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医薬部外品　研究報告　調査報告書
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識別番号・報告回数		回	報告日 年　月　日	第一報入手日 2009 年 2 月 17 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	Ebola-Reston in pigs and humans in the Philippines. www.who.int/csr/don/2009_02_03/en/print.html	公表国 スイス	
販売名（企業名）						

研究報告の概要	使用上の注意記載状況・その他参考事項等
2009 年 1 月，フィリピン政府はエボラレストンウイルス株（ERV）罹患ブタからヒトへの最初の伝播が認められた可能性が高いことを公表した。罹患ブタとの直接接触があったと考えられた 5 名は抗 ERV 抗体に対して陽性結果を示しているもののいずれも良好な健康状態にあると考えられ，臨床徴候を呈した者はいなかった。しかしながら，感染した 5 名は健康成人であり，当該ウイルスが高齢者，免疫が低下した者，妊婦，小児或いは基礎疾患のある者などの他の集団に及ぼし得る影響については不明である。フィリピン政府はこれら 5 名に関連する接触者の追跡などの ERV によるヒトおよび動物の健康リスクを制限する方策を実施中である。	BYL-2009-0369 The Lancet Infectious Disease 9; 148, 2009

報告企業の意見	今後の対応
米国ではアジアを起源とする ERV の感染が，動物において報告されており，そのため弊社の組換え製品の培養培地に用いる血漿分画製剤を製造するための血漿ドナーが，感染動物と接触していた可能性があるという理論上のリスクがある。しかしながら，こうした状況に至る可能性は極めて低く，また，エボラウイルスはエンベロープウイルスであるため，製造工程におけるウイルス除去・不活化工程が有効である。	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。 今後，米国における ERV 感染のアウトブレイクが発生した場合には，動物からヒトへの感染の情報収集に努める。

World Health Organization

Ebola Reston in pigs and humans in the Philippines

3 February 2009 -- On 23 January 2009, the Government of the Philippines announced that a person thought to have come in contact with sick pigs had tested positive for Ebola Reston Virus (ERV) antibodies (IgG). On 30 January 2009 the Government announced that a further four individuals had been found positive for ERV antibodies: two farm workers in Bulacan and one farm worker in Pangasinan - the two farms currently under quarantine in northern Luzon because of ERV infection was found in pigs - and one butcher from a slaughterhouse in Pangasinan. The person announced on 23 January to have tested positive for ERV antibodies is reported to be a backyard pig farmer from Valenzuela City - a neighbourhood within Metro Manila.

The Philippine Department of Health has said that the people who tested positive appear to be in good health and have not suffered from any significant illnesses in the past 12 months. The investigation team reported that it was possible that all 5 individuals had been exposed to the virus as a result of direct contact with sick pigs. The use of personal protective equipment (PPE) is not common practice among these animal handlers.

From these observations and previous studies of ERV, the virus has shown it can be transmitted to humans, without resulting in illness. However, the evidence available relates only to healthy adults and it would be premature to conclude the health effects of the virus on all population groups. The threat to human health is likely to be low for healthy adults but is unknown for all other population groups, such as immuno-compromised persons, persons with underlying medical conditions, pregnant women and children.

The Philippine Government is conducting contact tracing in relation to the five individuals who tested positive for antibodies. In addition, testing is ongoing for other persons who could have come into contact with sick pigs on the two quarantined farms in the provinces of Bulacan and Pangasinan where pigs co-infected with the Porcine Respiratory and Reproductive Syndrome (PRRS) and ERV were reported in 2008. The two farms remain under quarantine and the Philippine Government is maintaining its voluntary hold of exports of live pigs and fresh and frozen pork meat.

The Philippine Government has announced a combined Department of Health and Department of Agriculture strategy to limit the animal and human health risks of the Ebola Reston Virus and emphasized that local governments, the pig farming industry and the public will play a critical role in the strategy.

Along with its international partners, the WHO will continue to support the Philippine Government in its efforts to gain a better understanding of the Ebola Reston virus, its effects on humans, and the measures that need to be taken to reduce any risks to human health.

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
				2009. 2. 18	該当なし	
一般的名称	乾燥濃縮人血液凝固第Ⅷ因子		研究報告の公表状況	Hamaguchi T, Noguchi-Shinohara M, Nozaki I, Nakamura Y, Sato T, Kitamoto T, Mizusawa H, Yamada M. Emerg Infect Dis. 2009 Feb;15(2):265-71.	公表国 日本	
販売名(企業名)	クロスエイトM250(日本赤十字社) クロスエイトM500(日本赤十字社) クロスエイトM1000(日本赤十字社)					

研究報告の概要

○医学的処置と孤発性クロイツフェルト・ヤコブ病のリスク(日本、1999～2008年)
孤発性クロイツフェルト・ヤコブ病(sCJD)と医学的処置との関連性を解明するため、日本において1999～2008年の期間にCJDサーベイランス委員会により登録された患者の医学的処置(すべての外科治療、脳神経外科手術、眼科手術および輸血)について分析した。
sCJD患者753名および対照210名の年齢層別化症例対照調査および同一病院で神経外科的処置または眼科処置を受けた患者についての調査を行った。比較的小規模な対照群であったが、sCJD発症前に施行された当該医学的処置によりプリオン病が感染したという証拠は見つからなかった。sCJD発症後にsCJD患者の4.5%が手術を受けた(脳外科手術0.8%、眼科手術1.9%を含む)。プリオン病伝播に対する特別な予防措置はとられなかったが、幸いにも、これらの手術に起因するプリオン病患者は特定されなかった。
我々の所見は、外科的処置または輸血はsCJDの発生にほとんど影響を及ぼさないことを示している。

使用上の注意記載状況・その他参考事項等

クロスエイトM250
クロスエイトM500
クロスエイトM1000

血液を原料とすることに由来する感染症伝播等
vCJD等の伝播のリスク

報告企業の意見

日本において1999～2008年の期間にCJDサーベイランス委員会により登録された患者の医学的処置と孤発性クロイツフェルト・ヤコブ病(sCJD)との関連性について分析した結果、外科的処置または輸血はsCJDの発生にほとんど影響を及ぼさないことを示しているとの報告である。

今後の対応

本報告を含めて、これまでの疫学研究等では、血液製剤を介して古典的CJD(弧発性、遺伝性および医原性CJD)が伝播するという証拠はない。またCJDの病原因子とされる異常プリオンが本製剤の製造工程で効果的に除去されるとの成績もあるが、第Ⅷ因子製剤を介しvCJDに感染する可能性が示唆された報告もあることから、今後も引き続き情報の収集に努める。なお、日本赤十字社は、CJD、vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴(旅行及び居住)、CJDの既往歴(本人、血縁者)、hGH製剤投与の有無を確認し、該当するドナーを無期限に献血延期としている。

(17)

Medical Procedures and Risk for Sporadic Creutzfeldt-Jakob Disease, Japan, 1999–2008

Tsuyoshi Hamaguchi, Moeko Noguchi-Shinohara, Ichiro Nozaki, Yosikazu Nakamura, Takeshi Sato, Tetsuyuki Kitamoto, Hidehiro Mizusawa, and Masahito Yamada

To elucidate the association between medical procedures and sporadic Creutzfeldt-Jakob disease (sCJD), we analyzed medical procedures (any surgical procedure, neurosurgery, ophthalmic surgery, and blood transfusion) for patients registered by the CJD Surveillance Committee in Japan during 1999–2008. We conducted an age-stratified case–control study with 753 sCJD patients and 210 controls and a study of patients who underwent neurosurgical or ophthalmic surgical procedures at the same hospital. Although the control group was relatively small, no evidence was found that prion disease was transmitted through the investigated medical procedures before onset of sCJD. After onset of sCJD, 4.5% of the sCJD patients underwent operations, including neurosurgical for 0.8% and ophthalmic for 1.9%; no special precautions against transmission of prion diseases were taken. Fortunately we have not identified patients with prion disease attributed to these operations. Our findings indicate that surgical procedures or blood transfusion had little effect on the incidence of sCJD.

Prion disease is characterized by spongiform change and abnormal prion protein deposition in the brain and is transmissible under certain situations. Human prion disease is divided into 3 categories: genetic prion diseases with mutations of the prion protein (PrP) gene; prion diseases acquired by transmission of the prion through exposure to contaminated materials, including iatrogenic transmission; and sporadic Creutzfeldt-Jakob disease (sCJD) with no PrP mutation or evidence of exposure to prion. To date, >400 patients with iatrogenic CJD, who received prions through contaminated neurosurgical instruments, intracerebral electroencephalographic electrodes, human pituitary hormone, corneal transplants, or dura mater grafts, have been reported (*1*). Furthermore, some case–control studies reported that medical procedures were possible risk factors for sCJD (*2–6*). However, other studies did not demonstrate any significant association between medical procedures and sCJD (*7–10*).

After a results of a case–control study that found an association between CJD and medical procedures was reported from Japan in 1982 (*2*), 132 patients with dura mater graft–associated CJD (dCJD) have been found in Japan (*11,12*); however, no recent studies have investigated medical procedures as a risk for acquiring sCJD. In Japan, 66 (8.6%) of 766 patients with prion diseases had iatrogenic cases that were all dCJD (*12*), and the outbreak of iatrogenic CJD required a new study about the association between sCJD and medical procedures in Japan. Here we analyzed the role of medical procedures in cases of sCJD by using relevant data from CJD surveillance in Japan.

Methods

Patients

We investigated 1,339 patients with suspected prion diseases who had been registered by the CJD Surveillance Committee in Japan from April 1999 through February 2008. The surveillance system was initiated in April 1999, and each patient was prospectively assessed with a surveillance protocol that assembled information about life

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history; previous medical history, including the history of surgical treatment and blood transfusion; clinical history; laboratory data; and results of molecular genetic and pathologic examinations. Information on patients with suspected prion diseases were obtained through 1) the application for registration with the Japanese Intractable Diseases Information Center (www.nanbyou.or.jp/english/nan_kenkyu_45.htm) by each patient's family, 2) the law on infectious diseases, or 3) request for genetic or cerebrospinal fluid analyses sent to members of the CJD Surveillance Committee by the physicians. In Japan, 123 diseases have been defined as intractable disease, and for 45 of them, including prion diseases, patients receive additional economic support for medical costs. Furthermore, medical doctors must report patients suspected of having prion disease to the local public health department within 7 days after the diagnosis, according to the law on infectious diseases (which has been enforced since April 1999 in Japan to monitor some specific infectious diseases). After written consent approved by the Institutional Ethics Committee was obtained from each patient's family, members of the CJD Surveillance Committee directly examined the patient and collected data from the clinical records. For each patient with a history of surgery, we collected information about the underlying disease from the patient's family, including the date and hospital in which the operation was performed. For each patient with a history of blood transfusion, we collected information about the date of blood transfusion. Most information was collected by interviewing the patient's family members.

On the basis of discussions by the CJD Surveillance Committee, we confirmed or denied the diagnosis of prion disease in each case. In patients with a confirmed diagnosis of prion disease, we classified prion diseases into 4 categories: sCJD, acquired prion disease, genetic prion disease, and unclassified prion disease. sCJD was diagnosed according to the revised classical criteria established by Masters et al. (*13*): definite CJD (neuropathologically confirmed spongiform encephalopathy or abnormal prion protein deposition in the brain); and probable CJD (neuropathologically unconfirmed cases showing progressive dementia, periodic sharp-wave complexes on electroencephalogram, and at least 2 of the following features: myoclonus, pyramidal signs/extrapyramidal signs, cerebellar signs or visual symptoms, and akinetic mutism). Acquired prion diseases included iatrogenic CJD, in which the criteria for sCJD were applied for a diagnosis with a history of iatrogenic exposure, and variant CJD, in which the diagnosis was based on the World Health Organization (WHO) 2001 criteria (*14*). Regarding the accuracy of the diagnosis of genetic prion diseases, pathologically verified cases were defined as "definite," and cases demonstrating mutations in the PrP gene and neuropsychiatric manifestations compatible with prion diseases were defined as "probable." We selected patients with definite or probable sCJD for analysis.

Patients who did not receive a diagnosis of prion diseases were classified into 3 categories: prion diseases definitely denied; prion diseases probably denied; and diagnosis unclear. "Prion diseases definitely denied" indicated patients whose conditions were definitively diagnosed as diseases other than prion diseases, and "prion diseases probably denied" indicated patients for whom the diagnosis of prion diseases was clearly unlikely due to the improving or nonprogressive disease course or for other reasons, although a definitive diagnosis of another disease was not established. Because patients with "prion diseases definitely denied" or "prion disease probably denied" had no or little possibility of prion disease, we selected these cases as the controls in our case–control study.

Surgical Procedures and Blood Transfusions before Onset of sCJD

To estimate the risk for sCJD through past surgery or blood transfusion, we performed a case–control study. Operations were divided into the following categories: neurosurgery, ophthalmic surgery, and surgery other than neurosurgery or ophthalmic surgery (other surgery), because neurosurgery or ophthalmic surgery for those with prion diseases are categorized in the guidelines of the CJD Incident Panel in the United Kingdom as high- or medium-risk procedures for transmission of infective PrP (*15*). In these guidelines, procedures involving the olfactory epithelium are also categorized as medium risk (*15*). However, the number of persons who underwent the operation possibly involving the olfactory epithelium is too small to be estimated by statistical analysis (2 sCJD patients and 2 controls underwent surgery for sinusitis), and we categorized these operations as other surgery. Neurosurgery included operations on the brain, cerebral blood vessels, and spinal cord. Ophthalmic surgery included all operations involving the eyeball and optic nerve. Other surgery included all surgical procedures other than neurosurgery and ophthalmic surgery. Furthermore, the committee performed a detailed investigation of sCJD patients who underwent neurosurgery or ophthalmic surgery at a hospital where other patients with any type of prion disease had ever undergone neurosurgery or ophthalmic surgery.

Surgical Procedures after Onset of sCJD

We analyzed sCJD patients who underwent surgical procedures after the onset of sCJD because such procedures might cause secondary transmission of the disease through contaminated instruments. In particular, for neurosurgery and ophthalmic surgery, we investigated the reason for the operation, interval between the operation and onset of sCJD symptoms, age at onset of sCJD, and symptoms at onset of sCJD.

Statistical Analyses

Between the sCJD and control groups, age at onset was compared by Student *t* test, and medical procedures before the onset of diseases were compared by Fisher exact test. The case–control study of surgical procedures and blood transfusions before the onset of diseases was estimated by logistic-regression analysis. Because age at onset was different among sCJD patients (mean ± SD, 67.7 ± 9.5 years) and controls (59.3 ± 16.6 years) ($p<0.0001$), we divided the sCJD patients and controls into 3 categories according to age at disease onset; 31–50 years, 51–70 years, and ≥71 years. We performed a single regression analysis for any operation, neurosurgical procedure, ophthalmic surgical procedure, other operation, and blood transfusion in each age group. The strength of association between sCJD and putative risk factors was assessed by the odds ratios and 95% confidence intervals. Significance was defined as $p<0.05$. Statistical analyses were performed by using StatView J-7.5 (Abacus Concepts, Berkeley, CA, USA).

Results

A total of 990 patients received a diagnosis of definite or probable prion disease. Summary of the characteristics of patients with prion diseases is shown in Table 1, in which 760 patients with sCJD are included. There were 221 patients with "prion disease definitely denied" and "prion disease probably denied." Seven sCJD patients and 11 control patients were excluded from the case–control study because information on medical history was not sufficient for analysis. Diagnoses of the 210 control patients is shown in Table 2.

Medical Procedures before Onset of sCJD

Frequencies of medical procedures before the onset of sCJD in sCJD patients and in controls are compared in Table 3. For both the sCJD and control groups, ≈50% had a history of surgery, and ≈10% had received a blood transfusion. No significant differences were found between them in frequency of any surgery, neurosurgery, ophthalmic surgery, other surgery, or blood transfusion (Table 3). In the logistic-regression analysis, no significant risk was associated with any medical procedures investigated in this study (Table 4).

Five sCJD patients had a history of neurosurgery or ophthalmic surgery at hospitals where neurosurgery or ophthalmic surgery had been performed on patients in whom prion disease later developed (Table 5); intervals between operations at the same hospitals were >3 years (Table 5).

Table 1. Characteristics of patients with definite or probable prion disease, Japan, 1999–2008*

Type of prion disease	No. (%) patients
Sporadic CJD	760 (76.8)
Genetic prion diseases	167 (16.9)
Acquired prion diseases†	62 (6.3)
Unclassified CJD	1 (0.1)
Total	990

*CJD, Creutzfeldt-Jakob disease.
†Acquired prion diseases included 61 cases of dura mater CJD and 1 case of variant CJD.

Surgical Procedures after Onset of sCJD

Except for 2 patients suspected of having prion disease, who had undergone brain biopsy with disposable instruments, 34 (4.5%) of 760 sCJD patients underwent some type of surgical procedure before the diagnosis of prion disease, including neurosurgery in 6 (0.8%), ophthalmic surgery in 14 (1.8%), and other surgery in 16 (2.1%). The 6 case-patients who underwent neurosurgery had these operations within 3 months after sCJD onset: procedures performed for subdural hematoma (n = 3), aneurysm (n = 2), and menigioma (n = 1) (Table 6). All 14 case-patients who underwent ophthalmic surgery underwent operations for cataracts, and 7 of these patients had had visual disturbance as an initial symptom of sCJD (Table 7). Among 5 patients for whom information on the effects of ophthalmic surgery could be obtained, 2 had some improvement of visual symptoms after surgery, but the other 3 patients had no improvement. Although both cataracts and sCJD could contribute to the visual symptoms, sCJD would contribute to visual symptoms in patients who had no effects of ophthalmic surgery. We have obtained information about instrument cleaning and sterilization procedures for 3 of 5 patients who underwent neurosurgery and for 5 of 14 patients who underwent ophthalmic surgery after the onset

Table 2. Diagnoses for 210 controls in case–control study of sCJD, Japan, 1999–2008*

Disease	No. diagnoses
Encephalitis	27
Alzheimer disease	21
Frontotemporal dementia	15
Metabolic encephalopathy	15
Cerebrovascular disorders	12
Spinocerebellar degeneration	12
Corticobasal degeneration	9
Epilepsy	7
Psychiatric disorders	7
Hypoxic encephalopathy	7
Hashimoto encephalopathy	6
Dementia with Lewy bodies	6
Paraneoplastic syndrome	5
Mitochondrial encephalopathy	4
Malignant lymphoma	3
Other disorders	54

*sCJD, sporadic Creutzfeldt-Jakob disease.

Table 3. Medical procedures before disease onset, case–control study of sCJD, Japan, 1999–2008*

Medical procedures	sCJD case-patients, no. (%), n = 753	Controls, no. (%), n = 210
Surgery	372 (49.4)	104 (49.5)
Neurologic	25 (3.3)	13 (6.2)
Ophthalmic	42 (5.6)	11 (5.2)
Other	337 (44.8)	89 (42.4)
Blood transfusion	78 (10.4)	20 (9.5)

*sCJD, sporadic Creutzfeldt-Jakob disease. p values were not significant.

of sCJD. All surgeons reused some of the surgical instruments, but according to the WHO guidelines (*16*), the sterilization methods of the instruments were not appropriate for eliminating infectious PrP, including the use of ethylene oxide gas or incomplete autoclaving.

Discussion

In this case–control study, we found no evidence of increased sCJD risk associated with patient's history of surgical procedures or blood transfusions. In the previous case–control study and in our study, receipt of a blood transfusion was not shown to be a significant risk for CJD (*2–10*). However, whether surgical procedures contribute to the risk for sCJD has been controversial. Our results, in which any operation was not a significant risk for sCJD, were consistent with results of 2 previous large case–control studies (*8,9*) and a reanalysis of results of 3 case–control studies (*10*). Even in the studies with positive results, some different results were provided when the surgical procedures were categorized by affected organ. One previous case–control study indicated significant risk for sCJD after neurosurgical procedures (*3*), but no significant risk was shown in other studies (*5,6,8–10*). Ophthalmic surgery was reported as causing significant risk for sCJD in a case–control study in Australia (*4*) but not in other studies (*5,6–10*).

In a recent study in the United Kingdom (*6*), the increased risk associated with having undergone surgical procedures was restricted to the category "other surgery," which included such procedures as sutures to skin, and the association largely disappeared when the whole of the other-surgery category was excluded. These different results may show little possibility for transmission of infectious PrP through surgical procedures, although we cannot exclude the possibility that such transmission occurs occasionally because iatrogenic CJD exists.

The conflicting results in case–control studies, including ours, may be explained by differences in the area, race, period in which studies were performed, number of patients, and methods as discussed below. Our study, which attempted to determine when medical procedures were associated with an increased risk for sCJD, had the largest number of sCJD patients in case–control studies to date. The relatively small number of controls is a potential limitation. In case–control studies, methods of obtaining data from controls should be the same as those from patients. In our study, patients in the groups "prion diseases definitely denied" or "prion diseases probably denied" in our CJD surveillance, who had no or little possibility of having prion disease, were used as the controls. Therefore, data from controls could be collected at the same level of precision as those from the sCJD cases. Because the ages of the sCJD patients and controls were significantly different, age-stratified analysis was required in our study. A recent study reported that some methodologic differences might partially explain conflicting data regarding the association between surgical procedures and CJD (*17*). The report suggested that the use of controls from the community would be preferable to using those from the hospital because community-based controls are often more representative and would result in a more valid comparison (*17*). Furthermore, using proxy informants for controls may be advisable for the purpose of comparability with case-patients, although this practice does not necessarily offset biases in data ascertainment (*17*). In our case–control study, we used proxy informants for controls who were recruited from hospitals under the same condition as the sCJD case-patients.

Table 4. Medical procedures and risk for sCJD, by age at disease onset, Japan, 1999–2008*

Age range, y	Data category	Total no. patients	Any surgery	Neurosurgery	Ophthalmic surgery	Other surgery	Blood transfusion
31–50	sCJD	32	50.0%	6.3%	6.3%	40.6%	3.1%
	Control	37	45.9%	10.8%	2.7%	37.8%	5.4%
	OR		1.66	0.38	2.15	0.78	0.64
	95% CI		0.04–74.09	0.02–6.64	0.05–101.51	0.02 – 33.39	0.05–9.09
	p value		0.79	0.50	0.70	0.90	0.74
51–70	sCJD	414	43.7%	1.7%	2.2%	41.8%	9.4%
	Control	97	46.4%	5.2%	3.1%	40.2%	11.3%
	OR		0.18	0.69	2.71	5.57	0.84
	95% CI		0.02–1.73	0.13–3.62	0.24–30.38	0.62–50.05	0.40–1.77
	p value		0.14	0.66	0.42	0.13	0.64
≥71	sCJD	317	57.0%	5.2%	10.1%	49.2%	12.4%
	Control	60	65.0%	6.7%	10.0%	56.7%	11.7%
	OR		0.81	0.76	1.15	0.83	1.27
	95% CI		0.15–4.37	0.15–3.80	0.38–3.48	0.17–4.02	0.52–3.10
	p value		0.80	0.74	0.81	0.82	0.60

*sCJD, sporadic Creutzfeldt-Jakob disease; OR, odds ratio; CI, confidence interval.

Regarding the 5 sCJD patients with a history of neurosurgical or ophthalmic surgical procedures at hospitals where other patients with prion disease had previously undergone such procedures, we consider that the possibility of transmission through these procedures was extremely limited because the intervals between procedures and the acquisition of sCJD had been >3 years for all patients. According to the Incident Panel in the United Kingdom, most instruments that have gone through 10 cycles of use and decontamination are unlikely to pose a substantial risk (*15*). We assume that all instruments had gone through >10 cycles of use during the 3-year interval, and almost no infectivity remained on the instruments. In Japan, a large number of dCJD patients have been recognized with no other types of iatrogenic CJD (*11,12*); this study confirmed that no surgically transmitted cases occurred among patients with sCJD.

It is noteworthy that 4.5% of the sCJD patients underwent some types of surgical procedures after the disease onset, including neurosurgical (0.8%) and ophthalmic procedures (1.8%). Through surgical instruments, neurosurgical operations may transmit high infectivity from the brain tissues of sCJD patients, and ophthalmic operations may transmit moderate infectivity of the eye tissues in cases of cataracts (*15*). In this study, all these neurosurgical and ophthalmic procedures were performed without suspicion of prion diseases or special precautions to reduce the risk for secondary transmission of prion infection through the instruments. These findings suggest that delayed diagnosis of sCJD would be linked to increased risk for secondary transmission of prion diseases through surgical instruments. In neurosurgical procedures, the symptoms of sCJD were misdiagnosed as those of other neurologic diseases, and operations were performed near the time of disease onset. In terms of ophthalmic surgery, all patients underwent operations for cataracts, and 7 (50%) of 14 patients had visual disturbances as an initial symptom of sCJD. These data are similar to those in a report from the United Kingdom (*18*). Visual disturbances might prompt ophthalmic surgery. More seriously, 3 patients underwent operations ≥8 months after sCJD onset. In this study, all surgeons who provided information reused the surgical instruments with incomplete sterilization, and the potential for infection was the same as in our previous study of ophthalmic surgery (*19*).

Neurosurgeons and ophthalmologists should become better informed about prion diseases and the necessity of using disposable instruments whenever possible. Further-

Table 5. Characteristics of 5 sCJD patients who underwent neurosurgery or ophthalmic surgery at hospitals where other patients with prion diseases had previously undergone neurosurgery or ophthalmic surgery, Japan, 1999–2008*

Patient	Type of CJD	Onset of CJD	Date of surgery	Reason for surgery
1	sCJD	2003 Aug	1991 Aug	Subarachinoid hemorrhage
	dCJD	2001 May	1976	Spinal cord tumor
			1986 Aug	Spinal cord tumor
2	sCJD	2002 Feb	1994 Sep	Subdural hematoma
			1997 Sep	Cataract
	dCJD	1998 Jan	1987 Jan	Meningioma
3	sCJD	2001 Jan	1989 Apr	Subarachinoid hemorrhage
	dCJD	1995 Jul	1980 Jul	Aneurysm
4	sCJD	2001 Jul	1999	Spinal cord lesion (details unknown)
	dCJD	2001 Aug	1978 Sep	Astrocytoma
5	sCJD	2002 May	2002 Apr	Cataract
	sCJD	2002 May	1997 Aug	Cataract
			1999 Jan	Cataract

*CJD, Creutzfeldt-Jakob disease; sCJD, sporadic CJD; dCJD, Creutzfeldt-Jakob disease associated with cadaveric dura mater graft.

Table 6. Data for sCJD patients who underwent neurosurgery after onset of sCJD symptoms, Japan, 1999–2008*

Patient no.	Reason for surgery	Interval between onset of sCJD symptoms and surgery, mo	Age at onset of sCJD, y	Symptom at onset of sCJD
1	Subdural hematoma	0	71	Dementia
2	Subdural hematoma	0	77	Apathy
3	Subdural hematoma	1	57	Dementia
4	Meningioma	1	74	Vertigo
5	Aneurysm	2	46	Dementia
6	Aneurysm	3	67	Vertigo

*sCJD, sporadic Creutzfeldt-Jakob disease.

Table 7. Data for sCJD patients who had ophthalmic surgery for cataracts after onset of sCJD symptoms, Japan, 1999–2006*

Patient no.	Interval between onset of sCJD symptoms and surgery, mo	Age at onset of sCJD, y	Symptom at onset of sCJD
1	0	60	Gait disturbance
2	0	61	Dementia
3	0	63	Visual impairment
4	0	71	Visual impairment
5	0	74	Visual impairment
6	0	74	Visual impairment
7	1	66	Dementia
8	1	74	Depression
9	1	85	Visual impairment
10	2	79	Tremor
11	4	81	Visual impairment
12	8	77	Anxiety
13	10	57	Dementia
14	14	64	Visual impairment

*sCJD, sporadic Creutzfeldt-Jakob disease.

more, a more sensitive method for early diagnosis of sCJD is needed because clinical diagnosis is sometimes difficult, particularly in atypical sCJD cases, such as MM2, MV2, VV1, or VV2 types (*20–23*), according to 6 phenotypes of sCJD divided by codon 129 polymorphisms of PrP (methionine/valine) and type of infectious PrP by Western blotting (*24*). Even neurologists may misdiagnose the initial stage of the atypical sCJD cases as being another neurodegenrative disease such as Alzheimer disease and progressive supranuclear palsy (*20*). Moreover, patients who have undergone surgical procedures with possibly contaminated instruments need to undergo a risk assessment with long-term follow-up after careful ethical consideration. Since June 2004, we have identified and monitored all patients who underwent neurosurgical procedures with possibly contaminated instruments, CJD has developed in none of those patients.

In conclusion, we did not demonstrate any evidence of increased risk for sCJD associated with a history of surgery or blood transfusion in the Japanese surveillance system. However, the fact that some patients had surgeries, including neurosurgery, even after the onset of sCJD indicates that we cannot deny any possibility of transmission of prion diseases by medical procedures. Neurosurgeons, ophthalmologists, and other surgeons need to focus more attention on prion diseases to reduce the iatrogenic risk, as well as realize that prolonged, careful surveillance of prion diseases is necessary.

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別紙様式第2−1

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 2009年2月9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	CDC／Travelers' Health (Updated: February 04, 2009)	公表国 ジンバブエ	
販売名(企業名)	別紙のとおり					

研究報告の概要	使用上の注意記載状況・その他参考事項等
問題点：ジンバブエにおけるコレラのアウトブレイクで61,304人の感染疑い例、3,181人の死亡例が報告されている。 ジンバブエの保健当局からコレラのアウトブレイクについて報告されている。国連人道問題調整事務所によると、2008年8月26日から2009年1月31日までにジンバブエ国内で61,304人の感染疑い例、3,181人の死亡例が報告されている。被害が大きい地域は、首都のHarare (14,126人感染、592人死亡)、Mashonaland WestManicaland South (7,081人感染、458人死亡) である。コレラの発生例は、ジンバブエの全ての州から報告されている。また、ボツワナ、モザンビーク、ケニヤ、マラウイ、ナミビア、ナイジェリア、ギニアビサウ及びトーゴといった周辺国からも発生例が報告されている。	記載なし

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。

MedDRA/J ver.11.1

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別紙

一般的名称	①人血清アルブミン、②人血清アルブミン、③人血清アルブミン*、④人免役グロブリン、⑤乾燥ペプシン処理人免疫グロブリン、⑥乾燥スルホ化人免疫グロブリン、⑦乾燥スルホ化人免疫グロブリン*、⑧乾燥濃縮人活性化プロテインC、⑨乾燥濃縮人血液凝固第Ⅷ因子、⑩乾燥濃縮人血液凝固第Ⅸ因子、⑪乾燥抗破傷風人免疫グロブリン、⑫抗HBs人免疫グロブリン、⑬トロンビン、⑭フィブリノゲン加第ⅩⅢ因子、⑮乾燥濃縮人アンチトロンビンⅢ、⑯ヒスタミン加人免疫グロブリン製剤、⑰人血清アルブミン*、⑱人血清アルブミン*、⑲乾燥ペプシン処理人免役グロブリン*、⑳乾燥人血液凝固第Ⅸ因子複合体*、㉑乾燥濃縮人アンチトロンビンⅢ
販売名(企業名)	①献血アルブミン20“化血研”、②献血アルブミン25“化血研”、③人血清アルブミン“化血研”*、④“化血研”ガンマーグロブリン、⑤献血静注グロブリン“化血研”、⑥献血ベニロンーⅠ、⑦ベニロン*、⑧注射用アナクトC2,500単位、⑨コンファクトF、⑩ノバクトM、⑪テタノセーラ、⑫ヘパトセーラ、⑬トロンビン“化血研”、⑭ボルヒール、⑮アンスロビンP、⑯ヒスタグロビン、⑰アルブミン20%化血研*、⑱アルブミン5%化血研*、⑲静注グロブリン*、⑳ノバクトF*、㉑アンスロビンP1500注射用
報告企業の意見	コレラは代表的な経口感染症の1つで、コレラ菌で汚染された水や食物を摂取することによって感染する。コレラ菌は、菌体表面のO抗原（リポ多糖体）の違いによって、現在205種類（11種類は未発表）に分類されている。このうち、コレラを起こすのはO1およびO139血清型のみである。わが国におけるコレラは、最近はほとんどが輸入感染症として発見される。すなわち熱帯・亜熱帯のコレラ流行地域への旅行者の現地での感染例である。国内での感染例の報告もあるが、輸入魚介類などの汚染が原因であろうと推定されていて、二次感染例と思われる例はほとんど無い。(http://idsc.nih.go.jp/idwr/kansen/k00-g15/k00_01/k00_01.html) 仮に、本剤の原材料であるヒト血液にコレラ菌が混入していたとしても、弊所で製造している全ての血漿分画製剤の製造工程には、約0.2μmの「無菌ろ過工程」および、コレラ菌よりも小さいウイルスの除去を目的とした平均孔径19nm以下の「ウイルス除去膜ろ過工程」が導入されているので、これらの工程により除去されるものと考えられる。更に、これまでに本剤によるコレラ菌感染の報告例は無い。 以上の点から、本剤はコレラ菌感染に対して一定の安全性を確保していると考えるが、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。

*現在製造を行っていない

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Centers for Disease Control and Prevention Travelers' Health
Your Online Source for Credible Health Information

Outbreak Notice

Cholera in Zimbabwe and Neighboring Countries

This information is current as of today, February 11, 2009 at 23:51

Updated: February 04, 2009

An outbreak of cholera has been reported by health officials in Zimbabwe. According to the United Nations Office of the Coordination of Humanitarian Affairs, from August 26 through January 31, 2009, 61,304 suspected cases and 3,181 deaths have been reported in the country. The worst-affected areas are the capital city of Harare (14,126 cases and 592 deaths), Mashonaland West (14,259 cases and 685 deaths), Manicaland South (7,081 cases and 458 deaths). Cases of cholera have been reported in all of Zimbabwe's provinces. Cases have also been confirmed in the neighboring countries of Botswana, Mozambique, South Africa, and Zambia. Additional sources have reported cases in Angola, Burundi, Democratic Republic of Congo, Kenya, Malawi, Namibia, Nigeria, Guinea-Bissau and Togo.

Cholera is a potentially fatal bacterial infection that causes severe diarrhea and dehydration. The disease is spread through untreated sewage and contaminated drinking water. There is no cholera vaccine available in the United States.

Advice for People Traveling to Zimbabwe

Most travelers are not at high risk for getting cholera, but travelers should be aware of the outbreak and make sure they are taking steps to prevent getting sick. Although no cholera vaccine is available in the United States, U.S. travelers can greatly reduce their risk for cholera by following CDC's safe food and water advice:

- Before departing for Zimbabwe, talk to your doctor about getting a prescription for an antibiotic to treat traveler's diarrhea.
- Drink water that you have boiled for at least one minute or treated with chlorine or iodine. Other safe beverages include tea and coffee made with boiled or treated water, as well as drinks that have been bottled and sealed (such as bottled water, carbonated drinks, and sports drinks).
- Do not put ice in drinks, unless the ice is made from boiled or treated water.
- Eat only foods that have been thoroughly cooked and are still hot, or fruit that you have peeled yourself.
- Do not eat undercooked or raw fish or shellfish, including ceviche.
- Make sure all vegetables are cooked. Do not eat salads or other raw vegetables.
- Do not eat foods and drink beverages from street vendors.
- Do not bring perishable seafood back to the United States.

A simple rule of thumb for safe food and water is "*Boil it, cook it, peel it, or forget it.*"
If you are traveling in Zimbabwe or neighboring countries and have severe watery diarrhea seek medical care right away. It is important to remember to drink fluids and use oral rehydration solution (ORS) to prevent dehydration.

More Information

The United Nations Office for the Coordination of Humanitarian Affairs in Zimbabwe has reported that new cases and deaths due to cholera are increasing. Although Zimbabwe has reported several smaller cholera outbreaks in recent years, this outbreak is more severe and may worsen with the onset of the rainy season. On December 3, the government of Zimbabwe declared a national emergency and appealed for international assistance. The humanitarian community has already been responding to this outbreak with water, sanitation, and hygiene initiatives in outbreak areas. WHO and its Health Cluster partners are finalizing a "Cholera Response Operational Plan" to evaluate and control the current outbreak.

For more information about the cholera outbreak in Zimbabwe, including maps:

- Weekly Situation Report (/travel/forward.aspx?t=aHR0cDovL29jaGFvbmxpbmUudW4ub3JnL0RlZmF1bHQuYXNweD9hbGlhcz1vY2hhb25saW5lLnVuLm9yZy96aW1iYWJ3ZQ%3d%3d-uddp6JMnq70%3d) —United Nations Office for the Coordination of Humanitarian Affairs (February 3, 2009)
- Cholera in Zimbabwe (/travel/forward.aspx?t=aHR0cDovL3d3dy53aG8uaW50L2Nzci9kb24vMjAwOF8xMl8wMi9bi9pbmRleC5odG1s-SD6LRlB9hkU%3d) —World Health Organization (December 2, 2008)
- Relief Web (/travel/forward.aspx?t=aHR0cDovL3d3dy5yZWxpZWZ3ZWIuaW50L3J3L2RiYy5uc2YvZG9jMTE1P09wZW5Gb3JtJnJPTE%3d-HYAld4y5GyY%3d) , Zimbabwe—United Nations, Office of the Coordination of Humanitarian Affairs, (January 31, 2009)

For more information for travelers:

- Warden Message about cholera, November 26, 2008 (/travel/forward.aspx?t=aHR0cDovL2hhcmFyZS51c2VtYmFzc3kuZ292LzExLzI2LzMvDQuaHRtbA%3d%3d-l2qel6aC740%3d) —American Embassy in Harare, Zimbabwe Warden messages (/travel/forward.aspx?t=aHR0cDovL2hhcmFyZS51c2VtYmFzc3kuZ292L3dhcmRlbi5odG1s-PuVXy907AcA%3d)
- Travel Warning about cholera, December 12, 2008 (/travel/forward.aspx?t=aHR0cDovL2hhcmFyZS51c2VtYmFzc3kuZ292L3ppbWJhYndlX3RyYXZlbHdhcm5pbmoyLmh0bVw%3d-dhUsw6uJ%2bDU%3d) —American Embassy in Harare, Zimbabwe

- Cholera (yellowBookCh4-Cholera.aspx) (from *CDC Health Information for International Travel 2008*)
- Safe food and water (contentSafeFoodWater.aspx) (CDC Travelers' Health website)

For more information about cholera, see the following CDC links:

- Cholera (http://www.cdc.gov/nczved/dfbmd/disease_listing/cholera_gi.html) (from CDC, Division of Foodborne, Bacterial, and Mycotic Diseases)
- Cholera (yellowBookCh4-Cholera.aspx) (from *CDC Health Information for International Travel 2008*)

To find medical care in Zimbabwe:

- On the web: List of local medical specialists (/travel/forward.aspx?t=aHR0cDovL2hhcmFyZS51c2VtYmFzc3kuZ292L21fZGJjYWxfaW5mb3JtYXRpb24uaHRtbA%3d%3d-U8dFKbSICao%3d) (Embassy of the United States, Harare, Zimbabwe)
- By phone: 263-4-250593/4 Consular section of the United States Embassy, Harare, Zimbabwe: American Citizen Services

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  National Center for Preparedness, Detection, and Control of Infectious Diseases

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