Kyoto man bitten by dog in R.P. dies of rabies

The Yomiuri Shimbun

A Kyoto man in his 60s died of rabies on his return to Japan after a stray dog bit his hand in the Philippines, the Public Health and Welfare Bureau in Kyoto said Friday.

The man, who fell into a coma before his death, was the first Japanese to be diagnosed with the virus in 36 years, the Health, Labor and Welfare Ministry said.

According to the ministry, the man was bitten by the dog at the end of August and returned to Japan on Nov. 1. He visited a doctor in Kyoto on Nov. 9 with cold symptoms before developing characteristic signs of rabies such as hallucinations and a fear of water and wind.

The National Institute of Infectious Diseases diagnosed the man with rabies after testing his saliva.

(Nov. 18, 2006)

National go

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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 2006 年 12 月 6 日	新医薬品等の区分	厚生労働省処理欄
一般的名称	①②③人血清アルブミン ④乾燥濃縮人血液凝固第Ⅷ因子 ⑤乾燥濃縮人血液凝固第Ⅸ因子	研究報告の公表状況	NIKKEI NET/20061205	公表国 日本		
販売名 (企業名)	①献血アルブミン-Wf（ベネシス） ②献血アルブミン(5%)-Wf（ベネシス） ③アルブミン-Wf（ベネシス） ④コンコエイトーHT（ベネシス） ⑤クリスマシンーM（ベネシス）					

研究報告の概要

既存の治療薬がほとんど効かず、世界保健機関（WHO）が警戒を呼び掛けている「超多剤耐性」の結核菌が、国内でも入院患者の 0.5%から検出されたことが、結核研究所の調査で 5 日までに分かった。
結核菌は、薬の服用を途中でやめるなど誤った治療で耐性が生じやすく、既に国内でも問題になっているが、それより治療が格段に難しい超耐性菌の確認は初めて。
検出例の半数は薬の服用歴がなかったことから、他の患者から感染した可能性が高い。調査した同研究所の御手洗聡細菌検査科長は「菌の耐性の強さに応じた個室療養を可能にするような治療態勢の見直しが必要だ」と指摘している。
御手洗科長らは、2002 年 6―11 月にかけて国内 99 の結核治療施設の入院患者 3122 人から採取した結核菌を分析した。
効き目が強い 2 種類の第 1 選択薬がともに効かない多剤耐性菌が 55 人(全体の 1.8%)に見つかったが、うち 17 人(同 0.5%)から検出された菌は、補助的に用いられる第 2 選択薬も複数の種類が効かない超多剤耐性菌だった。

使用上の注意記載状況・その他参考事項等

代表として献血アルブミン-Wf 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、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人アルブミンを精製し、アルブミン濃度 25w/v%に調整した製剤であり、ウイルス不活化を目的として、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。

報告企業の意見	今後の対応
既存の治療薬がほとんど効かず、世界保健機関（WHO）が警戒を呼び掛けている「超多剤耐性」の結核菌が、国内からも検出されたとの報告である。 血漿分画製剤からの結核菌伝播の事例は報告はされていない。万一原料血漿に結核菌が混入したとしても、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。

BENE2006-026

「超耐性」結核菌を国内で確認、入院患者の0.5%で検出

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[2006年12月5日/共同]

別紙様式第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	第一報入手日 2006年10月16日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称			研究報告の公表状況	Continuing Mycobacterium bovis transmission from animals to humans in New Zealand Epidemiology and Infection 2006,134/5 (1068-1073)	公表国 英国	
販売名（企業名）	タココンブ（CSL ベーリング株式会社）					

研究報告の概要

問題点（ニュージーランドにおける動物から人への Mycobacterium bovis 伝播）

M. bovis はニュージーランドの野生動物や家畜の牛などで一般的な感染症である。M. bovis は結核菌による疾患と臨床上区別できない疾病を起こす。今回の研究で、現在のニュージーランドのヒトにおける M. bovis 感染の疫学を述べ、1995 年から 2002 年の間の疫学調査や臨床検査結果から M. bovis 感染の可能な感染源を調査した。

当該調査期間中に 54 例の M. bovis 感染が確認され、年平均 6.8 例であった。その中の 34 例を詳細に検討できた。年平均 M. bovis 感染率を性別、年齢別に比較すると、60-69 歳の群が最も高率で、次に 70 歳以上の群であった。男女比は、3:1 であった。出生国はニュージーランドが 71.9%で、残りの 28.9%はニュージーランドに移ってきていた。感染部位は呼吸器感染症が 56.7%あった。その他に腹膜、リンパ節、腕・手首などであった。73.1%の感染者は入院した。ヒトから分離された M. bovis の REA タイプの 61%が、牛などから分離されたタイプと同一であった。

M. bovis 感染は 1940 年代のミルク加熱処理導入前の汚染ミルクにより頻繁に生じ、大部分が肺以外の感染であった。

ニュージーランドにおいて、動物からヒトに低レベルで持続的な M. bovis 感染があることを示していることが判った。

本研究でヒトが M. bovis 感染源であることを除外することができなかったが、ヒトは一般的に重要な感染源ではない。

使用上の注意記載状況・その他参考事項等

報告企業の意見	今後の対応
本成分のトロンビンは、牛血液を原料としている。牛がM. bovisに感染していたとしても、本剤の製造工程で不活化されると考えられる。	今後とも新しい感染症に関する情報収集に努める所存である。

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Epidemiol. Infect. (2006), 134, 1068–1073. © 2006 Cambridge University Press
doi:10.1017/S0950268806005930 Printed in the United Kingdom

Continuing *Mycobacterium bovis* transmission from animals to humans in New Zealand

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(*Accepted 10 December 2005, first published online 29 March 2006*)

SUMMARY

New Zealand has a large reservoir of *Mycobacterium bovis* infection in wild and farmed animals. This study aimed to assess the extent of human infection with this organism and the potential contribution of these animal sources. Combined epidemiological and laboratory investigation of human tuberculosis cases over the period 1995–2002 showed that *M. bovis* accounted for 2·7% (54/1997) of laboratory-confirmed human tuberculosis cases, a rate of 0·2/100 000 population. *M. bovis* isolates from humans (23) were typed using restriction endonuclease analysis (REA) and compared with isolates from wild and domestic animals (2600). Fourteen (61%) of the human isolates had REA patterns that were identical to patterns for isolates from cattle, deer, possums, ferrets, pigs, and occasionally cats. These results suggest a low level of ongoing *M. bovis* transmission from animal reservoirs to humans in New Zealand.

INTRODUCTION

Mycobacterium bovis can cause disease in humans that clinically is indistinguishable from that due to *Mycobacterium tuberculosis*. Although now uncommon in most developed countries, *M. bovis* remains an important cause of tuberculosis in developing countries [1, 2]. *M. bovis* is a common infection in wild animals in New Zealand, notably introduced Australian brushtail possums (*Trichosurus vulpecula*), and these occasionally infect farmed cattle and deer [3]. This situation raises the potential for animal-to-human transmission of this pathogen.

A previous review of human infection with *M. bovis* in New Zealand, identified 60 cases over the period from January 1985 to July 1995 [4]. The majority of these cases occurred in elderly people and probably represent infections acquired before introduction of milk pasteurization and herd testing in the 1940s and 1950s. However, this total included some younger cases (15 under 40 years of age) who should not have been exposed to unpasteurized milk.

This study, therefore, aimed to describe the current epidemiology of human *M. bovis* infection in New Zealand and determine the possible sources of these infections using combined epidemiological and laboratory investigation of cases over the 1995–2002 period.

METHODS

Human *M. bovis* and *M. tuberculosis* infections from 1995 to 2002 were identified using notification records supplemented by laboratory detection data from New Zealand's three tuberculosis referral laboratories. Cases occurring from 1998 to 2002 were analysed in

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detail, including key demographic and risk factor information. This period was chosen because few human isolates were stored before 1998. Rates were calculated using population data from the 2001 Census. Epi-Info (CDC, Atlanta, GA, USA) was used to calculate crude rate ratios (RR) and 95% confidence intervals 95% CI and the χ^2 test for linear trend.

The three tuberculosis laboratories sent all stored human *M. bovis* isolates to AgResearch, Wallaceville for DNA fingerprinting. AgResearch carried out this characterization of human isolates using restriction endonuclease analysis (REA). Each isolate was separately digested with three restriction enzymes, *Bst*EII, *Pvu*II and *Bcl*I. This process generated three gels and associated band pattern for each isolate. This was the same method as had been used to type 2600 *M. bovis* isolates collected from a wide variety of domestic and wild animals in New Zealand over the 1982–2003 period [5–7]. These animal isolates had been characterized into 270 different REA types and the information stored in a DNA database. The restriction types of the human *M. bovis* isolates were compared to these animal types.

The epidemiological information was analysed in conjunction with the results of the DNA fingerprinting of the *M. bovis* strains recovered from the patients. This process aimed to determine the likelihood of the human infections being acquired from specific animal exposures in New Zealand or from overseas.

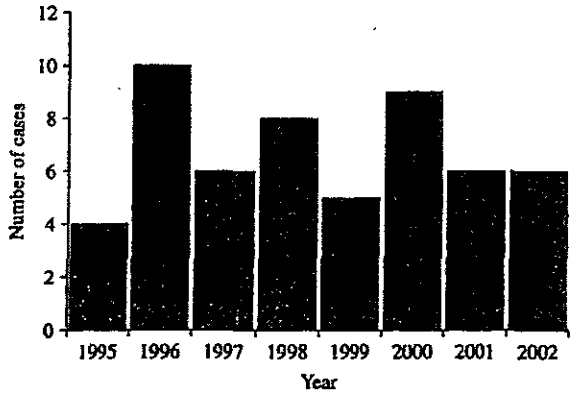

Fig. 1. Human *M. bovis* infections in New Zealand by year, 1995–2002.

Fig. 2. Human *M. bovis* infection incidence by age and sex, average annual rate per 100 000 population, 1998–2002.

RESULTS

Epidemiology of *M. bovis* infection

Notification and laboratory data identified a total of 54 human cases of *M. bovis* (excluding *M. bovis* BCG) infection from 1995 to 2002. There were a further 1943 cases of infection with *M. tuberculosis*, so *M. bovis* represented 2·7% (54/1997) of the laboratory-confirmed tuberculosis cases detected over that period.

The incidence of newly diagnosed *M. bovis* infections (Fig. 1) did not increase over the period 1995–2002 (χ^2 for linear trend, $P=1{\cdot}0$). The average number of bovine tuberculosis cases in the 8-year period was 6·8 per year.

The 34 *M. bovis* infections occurring from 1998 to 2002 were reviewed in detail. Over this 5-year period, cases occurred in 16 of New Zealand's 21 district health board areas, with an average rate of 0·18/100 000 cases. Rates ranged from 0 to 1·32/100 000, although these figures are based on small numbers. Areas reporting rates above the national average were West Coast, Wairarapa, Hutt, Lakes, Tairawhiti, Waikato, Counties Manukau, Eastern Bay of Plenty, Capital Coast and Whanganui districts.

Figure 2 shows the average annual rates of *M. bovis* infection by age group and sex. Highest rates were in the 60–69 years age group, followed by those ⩾70 years of age. Gender was recorded for all 34 cases. Male cases outnumbered females by 3:1.

Country of birth information was available for 32 cases of whom 23 (71·9%) were born in New Zealand and the remaining nine (28·1%) had migrated to New Zealand. Six of the immigrant cases had been born in developing countries. The rates for Maori (2·1/100 000) and Pacific people (1·5/100 000) and people of other ethnicity (1·2/100 000) were higher than for Europeans (0·5/100 000).

The site of infection was recorded for 88·2% of cases (30/34). Pulmonary infection was the most common site, accounting for 56·7% (17/30). The remaining extra-pulmonary sites included: peritoneum,

Table 1. *Comparison of the epidemiological characteristics of human* M. bovis *and* M. tuberculosis *infections, 1998–2002*

Characteristic	*M. bovis* infection (% recorded)	*M. tuberculosis* infection (% recorded)
Sex		
Male	25 (73·5)	696 (52·4)
Female	9 (26·5)	632 (47·6)
Median age (yr)	57	37
Age group (yr)		
0–19	1 (2·9)	153 (11·5)
20–59	17 (50·0)	866 (64·9)
⩾60	16 (47·1)	316 (23·7)
Ethnicity		
European	14 (45·2)	169 (13·1)
Maori	11 (35·5)	217 (16·8)
Pacific	3 (9·7)	240 (18·6)
Other	3 (9·7)	665 (51·5)
Region		
North Island	26 (76·5)	1183 (88·5)
South Island	8 (23·5)	153 (11·5)
Site		
Pulmonary	17 (56·7)	685 (56·9)
Non-pulmonary	10 (33·3)	383 (31·8)
Both pulmonary and non-pulmonary	3 (10·0)	134 (11·1)
Birth		
Inside New Zealand	23 (71·9)	360 (29·6)
Outside New Zealand	9 (28·1)	855 (70·4)
Total 1998–2002	34	1336

lymph nodes, arm/wrist (tenosynovitis), genitourinary system, hip joint, and proximal interphalangeal joint. Most cases were hospitalized (19/26 or 73·1%). The case- fatality rate was 15·4% (4/26).

Comparison of *M. bovis* and *M. tuberculosis* infection

Table 1 compares the characteristics of *M. bovis* and *M. tuberculosis* cases for the 5-year period 1998–2002. People infected with *M. bovis* were significantly more likely to be male (RR 2·5, 95% CI 1·2–5·3), over 60 years of age (RR 2·5, 95% CI 1·2–5·3), European (RR 6·2, 95% CI 3·1–12·1) or Maori (RR 2·2, 95% CI 1·1–4·6), to have been born inside New Zealand (RR 4·6, 95% CI 2·0–10·6) rather than migrated there, and to be living in the South Island at the time of diagnosis (RR 2·3, 95% CI 1·1–5·0). Of note is that *M. bovis* infection was not more commonly associated with extra-pulmonary sites of infection than was *M. tuberculosis*.

Laboratory investigation of human *M. bovis* infections

The three tuberculosis referral laboratories located 23 viable human *M. bovis* isolates for the 1998 to 2002 period, out of a possible total of 34. The AgResearch laboratory at Wallaceville typed these isolates and compared their patterns to REA results for animal isolates held in their database (Table 2).

Eight isolates were classified as 'foreign' strains as their REA pattern has not been seen previously in a New Zealand animal isolate. Of this group, four of the source patients were recorded as having been born overseas (one in Fiji, one in the Cook Islands, one in England and one in Scotland), and four were born in New Zealand. One isolate was the strain (AN5) used for making bovine purified protein derivative (PPD). This infection was a result of an accidental exposure that occurred in a laboratory manufacturing tuberculin.

This left 14 isolates that had an REA pattern that was identical to one that has been seen previously in wild or domestic animals in New Zealand. These isolates included nine different unique REA patterns. Of these, five isolates had the same REA type (115) that is found very commonly in the Central North Island in a wide range of animal reservoirs. Two isolates had the same type (21) that is found very commonly in the Wairarapa and on the West Coast of the South Island, again in a wide range of reservoir animals. The remaining seven REA types were all represented by a single isolate. The types found in humans had all been isolated from bovine reservoirs (14/14 isolates). There was also a high degree of overlap with those found in deer (12/14), ferrets (10/14) and possums (11/14).

Of these 14 cases with REA patterns that matched specimens from animals in New Zealand, eight had risk factor information recorded. Of these, five reported animal contact that could potentially have given rise to infection. These contacts included living or working on a farm, being an abattoir worker, consumption of unpasteurized milk, and working as a veterinary receptionist. One case was infected following accidental inoculation during necropsy of a tuberculous possum, as specifically reported elsewhere [8].

DISCUSSION

Findings from this study suggest a continuing low level of *M. bovis* transmission from animals to humans in New Zealand. Although *M. bovis* is a relatively uncommon cause of human tuberculosis in New

Table 2. *Human* M. bovis *isolates (1998–2002), and animal isolates (1982–2003) by REA type (see references [5–7] for details of REA types)*

REA type	No. of human isolates (% of total human isolates)	No. of animal isolates	No. of isolates from each animal species (% of total isolates for that species)					
			Bovine	Cervine	Ferret	Possum	Porcine	Feline
Foreign*	8 (34·8)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
115	5 (21·7)	417	308 (24·1)	51 (10·6)	15 (7·7)	27 (6·4)	15 (8·1)	1 (2·4)
21	2 (8·7)	97	41 (3·2)	15 (3·1)	11 (5·6)	18 (4·3)	11 (5·9)	1 (2·4)
AN5*	1 (4·3)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
6	1 (4·3)	3	3 (0·2)	0	0	0	0	0
9	1 (4·3)	3	2 (0·2)	1 (0·2)	0	0	0	0
19	1 (4·3)	33	7 (0·5)	24 (5·0)	1 (0·5)	1 (0·2)	0	0
27	1 (4·3)	30	1 (0·1)	3 (0·6)	0	13 (3·1)	13 (7·0)	0
62	1 (4·3)	109	50 (3·9)	11 (2·3)	16 (8·2)	10 (2·4)	17 (9·2)	5 (11·9)
151	1 (4·3)	111	78 (6·1)	18 (3·7)	7 (3·6)	6 (1·4)	1 (0·5)	1 (2·4)
158	1 (4·3)	3	3 (0·2)	0	0	0	0	0
Other	0	1794	783 (61·4)	359 (74·5)	146 (74·5)	344·(82·1)	128 (69·2)	34 (81·0)
Total	23	2600	1276	482	196	419	185	42

REA, Restriction endonuclease analysis; n.a., not applicable.
* Never found in animals in New Zealand.

Zealand, accounting for about 2·7% of human disease, this contribution is higher than that seen in other developed countries. In Australia *M. bovis* caused ~1% of human disease over the 1970–1994 period [9] and in Britain it accounted for 1·2% of cases from 1986 to 1990 [10]. Another indication of *M. bovis* transmission within New Zealand comes from the observation that most cases (71·9% over the 1998–2002 period) were born in New Zealand. This proportion is significantly higher than that seen for infection with *M. tuberculosis* where a minority of cases are New Zealand born (only 29·6% during this period).

There has been little increase over 17 years in the incidence of human infection with *M. bovis* in New Zealand. A previous analysis by Richard Pooley identified 60 cases over the $11\frac{1}{2}$-year period from January 1985 to July 1995, an average of 5·2 cases a year [4]. This present study identified an average of 6·8 cases a year for the 8-year period from 1995 to 2002.

The site of tuberculosis infection gives an indication of the possible route of transmission. The majority (56·7%) of *M. bovis* infections are pulmonary, which is a similar proportion to that seen for *M. tuberculosis* infection. This contrasts with the pattern prior to pasteurization of milk in the 1940s when infection was frequently transmitted via contaminated milk and the majority of infections were non-pulmonary [11].

The ages of human *M. bovis* cases suggest that many are reactivations of old infections rather than newly acquired disease. Among the New Zealand-born cases, most (80%) were >30 years of age which is similar to the 85% found by Pooley [4]. The median age of *M. bovis* infections (57 years) is much older than that for *M. tuberculosis* infection (37 years). Despite this, there are still *M. bovis* infections occurring in relatively young New Zealanders with four <30 years of age at the time of diagnosis. They were all born after control measures were introduced to limit transmission through contaminated milk. These measures included the compulsory testing of dairy cattle from 1961 and steady introduction of milk pasteurization from the 1940s to the early 1970s. These cases are likely to have acquired infection from other sources. The 3:1 preponderance of males compared to females suggests that occupational settings may be important sources of *M. bovis* exposure. A similar overrepresentation of males is seen for leptospirosis in New Zealand, and has been attributed to the larger proportion of males working as farm and abbatoir workers where most exposure to this pathogen occurs [12].

Combined results of molecular and epidemiological investigation can provide evidence of the sources of human infections. For the two *M. bovis* infections resulting from well-documented occupational exposures, the source of infection was clearly identified. Five other cases in this present study reported animal contact that could potentially have given rise to

infection and had REA patterns that were the same as ones found in wild and domestic animals in New Zealand. Here the evidence is suggestive of local infection but more detailed investigation would be required to identify specific sources. Far less can be concluded about the source of infection for the remaining cases, including the eight others with REA patterns that were the same as ones found in wild and domestic animals in New Zealand.

There are few reported studies that have used molecular methods to investigate sources of human *M. bovis* infection. One study analysed 20 human and 58 animal isolates from Argentina and 47 human and 13 animal isolates from The Netherlands using restriction fragment length polymorphism (RFLP) patterns probed by the insertion element IS*6110* [13]. It found that most human isolates in Argentina were of a single type that also predominated among cattle isolates. This situation contrasted with The Netherlands where the *M. bovis* fingerprints of strains from humans were very diverse and none were found among *M. bovis* strains of animal origin. A study in Sweden used similar methods to characterize isolates from 11 humans and 28 farmed deer sampled from an outbreak affecting five herds. The *M. bovis* fingerprints of the human isolates were diverse, whereas the isolates from the deer all had a different and very specific pattern [14]. The molecular epidemiology of human *M. bovis* infection in New Zealand, characterized by human infection with a diverse range of REA types, resembles the situation seen in The Netherlands and Sweden more than that in Argentina, but differs from Sweden and Argentina in having many of these types infect both animals and humans.

This study cannot exclude human sources for some *M. bovis* infections. For example, one case in our series reported contact with another case of human *M. bovis* infection. Human-to-human [15], and even human-to-animal transmission of *M. bovis* has been documented [16], and a recently reported contact investigation study suggests that in some circumstances *M. bovis* may be almost as efficient at human-to-human transmission as *M. tuberculosis* [17]. Despite these observations, humans are usually a 'dead-end' host for *M. bovis* infections and human contact is not generally an important source of infection.

The major limitations of this present study are its small size and the lack of complete epidemiological information on human cases. Continuing the typing of human isolates prospectively would increase the size of this study sample over time. It would also be useful to undertake more detailed epidemiological investigation of these human cases, including their history of animal contact and geographic areas where they have lived in the past, so that these results could be compared with the extensive information held on *M. bovis* distribution in animals. A case-control study should also be considered to provide a more precise estimate of the risk of human infection associated with specific forms of animal contact.

ACKNOWLEDGEMENTS

Staff of New Zealand's three tuberculosis referral laboratories are acknowledged for the isolation of the *M. bovis* strains and forwarding them to Wallaceville for DNA fingerprinting: Ross Vaughan, Mycobacteria Laboratory, Auckland Hospital; Jane Wakefield, Kathryn Coley, Vivienne Talbot, Mycobacteria Laboratory, Waikato Hospital; Leo McKnight, Mycobacteria Laboratory, Wellington Hospital. Gary Yates, AgResearch, is thanked for culturing the *M. bovis* isolates for DNA fingerprinting. This study was contracted by the Animal Health Board.

DECLARATION OF INTEREST

None.

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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		回	報告日 年　月　日	第一報入手日 2006 年 10 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			研究報告の公表状況	Evaluation of inactivation methods for severe acute respiratory syndrome coronavirus in noncellular blood products Miriam E.R. et. al Transfusion. 46; 1770-77	公表国 米国	
販売名（企業名）						

研究報告の概要

背景:
重症急性呼吸器症候群コロナウイルス (SARS-CoV) が感染患者の血液内で検出された。このことから，献血や血漿分画製剤の汚染の可能性が考えられる。この報告書ではタンパク溶液中の SARS-CoV 不活化に有効な方法を報告している。
研究方法:
熱，紫外線 (UV) 照射法，オクタン酸，及び有機溶媒/界面活性 (S/D) 処理が，擬似的な血漿分画製剤タンパク溶液中の SARS-CoV に対し不活化効果を示すか実験を行った。処理サンプルにおける組織培養増殖アッセイを行い，不活化効果を評価した。
結果:
60 度の熱処理では SARS-CoV の不活化に 15-30 分必要であった。UVC (200-280nm) は 40 分で効果的に SARS-CoV を不活化したが，一方，UVA (320-400nm) ではウイルス不活化を高めるためにソラーレンの添加が必要であった。ウシ血清アルブミンは UVC と UVA の SARS-CoV の不活化能力を制限し，オクタン酸処理はスパイクされた溶液中の SARS-CoV 感染力を低減しなかった。S/D 処理では，Triton X-100, Tween80，及びナトリウムコール酸で SARS-CoV を不活化するのにそれぞれ 2，4，及び 24 時間必要であった。
結論:
事実上，熱，UVC 照射法，及び S/D 処理により SARS-CoV の不活化が可能であった。
オクタン酸処理はウイルス不活化には不十分であった。

報告企業の意見	今後の対応
本研究によって，SARS-CoV のエンベロープ構造を考慮した，S/D 処理，UVC 照射，および 60℃の加熱処理という通常のウイルス不活化によって，SARS-CoV が短時間で不活化されることが確認された。	血漿分画製剤の製造工程におけるウイルス除去工程で，SARS-CoV は不活化されることが確認されていることから，現時点で新たな安全対策上の措置を講じる必要はないと考える。

使用上の注意記載状況・その他参考事項等

BYL-2007-0245