is forbidden to move small ruminants between counties. The local animal health authority may, however, grant permissions. Furthermore, it is only permitted to take sheep and goats into a flock from a flock classified on an equal or higher level. Currently almost all flocks in Norway are in [highest] class 5 [under surveillance for at least 8.5 years]. If animals of unknown surveillance status are introduced illegally into a flock, the said flock will be degraded to the lowest class.

4. Laboratory examination procedures

The national reference laboratory for TSE in Norway is the Norwegian Veterinary Institute in Oslo. The samples are analyzed according to the conditions laid down in Regulation (EC) No 999/2001 [see <http://ec.europa.eu/food/fs/afs/marktlab/marktlab14_en.pdf>].

Clinically suspect animals are subject to histopathological examination of brain tissue and immunohistochemical examination of brain and lymphoid tissue for PrPSc. In addition, a rapid test (TeSeE (R) Bio-Rad) is performed on brain and lymphoid tissues.

From fallen stock a pooled brain tissue sample (obex and cerebellum) is initially examined by the rapid test. Immunohistochemistry and Western blot (WB) are used as confirmative tests.

Western blot (TeSeE sheep/goat WB Bio-Rad) differentiates between classical and atypical scrapie (Nor98). Immunohistochemistry is performed using a monoclonal anti-PrP-antibody (F89/160.1.5). A commercially available kit (Envision+ (R) System HRP [AEC] DakoCytomation) is used to enhance the sensitivity of the method.

The confirmative tests, immunohistochemistry and Western blot analyses for PrPSc (TeSeETM sheep/goat Western Blot Bio-Rad), are carried out at the Norwegian Veterinary Institute in Oslo.

5. Components of the programme

Education, notification of suspect cases, official inspections, identification and registration of sampled flocks are essential elements to fulfill the surveillance program.

a. Education
To ensure that the persons who are handling small ruminants have knowledge about their obligations and the disease, information, and education campaigns have been carried out. Farmers as well as local veterinary officers (VOs) have been trained.

b. Notification
There is an obligation for private practitioners to notify any clinical suspect animal detected while carrying out private work on-farm. The same obligation exists for the keeper, transporter, or other responsible for the animal. This obligation also applies for all fallen stock older than 18 months.

c. Official inspections
The local VOs inspect all sheep and goat flocks in Norway regularly, at least every 10th year. Farms with restrictions are visited every year. The visits include both inspections of the animals and the holding, as well as inspection of the identification marking of the animals and the records, in particular records concerning the health situation (including treatments) of the animals.

All clinically suspect animals are examined by the VO. Selected animals may be re-inspected after 2 weeks, or killed and submitted to testing. The animal may also be transferred to an isolated pen for further observation and later examination.

Thorough inspections of the live animals to detect possible cases of scrapie are being conducted by the farmers themselves, by the VOs on their regular visits to the farms, and by extended ante mortem examinations of all sheep older than 2 years. The antemortem examinations are usually performed in the abattoirs. In flocks with official restrictions due to

suspicion of scrapie, it has to be performed by the VO on the farm prior to transport to the abattoir.

d. Identification and registration of animals
All holdings of small ruminants and animals belonging to them are registered with unique identifiers in a central database.

In addition to the above mentioned requirement the farmers are obliged to keep holding registers and movement documents containing information referred to in Council Regulation (EC) No 21/2004 [see <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:005:0008:0017:

e. Sampling
* Animals slaughtered for human consumption
- 10 000 sheep above 18 months of age randomly selected from the sub-population of normally slaughtered animals
- all imported ovine and caprine animals irrespective of age
- all slaughtered ovine and caprine animals above 18 months of age from holding subject to restriction due to the TSE control and eradication programme
* Animals not slaughtered for human consumption
- all ovine (goal 10 000) and caprine (goal 500) animals above 18 months of age which have died or have been killed for other reasons than slaughter for human consumption
- all dead or killed for destruction ovine and caprine animals above 18 months of age from holding subject to restriction due to the TSE control and eradication programme
* Sampling following notification
- all sheep and goats showing signs of nervous disorders or behavioural changes irrespective of age when it is not entirely clear whether this was caused by injuries or other infections
* Registration of sampled flocks

All flocks sampled will be registered at the Norwegian Veterinary Institute. This register can be compared to the national register of animal holdings and large flocks where no animals are tested for TSEs might be identified for following up by the local VO.

6. Control measures
---
a. Classical scrapie: measures as a consequence of scrapie confirmation
When classical scrapie is confirmed in a flock, the entire holding of small ruminant animals is killed. The carcasses are treated as category 1 material according to Regulation (EC) No 1774/2002. Any sheep in contact flocks that were born on the affected holding, and offspring of ewes that were born on the affected holding, are killed, destroyed, and compensation is paid by the authorities.

The prion protein genotype has since 2003 been determined for all animals that are killed as a part of the eradication measures for classical scrapie.

After an affected flock has been killed, extensive measures are taken to eliminate the infectious agent from the holding. Buildings where sheep have been kept are subjected to strict sanitation measures. If satisfactory cleaning and disinfection is considered impossible, the building is demolished.

The sanitation measures required for indoor areas include the removal of manure, removal and burning of all wooden materials and other not washable material that has been in direct contact with the sheep (flooring, walls, drinking basins, etc), cleaning and disinfection of remaining indoor areas, painting of least the bottom 1.5 m [4.5 feet] of the walls of the building (including window panes), and fitting of new floors, doors, walls, etc, according to the condition on the farm.

Sanitation measures for outdoor areas include changing of the upper layer on surrounding unpaved roads, washing, disinfection, and if necessary painting of the outside wall of relevant buildings, ploughing and/or burning of grass on grazing areas, and disinfection or fitting of new fences on areas that have been in contact with sheep.

After completion of the sanitation measures, the farm must be left empty for at least 2 years, before restrictions are lifted and new sheep and goats are allowed to enter the farm.

Restrictions are put on pasture too. The 1st harvest after re-cultivation (ploughing) of home fields cannot be fed to sheep and goats. If proper re-cultivation of the fields is not possible, the land must lie fallow for

5 years. The extent of restrictions on outlying fields may vary depending on the present circumstances, such as grazing load and vegetation. Normally, keeping susceptible animals away from pasturage in a 2 years time is considered sufficient.

Full compensation is paid to the owner to cover the value of the herd and the expenses related to the sanitation measures.

b. Classical scrapie: suspect animals and contacts
Suspicion of occurrence of classical scrapie may arise due to earlier contact between the flock and affected flocks, or the result of a suspect animal found within a flock. Suspect animals are followed up by the local VO.

All farms or flocks that have either sold sheep to a scrapie-affected flock, or bought sheep from a scrapie-affected flock, or kept sheep from scrapie-affected flocks temporarily on their farms within the last 10 years prior to the diagnosis, are put under official restrictions for at least 5 years. The restrictions include a ban on transfer of live sheep to any other farm, to exhibitions, and to introduce animals into the farm.

In farms that have had ewes from affected flocks in their buildings in the lambing period, the restriction includes a ban on taking the flock to pastures that are shared with other flocks. If these farms agree to kill or slaughter all their sheep and goats the authorities offer economic compensation for each animal, provided that sanitary measures are carried out also in the indoor area after the culling.

Since 2003 all animals older than 18 months from flocks put under restrictions are tested for scrapie when slaughtered.

Sheep in some contact flocks are considered as being of particular risk of developing classical scrapie. The alternative criteria for being included in this group are as follows:
1) if the flock has a close contact with an affected flock, or 2) if the flock has recruited a more than 30 per cent of its animals from the affected flock, or 3) if the sheep that developed classical scrapie in the affected flock, originated from the contact flock.

Such flocks are treated in the same way as if classical scrapie was confirmed.

c. Scrapie Nor98 ['atypical scrapie]:
Measures: until 2004 confirmed cases of scrapie Nor98 were mainly handled as classical scrapie cases. However, as increasing knowledge about the low transmissibility of scrapie Nor98 was obtained, the eradication measures were adjusted. The current control strategy only consists of movement restrictions and increased surveillance for a 2 years period of time.
- movement restrictions: animals or germinal products may not be moved from the holding except animals for slaughter following a permit from the local VO. Animals from holding with movement restrictions may nevertheless share pasture with sheep and goat from other holdings.
- increased surveillance: all dead or killed for destruction animals above 18 months of age are tested as well as those (older than 18 months) slaughtered for human consumption.

d. Genotyping
A proportion of adult ovine animals are genotyped.

Measures are restricted to the index flocks, contact flocks are defined only in rare circumstances.

7. Additional guarantees and requirements applicable to intra EEA [European Economic Area]-trade, imports, and placing on the domestic market
---
The following requirements apply both for EEA-trade from countries not listed in the annex in Commission Regulation (EC) No 546/2006 and placing on market in Norway:

Ovine and caprine animals destined for Norway or placed on the domestic market must have been kept continuously, since birth, on holdings which have satisfied the following conditions for a period of at least 7 years prior to date of dispatch of such animals:
a. no cases of TSE in small ruminants, except scrapie Nor98, have been confirmed irrespective of the animals' genotypes,
b. no eradication measures have been applied because of TSE in small ruminants, except scrapie Nor98, and
c. the holdings have not contained animals identified as animals at risk referred to in Article 13(1)(b) Regulation (EC) No 999/2001.

--
communicated by:
ProMED-mail
<promed@promedmail.org>

[Norway's experience in controlling classical scrapie with impressive success may be useful for other countries engaged with similar problems, including Japan. Having also the longest experience with atypical scrapie ('scrapie Nor98'), Norway's policy in addressing this new disease entity deserves attention. Atypical scrapie has already been discovered in aged sheep in at least 7 other European countries, as well as USA, Canada, Falk Islands, New Zealand, and Australia (The Australian suspected case has eventually been confirmed; see
<http://www.animalhealthaustralia.com.au/fms/Animal%20Health%20Australia/ADSP/A

The European Food Safety Authority (EFSA) Panel on Biological Hazards (BIOHAZ), published in EFSA Journal of 27 Jan 2011; 9(1): 1945, a "Joint Scientific Opinion on any possible epidemiological or molecular association between TSEs in animals and humans". One of the issues discussed was atypical scrapie. Among the panel's conclusions:

"The opinion concludes that, at present, the only TSE agent demonstrated to be zoonotic is the classical BSE agent."

"The opinion highlights that the active screening has allowed the identification of 3 new forms of animal TSEs (L-type atypical BSE, H-type atypical BSE, and atypical scrapie), but that the information obtained has major limitations due to the unknown sensitivity of the current monitoring system for these TSEs. There is no epidemiological evidence to suggest that classical scrapie is zoonotic. The epidemiological data are too limited to conclude whether the atypical scrapie agent has a zoonotic potential."

Additional information, including results of infection trials in primates, is available at <http://www.efsa.europa.eu/en/efsajournal/pub/1945.htm>.

Hazards related to atypical scrapie are also reviewed in ProMED-mail 20101206.4364 (items 5 & 6). - Mod.AS]

[see also:
2010

Prion disease update 2010 (11) 20101206.4364
Scrapie, atypical, ovine - Australia: (WA) susp 20100312.0803
2005

Scrapie, sheep - Japan: OIE 20050430.1210
2003

Scrapie - Norway: new phenotype 20031117.2857
Scrapie, sheep - Japan (03): OIE 20031026.2675
Scrapie, sheep - Japan (02): (OIE) 20030929.2451
Scrapie, sheep - Japan 20030922.2390
Scrapie, sheep - Japan 20011101.2703
1999

Scrapie - Japan 19991027.1944]

.....arn/mj/lm/sh

an individual moderator). If you do not give your full name name and affiliation, it may not be posted. You may unsubscribe at <http://www.isid.org/promedmail/subscribe.lasso>. For assistance from a human being, send mail to: <postmaster@promedmail.org>.
##
##

医薬品　研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄

一般的名称	－	研究報告の公表状況	Transfusion medicine reviews (United States) Apr 2011, 25 (2) p133-44	公表国 米国
販売名(企業名)	－			

研究報告の概要

輸血時の変異型クロイツフェルト・ヤコブ病(vCJD)感染を阻止するため、欧州では全例の白血球除去処理が導入されている。楽観的な感染性の想定においてさえも、残存する血漿の感染性は受血者への感染に十分であり、白血球除去処理によりvCJDの感染を阻止できないことが、齧歯類モデルから示唆されている。
一方、羊モデルにおける予備データでは白血球除去処理後の輸血による感染を認めず、ヒトでも白血球除去赤血球の輸血でのvCJDの感染の報告はない。
また、プリオン除去フィルターにより齧歯類において残存する血漿の感染性を取り除くことができることがわかっており、英国においてプリオンフィルトレーションの予防的導入が牛海綿状脳症への食事による暴露がない患者(1996年1月1日以降に生まれた患者)に対して実施されることは、英国において同様の患者に導入されている新鮮凍結血漿の低リスク国からの輸入と同様の措置であり、通常の白血球除去がヒトにおける輸血感染を阻止に無効であることを意味しているわけではない。
これらのことから、現在、欧州において実施されているvCJDの輸血による感染を阻止するための全例の白血球除去処理は継続されるべきである。

報告企業の意見	今後の対応
EUでのvCJD対策における白血球除去については、今後も継続されるべきと述べている。 現時点まで血友病以外で血漿分画製剤からvCJD伝播が疑われた報告はなく、血漿分画製剤の製造工程でプリオンが除去できるとの情報もある。 なお、当社血漿分画製剤の原料血漿は現在まで英国の血漿を使用していない。	今後ともvCJDに関する安全性情報等に留意していく。

使用上の注意記載状況・その他参考事項等

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

10

Universal White Blood Cell Reduction in Europe: Has Transmission of Variant Creutzfeldt-Jakob Disease Been Prevented?

Eleftherios C. Vamvakas

Universal white blood cell (WBC) reduction was introduced in Europe to prevent transmission of variant Creutzfeldt-Jakob disease (vCJD) by transfusion. Findings from rodent models indicate that WBC reduction should not prevent vCJD transmission because the residual plasma infectivity suffices to infect transfusion recipients even under optimistic infectivity assumptions. Although infectivity in human blood may not partition in the manner in which it is distributed in rodents, prion-reduction filters remove the residual plasma infectivity in rodent models. Precautionary introduction of prion filtration in the UK—for patients without dietary exposure to bovine spongiform encephalopathy and in the absence of a reported case of vCJD transmission attributable to infectivity residing in plasma—is consistent with the (already in place for such subjects) precautionary importation to the UK of fresh frozen plasma from low-risk countries. Thus, implementation of prion filtration in the UK does not imply that universal WBC reduction—as currently practiced in Europe—does not abrogate transmission of vCJD. Because neither a human case of vCJD transmission through transfusion of WBC-reduced red blood cells nor a case of experimental bovine spongiform encephalopathy transmission by WBC-reduced transfusion to sheep has been reported, it cannot be concluded that ordinary WBC reduction is ineffective in preventing transfusion transmission in humans. Accordingly, universal WBC reduction for the prevention of vCJD in Europe should continue.

IN 1999, WHEN the possibility of transfusion transmission of variant Creutzfeldt-Jakob disease (vCJD) was merely theoretical—owing to the finding of abnormal prion protein in the lymphoid tissues of patients with vCJD—the UK, Ireland, and Portugal implemented universal white blood cell (WBC) reduction in order to prevent donor lymphocytes from contaminating the transfusion recipient's blood-stream with prions.[1] France had already implemented universal WBC reduction in 1998 to enhance overall blood safety, although it has subsequently listed that this intervention was among the precautionary measures introduced to reduce the risk of transfusion transmission of vCJD. Around the same time, at the turn of the 21st century, universal WBC reduction was implemented in Canada and the appropriateness of introducing it was extensively debated in the US.[2-4]

In the absence of considerations of cost, universal WBC reduction of all transfused cellular blood components could extend to all patients the 3 proven benefits of WBC reduction in preventing febrile, non-hemolytic transfusion reactions, refractoriness to random-donor platelet transfusion secondary to HLA alloimmunization, and transmission of Cytomegalovirus.[2-4] For patients at risk, however, these benefits had already been secured through selective WBC reduction, and the North-American debate focused primarily, albeit not exclusively, on the examination of the efficacy of WBC reduction in abrogating the purported deleterious effects of allogeneic blood transfusion-related immunomodulation (TRIM).[5-7] Like the prevention of vCJD transmission by transfusion, prevention of these TRIM effects would apply to *all* patients, thereby justifying *universal* WBC reduction. The precautionary principle[8-10] could be invoked to justify introducing universal WBC reduction either for the prevention of the transmission of vCJD or for the abrogation of the purported TRIM effects (which include postoperative mortality[7]).

Ten years after the implementation of universal WBC reduction in Europe, and the conclusion of the debate over whether to implement universal WBC reduction in the United States, it is appropriate to consider whether the decision made in Europe at the turn of the century achieved the desired benefit; or whether further measures should be implemented at this time to enhance blood safety. This is because other interventions are becoming available for reducing the risk of the transfusion transmission of vCJD, posing a policy question of not so much whether universal WBC reduction has been (in)effective but whether it needs to be

From the Cedars-Sinai Medical Center, Los Angeles, CA.
Address reprint requests to Eleftherios C. Vamvakas, MD, PhD, MPH, Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Room 3733, Los Angeles, CA 90048. E-mail: vamvakase@cshs.org
0887-7963/$ - see front matter

doi:10.1016/j.tmrv.2010.11.005

augmented by the further step of prion filtration. This policy question is not posed in the United States at this time, but it may become relevant in the foreseeable future.

TRANSFUSION TRANSMISSION OF vCJD IN THE UK: AN UPDATE

The bovine spongiform encephalopathy (BSE) epidemic in the UK started in 1980, peaked in 1992, and has since been contained. UK residents born after January 1, 1996, are considered not to have evidence of dietary exposure to BSE. One hundred seventy cases of vCJD had occurred in the UK by the end of 2009.[11] The epidemic peaked in 2000—with 28 deaths—and subsequently declined, with only 1 death recorded in 2009.[11] With the incidence of the disease thus falling, one mathematical model has predicted only about 70 more cases of disease (95% confidence interval [CI], 10-190) to occur in the UK.[12] Although a peak has passed there could be further peaks, possibly in different genetic groups. All vCJD patients with clinical disease have been methionine homozygous at codon 129 of the *PRNP* prion protein gene—a genotype present in 40% of the white population.

Only one individual with subclinical disease has been tested, and s/he was found to be methionine/valine heterozygous at this codon. That patient—who died 5 years post-transfusion from unrelated causes—had received non–WBC-reduced red blood cells (RBCs) from a blood donor who later developed vCJD. Although 5 years is too short a period compared to the usual incubation period of vCJD contracted from BSE/dietary sources, it is perhaps significant that the only known patient with sub-clinical disease (ie, without any symptoms or signs of vCJD and with presence of abnormal prion protein in the spleen and a lymph node although not in the brain) was codon-129 heterozygous.

A retrospective study of UK tonsil and appendix samples[13] found that 3 of 12 674 samples were positive for abnormal prion protein on western blot analysis. The sensitivity and specificity of the employed assay is uncertain in this context, making the reported estimate a likely under- or overestimate. The simplest interpretation of this estimate, however, corresponds to a prevalence figure for the UK population of approximately 1 per 4000 (235 per million, 95% CI, 49-692 per million). Two of the 3 positive samples[13] were tested for codon-129 polymorphism of their *PRNP* gene, and both individuals were found to be valine homozygotes.

Fourteen years after the beginning of the human epidemic in 1996, the median age of death (28 years for the 170 cases recorded to the end of 2009) has remained the same. This stable age of death is not compatible with what would be expected if a particular cohort of individuals had been exposed to infection during a specified window of time. The best-fit mathematical model for explaining these observations suggests an age-dependent exposure/susceptibility variation that makes children and adolescents more susceptible to infection than adults. Based on such an age-dependent model and the tonsil-and-appendix data,[13] we can expect 3000 (95% CI, 520-6,810) future vCJD cases in the UK, mainly in persons aged 10 to 30 years—cases that have not yet occurred perhaps owing to a prolonged asymptomatic phase in codon-129 heterozygotes or valine homozygotes.[14]

No case of clinical vCJD in a codon-129 heterozygote or valine homozygote has yet been reported.[15] The most optimistic scenario holds that such individuals have natural resistance to the disease: they do not develop clinical vCJD and they will live their lives without attaining a level of infectivity in peripheral blood capable of infecting transfusion recipients. The worst-case scenario, however, holds that codon-129 heterozygotes or valine-homozygotes enter a long (or even life-long) asymptomatic phase during which they have sufficient infectivity in their blood to infect susceptible (methionine homozygous) transfusion recipients. Susceptible transfusion recipients then develop disease before the infection becomes manifest in the infectious donor who therefore continues to donate blood and to cause disease in susceptible recipients. This possibility is consistent with long-term human studies in kuru.[16]

A further distinction is made between pre-clinical and sub-clinical disease. In the latter case, there is no prion-protein deposition in the brain, and it remains unknown whether the prion-protein deposition in peripheral tissues corresponds to the aforementioned best or worst-case scenario. In preclinical disease, there is prion-protein deposition in the brain and—although the patient is still asymptomatic—s/he is believed to be bound to develop vCJD.

To fit both the falling incidence (1 death in 2009)[11] and high prevalence[13] data, Clark and Ghani[14] presented a statistical model which

considered that 93% (95% CI, 60% to 97%) of infected individuals do not go on to develop clinical disease. While this assumption best fits both sets of data, such a high proportion of infections not resulting in clinical disease may (or may not) be plausible. Clark and Ghani's model is compatible with both of the described (most optimistic and most pessimistic) scenarios.

If even a fraction of such asymptomatic carriers[13] accumulate sufficient infectivity in their blood to infect transfusion recipients, secondary transmission from infected individuals via transfusion or tissue transplantation could extend the outbreak of the disease in the UK.[17] Because no interspecies barrier is involved, transmission through transfusion could be more effective compared with the BSE/dietary route. As evidence is accumulating to suggest that all codon-129 genotypes may be susceptible to vCJD infection,[18-20] the presumed number of UK residents infected by the BSE/dietary source who can potentially accumulate sufficient infectivity in their peripheral blood to infect transfusion recipients increases. At the same time, transmissibility of vCJD by blood transfusion has been established by the hitherto reported human cases of transmission amongst a small number of "at-risk" individuals, as well as by effective experimental transmission in sheep.

Cases of Human-to-Human Transmission by Transfusion

Eighteen UK vCJD patients had been blood donors and 66 patients were identified as having received a labile blood component from a donor who later developed vCJD. Thirty-two of these subjects (of whom 13 can be expected to be methionine homozygous) have hitherto survived for 5 years or more after the implicated transfusion. Only one deceased recipient was examined at postmortem for the presence of abnormal prion protein and, as already described, was found to have evidence of subclinical infection in the spleen and a lymph node and to be heterozygous at codon 129. Three of the (likely) 13 methionine homozygotes have developed vCJD,[21-23] indicating a 23% probability for methionine homozygotes surviving for 5 years or more to develop clinical vCJD after receiving the non–WBC-reduced RBCs of a donor who later developed vCJD.

This probability most likely *under*estimates the risk since the identification of a case of transfusion-transmitted vCJD requires that the vCJD infection be recognized in both the donor and the recipient. Nonetheless, the 23% estimate *far* exceeds the expected incidence of disease acquired from dietary/BSE sources among UK methionine homozygotes. Moreover, 2 of the 4 probable transfusion-transmitted cases were contracted from the same donor, with the index donations separated by just 4 months[24]; 3 of the 4 recipients were older than 60 years—an unusual occurrence for vCJD acquired from dietary/BSE sources; and the donors developed clinical signs of vCJD between 17 and 42 months after donating, indicating that they were at an advanced stage of the incubation period when they made the donation which transmitted vCJD.

All 4 recipients who apparently contracted vCJD from transfusion had received non-WBC-reduced RBCs between 1996 and 1999. They had been exposed to 5, 8 to 10, 23, and 56 donors, and 3 of the 4 developed vCJD between 6 and 8.5 years after the index transfusion—a short incubation period compared with the incubation period associated with vCJD acquired from BSE/dietary sources.[25] This short incubation period perhaps indicates the effectiveness of human-to-human transmission of vCJD through transfusion.[25]

Recently, circumstances raised the possibility of an additional 2 cases of transfusion-transmitted vCJD.[26] These vCJD cases were linked by a possible common donor of non-WBC-reduced RBCs who has *not* developed vCJD. The codon-129 genotype of this donor is unknown. Between 1989 and 2005, blood components from this donor were transfused to 27 additional recipients who have not been traced because the donor has not developed vCJD. Nevertheless, except for the aforementioned 2 patients who developed vCJD at 18 or 41 years of age—after possibly contracting the infection from the identified common donor, in 1989 or 1993, respectively—no other vCJD patient has been linked to this donor by the UK's comprehensive vCJD surveillance system.[26]

Cholan et al[26] demonstrated that this pattern of events (2 patients with vCJD being associated by means of a possible common donor) would *not* be *un*expected in the absence of any causal link between the 2 cases. The first patient was transfused with non-WBC-reduced RBCs from (probably) 4 different donors when s/he was a premature neonate in 1989. Although blood from the common donor

would have been at the hospital's inventory at that time, it would have been 13 days old on the day of the transfusion and thus unlikely to have been used for transfusion to a neonate. Had the patient contracted vCJD from that transfusion, however, the incubation period of transfusion-transmitted vCJD would have been extraordinarily long compared with that seen in the previously-reported cases.[21-23] Experimental exposure of neonatal mice to scrapie is also associated with extension of the incubation period owing to inefficient infection of the premature spleen.[27] The second patient was exposed to 103 donors and could have been exposed to the identified common donor in 1993 —a possibility that cannot be confirmed because in 1989 to 1993 systems were not in place in the UK to ensure full traceability of the components issued for transfusion.[26] It is because this second recipient was exposed to so many donors that a possible common donor could have been identified by coincidence for these 2 vCJD cases.

The authors thus concluded that the circumstances did not support the interpretation that 1 (or perhaps 2) additional vCJD transmissions by transfusion had occurred.[26] Transfusion remains just as likely a source of infection, however, as the dietary/BSE route, because of the extremely low probability for each of these patients to have contracted vCJD from dietary/BSE sources: 0.39 and 0.08 per million, respectively, for the 18- or 41-year-old patient.[26] This latter interpretation of transfusion transmission would have significant implications for the length of the period during which an asymptomatic blood donor can transmit infection—implications that reproduce the pessimistic scenario discussed above because the donor in question is alive and well more than 20 years after having made the first implicated donation.

At least 174 "implicated" batches of plasma products have been identified as having been manufactured from a pool of plasma to which an individual who later developed vCJD had contributed.[25] No individuals with hemophilia have hitherto developed vCJD and a retrospective study of autopsy samples from individuals with hemophilia showed no evidence of subclinical infection.[28] At the March 2009 meeting of the UK Spongiform Encephalopathy Advisory Committee (SEAC), however, it was reported that a hemophilia patient who died of non-vCJD causes had been found at postmortem to have abnormal prion protein in his spleen.[29] In that discussion, the SEAC deemed that it was more likely that the infection had occurred from the administration of clotting factors prepared from the plasma of a donor who had later developed vCJD than from dietary exposure to BSE. The specifics of this case have not yet been reported in the peer-reviewed literature, and the ensuing discussion assumes that no case of vCJD transmission through the vCJD infectivity that resides in human plasma has hitherto been documented.

Experimental vCJD Transmission by Transfusion in Sheep

Infectivity remains undetectable in the peripheral blood of patients with vCJD, although clinical transmission of disease through human blood has clearly occurred. This apparent contradiction can be explained by the technical challenge of developing a test capable of detecting the presence of abnormal prion protein in peripheral blood. Infection-associated forms of the prion protein constitute only a minuscule proportion of the total prion protein in blood, thereby representing a formidable obstacle to detecting infectivity in blood even in patients with full-blown disease. In the rodent models hitherto employed for this purpose, the contradiction is further explained by the presence of a species barrier between man and mouse and the limited volumes of blood that can be inoculated into such small animals. The relative similarity in size of sheep and humans means that volumes of blood comparable to those transfused in humans can be collected from and transfused into sheep. Houston et al[30] nonetheless took 9 years to complete a blood transfusion experiment in sheep, concluding that blood transfusion represents an effective route of transmission.

Two different transmissible spongiform encephalopathy (TSE) agents (scrapie and BSE) could be effectively transmitted between sheep by transfusion.[30] The overall transmission rates (percentage of all recipients who became infected) were 36% for BSE and 43% for scrapie. More specifically, 22 sheep received blood from BSE-exposed donor sheep; 5 recipient sheep developed clinical disease and 3 showed histopathologic evidence of infection—when they were sacrificed at 7 years post-exposure—without having developed any symptoms or signs of disease. In addition, 9 of 21 recipients of blood from scrapie-exposed sheep developed clinical scrapie. The incubation period of

the 5 sheep who developed clinical disease after they had received blood from BSE-exposed donor sheep varied between 531 and 610 days (ie, it was <2 years). The incubation period of the 9 sheep who developed clinical disease after they had received blood from scrapie-exposed donor sheep varied between 575 and 1,138 days (ie, it was <3.2 years). Two of the 5 BSE-exposed recipient sheep that developed clinical disease had received blood from donor sheep with preclinical disease. All but one scrapie-exposed recipient sheep that developed clinical disease had received blood from donor sheep with preclinical disease.

The effect of the stage of the incubation period in the donor animal when each donation was made could best be deduced from the results of the scrapie experiment, because the *PRNP* genotype of the sheep used made them almost 100% susceptible to natural and experimental infection.[30] These results were consistent with a gradual increase in infectivity in peripheral blood as the incubation period progressed (Fig 1). Moreover, when blood was collected early (at 20%-50% of the estimated incubation period in the donor animals), the incubation period of scrapie in the recipient animals was longer.

Risk of vCJD Transmission by Transfusion in the UK

Although vCJD is transmissible by transfusion, the magnitude of the risk of transmission is hard to estimate.[31] The scenarios that the UK currently uses for risk management employ combinations of "high" and "low" values for three determinants of the risk: the prevalence of subclinical disease in the blood-donor population, the infectivity of blood components and the susceptibility of blood recipients to clinical disease. Because a number of these scenarios have overestimated the number of cases hitherto recorded, at its March 2010 meeting, the SEAC requested that the scenarios used be calibrated against the observed data or that the assumptions made be refined to better approximate the observed data.[32]

The UK Institute of Neurology tested 10,075 samples of tonsils and 1 of these samples showed one positive follicle in one section by immunohistochemistry (although the other sections from the same block and two other blocks were negative).[32] Although the presence of abnormal prion protein in the tonsils of patients with vCJD is variable, this series of tonsils would suggest a prevalence of 1 per 10,000 for subclinical disease in the UK population. At its March 2010 meeting, however, the SEAC opted to continue to use the previous (1 per 4000) estimate[13] for risk management purposes.[32] Although further examinations of tonsils and spleens of UK patients are planned and another series of 80,000 tonsils produced no positive result,[32] the interpretation of what these data mean—in terms of both the true prevalence of abnormal prion protein accumulation in the UK

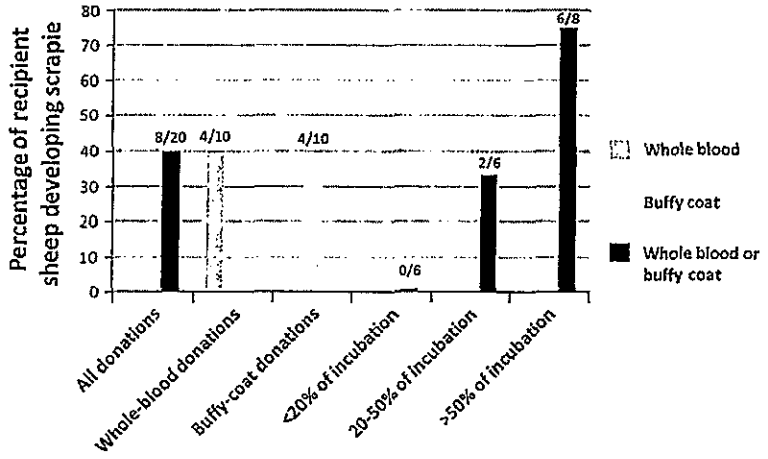


Fig 1. Proportion of recipient sheep developing scrapie after receiving whole-blood or buffy-coat transfusion from donor sheep exposed to scrapie and assumed to be at various stages (from <20% to >50%) of the estimated incubation period.[30] The number of sheep developing scrapie among all transfused sheep is shown above each column. A donation made by a donor sheep during the clinical phase of scrapie[30] is not included. One recipient sheep suspected of having scrapie clinically, but showing no evidence of infection on post-mortem examination,[30] is counted as not having disease.

population and the frequency of infectious blood donors—is uncertain.[31]

Despite this uncertainty, codon-129 methionine homozygotes born after the containment of the BSE epidemic (ie, after January 1, 1996) may have a risk as high as 1 per 100 000 to develop a fatal disease following exposure to vCJD through transfusion if they survive for 5 or more years after the transfusion. Such would be the risk of transfusion-acquired clinical disease if: (1) ordinary WBC reduction (as practiced in the UK today) did not prevent transmission of vCJD; (2) the probability of developing clinical disease after receiving blood from a donor who later developed vCJD were 23% (as derived above); (3) the prevalence of subclinical disease in the UK population were approximately 1 per 10,000 (the latest estimate from tonsil samples[32]); and (4) 40% of donors with subclinical disease were (infectious as was the case in the completed sheep scrapie experiment[30]) (Fig 1). A risk of this magnitude warrants preventive measures to protect recipients from a fatal transfusion-acquired disease.

WHY ORDINARY WBC REDUCTION SHOULD BE INEFFECTIVE IN PREVENTING TRANSFUSION TRANSMISSION OF vCJD

One refers to an "infectious dose" as the minimal dose capable of transmitting infection in an animal model for the mode of contamination given.[25] Studies in rodents[33-35] with TSE showed infectivity of 1 to 10 infectious doses per milliliter of whole blood. About 40% of this infectivity was distributed in the WBCs and the remainder in the plasma.[35] The latter form of infectivity probably predominated, because most of the cell-associated infectivity was loosely bound and could be washed off.[35] Infectious prions, however, may partition between the cellular and acellular fractions of human blood differently from the manner in which they partitioned in these rodent models.

Based on the findings from the animal models, it can expected that ordinary WBC reduction through filtration (as implemented in the UK in 1999) would remove 40% to 70% of the total infectivity present in a whole-blood unit[35] but would have little impact on the plasma-borne infectivity. Under optimal conditions, only 10 mL of donor plasma can be left in a RBC unit prepared in an additive solution, although—under the usual conditions of manufacturing RBCs by the buffy-coat method in the UK—20 mL of plasma usually remain in the supernatant fluid. If (1) 40% of the infectivity resides in the WBCs and 60% in the plasma, (2) the starting whole-blood infectivity is 10 infectious doses/mL, (3) the whole-blood unit is WBC reduced, and (4) the residual plasma volume at the completion of all manufacturing steps is 10 mL; 110 infectious doses would be left in the RBC unit distributed for transfusion[31] (Fig 2).

To achieve less than 1 infectious dose/transfused RBC component, a further 3-log reduction would be required (to successively reduce the total infectivity of

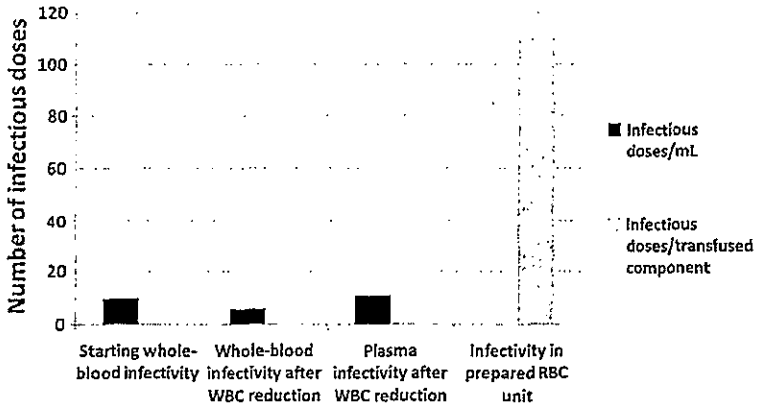


Fig 2. Infectivity residing in the plasma of a RBC unit manufactured in the UK under ideal conditions.[31] If the starting infectivity in whole blood is 10 infectious doses/mL, 6 infectious doses/mL are left in the whole-blood unit following WBC reduction, and all this infectivity resides in the unit's plasma. Assuming a 45% hematocrit for the donor, the concentration of infectivity in the unit's plasma is 11 infectious doses/mL. If only 10 mL of plasma are left in the component after the donor's plasma is replaced with additive solution, the total infectivity of the RBC unit distributed for transfusion is 110 infectious doses (11 infectious doses/mL times 10 mL of residual plasma).

the unit, for each successive log, to 11, 1.1, and 0.11 infectious dose[s]). Uncertainty about the starting level of whole-blood infectivity (1 vs 10 infectious doses per milliliter or more in published rodent models), and the volume of plasma left in a RBC unit distributed in the UK (10 vs ≥20 mL) can each affect the extent of the necessary reduction to remove plasma-borne infectivity by approximately 1 log.[31]

EFFICACY AND SAFETY OF PRION-REDUCTION FILTERS

Published studies[35-40] of the efficacy of prion-reduction filters in rodent models show a greater than 3-log reduction in infectivity on brain homogenate spikes and reduction to the limit of detection (>1 log) in endogenous infectivity studies. There are no data demonstrating removal of infectivity from the blood of infected humans, however, and fundamental questions relating to the relevance of brain-homogenate-spike material to the clinical setting remain unanswered.[31] Exogenous infectivity models generally use 10% homogenized infected brain tissue. This approach achieves extremely high infectivity levels, but it does not imply that the spike behaves in blood in the manner that endogenous abnormal prions (which would have naturally found their way to the peripheral blood of donors) behave. The form in which infectivity circulates in the blood of infectious donors is unknown, so that the behavior of spiked infectivity across a filter may not reflect the behavior of true endogenous infectivity across the same filter. Therefore, the assessment of the efficacy of prion-reduction filters in removing human peripheral-blood infectivity continues to represent a formidable challenge.

The potential for deleterious effects on the RBC concentrate itself is also a matter of concern, both in terms of the possibility of alterations to the rheological or antigenic profile of the RBCs and the RBC loss in the volume of the additional filter.[31] Nonetheless, in vitro studies by the manufacturers did not raise concerns other than the high hold-up volumes of approximately 50 mL in the filters.[38] In the recent evaluations of the MacoPharma (Tourcoing, France) filter—which were performed by the UK[41] and Irish[42] blood services under the conditions in which prion reduction filters would likely be put into use in the UK and Ireland—up to 7 to 8 g of donor hemoglobin were retained by the filter.[41] As a result, WBC-reduced RBCs prepared by the buffy-coat-reduced ("bottom-and-up") manufacturing method could not meet the European Union (EU) minimum standard for a therapeutic adult RBC dose as applied in the UK (where at least 75% of the RBC units must contain ≥40 g of donor hemoglobin): only 58% of the units prepared by this method contained the minimum amount of RBCs. When the whole-blood-filtration ("top-and-top") manufacturing method was used, however, the minimum hemoglobin requirement was met.[41]

The authors concluded that filtration had no detrimental effect on the expression of RBC antigens after passing through the filter,[41] although the employed methods would likely not have detected the generation of neoantigens.[43] Moreover, although appropriate adjustments to the filter sets could overcome the problem, 5.9% of the RBC units failed to filter properly. The response of treated cells to gamma irradiation and freezing was essentially unaffected and routine RBC quality measures (extracellular potassium, 2,3-disphosphoglycerate, and adenosine triphosphate) were satisfactory.[41]

A safety (phase I/II) clinical trial of the MacoPharma filter in volunteer allogeneic RBC recipients raised no safety concerns.[42] Twenty patients were uneventfully transfused one RBC unit that had undergone prion filtration and 6 of them received further prion-reduced units without adverse effects. Clinical events and laboratory test results (liver function tests and RBC antibody screen and antiglobulin test) were recorded during the transfusion, during the first 24 hours, and at a 6-week follow-up visit. The post-transfusion hemoglobin increment (mean ± SD) was 0.70 ± 0.50 g/unit (compared to 0.98 ± 0.30 g/unit in historical controls). Although the controls were not matched to the cases, both cases and controls were multitransfused hematology patients and the minimum EU standard for hemoglobin content (40 g/U) had been met in all the transfused units. Further studies of the safety of prion-reduction filters are warranted for extending these safety data to other adult (and especially pediatric) populations.

At least 3 manufacturers have pursued the development of prion-reduction filters. Pall (Port Washington, NY) extended the original use of WBC reduction filters to prion adsorption through a modification of the filter that rendered it capable of adsorbing infectious prions with a practicable degree of specificity and efficacy. Other manufacturers (PRDT, Cambridge, UK; and MacoPharma

in collaboration with Pathogen Removal and Diagnostic Technologies, Inc) incorporated in a prion filter separate from the WBC reduction filter ligands developed with combinatorial chemistry to bind specifically to the abnormal prion protein. The reported capability of these filters is the same.[35-40] The devices remove infectivity from plasma, or at least from the amount of plasma present in RBCs manufactured in additive solution. An excess of plasma—such as present in a unit of whole blood or fresh frozen plasma (FFP)—may interfere with the efficacy of the filter.[44]

Recently, it was reported at the March 2010 meeting of the SEAC, that the Advisory Committee on the Safety of Blood, Tissues, and Organs has recommended that blood prion filtration be used for transfusion recipients with no prior evidence of dietary exposure to BSE.[32] The UK Department of Health is presently considering this recommendation. Although testing individual donations is desirable, the technical challenges to developing such a test remain formidable.[45] Testing might be best at detecting donors with greater levels of infectivity in their blood—levels that might have the potential, perhaps, to overwhelm the filters' capacities.[44] The filters will be at their most efficacious in the presence of low levels of infectivity, which would be expected to occur early in the infectious phase of the incubation period or (perhaps) in life-long asymptomatic carriers.[44]

COULD ORDINARY WBC REDUCTION BE EFFECTIVE IN PREVENTING TRANSFUSION TRANSMISSION OF vCJD?

Hitherto, no case of transfusion-transmitted vCJD has been reported from the UK in a patient who received blood after the implementation of universal WBC reduction in October 1999. For blood donors acquiring vCJD from dietary/BSE sources, clinical disease would appear after a long incubation period (estimated at 16.7 years).[25] Therefore, such donors (infected during the years of the BSE epidemic in the 1980's) would have been in the preclinical phase of disease (with sufficient infectivity in their peripheral blood to infect transfusion recipients) in the late 1990s and/or early in the 21st century. If (1) vCJD transmission by transfusion continued to occur after the implementation of universal WBC reduction and (2) 3 recipients who contracted vCJD infection from transfusions given between 1996 and 1999 manifested clinical disease by 2006, making the incubation period of transfusion-acquired vCJD 6 to 8.5 years,[21-23] by the end of 2009, there should have been a few more cases of clinical vCJD contracted from transfusions given in 1999 to 2002.

Although current WBC reduction would not be expected to sufficiently reduce infectivity to prevent infection of a transfusion recipient according to our prevailing infectivity assumptions based on the findings from rodent models,[31] it remains possible that WBC reduction does afford protection. Four sources of uncertainty make this possible: (1) the starting level of infectivity in human whole blood (which may be lower than the 1 to 10 infectious doses/mL level observed in animal models); (2) the distribution of the infectivity between human plasma and WBCs (which may differ from the 60:40 ratio indicated by rodent models); (3) the effectiveness of human-to-human transmission; and (4) the susceptibility of transfused patients to infection from any given inoculum.

Until a case of transfusion-transmitted vCJD is reported to have been contracted through transfusion of a WBC-reduced component, we cannot conclude that the ordinary WBC reduction currently taking place in the UK and several European countries does not protect from transfusion transmission of vCJD. Any measure of safety (including complete protection) that such ordinary WBC reduction affords vis-à-vis vCJD transmission remains unknown. Therefore, the current universal WBC reduction for the prevention of vCJD in Europe should continue.

The effect of WBC reduction is being addressed in a follow-up study of the sheep experiment. In the completed sheep scrapie experiment,[30] transmission rates were the same in recipient sheep transfused with whole blood (4/10) and recipient sheep transfused with buffy coat (4/10—Fig 1). In the continuing sheep experiment, preliminary data (recorded at approximately 900 days post-transfusion) indicated that no sheep that had received WBC-reduced transfusion from BSE-infected donor sheep had succumbed to infection.[46]

Despite the findings from rodent models,[33-35] it is thus possible that—in sheep as well as in humans—WBC reduction alone can be effective in abrogating the risk of transfusion transmission of vCJD during the preclinical (or at least the subclinical) phase of disease. Alternatively, it could be that—in sheep as well as in humans—by removing the WBC-associated fraction of infectivity, WBC reduction

protracts the asymptomatic phase of disease in transfusion recipients infected with a low inoculum. If this were the case, although 900 days exceed the incubation periods of BSE observed in the completed experiment,[30] 900 days may be too short a period for BSE contracted through a WBC-reduced blood transfusion in sheep to manifest itself. Such a reduction in infectivity because of WBC reduction could also explain why no transfusion-transmitted cases (contracted in 1999-2002) were reported by the end of 2009. In other words, just as the reference to the risk of transmission of vCJD through transfusion moved from "theoretical" to "possible," "probable," and "definite" with the reporting of the 4 cases of transfusion-transmitted vCJD from non-WBC-reduced RBCs between 2003 and 2007,[21-24] the same scenario could unfold in the coming years as cases of transfusion-transmitted vCJD from WBC-reduced RBCs appear after a protracted incubation period.

SHOULD PRION-REDUCTION FILTERS BE INTRODUCED?

To protect recipients with no dietary exposure to BSE the UK implemented extraordinary measures for transfused FFP (Table 1), before there was a vCJD case linked to vCJD infectivity residing in human plasma. Thus, even without a reported case of vCJD contracted through the transfusion of WBC-reduced RBCs, the endorsement of prion-reduction filters for transfusion recipients without evidence of dietary exposure to BSE is consistent with the measures already adopted to prevent transmission of vCJD through FFP. The only caveat pertaining to this endorsement is that the UK blood services employ a manufacturing method ensuring that prion-reduced RBC units meet the EU minimum standard for hemoglobin content (40 g/unit). Like the importation of plasma from low-risk countries (Table 1), until a case of transmission of vCJD through WBC-reduced RBCs is reported, the initiative to introduce prion-reduction filters represents a precautionary measure.[8-10] As such, it can be deemed appropriate based on the existing precedent: if the measure for FFP intended for transfusion to UK patients born after January 1, 1996, is appropriate, provision to these same patients of WBC-reduced RBCs that have undergone the further step of prion filtration can be deemed appropriate as well.

Table 1. Measures Already Adopted in Europe to Reduce the Risk of Transmission of vCJD by Transfusion*

- Universal WBC reduction of all cellular blood components (all countries in which vCJD cases have arisen as well as neighboring countries)
- Reduction in allogeneic-donor exposures through the use of single-donor (as opposed to pooled) blood components:
  — Apheresis (as opposed to pooled whole-blood-derived) platelets (UK)
  — Single-donor (as opposed to pooled solvent/detergent-treated) plasma (The Netherlands)
- Deferral of all persons with a history of blood transfusion since 1980 from donating blood (UK, Ireland, France, The Netherlands)
- Cessation of use of indigenous plasma for the manufacturing of plasma derivatives (UK and Ireland)
- Specifically for patients born after January 1, 1996 and considered not to have had any dietary exposure to BSE: Importation of methylene-blue-treated FFP donated by donors in low-risk countries (UK and Ireland)
- Deferral of persons with a history of residence in the UK from donating blood (other European countries)
- Optimization of blood component use:
  — Assurance that blood components are transfused only when needed
  — Communication of the uncertainties about the risks of allogeneic blood transfusion to the patients and the public

*Countries that have adopted each measure are shown within parentheses.

An alternative could be to provide washed WBC-reduced RBCs to these young UK patients,[44] although—as the number of patients with no dietary exposure to BSE increases with each passing year—washing may prove just as disruptive to safeguarding an adequate blood supply as the use of prion-reduction filters. Nonetheless, the possibility of washing RBCs—which is surely a safe alternative with respect to any untoward effects of prion filtration and also offers some protection from TRALI[47]—should not be forgotten amidst the effort to validate and implement the new technology of prion filtration.

Elsewhere in Europe, there have been 41 cases of vCJD (Table 2). Remarkably, there has not yet been a case in Germany or other neighboring countries.[11] Nonetheless, the description in other countries—such as Spain and Saudi Arabia—of vCJD patients who had been blood donors in the past suggests that the problem has already taken on an international dimension,[25] warranting proportional responses from outside the UK as well. If we accept the prevalence of subclinical vCJD in the UK to be 1 per 10,000,[32] from the relative incidence of clinical disease between each particular country and the

Table 2. Prevalence of Subclinical vCJD in Europe

Country	Number of clinical vCJD cases*	Presumed prevalence	
		% of UK†	Estimate‡
UK	170	100	1 per 10 000
Ireland	2(4)*	17	1 per 60 000
France	25	14	1 per 70 000§
The Netherlands	3	6.5	1 per 150 000
Portugal	2	6.5	1 per 150 000
Spain	5	4	1 per 250 000
Italy	2	1	1 per 1 000 000

* As of the end of 2009. When cases had resided in the UK for longer than 6 months between 1980 and 1996, they are presumed to have been exposed to BSE in the UK. The total number of vCJD cases in Ireland (including the 2 cases probably exposed in the UK) is shown within parentheses.

† Based on the relative incidence of clinical disease between each country and the UK. The population of each country was obtained from http://en.wikipedia.org/wiki/Demographics_of_the_European_Union. The number of clinical vCJD cases by the end of 2009 was obtained from http://www.cjd.ed.ac.uk. Both accessed May 19, 2010.

‡ Approximation that does not take into account the differences in the epidemiologic curve of each country versus that of the UK. Based on the latest UK estimate of prevalence (1 positive tonsil among 10 075) discussed at the March 2010 meeting of the SEAC.[32]

§ Compared to the estimate of 1 per 120 000 generated from data on the French vCJD epidemic.[25]

UK, we can expect the prevalence of subclinical vCJD in Europe to be as shown in Table 2.

The prevalence in each country cannot be inferred simply from the relative incidence of clinical disease, because the epidemics in these other countries have lagged behind the UK epidemic and there has not yet been a sufficient number of cases to characterize each epidemiologic curve. Nonetheless, at least in the interim, decisions in these countries could be proportional to the relative incidence of clinical disease between each country and the UK. Hitherto, outside the UK and Ireland, the risk from transfusion of FFP has not been deemed worthy of the precautionary measures implemented in the UK and Ireland for patients born after January 1, 1996 (Table 1). Accordingly, at this point, the vCJD infectivity residing in the residual plasma of WBC-reduced RBCs should not be deemed worthy of prion filtration either.

Platelets[48] and RBCs[44] appear to contain no vCJD infectivity. The current opinion held by the SEAC[49] is that—while there may be interspecies differences in the distribution of TSE infectivity in the blood—based on data from animal models,[33] vCJD infectivity in human blood is likely to be partitioned between plasma and WBCs[50,51] and to be only minimally associated with RBCs and platelets. With regard to platelet concentrates—whether pooled whole-blood-derived platelets prepared by the buffy-coat method or single-donor (apheresis) platelets—minimization of plasma pooling and re-suspension in additive solutions rather than plasma would reduce the amount of residual plasma to 80-90 mL.[31] This amount of plasma would contain more than enough infectivity to transmit infection to the recipient under even optimistic infectivity assumptions.[31] Thus, efforts to minimize the plasma volume of platelets through replacement with additive solutions are likely to be ineffectual,[31] and the UK is in the process of converting its platelet supply from pooled whole-blood-derived to single-donor platelets (Table 1).

Prion-reduction filters are not currently applicable to either platelets or FFP. They may become available for pooled solvent/detergent-treated plasma in the near future, making pooled solvent/detergent-treated plasma perhaps superior to male-only FFP—at least in Europe—for the prevention of both transfusion-related acute lung injury[52] and transfusion transmission of vCJD.[53]

Reporting of cases of vCJD transmission through transfusion of WBC-reduced RBCs will change the risk estimates both inside and outside the UK. Such cases (contracted after 1999, that is, after the BSE epidemic had already been contained) would confirm the prediction of a UK vCJD epidemic sustained by blood transfusion.[54] It is for this reason that—on a precautionary basis—all transfusion recipients have already been deferred from donating blood in the UK, France, and The Netherlands (Table 1). Despite mathematical modeling indicating that this should not be done in Germany,[55] UK models[17] indicated that the deferral of all persons with a history of transfusion since 1980 has been both effective and timely.

If cases are contracted in the UK from transfusion of WBC-reduced RBCs, it can be appropriate for the UK to consider expanding the use of prion-reduction filters to RBCs given to patients other than those born after January 1, 1996. To ensure prevention of vCJD transmission, prion filtration for such older patients should be combined with importation of FFP from low-risk countries and use of single-donor platelets (Table 1). Although such older patients could have been infected during the BSE epidemic (1980-1996), they may well have

escaped infection in the past and be more susceptible to acquiring infection now through a transfusion (because no species barrier is involved in transfusion transmission).

Commensurately, for patients deemed to have no dietary exposure to BSE, the measures implemented in the UK when no cases of vCJD acquired by transfusion of WBC-reduced RBCs had been reported (Table 1) could be considered for adoption in other European countries. Based on a comprehensive risk analysis of the (presumed) vCJD prevalence in the population (Table 2) and the (as characterized as possible) epidemiologic curve of infection originating in dietary/BSE sources in each country, each jurisdiction should decide whether any of these measures should also be implemented for transfusion recipients who may have already been exposed to BSE.

CONCLUSION

Until a case of vCJD transmission through transfusion of non-WBC-reduced RBCs is reported, we cannot presume that the desired benefit derived from universal WBC reduction in Europe—that is, the prevention of transfusion transmission of vCJD—has not been achieved. If one reasons based on our prevailing infectivity assumptions that are based on the results of rodent models,[31] the argument that WBC reduction should be ineffective in abrogating vCJD transmission by transfusion appears incontrovertible. Nevertheless, the argument that these findings cannot be extrapolated to humans is just as persuasive. Thus, the current universal WBC reduction in Europe for the prevention of transfusion transmission of vCJD should continue. The introduction of prion filtration in the UK—for patients born after January 1, 1996, does not imply that the currently-performed universal WBC reduction has been ineffective in preventing transfusion transmission of vCJD. Such precautionary introduction of prion-reduction filters is consistent with the (already in place) precautionary importation of FFP from low-risk countries.

REFERENCES

1. Mabbott N, Turner M: Prion and the blood immune systems. Haematologica 90:542-548, 2005
2. Vamvakas EC, Blajchman MA: Universal white-cell reduction: The case for and against. Transfusion 41:691-712, 2001
3. Dzik S, AuBuchon J, Jeffries L, et al: Leukocyte reduction of blood components: Public policy and new technology. Transf Med Rev 14:34-52, 2000
4. Blajchman MA: The clinical benefits of leukoreduction of blood products. J Trauma 60:S83-S90, 2006
5. Blajchman MA: Allogeneic blood transfusions, immunomodulation and postoperative bacterial infection. Do we have the answers yet? Transfusion 37:121-125, 1997
6. Vamvakas EC, Blajchman MA (editors): Immunomodulatory Effects of Blood Transfusion. Bethesda, MD, AABB Press, 1999
7. Vamvakas E, Blajchman MA: Transfusion-related immunomodulation: An update. Blood Rev 21:327-348, 2007
8. Foster KR, Vecchia P, Repacholi MH: Risk management: Science and the precautionary principle. Science 288:978-981, 2000
9. Wilson K, Wilson M, Hébert PC, et al: The application of the precautionary principle to the blood system: The Canadian blood system's vCJD donor deferral policy. Transf Med Rev 17: 89-94, 2003
10. Wilson K, Ricketts MN: The success of precaution? Managing the risk of transfusion transmission of variant Creutzfeldt-Jakob disease. Transfusion 47:1475-1478, 2004
11. University of Edinburgh: UK Creutzfeldt-Jakob Disease Surveillance Unit. http://www.cjd.ed.ac.uk Accessed December 24, 2010
12. Ghani AC, Donnelly CA, Ferguson NM, et al: Updated projections of future vCJD deaths in the UK. BMC Infect Dis 3: 4, 2003
13. Hilton DA, Ghani AC, Conyers L, et al: Prevalence of lymphoreticular prion protein accumulation in UK tissue samples. J Pathol 203:733-739, 2004
14. Clark P, Ghani AC: Projections of future course of the primary vCJD epidemic in the UK: inclusion of subclinical infection and the possibility of wider genetic susceptibility. J R Soc Interface 2:19-31, 2005
15. Wadsworth JD, Asante EA, Desbruslais M, et al: Human prion protein with valine 129 prevents expression of variant CJD phenotype. Science 306:1793-1796, 2004
16. Collinge J, Whitfield J, Mckintosh E, et al: Kuru in the 21st century—an acquired human prion disease with very long incubation periods. Lancet 367:2068-2074, 2006
17. Clarke P, Will RG, Ghani AC: Is there a potential for an epidemic of variant Creutzfeldt-Jakob disease via blood transfusion in the UK? J R Soc Interface 4:675-684, 2007
18. Bishop MT, Hart P, Aitchison L, et al: Predicting susceptibility and incubation time of human-to-human transmission of vCJD. Lancet Neurol 5:393-398, 2006
19. Ironside JW, Bishop MT, Connolly K, et al: Variant Creutzfeldt-Jakob disease: prion protein genotype analysis of positive appendix tissue samples from a retrospective prevalence study. BMJ 332:1186-1188, 2006
20. Mead S, Joiner S, Desbruslais M, et al: Creutzfeldt-Jakob disease, prion-protein gene codon 129 VV, and a novel PrPSc type in a young British woman. Arch Neurol 64:1780-1784, 2007
21. Pincock S: Patient's death from vCJD may be linked to blood transfusion. Committee to discuss need for further precautions to prevent possible vCJD transmission through blood. Lancet 363:43, 2004

22. Llewelyn CA, Hewitt PE, Knight RS, et al: Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. Lancet 363:417-421, 2004

23. Hewitt PE, Llewelyn CA, Mackenzie J, et al: Creutzfeldt-Jakob disease and blood transfusion: Results of the UK Transfusion Epidemiology Review Study. Vox Sang 91:221-230, 2006

24. Health Protection Agency: Fourth case of transfusion-associated variant CJD. Health Prot Rep 1, 2007

25. Lefrère JJ, Hewitt P: From cows to sensible blood transfusion: The risk of prion transmission from labile blood components in the United Kingdom and France. Transfusion 49: 797-812, 2009

26. Cholan G, Llewelyn C, Mackenzie J, et al: Variant Creutzfeldt-Jacob disease in a transfusion recipient: Coincidence or cause? Transfusion 50:1003-1006, 2010

27. Irena M, Farguhar CF, Outram GW, et al: Resistance of neonatal mice to scrapie is associated with inefficient infection of the premature spleen. J Virol 80:474-482, 2006

28. Lee CA, Ironside JW, Bell JE, et al: Retrospective neuropathological review of prion disease in UK hemophilia patients. Thromb Haemost 80:909-911, 1998

29. Health Protection Agency: Asymptomatic vCJD abnormal prion protein in a hemophilia patient. Available at: http://www.hpa.org.uk/webw/HPAweb&HPAwebstandard/HPAweb_C/1195733818681?p=1225960597236.

30. Houston F, McCutcheon S, Goldmann W, et al: Prion diseases are efficiently transmitted by blood transfusion in sheep. Blood 112:4739-4745, 2008

31. Turner ML, Ludlam CA: An update on the assessment and management of the risk of transmission of variant Creutzfeldt-Jakob disease by blood and plasma products. Br J Haematol 144:14-23, 2009

32. SEAC: Minutes of the 104th meeting of the Spongiform Encephalopathy Advisory Committee, London, UK, March 5, 2010. Available at: http://www.seac.gov.uk/summaries/seac104-summary.pdf.

33. Brown P, Rohwer RG, Dunstan BC, et al: The distribution of infectivity in blood components and plasma derivatives in experimental models of transmissiform spongiform encephalopathy. Transfusion 38:810-816, 1998

34. Cervenakova L, Yakovleva O, McKenzie C, et al: Similar levels of infectivity in the blood of mice infected with human-derived vCJD and GSS strains of transmissible spongiform encephalopathy. Transfusion 43:1687-1694, 2003

35. Gregori L, Grugel PV, Lathorp JT, et al: Reduction in infectivity of endogenous transmissible spongiform encephalopathies present in blood by adsorption to selective affinity resins. Lancet 368:2226-2230, 2006

36. Gregori L, McCombie N, Palmer D, et al: Effectiveness of leukoreduction for removal of infectivity of transmissible spongiform encephalopathies from blood. Lancet 364:529-531, 2004

37. Gregori L, Lambert BC, Gurgel PV, et al: Reduction of transmissible spongiform encephalopathy infectivity from human red cells with prion protein affinity ligands. Transfusion 46:1152-1161, 2006

38. Saunders C, Herbert P, Rowe M, et al: In-vitro evaluation of the Pall Leukotrap affinity prion reduction filter as a secondary device following primary leukoreduction. Vox Sang 89:220-228, 2007

39. Sowemimo-Coker SO, Kascsak R, Kim A, et al: Removal of exogenous (spiked) and endogenous prion infectivity from red cells with a new prototype of leukocyte filtration filer. Transfusion 45:1839-1844, 2005

40. Sowemimo-Coker SO, Pesci S, Andrade F, et al: Pall leukotrap affinity prion-reduction filter removes exogenous infectious prions and endogenous infectivity from red cell concentrates. Vox Sang 90:265-275, 2006

41. Wiltshire M, Thomas S, Scott J, et al: Prion reduction of red blood cells: Impact on component quality. Transfusion 50: 970-979, 2010

42. Cahill MR, Murphy T, Khan M, et al: Phase I/II safety study of transfusion of prion-filtered red-cell concentrates in transfusion-dependent patients. Vox Sang 99:174-176, 2010

43. Dodd RY: Prions and precautions: be careful for what you ask. Transfusion 50:956-958, 2010

44. Eglin RP, Murphy WG: Beyond leukodepletion: Removing infectious prions by filtration. Transfusion 45:1836-1838, 2005

45. Brown P: Blood infectivity, processing, and screening tests in transmissible spongiform encephalopathy. Vox Sang 89: 63-70, 2005

46. Blanco AR, McCutcheon S, de Wolf C, et al: The effect of leukodepletion on transmission of BSE by transfusion of sheep blood components. Prion 2009—Transmissible Spongiform Encephalopathies Meeting, September 23-25. Greece, Thessaloniki-Chalkidiki; 2009

47. Benson AB, Moss M, Silliman CC: Transfusion-related acute lung injury (TRALI): A clinical review with emphasis on the critically ill. Br J Haematol 147:431-443, 2009

48. Holada K, Vostal JG, Theisen PW, et al: Scrapie infectivity in hamster blood is not associated with platelets. J Virol 76: 4649-4650, 2002

49. SEAC: Position statement: Position statement on TSE infectivity in blood. London, UK, Spongiform Encephalopathy Advisory Committee; 2006 [Updated 2006 August 21] Available at: http://www.seac.gov.uk/statements/statement0806.htm

50. Barclay GR, Hope J, Brickett CR, et al: Distribution of cell-associated prion protein in normal adult blood determined by flow cytometry. Br J Haematol 107:804-814, 1999

51. Sivakumaran M: Infectivity of buffy coat in variant CJD. Transfusion 40:754-755, 2000

52. Prowse C: Properties of pathogen-inactivated plasma components. Transfus Med Rev 23:124-133, 2009

53. MacLennan S, Barbara JA: Risks and side-effects of therapy with plasma and plasma fractions. Best Pract Res Clin Haematol 19:169-189, 2006

54. Farrugia A, Ironside JW, Giagrande P: Variant Creutzfeldt-Jakob disease transmission by plasma products: Assessing and communicating risk in an era of scientific uncertainty. Vox Sang 89:186-192, 2005

55. Dietz K, Raddatz G, Wallis J, et al: Blood transfusion and spread of variant Creutzfeldt-Jacob disease. Emerg Infect Dis 13: 89-96, 2007

B　個別症例報告概要

○　総括一覧表
○　報告リスト

個別症例報告のまとめ方について

個別症例報告が添付されているもののうち、個別症例報告の重複を除いたものを一覧表の後に添付した（国内症例については、資料3において集積報告を行っているため、添付していない）。

感染症定期報告の報告状況(2011/7/1～2011/9/30)

血対ID	受理日	番号	報告者名	一般名	生物由来成分名	原材料名	原産国	含有区分	文献	症例	適正措置報
100379	2011/7/15	110286	バクスター	ルリオクトコグアルファ(遺伝子組換え)	ルリオクトコグアルファ(遺伝子組換え)	遺伝子組換えチャイニーズハムスター卵巣細胞株	該当なし	有効成分	無	有	無
100380	2011/7/15	110287	バクスター	ルリオクトコグアルファ(遺伝子組換え)	アプロチニン	ウシ肺	ニュージーランド	製造工程	無	有	無
100381	2011/7/15	110288	バクスター	ルリオクトコグアルファ(遺伝子組換え)	インスリン(抗第Ⅷ因子モノクローナル抗体製造用)	ウシ膵臓	米国	製造工程	無	有	無
100382	2011/7/15	110289	バクスター	ルリオクトコグアルファ(遺伝子組換え)	ウシ血清アルブミン	ウシ血液	米国	製造工程	無	有	無
100383	2011/7/15	110290	バクスター	ルリオクトコグアルファ(遺伝子組換え)	ウシ胎児血清(抗第Ⅷ因子モノクローナル抗体製造用)	ウシ血液	オーストラリア	製造工程	無	有	無
100384	2011/7/15	110291	バクスター	ルリオクトコグアルファ(遺伝子組換え)	培養補助剤(抗第Ⅷ因子モノクローナル抗体製造用-1)	ウシ血液	米国	製造工程	無	有	無
100385	2011/7/15	110292	バクスター	ルリオクトコグアルファ(遺伝子組換え)	培養補助剤(抗第Ⅷ因子モノクローナル抗体製造用-2)	ウシ肝臓	米国又はカナダ	製造工程	無	有	無
100386	2011/7/15	110293	バクスター	ルリオクトコグアルファ(遺伝子組換え)	人血清アルブミン	人血漿	米国	添加物	無	有	無
100395	2011/8/26	110387	バクスター	ルリオクトコグ アルファ(遺伝子組換え)	ルリオクトコグアルファ(遺伝子組換え)	遺伝子組換えチャイニーズハムスター卵巣細胞	該当なし	有効成分	無	有	無
100414	2011/9/29	110538	バクスター	乾燥濃縮人血液凝固第Ⅷ因子	乾燥人血液凝固第Ⅷ因子	人血漿	米国	有効成分	無	有	無
100415	2011/9/29	110539	バクスター	乾燥濃縮人血液凝固第Ⅷ因子	人血清アルブミン	人血漿	米国	添加物	無	有	無
100416	2011/9/29	110540	バクスター	乾燥人血液凝固因子抗体迂回活性複合体	乾燥人血液凝固因子抗体迂回活性複合体	人血漿	米国	有効成分	無	有	無

別紙様式第４

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第16回	16-1	感染症および寄生虫症	非Ａ非Ｂ型肝炎	アルゼンチン	男	46歳	不明	回復	文献報告	当該製品	識別番号：11000001 報告日：2011年4月15日 MedDRA: Version(14.0)

100379	2011/7/15	110286	バクスター	ルリオクトコグアルファ(遺伝子組換え)	ルリオクトコグアルファ(遺伝子組換え)	遺伝子組換えチャイニーズハムスター卵巣細胞株	該当なし	有効成分	無	有	無
100380	2011/7/15	110287	バクスター	ルリオクトコグアルファ(遺伝子組換え)	アプロチニン	ウシ肺	ニュージーランド	製造工程	無	有	無
100381	2011/7/15	110288	バクスター	ルリオクトコグアルファ(遺伝子組換え)	インスリン(抗第Ⅷ因子モノクローナル抗体製造用)	ウシ膵臓	米国	製造工程	無	有	無
100382	2011/7/15	110289	バクスター	ルリオクトコグアルファ(遺伝子組換え)	ウシ血清アルブミン	ウシ血液	米国	製造工程	無	有	無
100383	2011/7/15	110290	バクスター	ルリオクトコグアルファ(遺伝子組換え)	ウシ胎児血清(抗第Ⅷ因子モノクローナル抗体製造用)	ウシ血液	オーストラリア	製造工程	無	有	無
100384	2011/7/15	110291	バクスター	ルリオクトコグアルファ(遺伝子組換え)	培養補助剤(抗第Ⅷ因子モノクローナル抗体製造用-1)	ウシ血液	米国	製造工程	無	有	無
100385	2011/7/15	110292	バクスター	ルリオクトコグアルファ(遺伝子組換え)	培養補助剤(抗第Ⅷ因子モノクローナル抗体製造用-2)	ウシ肝臓	米国又はカナダ	製造工程	無	有	無
100386	2011/7/15	110293	バクスター	ルリオクトコグアルファ(遺伝子組換え)	人血清アルブミン	人血漿	米国	添加物	無	有	無

別紙様式第４

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢	発現時期	転帰	出典	区分	備考
		器官別大分類	基本語								
第10回	10-2	感染症および寄生虫症	Ｃ型肝炎	アメリカ	男性	不明	1999年	不明	症例報告	当該製品	報告日：2011年7月22日（追加報告） 識別番号：C-09000005 当該調査期間より前に他剤で報告した症例であるが、当該調査期間中に、本剤投与歴のあることが初めて判明した。 MedDRA/J Version 14.0
	10-1	感染症および寄生虫症	非Ａ非Ｂ型肝炎	アルゼンチン	男性	46歳	不明	回復	文献報告	外国製品	報告日：2011年4月15日 識別番号：C-11000001 文献ID：Baxter2011-001 製剤名不明の第VIII因子製剤を投与された症例。 MedDRA/J Version 14.0

100395	2011/8/26	110387	バクスター	ルリオクトコグ アルファ(遺伝子組換え)	ルリオクトコグアルファ(遺伝子組換え)	遺伝子組換えチャイニーズハムスター卵巣細胞	該当なし	有効成分	無	有	無

別紙様式第4

感染症発生症例一覧

番号	感染症の種類 器官別大分類	基本語	発現国	性別	年齢（歳）	発現時期（年/月/日）	転帰	出典	区分	識別番号	報告日	備考 MedDRA (Ver.)	備考
第17回 17-1	感染症および寄生虫症	C型肝炎	イギリス	男性	不明	2005	不明	症例報告	外国製品	11000013	2011/8/30	14.0	
第17回 17-2	感染症および寄生虫症	C型肝炎	コロンビア	男性	8	不明	不明	症例報告	外国製品	11000011	2011/8/22	14.0	
第17回 17-3	感染症および寄生虫症	非A非B型肝炎	アルゼンチン	男性	46	不明	回復	症例報告	外国製品	11000001	2011/4/15	14.0	
第17回 13-2	感染症および寄生虫症	C型肝炎	アメリカ	男性	不明	1999	不明	症例報告	外国製品	09000005	2011/7/22	14.0	第17回症例番号13-2は前回報告における第15回症例番号13-2において報告したものの追加報告
第17回 7-6	感染症および寄生虫症	HIV感染	イギリス	男性	60	1986	不明	症例報告	外国製品	06000018	2011/8/25	14.0	第17回症例番号7-6は前回報告における第7回症例番号7-6において報告したものの追加報告
第17回 7-6	感染症および寄生虫症	C型肝炎	イギリス	男性	60	不明	不明	症例報告	外国製品	06000018	2011/8/25	14.0	第17回症例番号7-6は前回報告における第7回症例番号7-6において報告したものの追加報告
第17回 7-6	感染症および寄生虫症	B型肝炎	イギリス	男性	60	不明	不明	症例報告	外国製品	06000018	2011/8/25	14.0	第17回症例番号7-6は前回報告における第7回症例番号7-6において報告したものの追加報告

100414	2011/9/29	110538	バクスター	乾燥濃縮人血液凝固第Ⅷ因子	乾燥人血液凝固第Ⅷ因子	人血漿	米国	有効成分	無	有	無
100415	2011/9/29	110539	バクスター	乾燥濃縮人血液凝固第Ⅷ因子	人血清アルブミン	人血漿	米国	添加物	無	有	無

別紙様式第４

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第17回	17-1	臨床検査	抗ＨＢｓ抗体陽性	日本	男	23	2011/05/25	不明	症例報告	外国製品	登録番号：11000001 報告日：2011年7月11日 MedDRA: Version(14.0)
第16回	0*	0	0	0	0	0	0	0	0	0	

100416	2011/9/29	110540	バクスター	乾燥人血液凝固因子抗体迂回活性複合体	乾燥人血液凝固因子抗体迂回活性複合体	人血漿	米国	有効成分	無	有	無