別紙様式第 2-1

別紙 3

医薬品研究報告　調査報告書

識別番号・報告回数		回	報告日 年　月　日	第一報入手日 2012 年 12 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	BSE, Bovine-Brazil http://www.promedmail.org/direct.php?id=20121208.1443015	公表国 ブラジル	
販売名（企業名）						

研究報告の概要

2010 年 12 月 18 日に、ブラジルの Official Veterinary Services(OVS)は、Sertanopolis 自治体の農業借地所有者から、四肢を硬直させ横臥状態のウシについて報告を受けた。このウシは定期検査の際に発見されたとの報告であった。翌日に OVS がその農業借地を尋ねたところ、当該ウシは死亡したとの情報を入手した。
当該ウシは、肉牛繁殖用で、死亡時の年齢は 13 歳であった。OVS は関連情報を収集すると伴に死亡原因特定のための試料を採取した。この地区では草食動物における狂犬病の発生が認められていたので、国の指示に従い、狂犬病診断および鑑別診断のための検査試料が採取された。
神経疾患が疑われる場合に適応される規制と通常の手続きに従い、試料を用いて狂犬病の検査が施行されたが、結果は陰性であった。成獣であったので、試料は、牛海綿状脳症の監視体制のための分析研究所に送付された。
2011 年 4 月 11 日に、OVS 公認の研究所において、病理組織学的検査により牛海綿状脳症は陰性であるとの結果が得られた。
一方、試料は、National Reference Laboratory、National Agricultural Laboratory にも送付され、2012 年 6 月 15 日に、免疫組織化学的検査によって牛海綿状脳症が陽性であるとの結果が得られた。
同試料は、イギリスにある国際獣疫事務局の付託研究施設にも送付された。2012 年 12 月 6 日に、免疫組織化学検査により牛海綿状脳症陽性であることが確認された。今回の牛海綿状脳症はブラジルにおける最初の症例であった。

報告企業の意見	今後の対応
コージネイト FS の製造工程においてアフィニティークロマトグラフィーを用いているが、このリガンドであるマウス IgG モノクローナル抗体産生細胞の培養液にウシインスリンが添加されている。このウシインスリンの一連の製造・精製工程はプリオンを高率に除去できることが確認されている。従って，プリオンがコージネイト FS に混入する可能性は極めて低いと考えられる。	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。引き続き関連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

BYL-2013-0415

BSE, Bovine-Brazil
http://www.promedmail.org/direct.php?id=20121208.1443015

15

MedDRA version 15.1

ProMED-mail

BYL-2013-0415

1/4 ページ

Published Date: 2012-12-08 11:46:03
Subject: PRO/AH/EDR> BSE, bovine - Brazil: (PR)
Archive Number: 20121208.1443015

BSE, BOVINE - BRAZIL: (PARANA)
****
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: 7 Dec 2012

Source: OIE [edited]
http://www.oie.int/wahis_2/temp/reports/en_imm_0000012682_20121207_181754.pdf

Information received on 07 Dec 2012 from Dr Figueiredo Marques Guilherme Henrique, Director, Departamento de Saede Animal, Ministerio da Agricultura, Pecuaria e Abastecimento, Brasilia, Brazil

Summary:

Report type: Immediate notification

Date of start of the event 18 Dec 2012

Date of pre-confirmation of the event 15 Jun 2012

Report date: 07 Dec 2012

Date submitted to OIE: 07 Dec 2012

Reason for notification: 1st occurrence of a listed disease

Manifestation of disease: Sub-clinical infection

Causal agent Prion responsible for bovine spongiform encephalopathy

Nature of diagnosis Laboratory (advanced)

This event pertains to the whole country

New outbreaks

Summary of outbreaks: Total outbreaks: 1

Outbreak Location: Parana (Sertanopolis)

Total animals affected

Species / Susceptible / Cases / Deaths / Destroyed / Slaughtered

Cattle / 148 / 1 / 1 / 0 / 0

Outbreak statistics:

Species: Cattle

Apparent morbidity rate: 0.68 percent

Apparent mortality rate: 0.68 percent

Apparent case fatality rate: 100 percent

Proportion susceptible animals lost* 0.68 percent *

*Removed from the susceptible population through death, destruction and/or slaughter;

Epidemiology

Source of the outbreak(s) or origin of infection: Unknown or inconclusive

Epidemiological comments: On 18 Dec 2010, the Official Veterinary Services (OVS) were informed by the owner of a holding in the municipality of Sertanopolis (State of Parana) on a recumbent bovine showing limb stiffness which was detected during routine inspection. Next day, when the OVS were going to visit the holding, they were informed by the stockman that the animal was dead.

The OVS went to the holding to collect information and samples for the diagnosis of the cause of the death. As it is an area where rabies is present in herbivores, samples were taken for the diagnosis of this disease and for differential diagnosis, as recommended by the national protocol. The animal was properly buried on site. The animal was a beef breeding cow almost 13 years old at the time of death, according to information obtained during the epidemiological investigations.

According to regulations and routine procedures to be implemented in case of suspected neurological diseases, the sample was tested for rabies and it was negative. As it was an adult animal negative for rabies, the sample was sent for laboratory analysis within the surveillance system for bovine spongiform encephalopathy (BSE).

On 11 Apr 2011, a negative histopathological result for BSE was obtained in a laboratory accredited by the OVS. The sample was sent to the National Reference Laboratory, National Agricultural Laboratory (LANAGRO-PE), Recife, Pernambuco, for BSE diagnosis and it tested positive on 15 Jun 2012 by immunohistochemical test.

The delay between the 2 tests was caused by an incident occurred in one of the laboratories of the accredited network for the diagnosis of BSE. That led to overload the system and to prioritize the diagnosis of samples which met BSE-risk characteristics, as established by the OIE. The sample belonged to the group "fallen stock" and to the age group "over 9 years," according to the Article 11.5.22 of the OIE Terrestrial Animal Health Code. This classification led to consider the sample as showing a low diagnosis priority level, which resulted in a longer than expected delay from histopathological to immunohistochemical tests.

According to the procedure manual on response to the occurrence of a BSE event in Brazil and as it is

the 1st occurrence in the country, the sample was sent for confirmatory diagnosis to the OIE Reference Laboratory for this disease, Animal Health and Veterinary Laboratories Agency (AHVLA), Weybridge, United Kingdom. The sample tested positive in immunohistochemical test on 6 Dec 2012.

The epidemiological investigation shows that the animal's death was not caused by BSE and suggests that it may be an atypical case of the disease occurring in the oldest animals. Information collected during the epidemiological investigation shows also that the animal was reared in an extensive system on grazing.

Note by the OIE: Brazil is still recognized by the OIE as having a negligible BSE risk in accordance with Chapter 11.5. of the OIE Terrestrial Animal Health Code.

Control measures

Measures applied: No vaccination

No treatment of affected animals

Measures to be applied: No other measures

Diagnostic test results

Laboratory name and type: Animal Health Laboratory - IMA (National laboratory)

Tests and results

Species / Test / Test date / Result

Cattle / histological test / 11 Apr 2011 / Negative

Laboratory name and type: National Agricultural Laboratory (LANAGRO-PE) (National laboratory)

Tests and results:

Species / Tests / Test date / Result

Cattle / immunohistochemical tests / 15 Jun 2012 / Positive

Laboratory name and type: Animal Health and Veterinary Laboratories Agency (AHVLA) (OIE's Reference Laboratory)

Tests and results:

Species / Test / Test date / Result

Cattle / immunohistochemical test / 06 Dec 2012 / Positive

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Communicated by:

ProMED-mail

<promed@promedmail.org>

[This is the 1st report of BSE (Bovine Spongiform Encephalopathy) in Brazil. While the OIE regards Brazil as a negligible risk, there are some countries who may view this differently, especially as they look at meat that may be exported.

The determination of this case as a sporadic case may take some investigation or analysis. Without such an analysis to prove this was a sporadic case, there is a large shadow of doubt that may creep over countries importing product from Brazil.

Other countries and likely the OIE will be looking to see what type of surveillance program Brazil may put into effect. With an eye toward the export markets, Brazil will likely analyze the situation and put into place a surveillance mechanism and a thorough investigation of the situation.

Parana, Brazil, may be found on the interactive Healthmap/ProMED-mail map at:
http://healthmap.org/r/3yzA - Mod.TG]

See Also

BSE, bovine - USA (06): (CA) 20120805.1228663
BSE, bovine - USA (05): (CA) 20120504.1122322
BSE, bovine - USA (04): (CA) 20120501.1119136
BSE, bovine - USA (03): (CA) 20120429.1117352
BSE, bovine - USA (02): (CA) OIE 20120428.1116584
BSE, bovine - USA: (CA) 4th animal confirmed 20120425.1113102
2011
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BSE - Japan (03): NOT, official statement 20111202.3501
BSE - Japan (02): 37th case, NOT 20111129.3485
BSE - Japan: 37th case, atypical, RFI 20111129.3480
BSE - Switzerland (02): (BE) OIE 20110527.1621
BSE - Switzerland: (SG) OIE 20110504.1381
BSE, bovine - Canada: (MB), Correction (AB) 20110306.0725
BSE, bovine - Canada: (AB) 20110305.0720
BSE, bovine - Canada: (MB) 20110305.0720
BSE - Netherlands: (FR), OIE 20110122.0272
2010
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BSE - Netherlands (02): (NB), OIE 20101023.3843
BSE - Netherlands: new case 20100904.3176
BSE, bovine - Canada: (AB) 20100311.0792
.....as/tg/ejp/mpp

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
				2013年1月31日	該当なし。		
一般的名称	別紙のとおり。	研究報告の公表状況	重症熱性血小板減少症候群に関する報道発表資料（厚生労働省、2013年1月30日）		公表国	日本	
販売名（企業名）	別紙のとおり。						使用上の注意記載状況・その他参考事項等
							記載なし。

研究報告の概要

問題点：山口県において、中国で2009頃より発生が報告された、新規なフレボウイルス属ウイルスによる新しいダニ媒介性疾患「重症熱性血小板減少症候群（Severe Fever with Thrombocytopenia Syndrome：SFTS）」の国内最初の症例（患者１名：昨秋に死亡。最近の海外渡航歴なし。）が確認された。本ウイルスはSFTSウイルス（SFTSV）と命名され、クリミア・コンゴ出血熱やリフトバレー熱等の原因ウイルスと同じブニヤウイルス科に属し、ヒトへの感染はダニに咬まれることの他、患者体液との直接接触による感染も報告されている。潜伏期間は６日～２週間で、発熱、頭痛等の他、意識障害等の症状を呈することもあり、致死率は10%を超える。
厚生労働省では、都道府県等へ本疾患に関する情報提供を行うとともに、医療機関に対して、同様の患者を診察した際は情報提供するよう、自治体を通じて協力を要請している。

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。

16

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人免役グロブリン、⑥乾燥ペプシン処理人免疫グロブリン、⑦乾燥ペプシン処理人免疫グロブリン、⑧乾燥スルホ化人免疫グロブリン、⑨乾燥スルホ化人免疫グロブリン、⑩乾燥スルホ化人免疫グロブリン、⑪乾燥スルホ化人免疫グロブリン、⑫乾燥スルホ化人免疫グロブリン*、⑬乾燥濃縮人活性化プロテインC、⑭乾燥濃縮人血液凝固第Ⅷ因子、⑮乾燥濃縮人血液凝固第Ⅷ因子、⑯乾燥濃縮人血液凝固第Ⅷ因子、⑰乾燥濃縮人血液凝固第Ⅸ因子*、⑱乾燥濃縮人血液凝固第Ⅸ因子*、⑲乾燥濃縮人血液凝固第Ⅸ因子*、⑳乾燥濃縮人血液凝固第Ⅸ因子、㉑乾燥濃縮人血液凝固第Ⅸ因子、㉒乾燥濃縮人血液凝固第Ⅸ因子、㉓乾燥抗破傷風人免疫グロブリン、㉔抗 HBs 人免疫グロブリン、㉕トロンビン、㉖フィブリノゲン加第ⅩⅢ因子*、㉗フィブリノゲン加第ⅩⅢ因子、㉘乾燥濃縮人アンチトロンビンⅢ、㉙ヒスタミン加人免疫グロブリン製剤、㉚人血清アルブミン*、㉛人血清アルブミン*、㉜乾燥ペプシン処理人免役グロブリン*、㉝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ガンマーグロブリン筋注 450mg/3mL「化血研」、⑤ガンマーグロブリン筋注 1500mg/10mL「化血研」、⑥献血静注グロブリン "化血研"、⑦献血グロブリン注射用 2500mg「化血研」、⑧献血ベニロン－Ⅰ静注用 500mg、⑨献血ベニロン－Ⅰ静注用 1000mg、⑩献血ベニロン－Ⅰ静注用 2500mg、⑪献血ベニロン－Ⅰ静注用 5000mg、⑫ベニロン*、⑬注射用アナクトC2,500 単位、⑭コンファクトF注射用 250、⑮コンファクトF注射用 500、⑯コンファクトF注射用 1000、⑰ノバクトM注射用 250*、⑱ノバクトM注射用 500*、⑲ノバクトM注射用 1000*、⑳ノバクトM静注用 400 単位、㉑ノバクトM静注用 800 単位、㉒ノバクトM静注用 1600 単位、㉓テタノセーラ筋注用 250 単位、㉔ヘパトセーラ筋注 200 単位/mL、㉕トロンビン "化血研"、㉖ボルヒール*、㉗ボルヒール組織接着用、㉘アンスロビンP500 注射用、㉙ヒスタグロビン皮下注用、㉚アルブミン 20%化血研*、㉛アルブミン 5%化血研*、㉜静注グロブリン*、㉝アンスロビンP1500 注射用
報告企業の意見	Sever Fever with Thrombocytopenia syndrome virus (SFTSV) は新規なフレボウイルス属のウイルスで、核酸は一本鎖 RNA、エンベロープを有し、中国で 2009 年頃から報告されている重症熱性血小板減少症候群の原因ウイルスである。 今回の報告は、山口県で重症熱性血小板減少症候群の国内最初の症例が確認され、当該患者は死亡したとの報告である。 上記製剤の製造工程には、冷アルコール分画工程、ウイルス除去膜ろ過工程、加熱工程等の原理の異なるウイルスクリアランス工程が導入されており、各工程のウイルスクリアランス効果は「血漿分画製剤のウイルスに対する安全性確保に関するガイドライン（医薬発第 1047 号、平成 11 年 8 月 30 日）」に基づく、モデルウイルスを用いたウイルスプロセスバリデーションにより確認されている。今回報告した SFTSV のモデルウイルスには、エンベロープの有無、核酸の種類等から、ウシウイルス性下痢ウイルス（BVDV）が該当すると考えられるが、上記工程の BVDV クリアランス効果については上記バリデーションにより確認されている。また、これまでに上記製剤による SFTSV への感染報告例は無い。 以上の点から、上記製剤は新規フレボウイルス属のウイルス感染に対する安全性を確保していると考える。

*：現在製造を行っていない

INF2012-004

厚生労働省 Ministry of Health, Labour and Welfare

平成25年1月30日
【照会先】厚生労働省健康局結核感染症課
感染症情報管理室長　中嶋　建介（内線2389）
課長補佐　難波江　功二（内線2373）
（代表番号）03(5253)1111
（直通番号）03(3595)2257

報道関係者　各位

中国で近年報告されている新しいダニ媒介性疾患の患者が国内で確認されました

今般、中国において2009年頃より発生が報告され、2011年に初めて原因ウイルスが特定された新しいダニ媒介性疾患「重症熱性血小板減少症候群（Severe Fever with Thrombocytopenia Syndrome: SFTS）」の症例（患者1名：昨秋に死亡。最近の海外渡航歴なし。）が、山口県において確認されました（別添1）。
これを受けて、厚生労働省では、本疾患に関する資料（別添2、3）を作成し、都道府県等に情報提供を行うとともに、医療機関に対して、同様の患者を診察した際は情報提供するよう、自治体を通じて協力を要請したところです（別添4）。
厚生労働省では、引き続き、本疾患に関する情報収集や調査研究を実施し、適切な対応を行ってまいります。

- （別添1）病原微生物検出情報（IASR）速報　国内で初めて診断された重症熱性血小板減少症候群患者（PDF:KB）
- （別添2）重症熱性血小板減少症候群について（PDF:KB）
- （別添3）重症熱性血小板減少症候群に関するQ&A（PDF:KB）
- （別添4）厚生労働省結核感染症課長通知「重症熱性血小板減少症候群（SFTS）の国内での発生について（情報提供及び協力依頼）」（平成25年1月30日）（PDF:KB）

厚生労働省

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
				2013. 1. 30	該当なし	
一般的名称	新鮮凍結人血漿		研究報告の公表状況	病原微生物検出情報(IASR);Available from: http://www.nih.go.jp/niid/ja/sfts/sfts-iasrs/3142-pr3963.html	公表国 日本	
販売名(企業名)	新鮮凍結血漿-LR「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」成分採血(日本赤十字社) 新鮮凍結血漿-LR「日赤」120(日本赤十字社) 新鮮凍結血漿-LR「日赤」240(日本赤十字社) 新鮮凍結血漿-LR「日赤」480(日本赤十字社)					

研究報告の概要

○国内で初めて診断された重症熱性血小板減少症候群患者
国内で初めて、発熱や血小板減少等の症状を呈して亡くなった患者が、ウイルス学的に重症熱性血小板減少症候群ウイルス(SFTSV)による感染症であると診断された。
患者(海外渡航歴なし)は2012年秋、発熱、嘔吐、下痢(黒色便)を呈し入院したが、全身状態が悪化し死亡した。入院中に採取された血液からウイルスが分離され、SFTSVと同定された。また血液中にSFTSV遺伝子が含まれることが確認された。
SFTSVはクリミア・コンゴ出血熱やリフトバレー熱、腎症候性出血熱やハンタウイルス肺症候群の原因ウイルスと同様にブニヤウイルス科に属する。中国からの報告ではマダニからウイルスが分離されており、SFTSVの宿主はダニであると考えられている。ヒトへの感染はSFTSVを有するダニに咬まれることによるが、患者血液や体液との直接接触による感染も報告されている。SFTSVに感染すると6日～2週間の潜伏期を経て、発熱、消化器症状、頭痛、筋肉痛、神経症状、リンパ節腫脹、呼吸器症状、出血症状等の症状が出現し、致死率は10%を超える。
有効性が確認された治療法やワクチンはない。SFTSVに感染しないようにするには、ダニに咬まれないようにすることが重要である。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿-LR「日赤」
新鮮凍結血漿-LR「日赤」成分採血
新鮮凍結血漿-LR「日赤」120
新鮮凍結血漿-LR「日赤」240
新鮮凍結血漿-LR「日赤」480

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
発熱や血小板減少等の症状を呈して亡くなった海外渡航歴のない患者が、国内で初めて、ウイルス学的にブニヤウイルスに属する重症熱性血小板減少症候群ウイルス(SFTSV)による感染症であると診断されたとの報告である。	今後も引き続き情報の収集に努める。

17

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JRC20137-003

<速報> 国内で初めて診断された重症熱性血小板減少症候群患者

(掲載日 2013/1/30)

重症熱性血小板減少症候群(severe fever with thrombocytopenia syndrome, SFTS)はブニヤウイルス科フレボウイルス属に分類される新規ウイルス、SFTSウイルス(SFTSV)、によるダニ媒介性感染症である。2011年に中国でSFTSと命名された新規感染性疾患が報告されて以来1)、中国国内の調査から現在7つの省(遼寧省、山東省、江蘇省、安徽省、河南省、河北省、浙江省)で患者発生が確認されている1,2)。国内で初めて、発熱や血小板減少等の症状を呈して亡くなられた患者が、ウイルス学的にSFTSVによる感染症と診断されたので報告する。

2012年秋、海外渡航歴のない成人患者に、発熱、嘔吐、下痢(黒色便)が出現した。入院時身体所見では、明らかなダニ咬傷はなく、血液検査所見では、白血球数(400/mm^3)と血小板数(8.9×10^4/mm^3)が著明に低下していた。また、AST、ALT、LDH、CKの高値が認められた。血液凝固系の異常、フェリチンの著明な上昇も認められた。尿検査で血尿、蛋白尿が認められた。胸腹部単純CTでは右腋窩リンパ節腫大を認めた。骨髄穿刺検査により、マクロファージによる血球貪食像を伴う低形成髄の所見が認められた。その後に四肢脱力および肉眼的血尿と多量の黒色便を認め、全身状態が不良となり死亡した。入院中に採取された血液からウイルスが分離され、SFTSVと同定された。また血液中にSFTSV遺伝子が含まれることが確認された。血清はELISA、IF法によるSFTSVに対する抗体検査において陰性であった。病理組織においてSFTSVの抗原及び核酸が確認された。

SFTSVは3分節の1本鎖RNAを有するウイルスで、クリミア・コンゴ出血熱やリフトバレー熱、腎症候性出血熱やハンタウイルス肺症候群の原因ウイルスと同様にブニヤウイルス科に属する。中国からの報告では、マダニ[フタトゲチマダニ(*Haemaphysalis longicornis*)、オウシマダニ(*Rhipicephalus microplus*)]からウイルスが分離されており1, 3)、SFTSVの宿主はダニであると考えられている。また、ダニに咬まれることの多い哺乳動物からSFTSVに対する抗体が検出されていることから、これらの動物もSFTSVに感染するものと考えられる1)。ヒトへの感染は、SFTSVを有するダニに咬まれることによるが、他に患者血液や体液との直接接触による感染も報告されている4)。ウイルス血症を伴う動物との接触による感染経路もあり得ると考えられる。SFTSVに感染すると6日～2週間の潜伏期を経て、発熱、消化器症状(食欲低下、嘔気、嘔吐、下痢、腹痛)、頭痛、筋肉痛、神経症状(意識障害、けいれん、昏睡)、リンパ節腫脹、呼吸器症状(咳、咽頭痛)、出血症状(紫斑、下血)等の症状が出現し、致死率は10%を超える1, 5)。SFTSはダニ媒介性ウイルス感染症であることから、流行期はダニの活動が活発化する春から秋と考えられる。ダニは日本国内に広く分布する。ただし、詳細はこれからの研究を待たなくてはならない。

確定診断には、血液などからのSFTSVの分離・同定、RT-PCRによるSFTSV遺伝子検出、急性期及び回復期におけるSFTSVに対する血清IgG抗体価、中和抗体価の有意な上昇の確認が必要であり、現在国立感染症研究所ウイルス第一部で検査が可能である。治療に関しては、リバビリン使用の報告があるが2)、その有効性は確認されていない。基本的に対症療法となる。有効なワクチンはない。

医療機関における院内感染予防には、ヒトからヒトに感染する接触感染経路があることから4)、標準予防策の遵守が重要である。また、臨床症状が似た患者を診た場合にはSFTSを鑑別診断に挙げることが重要である。

SFTSVに感染しないようにするには、ダニに咬まれないようにすることが重要である。草むらや藪など、ダニの生息する場所に入る場合には、長袖の服、長ズボン、足を完全に覆う靴を着用し、肌の露出を少なくすることが重要である。

SFTSが疑われる患者を診た場合には、最寄りの保健所、または、国立感染症研究所問い合わせ窓口(info[アットマーク]nih.go.jp)に連絡していただきたい。
*[アットマーク]は@に置き換えて送信してください。

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別紙様式第2-1

No. 7

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
				2013. 2. 15	該当なし	
一般的名称	新鮮凍結人血漿		研究報告の公表状況	Tang X, Wu W, Wang H, Du Y, Liu L, Kang K, Huang X, Ma H, Mu F, Zhang S, Zhao G, Cui N, Zhu BP, You A, Chen H, Liu G, Chen W, Xu B. J Infect Dis. 2013 Mar;207(5):736-9. doi: 10.1093/infdis/jis748. Epub 2012 Dec 6.	公表国 中国	
販売名（企業名）	新鮮凍結血漿-LR「日赤」（日本赤十字社） 新鮮凍結血漿-LR「日赤」成分採血（日本赤十字社） 新鮮凍結血漿-LR「日赤」120（日本赤十字社） 新鮮凍結血漿-LR「日赤」240（日本赤十字社） 新鮮凍結血漿-LR「日赤」480（日本赤十字社）					

研究報告の概要

○感染血液との接触による重症熱性血小板減少症候群ブニヤウイルスのヒトからヒトへの伝播
2010年5月～6月に発生した重症熱性血小板減少症候群（SFTS）のアウトブレイクの感染経路を同定するために調査を行った。発端患者は58歳男性で、5月20日に発熱、疲労、筋肉痛、咳、悪心を呈し、5月30日に死亡した。6月6日～8日、発端患者と接触があった31人（医療従事者、家族、親戚と友人、葬儀屋）のうち4人（3人は家族）が二次感染し、SFTSと一致する症状を発症した。これらの二次感染患者には、ダニの咬傷、野生動物との接触、他のSFTS患者との接触がなかった。二次感染した3人の家族は、手袋等の防護をせずに患者の血液に触れており、その後発症した。患者の血液に触れていない家族や親戚、友人は発症しなかった。また、患者を診た医療従事者16人も、保護具を装着せずに診察した医師も含め、発症していない。
調査によると、二次感染には患者血液との接触が有意に関連していたが、呼吸器からの分泌物、尿、便との接触とは有意な関連性はなかった。発端患者の粘膜や皮膚の創傷からの血液への接触及び看護時の保護具の未装着がSFTSのリスクを用量反応的に上昇させた。発端患者及び二次感染した息子の急性期血清からSFTSウイルスが分離され、これら2分離株の全ゲノム配列は99.99%の類似性を示した。二次感染患者4人全員の回復期血清において、IgG抗体が陽性であった。無症状の接触者27人は、ウイルスRNA及びIgG抗体のいずれも陰性であった。
これらのことから、発端患者の血液との接触が二次感染者の感染源と推定できるが、他の感染源がある可能性もある。患者の家族及び医療従事者は、患者の血液や体液に直接触れないよう、防護策をとることを推奨する。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿-LR「日赤」
新鮮凍結血漿-LR「日赤」成分採血
新鮮凍結血漿-LR「日赤」120
新鮮凍結血漿-LR「日赤」240
新鮮凍結血漿-LR「日赤」480

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
2010年5月～6月に発生した重症熱性血小板減少症候群アウトブレイクの感染経路を調査した結果、発端患者の血液への接触が二次感染に有意に関連していたことが分かったとの報告である。	今後も引き続き情報の収集に努める。

18

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BRIEF REPORT

Human-to-Human Transmission of Severe Fever With Thrombocytopenia Syndrome Bunyavirus Through Contact With Infectious Blood

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We investigated an outbreak of severe fever with thrombocytopenia syndrome (SFTS) that occurred during May and June 2010, to identify the mode of transmission. Contact with the index patient's blood was significantly associated with development of SFTS ($P = .01$, by the χ^2 test for linear trend); the frequency of contact with the index patient's blood increased the risk of SFTS in a dose-response manner ($P = .03$, by the χ^2 test for linear trend). We concluded that human-to-human transmission caused this cluster of cases.

Keywords. severe fever with thrombocytopenia syndrome virus (SFTSV); human-to-human transmission; blood.

In May 2007, a life-threatening disease characterized by the sudden onset of fever, thrombocytopenia, and leukopenia was first reported in several provinces in central and northeast China [1, 2]. A novel bunyavirus was identified as the causative agent of this disease. The disease is referred to as fever, thrombocytopenia, and leukopenia syndrome (FTLS) or as severe fever with thrombocytopenia syndrome (SFTS), and the virus is designated FTLSV or SFTSV, respectively [1, 2]. Tick bites were presumed to be the mode of transmission, although no definitive evidence associated with this hypothesis has been identified [1, 2].

During May–June 2010, a cluster of 5 suspected cases of SFTS occurred in Henan Province in central China, with 1 death. We investigated this cluster to confirm the diagnosis and identify the mode of transmission.

METHODS

We defined a laboratory-confirmed case of SFTSV infection as the presence of ≥1 of the following findings: a blood culture positive for SFTSV, identification of viral RNA through reverse transcription polymerase chain reaction (RT-PCR), and seroconversion or a 4-fold increase in anti-SFTSV immunoglobulin G (IgG) titers between acute- and convalescent-phase sera.

We collected acute-phase serum from the index patient and paired sera from the ill contacts, with acute-phase sera collected <7 days after onset and convalescent-phase sera collected >6 weeks after onset. Sera were also collected from the asymptomatic contacts of the index patient 6 weeks after exposure. Ticks were collected from the domestic animals (2 cows and 1 dog) kept by the index patient. An immunofluorescence assay was used to detect anti-SFTSV IgG [1], and RT-PCR (QIAamp viral RNA Mini Kit 52904, Qiagen, Hilden, Germany), using a specific RNA-dependent RNA polymerase gene primer set, was performed to detect SFTSV RNA [1]. Virus was isolated by inoculating acute-phase sera into 2 wells of Vero E6 cells.

In a retrospective cohort study, we performed a verbal autopsy of the deceased index patient by questioning his wife, younger son, and daughter; the village clinic doctors; the head of the village; and the doctors and nurses who treated the patient. We also interviewed the ill and asymptomatic contacts of the index patient about their symptoms of SFTS and possible risk factors for infection, including their exposure to the index patient, exposure to wild animals, and history of tick bites. All participants provided verbal informed consent for anonymous use of their specimens and clinical information for research. The institutional review boards of all participating institutions approved this study.

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CASE REPORT

The index patient was a 58-year-old man, who, on 20 May 2010, experienced a sudden onset of fever (39.5°C), fatigue, myalgia, cough, and nausea. He initially received a diagnosis of influenza and was treated for 4 days in the village clinic with cefazolin, Shuanghuanglian (an herbal antiviral and antibiotic [3]), and dexamethasone (for fever reduction). On 25 May, his symptoms worsened, and he developed facial flushing and conjunctivitis and began vomiting, and he was transferred to municipal hospital A. On 26 May, he was transferred to municipal hospital B, where he received a diagnosis of suspected human granulocytic anaplasmosis [4] and was treated with doxycycline. However, his condition continued to deteriorate progressively; he developed nasal and oral bleeding at approximately 6:15 AM on 30 May and died at approximately 12:45 PM. During the verbal autopsy, the index patient's next of kin denied that the index patient had a history of tick bite before onset of illness. The index patient mostly worked in the field around his house during the 15 days prior to the onset of his illness. However, he often took cows to graze in the hills, and ticks were often found on the cows. During our investigation, we found that the index patient had 2 cows and 1 dog. We collected 9 ticks from the 2 cows, but no ticks were found on the family dog; all ticks, however, tested negative for SFTSV RNA by RT-PCR [1].

We identified 31 contacts with the index patient during his illness, including 16 healthcare workers, 10 family members, 4 relatives and friends, and the village funeral director. During 6–8 June, 4 of these individuals (13%) developed secondary SFTSV infection, with clinical signs and symptoms consistent with SFTS (Supplementary Figure 1) [1]. Of these 4 individuals, 3 were members of the index patient's family. Since 2006, one son (son 1) had resided in another city (Ninbo, Zhejiang Province), approximately 1300 km away, in which SFTSV infection has never been reported [1, 2]. Hearing of his father's grave illness, son 1 went directly to the hospital on 29 May and stayed at the bedside for 2 days, until his father's death. Son 1 became ill on 6 June. The index patient's other son (son 2) resided in the same village as the index patient, and he had visited his father every 3–5 days before his father became ill [1]. Son 2 began caring for the index patient on 25 May. The index patient's daughter resided in another county, approximately 20 km away, and went to the hospital to care for her father during 26–30 May. She had not seen her father during the 30-day period before 26 May. Son 2 and the daughter both became ill on 7 June. The only nonfamilial secondary case was the village funeral director, who resided in the same village and had unprotected contact with the index patient's blood from 1:00–4:00 PM on 30 May, after he sustained a cut on his right index finger while washing and clothing the body with his bare hands. He became ill on 8 June. All secondary cases denied tick bites, contact with wild animals, or exposure to other patients with SFTS during the 15-day period before the onset of their illness.

During the index patient's final hours of life, while he bled profusely from his mouth and nose, 5 of 10 family members were at the bedside; none wore rubber gloves or gowns. Three of these family members helped to wipe off the index patient's blood without wearing personal protection, and blood splashed onto their faces. All 3 became ill, showing clinical signs and symptoms consistent with SFTS [1]. The other 2 family members had no contact with the patient's blood but were only present in the ward; neither became ill. Four relatives and friends visited the index patient and talked with him during the early stages of his illness, when there was no bleeding, and none became ill.

The 16 healthcare workers with contact with the index patient consisted of 8 doctors and 8 nurses. Before the index patient was transferred to hospital B, 2 village doctors and 2 doctors in hospital A had unprotected contact with him during physical examinations, including taking his temperature and testing for coated tongue and lymph node enlargement, and intramuscular injection; none wore wear rubber gloves or gowns and none became ill. Following transfer of the index patient to hospital B, 4 healthcare workers had protected contact with the index patient before he developed bleeding, during physical examinations, including taking his temperature and testing for coated tongue and lymph node enlargement, and intravenous injections; none became ill. When he was bleeding on 30 May, 8 healthcare workers provided care, including wiping off his blood and administering intravenous injections, but only 1 did not wear rubber gloves, surgical masks, and gowns. None of these workers became ill.

RESULTS

Overall, contact with the index patient's blood was significantly associated with developing secondary illness ($P = .01$, by the χ^2 test for linear trend), whereas contact with the index patient's respiratory secretions, urine, and feces was not (Table 1). Of the various modes of exposure, contact with the index patient's blood on mucous membranes or skin wounds ($P < .01$, by the χ^2 test for linear trend) and not wearing personal protective equipment while providing care ($P = .01$, by the χ^2 test for linear trend) were significantly associated with disease risk. Additionally, frequency of contact with blood was associated with disease risk in a dose-response fashion ($P = .03$, by the χ^2 test for linear trend; Table 2).

Two isolates of SFTSV were obtained, one from the acute-phase sera of the index patient and the other from son 1. Whole-genome sequencing showed that the 2 isolates (GenBank accession numbers: HN01: HQ642766, HQ642767,

Table 1. Risk Factors for Secondary Severe Fever With Thrombocytopenia Syndrome Among 31 Close Contacts of the Index Patient, Henan Province, China, May–June 2010

Secretion	Close Contacts, No. Overall	Developed Secondary Case	Attack Rate, %	*P*[a]	OR (95% CI)[a]
Blood					
Exposed	12	4	33.33	.01	...
Unexposed	19	0	0		
Respiratory secretion					
Exposed	4	1	25.00	.44	2.67 (.21–34.56)
Unexposed	27	3	11.11		
Urine					
Exposed	5	1	20.00	.52	1.92 (.16–23.35)
Unexposed	26	3	11.54		
Feces					
Exposed	2	0	0	>.99	...
Unexposed	29	4	13.79		

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Calculated using the 2-sided Fisher exact test.

and HQ642768; HN69: JF682776, JF682777, and JF682778) were nearly identical (99.99% similarity). These 2 isolates showed slightly less similarity (99.83% and 99.83%, respectively) with an isolate obtained from a patient in Xinyang City on 23 June 2009 (GenBank accession numbers: HN20: JF682773, JF682774, JF682775).

Table 2. Risk Factors for Secondary Severe Fever With Thrombocytopenia Syndrome Among 12 Close Contacts Exposed to the Index Patient's Blood, Henan Province, China, May–June 2010

Variable	Close Contacts, No. Overall	Developed Secondary Case	Attack Rate, %	*P*
Exposure route				
Mucosa, mouth, nose, wound	4	4	100.00	<.01[a]
Skin, clothes, shoes	8	0	0	
Personal protective equipment				
Did not use	5	4	80.00	.01[a]
Use	7	0	0	
Exposure frequency, no. of episodes				
≥3	4	3	75.00	.03[b]
2	5	1	20.00	
1	3	0	0	

[a] Calculated using the Fisher exact test.

[b] Calculated using the 2-sided χ^2 test for trend.

The acute-phase sera from all 5 disease-positive patients were positive for SFTSV RNA by RT-PCR and negative for IgG to the virus. The convalescent-phase sera from the 4 secondary patients had IgG to SFTSV. The sera IgG titers were 1:80 (for son 1), 1:160 (for son 2), 1:640 (for the daughter), and 1:160 (for the funeral director). Sera from all 27 asymptomatic contacts tested negative for both viral RNA (by RT-PCR) and IgG to the virus.

Although contact with the index patient's blood was a point source of exposure, other exposures were also possible. We estimated that the incubation period of SFTSV for this mode of transmission was 7–13 days. However, our sample size was small, and this incubation period might not apply to other modes of transmission, such as tick- or mosquito-borne infection.

The index patient was treated with dexamethasone for fever reduction, during the first 4 days after onset of illness. Dexamethasone and other glucocorticoids lower innate immunity and increase the severity of viral infections [5, 6]. Although it was impossible to determine the role of dexamethasone in the severity of the index patient's illness, it is nonetheless advisable that dexamethasone not be used to treat simple fever. Steroids may have increased the number of circulating virions in his blood and excreted into other body fluids. This may have led to human-to-human transmission of SFTSV.

DISCUSSION

In summary, we have documented an outbreak of infection with the recently identified SFTSV and provided strong epidemiologic and viral genomic evidence that SFTSV can be transmitted between humans through contact with infected blood. This finding underscores the importance of protecting healthcare workers and patients' family members from exposure to blood. Our data also indicated that practicing standard isolation precautions [7] may minimize the risk of virus transmission by blood.

Since the submission of this manuscript, probable human-to-human transmission of SFTSV has been reported in patients who were not treated with steroids [8, 9]. We recommend that healthcare workers and family members caring for patients with suspected SFTS, as well as persons handling the bodies of those who have died of this disease, wear personal protective equipment, including gloves, gowns, eye protection, and masks, and avoid touching patients' blood and other body fluids. Patients with SFTS should be isolated until they no longer have detectable viremia, and all who come in contact with these patients should be monitored for fever until the end of the incubation period (>13 days). Those who develop symptoms should be isolated and tested.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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B. X. and W. C. are coprincipal investigators and jointly conceived of and designed the experiments. X. T., Y. D., H. W., K. K., X. H., H. M., S. Z., G. Z., N. C., B.-P. Z., H. C., A. Y., and G. L. isolated the virus and performed clinical virologic, serologic, epidemic, and data analysis. W. W., L. L., and F. M. performed the RT-PCR assays and virus sequencing.

Disclaimer. The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of this report.

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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別紙様式第２　　医薬品　　別紙 3-1

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 2013 年 1 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			研究報告の公表状況	Global Alert and Response http://www.who.int/csr/disease/coronavirus_infections/update_20121221/en/index.html	公表国 サウジアラビア、ヨルダン、カタール	
販売名（企業名）						

研究報告の概要

WHO は、2012 年 10～12 月の間に、9 症例の新種のコロナウイルスによる重症急性呼吸器感染症の報告を受けている。カタール（2 例）、サウジアラビア（5 例）およびヨルダン（2 例）において感染確定症例が報告されている。すべての症例は重症で、5 例が死亡している。サウジアラビアでは 5 例すべてが確認症例である。最初の 2 例は、サウジアラビアの異なる地域に居住していた。2 例のうち 1 例は死亡している。残り 3 例は、同じ住居で生活している家族で、2 例が死亡している。他の 1 例の症状は、確定症例で観察された症状と類似していたが、この症例は回復し、ウイルス検出結果は陰性であった。ヨルダンでは 2 例が確認されている。2 例とも死亡している。2012 年 4 月に医療従事者集団に肺炎症状が発現しており、この際、症状を発現した症例から採取した保存試料を調べたところ、2 例の感染が確認された。

WHO は 2012 年 4 月にヨルダンで発生した感染症例について検討を行った。感染が確定した 2 例と関係があった医療従事者のうち肺炎症状を呈する人に対して調査を行い、次のような結果を得ている。①感染集団における初発症例は特定できなかった。②すべての症例は、肺炎に類似した著しい呼吸器症状を呈していた。感染可能性症例の症状は、概して、軽症であった。③この集団において、腎不全の患者はいなかった。④肺炎を呈した 1 例は心膜炎を有していたことが判明した。この患者は確定症例で、転帰は死亡であった。2 番目の確定患者は、重度の呼吸器疾患の合併症として播種性血管内凝固症候を発現した。転帰は死亡であった。⑤暴露経路は不明であった。⑥確定症例および可能性症例の中で、旅行経験および動物との接触経験を有する者はいなかった。

確定症例および感染可能性症例の家族メンバーの大半、また、確定症例と接触があった医療関係者の大半は、呼吸器症状を発現しなかった。一方、個人的な接触があった家族の少なくとも二人、および、医療介護を提供した数名が肺炎症状を示しており、このことは、ヒト - ヒト感染の可能性を示唆している。しかし、共通の感染源への暴露があった可能性を完全に排除することはできない。

この新種ウイルスは SARS コロナウイルスの遠縁に該当するが、両者は異なっている。現時点の情報から判断し、この新種ウイルスは、SARS コロナウイルスと異なり、ヒト集団内で容易に感染したり、持続的に感染することはないようである。

報告企業の意見	今後の対応
新種のコロナウイルスによる重症急性呼吸器感染症の報告である。現時点で、持続的にヒトから人に感染する危険性は低いと考えられているが、WHO は注視が必要であるとしている。 コージネイト FS の製造工程における病原体除去・不活化処理は，脂質エンベロープをもつウイルス，および，エンベロープを持たないウイルスに対しても有効であることが報告されている。従って新種のコロナウイルスが本剤に混入する可能性は極めて低いと考えられる。	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。 今後も、新規人畜共通感染症や新たなウイルス感染症に関する情報収集に努める。

使用上の注意記載状況・その他参考事項等

BYL-2013-0416

Global Alert and Response
http://www.who.int/csr/disease/coronavirus_infections/update_20121221/en/index.html

19

MedDRA バージョン 15.1

BYL-2013-0416

World Health Organization

Global Alert and Response (GAR)

Background and summary of novel coronavirus infection – as of 21 December 2012

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Coronavirus Infections

More on coronavirus infections

Over the past three months, WHO has received reports of nine cases of human infection with a novel coronavirus. Coronaviruses are a large family of viruses; different members of this family cause illness in humans and animals. In humans, these illnesses range from the common cold to infection with Severe Acute Respiratory Syndrome (SARS) coronavirus (SARS CoV).

This summary provides the latest information on all reported cases and provides details of a WHO mission to Jordan, which has concluded since the last web update.

Thus far, the laboratory confirmed cases have been reported by Qatar (two cases), Saudi Arabia (five cases) and Jordan (two cases). All patients were severely ill, and five have died.

A total of five confirmed cases have been reported from Saudi Arabia. The first two are not linked to each other and lived in different parts of the country; one of these has died. Three other confirmed cases are epidemiologically linked and occurred in one family living within the same household; two of these have died. One additional family member in this household also became ill, with symptoms similar to those of the confirmed cases. This person has recovered and tested negative, by polymerase chain reaction (PCR) tests, for the virus.

Two confirmed cases have been reported in Jordan. Both of these patients have died. These cases were discovered through testing of stored samples from a cluster of pneumonia cases in health care workers that occurred in April 2012.

In November 2012 staff from WHO Headquarters and the Eastern Mediterranean Regional Office were invited to Jordan to assess severe acute respiratory infection (SARI) surveillance and infection prevention and control measures, and to review the April 2012 outbreak. The mission included hospital site visits, interviews with patients, relatives and caregivers, and review of case files. In addition to the two previously confirmed cases, a number of health care workers with pneumonia associated with the cases were also included in the review and are now considered probable case.

The main findings of this mission are:

- The index case among this cluster could not be determined.
- All patients had significant respiratory disease presenting as pneumonia. Disease was generally milder in the unconfirmed probable cases. One patient who is a probable case had symptoms that were mild enough to be managed at home and was not admitted to hospital.
- No patient in this cluster had renal failure.
- One patient presented with pneumonia and was discovered to also have pericarditis. This patient had laboratory confirmation of infection and has died.
- A second patient developed disseminated intravascular coagulation as a complication of severe respiratory disease. This patient also had laboratory confirmation of infection and has died.
- The method of exposure is uncertain.
- There was no history of travel or contact with animals among confirmed or probable cases.

Most family members and health care workers who were closely exposed to confirmed and probable cases did not develop respiratory disease. However, the appearance of pneumonia in some who provided care and in at least two family members with direct personal contact increases the suspicion that person-to-person transmission may have occurred. The possibility of exposure to a common source has not been definitively excluded. Further investigation with serological testing (when it becomes available) to confirm additional cases may help determine the types of exposures that result in infection.

The current understanding of this novel virus is that it can cause a severe, acute respiratory infection presenting as pneumonia. The additional unconfirmed probable cases in Jordan indicate that milder presentations may also be a part of the clinical appearance associated with infection. Acute renal failure has occurred in five of the nine confirmed cases but was not a prominent feature of the Jordanian cluster. In addition, pericarditis and disseminated intravascular coagulation have now been seen in two confirmed cases.

WHO recognizes that the emergence of a new coronavirus capable of causing severe disease raises concerns because of experience with SARS. Although this novel coronavirus is distantly related to the SARS CoV, they are different. Based on current information, it does not appear to transmit easily or sustainably between people, unlike the SARS virus.

WHO has closely monitored the situation since detection of the first case and has been working with partners to ensure a high degree of preparedness should the new virus be found to be sufficiently transmissible to cause community outbreaks. Some viruses are able to cause limited human-to-human transmission under condition of close contact, as occurs in families, but are not transmissible enough to cause larger community outbreaks.

Actions taken by WHO in coordination with national authorities and technical partners include the following:

- Investigations are ongoing to determine the likely source of infection and the route of exposure. Close contacts of confirmed cases are being identified and followed up.

- An interim surveillance recommendation has been updated to assist clinicians to determine which patients should undergo laboratory testing for the presence of novel coronavirus.
- Laboratory assays for the virus have been developed. Reagents and other materials for testing are available, as are protocols, algorithms and reference laboratory services. WHO has activated its laboratory network to assist in testing and other services. WHO has now issued preliminary guidance for laboratory biorisk management.
- The three affected countries either have already or are in the process of acquiring the capacity to test for the novel coronavirus in national laboratories and have enhanced their surveillance activities according to WHO guidance along with other countries in the area.
- WHO has created a webpage for coronavirus infections, with guidance for surveillance, infection control, biorisk management, and laboratory testing, which can be found at: http://www.who.int/csr/disease/coronavirus_infections/en/index.html

Based on the current situation and available information:

- WHO encourages all Member States to continue their surveillance for severe acute respiratory infections (SARI) and to carefully review any unusual patterns.
- Further, testing for the new coronavirus of patients with unexplained pneumonias should be considered, especially in persons residing in or returning from the Arabian peninsula and neighboring countries. Any new cases should be promptly reported both to national health authorities and to WHO.
- When collecting specimens for testing, priority should be given to collection of lower respiratory tract specimens such as sputa and endotracheal aspirates (for intubated patients).
- In addition, any clusters of SARI or SARI in health care workers should be thoroughly investigated, regardless of where in the world they occur. These investigations will help determine whether the virus is distributed more widely in the human population beyond the three countries that have identified cases.
- Health care workers should be advised to scrupulously adhere to standard infection control precautions for all patients. Droplet precautions should be added to standard precautions for any patient known or suspected to have an acute respiratory infection, including patients with suspected or confirmed infection with novel coronavirus. Airborne precautions should be used for aerosol-generating procedures, including intubation and related interventions. Details can be found on the website listed above.
- WHO does not advise special screening at points of entry with regard to this event nor does it recommend that any travel or trade restrictions be applied.

WHO continues to monitor this situation closely. Unless information is received that changes our understanding of this virus and the disease it causes, the next web update is expected to be posted during the second week of January 2013.

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
				2013. 2. 14	該当なし	
一般的名称	新鮮凍結人血漿				公表国	
販売名(企業名)	新鮮凍結血漿-LR「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」成分採血(日本赤十字社) 新鮮凍結血漿-LR「日赤」120(日本赤十字社) 新鮮凍結血漿-LR「日赤」240(日本赤十字社) 新鮮凍結血漿-LR「日赤」480(日本赤十字社)		研究報告の公表状況	ProMED 20130213.1541531	英国ほか	

研究報告の概要

○新型コロナウイルス:英国、ヒトーヒト感染の疑い
新型コロナウイルス関連の重症下気道疾患症例
英国健康保護局(HPA)は2013年2月13日、新型コロナウイルス(NCoV)感染が既に確定している患者の家族1人に、NCoV感染が2013年2月11日に確認されたと発表した。この患者は、短期間の呼吸器症状を呈して2月9日に入院し、呼吸器感染症に罹患しやすい基礎疾患があった。最近の海外渡航歴はなく、現在は集中治療を受けている。
現時点で、NCoVによる重症肺炎の検査確定患者は全部で11人となった。
これまでの情報によると、この家族内でのNCoVのヒトーヒト感染が示唆される。
HPAは英国国際ガイドラインに従い、2患者と密接に接触した家族及び治療に携わった医療従事者の監視を継続中であると報告した。現在NCoVと一致する症状を呈する者はいない。
家族内でのNCoVヒトーヒト感染を考慮し、欧州疾病管理センターは2012年12月7日に発表されたリスクアセスメントの更新を現在進めている。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿-LR「日赤」
新鮮凍結血漿-LR「日赤」成分採血
新鮮凍結血漿-LR「日赤」120
新鮮凍結血漿-LR「日赤」240
新鮮凍結血漿-LR「日赤」480

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
新型コロナウイルス(NCoV)感染確定患者と接触していた家族1人(渡航歴なし)にNCoV感染が確認され、家族内でのヒトーヒト感染が示唆されたとの報告である。	日本赤十字社では、輸血感染症対策として受付時に海外滞在歴の有無を確認し、帰国(入国)後4週間は献血不適としているほか、発熱などの体調不良者を献血不適としている。また、同様のウイルス性疾患である重症急性呼吸器症候群(SARS)患者または罹患の疑いがある場合や既往がある場合は献血不適とし、SARS患者または罹患疑いのある者と接触した場合は、発熱等の症状の有無に拘わらず、最後に接触した日から3週間は献血不適としている。今後も引き続き情報の収集に努める。

20

MedDRA/J Ver.15.1J

JRC2013T-007

Published Date: 2013-02-13 18:16:29
Subject: PRO/AH/EDR> Novel coronavirus - Eastern Med. (04): UK, pers to pers trans susp
Archive Number: 20130213.1541531

NOVEL CORONAVIRUS - EASTERN MEDITERRANEAN (04): UK, PERSON TO PERSON TRANSMISSION SUSPECTED
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A ProMED-mail post
http://www.promedmail.org
ProMED-mail is a program of the
International Society for Infectious Diseases
http://www.isid.org

In this report:

[1] HPA press release

[2] ECDC

[3] *WHO GAR update*

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[1] HPA press release

Date: 13 Feb 2013
Source: HPA UK Press Release [edited]
http://www.hpa.org.uk/NewsCentre/NationalPressReleases/130213statementonlatestcoronaviruspatient/

The Health Protection Agency (HPA) can confirm a further case of novel coronavirus infection in a family member of the case announced on Monday [11 Feb 2013]. The patient, who is a UK resident, does not have any recent travel history and is currently receiving intensive care treatment at The Queen Elizabeth Hospital, Birmingham. It is understood that this patient has an existing medical condition that may make them more susceptible to respiratory infections. This latest case brings the total number of confirmed cases globally to 11, of which 3 have been diagnosed in the UK.

Professor John Watson, head of the respiratory diseases department at the HPA, said: "Confirmed novel coronavirus infection in a person without travel history to the Middle East suggests that person-to-person transmission has occurred and that it occurred in the UK. This case is a family member who was in close personal contact with the earlier case and who may have been at greater risk of acquiring an infection because of their underlying health condition. To date, evidence of person-to-person transmission has been limited. Although this case provides strong evidence for person to person transmission, the risk of infection in most circumstances is still considered to be very low. If novel coronavirus were more infectious, we would have expected to have seen a larger number of cases than we have seen since the 1st case was reported 3 months ago. However, this new development does justify the measures that were immediately put into place to prevent any further spread of infection and to identify and follow up contacts of known cases. We will continue to provide advice and support to healthcare workers looking after the patients and to contacts of both cases. In light of this latest case, we would like to emphasise that the risk associated with novel coronavirus to the general UK population remains very low. The HPA will continue to work closely with national and international health authorities and will share any further advice with health professionals and the public if and when more information becomes available."

Notes to editors:

Laboratory confirmed cases to date: 11
Saudi Arabia: 5 (3 deaths)
Jordan: 2 (2 deaths)
UK: 3 (1 patient from Qatar - receiving treatment, 2 patients from UK, 1 with recent travel to Pakistan and Saudi Arabia - both receiving treatment)
Germany: 1 (patient from Qatar - discharged)

Coronaviruses are causes of the common cold but can also include more severe illness, such as SARS (severe acute respiratory syndrome). This new coronavirus was 1st identified in September 2012 in a patient who died from a severe respiratory infection in June 2012. The virus has so far only been identified in a small number of cases of acute, serious respiratory illness who presented with fever, cough, shortness of breath, and breathing difficulties.

For further information, see the HPA's coronavirus web pages, which include a Q&A page on this topic [see http://www.hpa.org.uk/webw/HPAweb&Page&HPAwebAutoListName/Page/1317136202637].

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

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[2] ECDC Update
Date: 13 Feb 2013
Source: ECDC (European Centre for Disease Control) [edited]
http://ecdc.europa.eu/en/press/news/Lists/News/ECDC_DispForm.aspx?List=32e43ee8-e230-4424-a783-85742124029a&ID=844&RootFolder=%2Fen%2Fpress%2Fnews%2FLists%2FNews

Epidemiological update: Case of severe lower respiratory tract disease associated with a novel coronavirus:

On [13 Feb 2013], the HPA announced that one family contact of the previously-confirmed case reported on [11 Feb 2013] was laboratory-confirmed to be infected with the novel coronavirus (NCoV). This 2nd case from the same family was hospitalised on [9 Feb 2013] with a short history of respiratory symptoms. The patient has an existing medical condition that may make him more susceptible to respiratory infections. *He does not have a recent travel history and* is currently receiving intensive care treatment.

The cases have been notified through the EU alerting system for communicable diseases.

This brings the total of laboratory-confirmed cases of severe pneumonia caused by the NCoV to 11 globally (see table below).

The information available suggests human-to-human transmission of the NCoV in this family cluster.

The HPA reports that surveillance of family, close contacts of the 2 patients, and healthcare workers treating the 2 patients is ongoing, as per the UK National Guidelines. None are currently presenting with symptoms consistent with NCoV.

The HPA is also following-up regarding passengers who may have been exposed while flying with the case announced on [11 Feb 2013] and are in contact with the airline concerned.

In light of this human-to-human transmission of the NCoV within the family cluster, ECDC is now updating its risk assessment, previously published on [7 Dec 2012].

Case No: Date Onset / Age (years) / Sex / Probable place of infection / Date reported / Source / Outcome

1: April 2012 / 45/ F / Jordan** / 30 Nov 2012 / WHO/IHR / Dead

2: April 2012 / 25 / M / Jordan** / 30 Nov 2012 / WHO/IHR / Dead

3: 13 Jun 2012 / 60 / M / Kingdom of Saudi Arabia* / 20 Sep 2012 / Kingdom of Saudi Arabia, ProMED / Dead

4: 3 Sep 2012 / 49 / M / Qatar / Kingdom of Saudi Arabia*** / 22 Sep 2012 / HPA/WHO / Alive

5: NK / NK / NK / Kingdom of Saudi Arabia* / 4 Nov 2012 / Kingdom of Saudi Arabia, ProMED, SMJ / Alive

6: 12 Oct 2012 / 45 / M / Qatar
**** / 23 Nov 2012 / RKI/WHO / Alive

7: NK / NK / M / Kingdom of Saudi Arabia* / 19-23 Nov 2012 / Kingdom of Saudi Arabia, ProMED, WHO / Alive

8: 28 Oct 2012 / NK / M / Kingdom of Saudi Arabia* / 23 Nov 2012 / WHO / Dead

9: October 2012 / NK / M / Kingdom of Saudi Arabia* / 28 Nov 2012 / WHO / Dead

10: 24 Jan 2013 / 60 / M / Pakistan, Kingdom of Saudi Arabia*/ 8 Jan 2013 / EWRS / Alive, Hospitalised

11: 6 Feb 2013 / NK / M / United Kingdom* / 12 Feb 2013 / HPA / Alive, Hospitalised

* Part of family cluster
** Healthcare worker and part of outbreak linked to hospital
*** Patient transferred to UK

**** Patient transferred to Germany
NK: not known

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

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[3] WHO GAR update
Date: 13 Feb 2013
Source: WHO GAR [edited]
http://www.who.int/csr/don/2013_02_13/en/index.html

Novel coronavirus infection - update [13 Feb 2013]:

The United Kingdom (UK) has informed WHO of another confirmed case of infection with the novel coronavirus (NCoV). The patient is a UK resident and a relative of the case announced on [11 Feb 2013].

The latest confirmed case does not have any recent travel history outside the UK and is currently hospitalized in an intensive care unit. It is understood that this patient has pre-existing medical conditions that may have increased susceptibility to respiratory infections.

Confirmed NCoV in a person without recent travel history indicates that infection was acquired in the UK. To date, evidence of person-to-person transmission has been limited. Although this case is suggestive of person-to-person transmission, on the basis of current evidence, the risk of sustained person-to-person transmission appears to be very low.

The Health Protection Agency (HPA) is following up on all close contacts (family and healthcare workers) who may have been exposed to either of these 2 new confirmed cases.

As of [13 Feb 2013], a total of 11 confirmed cases of human infection with NCoV have been notified to WHO, with no change in the number of fatalities i.e., 5 deaths since April 2012.

Based on the current situation and available information, WHO encourages all Member States to continue their surveillance for severe acute respiratory infections (SARI) and to carefully review any unusual patterns. Testing for the

new coronavirus should be considered in patients with unexplained pneumonias, or in patients with unexplained severe, progressive, or complicated respiratory illness not responding to treatment.

Any clusters of SARI or SARI in healthcare workers should be thoroughly investigated, regardless of where in the world they occur.

New cases and clusters of the NCoV should be reported promptly both to national health authorities and to WHO.

WHO does not advise special screening at points of entry with regard to this event nor does it recommend that any travel or trade restrictions be applied.

WHO continues to monitor the situation closely.

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Communicated by:
ProMED-mail Rapporteur Marianne Hopp

[The above mentioned case of severe acute respiratory infection (SARI) is currently the 11th confirmed case of severe respiratory disease attributable to infection with the novel CoV 1st identified in a fatal case in Saudi Arabia (see prior ProMED-mail posts listed below). It is also the 3rd incident of infection with this novel CoV that occurred in a close contact of an earlier confirmed case, suggesting possible person to person transmission of the virus. There was a cluster of 3 confirmed cases in a family in Saudi Arabia in November 2012 and a cluster of 2 confirmed cases among ICU staff in a hospital in Jordan in May 2012. As stated clearly in the 3 reports of this update, evidence thus far does not seem to suggest an ease and facility of person-to-person contact of this organism as yet.

The table of cases presented in the ECDC report above is a very useful presentation and summary of the current publicly available information on the descriptive epidemiology of known confirmed cases of severe acute respiratory illness due to infection with this novel CoV. Information on exposure histories of each of the patients is not available (some of the earlier cases were reported to have had contact with farm animals in Saudi Arabia and Qatar, but similar information was not available on all cases). To date, cases that have been confirmed have been linked to geographic presence in the Middle East prior to onset of illness (Jordan, Saudi Arabia or Qatar; with one case also having visited Pakistan during the period prior to onset of illness). The absence of cases reported from other areas among individuals without history of contact with this region of the world may or may not reflect the true geographic distribution of this novel CoV, as there may be a bias against testing for this virus in the absence of such stated exposure history ("seek and ye shall find," or the corollary, "don't look and you won't find").

The scientific community is eagerly awaiting the details of epidemiologic investigations conducted on the 11 previously confirmed cases of infection with the novel CoV, especially those addressing exposure to possible animal sources (bats, bat saliva and excrement, farm animals, etc.) and dates of contacts/dates of onset of previous clusters. In addition, information on field studies on bats and farm animals in the Middle Eastern countries addressing infection of animals with the novel CoV is eagerly awaited as well.

For the interactive HealthMap/ProMED map of the UK, see http://healthmap.org/r/1INY. For the interactive HealthMap/ProMED map of the Middle East, see http://healthmap.org/r/1HAJ. - Mod.MPP]

See Also

Novel coronavirus - Eastern Med. (03): Saudi comment 20130212.1540011
Novel coronavirus - Eastern Med. (02): UK ex Saudi Arabia, Pakistan 20130212.1539086
Novel coronavirus - Eastern Mediterranean: bat reservoir 20130122.1508656
2012

Novel coronavirus - Eastern Mediterranean (06): comments 20121225.1468821
Novel coronavirus - Eastern Mediterranean (05): WHO, transmission route 20121223.1465597
Novel coronavirus - Eastern Mediterranean (04): receptor charact. 20121211.1446670
Novel coronavirus - Eastern Mediterranean (03): research, ISARIC (UK) 20121208.1443486
Novel coronavirus - Eastern Mediterranean (02): diagnostics 20121207.1442473
Novel coronavirus - Eastern Mediterranean: WHO, Jordan, conf., RFI 20121130.1432498
Novel coronavirus - Saudi Arabia (19): Singapore: NOT 20121129.1430397
Novel coronavirus - Saudi Arabia (18): WHO, new cases, cluster 20121123.1421664
Novel coronavirus - Saudi Arabia (17): 4th case, RFI 20121121.1418018
Novel coronavirus - Saudi Arabia (16): whole genome sequence 20121114.1409556
Novel coronavirus - Saudi Arabia (15): new case 20121104.1391285
Novel coronavirus - Saudi Arabia (14): KSA MOH 20121022.1358297
Novel coronavirus - Saudi Arabia (13): history, collateral damage 20121021.1356623
Novel coronavirus - Saudi Arabia (12): RFI 20121019.1353615
Novel coronavirus - Saudi Arabia (11): clin. lab. & epi. investigations 20121004.1324712
Novel coronavirus - Saudi Arabia (10): WHO, revised case def. 20120930.1315960
Novel coronavirus - Saudi Arabia (09): real-time RT-PCR, addition 20120929.1315725
Novel coronavirus - Saudi Arabia (08): real-time RT-PCR assay 20120928.1314254
Novel coronavirus - Saudi Arabia (07): Eurosurveillance reports 20120928.1313337
Novel coronavirus - Saudi Arabia (06) 20120927.1311743
Novel coronavirus - Saudi Arabia (05): WHO, case def., nomenclature 20120926.1309747
Novel coronavirus - Saudi Arabia (04): RFI, Jordan, April 2012 20120925.1308001
Novel coronavirus - Saudi Arabia (03): UK HPA, WHO, Qatar 20120923.1305982
Novel coronavirus - Saudi Arabia (02): additional cases, RFI 20120923.1305931
Novel coronavirus - Saudi Arabia: human isolate 20120920.1302733
.....mpp/msp/dk

別紙様式第 2-1
番号 9

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 2013 年 1 月 17 日	新医薬品等の区分	厚生労働省処理欄

一般的名称	①②③⑨⑩pH4 処理酸性人免疫グロブリン ④⑤⑥⑦⑧ポリエチレングリコール処理人免疫グロブリン ⑪⑫人免疫グロブリン	研究報告の公表状況	共同通信社/2013/01/16	公表国 アメリカ
販売名 (企業名)	①日赤ポリグロビン N5%静注 0.5g/10mL（日本血液製剤機構） ②日赤ポリグロビン N5%静注 2.5g/50mL（日本血液製剤機構） ③日赤ポリグロビン N5%静注 5g/100mL（日本血液製剤機構） ④献血ヴェノグロブリン IH5%静注 0.5g/10mL（日本血液製剤機構） ⑤献血ヴェノグロブリン IH5%静注 1g/20mL（日本血液製剤機構） ⑥献血ヴェノグロブリン IH5%静注 2.5g/50mL（日本血液製剤機構） ⑦献血ヴェノグロブリン IH5%静注 5g/100mL（日本血液製剤機構） ⑧献血ヴェノグロブリン-IH ヨシトミ（日本血液製剤機構） ⑨日赤ポリグロビン N10%静注 5g/50mL（日本血液製剤機構） ⑩日赤ポリグロビン N10%静注 10g/100mL（日本血液製剤機構） ⑪グロブリン筋注 450mg/3mL「ベネシス」（日本血液製剤機構） ⑫グロブリン筋注 1500mg/10mL「ベネシス」（日本血液製剤機構）			

研究報告の概要

米国疾病対策センター(CDC)当局者は 13 日、米国各地でインフルエンザ・ウイルスが急速に拡大していると指摘、感染リスクの高い人だけでなく国民全員がワクチンの接種を受けるよう呼び掛けた。CDC のウェブサイトによると、インフルエンザの広範な流行がみられるのは全米 50 州のうち 47 州と、前週の 41 州から拡大。生後 6 カ月以上の国民は例外なくワクチンを接種すべきだとし、幼児、妊婦のほか、ぜんそくや糖尿病などの既往症を抱えている人、65 歳以上の高齢者は特にワクチンが重要だと警告している。
一方、ニューヨーク州はインフルエンザの流行が過去最悪といわれる状態まで広がっており、クオモ同州知事は 12 日、公衆衛生非常事態宣言を発令した。同州ではこれまでにインフルエンザで幼児 2 人と高齢者 10 人が死亡している。今シーズンの感染者も 19,000 人以上と、前シーズンの 4,400 人から急増し、現在も 2,884 人が入院中という。

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

別紙様式第 2-1
番号 9

医薬品
医薬部外品　　研究報告　調査報告書
化粧品

報告企業の意見	今後の対応	
インフルエンザウイルス（influenza virus）は、オルトミクソウイルス科に属する A型インフルエンザウイルス（influenzavirus A）、B型インフルエンザウイルス（influenzavirus B）、C型インフルエンザウイルス（influenzavirus C）の3属を指す。ウイルスの大きさは直径80～120nmの球形粒子で、エンベロープを有するRNAウイルスで、万一原料血漿にインフルエンザウイルスが混入したとしても、Human immunodeficiency virus-1（HIV-1）、或いはBVDVをモデルウイルスとしたウイルスクリアランス試験成績から、本剤の製造工程において不活化・除去されると考えている。	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。	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。

JBPO 2013-001

米当局が全国民にインフル・ワクチン接種を呼び掛け　ＮＹ州は非常事態宣言

共同通信社 1月16日(水)配信

【ワシントンＤＰＡ＝共同】米疾病対策センター（ＣＤＣ）当局者は１３日、米国各地でインフルエンザ・ウイルスが急速に拡大していると指摘、感染リスクの高い人だけでなく国民全員がワクチンの接種を受けるよう呼び掛けた。

ＣＤＣのウェブサイトによると、インフルエンザの広範な流行がみられるのは全米５０州のうち４７州と、前週の４１州から拡大。生後６カ月以上の国民は例外なくワクチンを接種すべきだとし、幼児、妊婦のほか、ぜんそくや糖尿病などの既往症を抱えている人、６５歳以上の高齢者は特にワクチンが重要だと警告している。

一方、ニューヨーク州はインフルエンザの流行が過去最悪といわれる状態まで広がっており、クオモ同州知事は１２日、公衆衛生非常事態宣言を発令した。同州ではこれまでにインフルエンザで幼児２人と高齢者１０人が死亡している。今シーズンの感染者も１万９０００人以上と、前シーズンの４４００人から急増し、現在も２８８４人が入院中という。

クオモ知事はこうした事態に対処するため、薬剤師が１８歳以下の子どもにワクチンを接種することを認可した。同州の薬剤師は従来、１８歳以上の人にだけに接種することが許可されていたが、今後３０日間はその範囲が生後６カ月以上に拡大される。

マサチューセッツ州ボストン保健当局も９日、インフルエンザの急拡大を受けて公衆衛生非常事態を宣言しており、他の州当局も事態を注視するとともに、住民にワクチン接種を呼び掛けている。

別紙様式第2-1

No. 4

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
				2012. 10. 20	該当なし	
一般的名称	新鮮凍結人血漿		研究報告の公表状況	Grard G, Fair JN, Lee D, Slikas E, Steffen I, Muyembe JJ, Sittler T, Veeraraghavan N, Ruby JG, Wang C, Makuwa M, Mulembakani P, Tesh RB, Mazet J, Rimoin AW, Taylor T, Schneider BS, Simmons G, Delwart E, Wolfe ND, Chiu CY, Leroy EM. PLoS Pathog. 2012 Sep;8(9):e1002924. doi: 10.1371/journal.ppat.1002924. Epub 2012 Sep 27.	公表国	
販売名（企業名）	新鮮凍結血漿-LR「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」成分採血(日本赤十字社) 新鮮凍結血漿-LR「日赤」120(日本赤十字社) 新鮮凍結血漿-LR「日赤」240(日本赤十字社) 新鮮凍結血漿-LR「日赤」480(日本赤十字社)				ガボン共和国	

研究報告の概要

○中央アフリカの急性出血熱に関連する新規ラブドウイルス
大規模シークエンシングにより、アフリカのコンゴ民主共和国マンガラ村において2009年に発生した急性出血熱患者3人に関連する新規ラブドウイルス(Bas-Congoウイルス:BASV)を発見した。3週間の間に報告されたこれらの症例は高熱、粘膜出血を突然発症し、さらに2人は3日以内に死亡した。唯一の生存者の急性期検体から1.09×10^{6}RNAコピー/mLの濃度でBASVが検出され、ゲノム配列の98.2%が読み取れた。系統樹解析の結果、BASVは他のラブドウイルスと離れており、アミノ酸の一致は34%未満であった。生存者及び同患者を直接担当した無症候の看護師1人(2人はいずれも医療従事者)から高値の中和抗体(1:1,000)が検出されたことから、BASVがヒトからヒトに伝播することが示唆された。本ウイルスの自然宿主動物あるいは媒介節足動物、正確な伝播様式はいまだに不明である。BASVは、アフリカにおいて急性出血熱の原因となる新たなヒト病原体である。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿-LR「日赤」
新鮮凍結血漿-LR「日赤」成分採血
新鮮凍結血漿-LR「日赤」120
新鮮凍結血漿-LR「日赤」240
新鮮凍結血漿-LR「日赤」480

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
中央アフリカで急性出血熱の原因となる新規のヒト病原体Bas-Congoウイルスが同定されたとの報告である。	今後も引き続き情報の収集に努める。

22

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A Novel Rhabdovirus Associated with Acute Hemorrhagic Fever in Central Africa

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Abstract

Deep sequencing was used to discover a novel rhabdovirus (Bas-Congo virus, or BASV) associated with a 2009 outbreak of 3 human cases of acute hemorrhagic fever in Mangala village, Democratic Republic of Congo (DRC), Africa. The cases, presenting over a 3-week period, were characterized by abrupt disease onset, high fever, mucosal hemorrhage, and, in two patients, death within 3 days. BASV was detected in an acute serum sample from the lone survivor at a concentration of 1.09×10^6 RNA copies/mL, and 98.2% of the genome was subsequently *de novo* assembled from ~140 million sequence reads. Phylogenetic analysis revealed that BASV is highly divergent and shares less than 34% amino acid identity with any other rhabdovirus. High convalescent neutralizing antibody titers of >1:1000 were detected in the survivor and an asymptomatic nurse directly caring for him, both of whom were health care workers, suggesting the potential for human-to-human transmission of BASV. The natural animal reservoir host or arthropod vector and precise mode of transmission for the virus remain unclear. BASV is an emerging human pathogen associated with acute hemorrhagic fever in Africa.

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Competing Interests: The authors have filed a patent application related to BASV. This does not alter the authors' adherence to all PLOS Pathogens policies on sharing data and materials.

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Introduction

Viral hemorrhagic fever (VHF) encompasses a group of diseases characterized by fever, malaise, bleeding abnormalities, and circulatory shock [1,2,3]. Quality research on these infections is hindered by the fact that they are sporadic and often occur in geographically remote and politically unstable regions of the developing world. Most VHF diseases are associated with a short incubation period (2–21 days), abrupt onset, rapid clinical course, and high mortality, placing VHF agents amongst the most virulent human pathogens [4]. All known VHFs are zoonoses, and to date have been attributed to only four families of enveloped, single-stranded RNA viruses – *Arenaviridae*, *Bunyaviridae*, *Filoviridae* and *Flaviviridae*. Viruses from these families have caused major deadly outbreaks on the African continent (Fig. 1). Lassa fever virus (*Arenaviridae*) causes an estimated 500,000 cases each year in West Africa [5]. Crimean-Congo hemorrhagic fever (CCHF) and Rift Valley Fever viruses (*Bunyaviridae*) are associated with outbreaks in

Author Summary

We used deep sequencing, a method for generating millions of DNA sequence reads from clinical samples, to discover a novel rhabdovirus (Bas-Congo virus, or BASV) associated with a 2009 outbreak of 3 human cases of acute hemorrhagic fever in Mangala village, Democratic Republic of Congo (DRC), Africa. The cases, presenting over a 3-week period, were characterized by abrupt disease onset, high fever, bloody vomiting and diarrhea, and, in two patients, death within 3 days. BASV was present in the blood of the lone survivor at a concentration of over a million copies per milliliter. The genome of BASV, assembled from over 140 million sequence reads, reveals that it is very different from any other rhabdovirus. The lone survivor and a nurse caring for him (with no symptoms), both health care workers, were found to have high levels of antibodies to BASV, indicating that they both had been infected by the virus. Although the source of the virus remains unclear, our study findings suggest that BASV may be spread by human-to-human contact and is an emerging pathogen associated with acute hemorrhagic fever in Africa.

West, South and East Africa [6]. Ebola and Marburg viruses (*Filoviridae*) have caused several sporadic human outbreaks with high mortality (50–90%) in Central Africa, where they have also decimated local great ape populations [7]. Yellow fever and dengue viruses (*Flaviviridae*) are widely distributed throughout Sub-Saharan Africa where they cause both endemic and sporadic epidemic diseases in human populations [8].

Rhabdoviruses are members of the family *Rhabdoviridae* and order *Mononegavirales* and are enveloped viruses with single-stranded, negative-sense RNA genomes [9]. Their genomes encode at least five core proteins in the following order: 3′-nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G) and large protein, or RNA-dependent RNA polymerase (L)-5′ (N-P-M-G-L). Rhabdoviruses are currently divided into six genera, with the two genera *Ephemerovirus* and *Vesiculovirus*, together with about 130 unclassified viruses, forming the dimarhabdovirus supergroup ("dipteran mammal-associated rhabdovirus") [10]. Notably, although rhabdoviruses span all continents and exhibit a wide host range, infecting plants, invertebrates, vertebrate animals, and humans, relatively few are known to cause human infections. Rabies virus (RABV) and related viruses from the *Lyssavirus* genus and Chandipura virus (CHPV) from the *Vesiculovirus* genus are known to cause acute encephalitis syndromes [11,12]. Other viruses from the genus *Vesiculovirus* cause vesicular stomatitis (mucosal ulcers in the mouth) and "flu-like" syndromes in both cattle and humans [13].

Unbiased next-generation or "deep" DNA sequencing is an emerging method for the surveillance and discovery of pathogens in clinical samples [14]. Unlike polymerase chain reaction (PCR), deep sequencing does not rely on the use of target-specific primers. Thus, the technique is particularly useful for the identification of novel pathogens with high sequence divergence that would elude detection by conventional PCR assays. Deep sequencing has been used previously to discover a new hemorrhagic fever-associated arenavirus from southern Africa, Lujo virus [15], as well as a new polyomavirus in human Merkel cell carcinoma [16]. With the depth of sequence data now routinely extending to >100 million reads, *de novo* genome assembly of novel viruses directly from primary clinical samples is feasible, as demonstrated by assembly of the 2009 pandemic influenza H1N1 virus genome from a single patient's nasal swab without the use of a reference sequence [17]. Here we report the critical role of deep sequencing in the discovery of a novel rhabdovirus associated with a small outbreak of fulminant hemorrhagic fever in the remote village of Mangala, Bas-Congo province, Democratic Republic of Congo (DRC), between May 25 and June 14, 2009.

Results

Case Reports from an Acute Hemorrhagic Fever Outbreak

Patient 1. The first case was a 15-year-old boy who presented to the health center in Mangala village (Boma Bungu Health Zone) on May 25, 2009 with malaise, epistaxis (nose bleeding), conjunctival injection, gingival bleeding, hematemesis (vomiting with blood), and watery diarrhea with blood (Table 1). No fever or respiratory symptoms were noted. Hemorrhagic symptoms initially appeared on May 24, and the patient died 2 days later from sudden circulatory collapse. The patient lived in the Tshela neighborhood of Mangala village and attended the local public school. All close contacts were monitored for 21 days, and none developed any signs of illness.

Patient 2. The second case was a 13-year-old girl. She attended the same public school as Patient 1 but was in a different class. She also lived in the Tshela neighborhood of Mangala village, about 50 meters from Patient 1's house. They knew each other but had no known face-to-face contact during the previous weeks. This patient presented to the health center on June 5, 2009 with headache, fever, abdominal pain, epistaxis, conjunctival injection, mouth bleeding, hematemesis, and diarrhea with blood. She was examined by a nurse and received acetaminophen and dipyrone for fever and quinine for possible malaria. Symptoms appeared on June 4, and the patient died suddenly on June 7, three days after onset. None of her close contacts developed symptoms during the 21 days of monitoring after her death.

Patient 3. The third case was a male nurse aged 32 years working in the health center visited by Patients 1 and 2. His disease appeared suddenly on June 13, 2009 with epistaxis, ocular and oral hemorrhage, hematemesis, and diarrhea with blood. Two days after the onset of hemorrhagic symptoms, he developed fever, anorexia, headache, fatigue, and abdominal pain. He was transferred to the regional general hospital of Boma (Fig. 1), a city of about 200,000 inhabitants, where a serum sample was obtained on June 15, just prior to treatment with fluid resuscitation, blood transfusion, and empiric antibiotics. Laboratory tests for malaria, tuberculosis, dengue, and bacterial sepsis were negative, and the patient recovered spontaneously a few days later. All persons in Mangala and Boma who had contact with Patient 3 were monitored for 21 days, and none became ill. Patient 3, like the two other patients, lived in the Tshela neighborhood of Mangala village, about 50 meters from Patients 1 and 2. Importantly, patient 3 was directly involved in the care of Patients 1 and 2 when they presented to the health center with hemorrhagic symptoms.

No disease outbreaks had been reported in the past in Boma Bungu Health Zone with the exception of a cholera diarrheal outbreak in 2006, and, notably, no cases of hemorrhagic disease had previously been reported. In addition, although DRC is a country endemic for filovirus infection (Fig. 1), no outbreaks of Ebola or Marburg fever have ever been described in Bas-Congo province. No animal die-offs or other unusual events in association with these cases were noted.

Initial Sample Collection and Diagnostic Testing

A cluster of three human cases of typical acute hemorrhagic fever occurred between May 25 and June 13, 2009 in Mangala village,

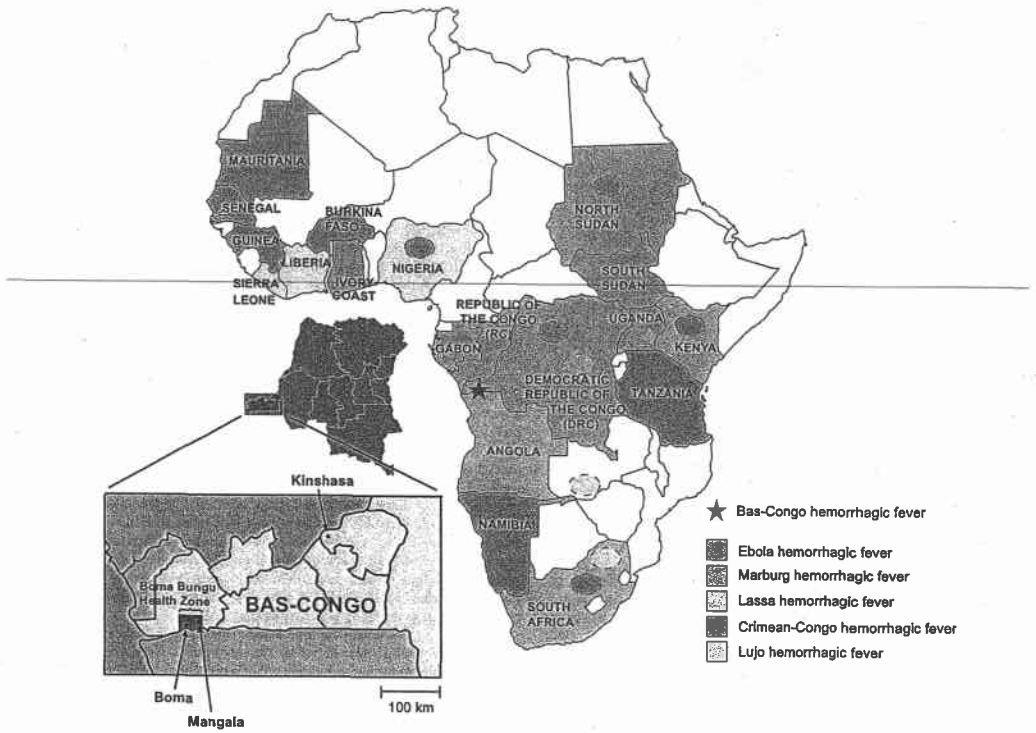

Figure 1. Map of Africa showing countries that are affected by viral hemorrhagic fever (VHF) outbreaks. Ebola VHF is pictured in orange, Marburg VHF in green, Crimean-Congo HF in violet, Lujo VHF in pink, and Lassa VHF in blue. Yellow fever and dengue VHF, which exhibit a wide geographic distribution throughout Sub-Saharan Africa, are not shown. Mangala village, located in the Bas-Congo province in DRC, is represented by a red star.
doi:10.1371/journal.ppat.1002924.g001

located in a remote tropical forest region in Central Africa. Cases were characterized by abrupt disease onset, high fever of >39°C when present, overt hemorrhagic symptoms with epistaxis, conjunctival injection, mouth and gastrointestinal bleeding, followed by death within 3 days of symptom onset in two patients (Table 1). The first patient, who died <48 hours after presentation, exhibited hemorrhagic symptoms without a documented fever, and only the third adult patient recovered from his illness. All three patients lived within a 2500-m^2 area in the same neighborhood of Mangala, a remote village in Bas-Congo province of DRC (Fig. 1). The first two patients died rapidly in Mangala village, and no blood samples were collected. A blood sample was collected from the third surviving patient threedays after symptom onset and sent to Centre International de Recherches Médicales de Franceville (CIRMF) for etiological diagnosis. The sample tested negative by TaqMan real-time PCR assays for all viruses known to cause acute hemorrhagic fever in Africa (data not shown).

Discovery and Genome Assembly of the BASV Rhabdovirus

To identify a potential causative pathogen in the third surviving patient with unknown hemorrhagic fever, RNA extracts from the serum sample were analyzed using unbiased deep sequencing (Fig. 2). The initial Roche 454 pyrosequencing library yielded a total of 4,537 sequence reads, of which only a single 220 bp read (0.022%) aligned with any annotated viral protein sequence in GenBank. The translation product showed similarity to a segment of the L protein, or RNA-dependent RNA polymerase, from Tibrogargan and Coastal Plains rhabdoviruses, with 41% identity to Coastal Plains virus (GenBank ADG86364; BLASTx E-score of 2×10^{-6}). This finding suggested the presence of a novel, highly divergent rhabdovirus in the patient's serum. Attempts to extend the initial sequence by primer walking or PCR using rhabdovirus consensus primers failed due to limited sample availability; thus, we resorted to ultra-deep sequencing on an Illumina HiSeq 2000.

Table 1. Demographics of and clinical symptoms developed in the three patients suspected to be infected by Bas-Congo virus (BASV).

	Patient 1	Patient 2	Patient 3
Sex	Male	Female	Male
Age	15	13	32
Village	Mangala	Mangala	Mangala
Neighborhood	Tshela	Tshela	Tshela
Occupation	Schoolboy	Schoolgirl	Nurse
Disease onset	May 24	June 4	June 13
Time until death	2 days	3 days	survived
Fever (T>39°C)	No	Yes	Yes
Weakness	No	No	Yes
Malaise	Yes	No	No
Headache	No	Yes	Yes
Abdominal pain	No	Yes	Yes
Epistaxis (nose bleeding)	Yes	Yes	Yes
Ocular hemorrhage/conjunctival injection (eye bleeding)	Yes	Yes	Yes
Oral hemorrhage (mouth bleeding)	Yes	Yes	Yes
Hemorrhagic vomiting	Yes	Yes	Yes
Hemorrhagic diarrhea	Yes	Yes	Yes

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Out of the 140,164,344 reads generated from Illumina sequencing, 4,063 reads (0.0029%) had nucleotide or protein homology to rhabdoviruses with an E-score of $<10^{-5}$. These reads were used as "seeds" for iterative *de novo* assembly, resulting in construction of an estimated 98.2% of the genome of the novel rhabdovirus. We provisionally named this rhabdovirus BASV, or Bas-Congo virus, referring to the province from which the outbreak originated.

The coverage of BASV achieved by deep sequencing was at least 10-fold across nearly the entire genome and included 29,094 reads out of ~140 million (0.021%) (Fig. 2). The viral load in the patient's serum was 1.09×10^6 RNA copies/mL by quantitative RT-PCR. The only moderately high titer is consistent with the fact that the sampled patient was a survivor of BASV infection and would thus be anticipated to have relatively lower viral titers in the blood, as also seen for survivors of Ebola virus infection [18].

Cultivation of the patient's serum in Vero, BHK, LLC-MK_2 (rhesus monkey kidney), CCL-106 (rabbit kidney) and C6/36 (*Aedes albopictus* mosquito) cell cultures failed to show cytopathic effect, and serial quantitative BASV RT-PCR assays on primary and passaged cell culture supernatants turned negative. Subsequent electron microscopy of inoculated cell cultures was negative for viral particles. In addition, no illnesses or deaths occurred in suckling mice inoculated intracerebrally with the BASV-positive serum and observed over 14 days.

Phylogenetic Analysis of BASV and Comparison with other Rhabdoviruses

Phylogenetic trees reveal that BASV belongs to the *dimarhabdoviridae* supergroup and is distantly related to members of the Tibrogargan group and the *Ephemerovirus* genus, although it clusters separately from other rhabdoviruses in an independent deeply rooted branch (Figs. 3 and 4; Fig. S1). Comparative analysis of the concatenated BASV proteins with representative dimarhabdoviruses reveals very low overall amino acid pairwise identity of 25.0 to 33.7%, depending on the virus (Fig. 5). Notably, BASV diverges significantly from either of the two main recognized human pathogens among rhabdoviruses, rabies virus or Chandipura virus.

The sequence divergence of BASV relative to other rhabdoviruses is also correlated with differences in genome structure (Fig. 5). The prototype genome organization of rhabdoviruses, found in lyssaviruses, is N-P-M-G-L. However, molecular analysis of novel rhabdoviruses has often revealed more complex genomes, with up to 10 additional open reading frames (ORF) located within an existing gene or interposed between the five core genes [19,20,21]. Rhabdoviruses from the Tibrogargan group (TIBV and CPV) share a distinctive genome structure with three additional genes, two between M and G (U1 and U2) and one between G and L (U3) [22]. Interestingly, BASV also has these three additional genes (U1–U3), confirming the phylogenetic relationship and overall structural similarity to the Tibrogargan group viruses. Based on their size, the U3 proteins of TIBV, CPV, and presumably BASV are candidate viroporins [22]. BASV is more distant structurally and phylogenetically from the Ephemero and Hart Park Group rhabdoviruses (Figs. 3 and 4), which do not contain U1 or U2 genes, but rather an additional two or three genes between G and L (including a putative U3 viroporin in BEFV referred to as the alpha-1 protein) (Fig. 5, asterisk). Moussa virus (MOUV), another rhabdovirus recently discovered in Africa (Fig. 4), does not contain any accessory genes but instead, shares the prototype N-P-M-G-L rhabdovirus structure [23].

BASV Serological Testing of the Case Patient and Close Contacts

To confirm that BASV is infectious to humans, convalescent sera were collected in early 2012 from surviving Patient 3 as well as five additional health care workers from Mangala identified as close contacts and tested in a blinded fashion for the presence of neutralizing antibodies to BASV (Fig. 6). Two of the six sera tested strongly positive with 50% protective doses between 1:1,000 and

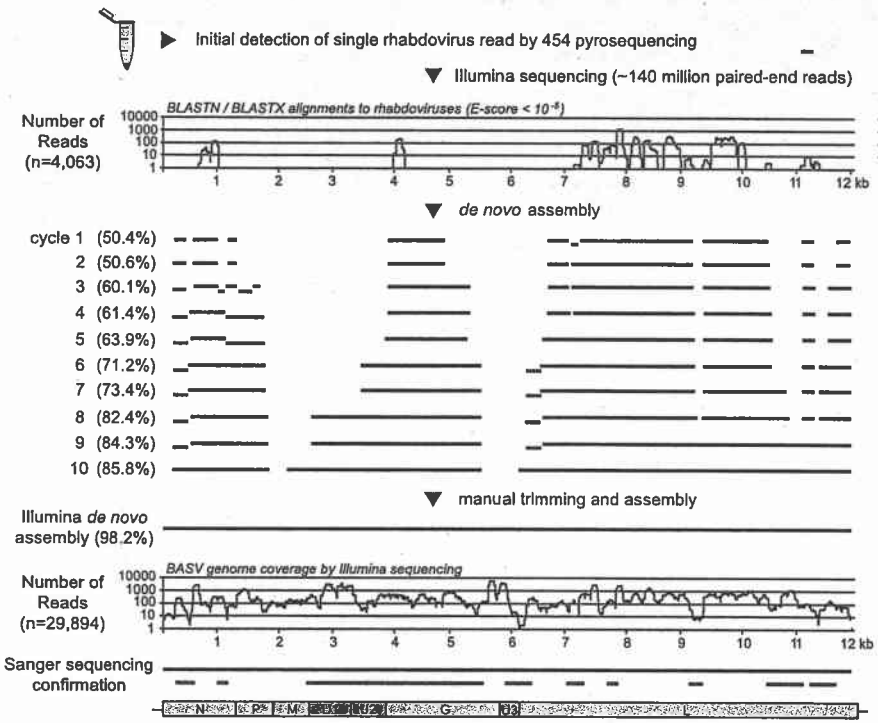

Figure 2. Deep sequencing and whole-genome *de novo* assembly of BASV. After initial discovery of BASV from a single 454 pyrosequencing read, 98.2% of the BASV genome was assembled *de novo* from >140 million paired-end Illumina reads. The horizontal lines (red) depict regions of the genome successfully assembled at the end of each cycle. PCR and Sanger sequencing were performed to confirm the assembly and genomic organization of BASV (green lines).
doi:10.1371/journal.ppat.1002924.g002

1:5,000 (Figs. 6A and 6F). Moreover, the observed neutralization was highly specific for BASV-G, since no neutralization was observed with pseudoviruses harboring the vesicular stomatitis virus glycoprotein (VSV-G). One of the neutralizing sera had been collected from surviving Patient 3 (Fig. 6A, "Patient 3"), whereas the other serum sample, containing even higher titers, corresponded to an asymptomatic nurse directly caring for Patient 3 during his period of acute hemorrhagic illness (Fig. 6F, "Contact 5"). Specifically, Contact 5 was the primary health care provider to Patient 3 at the health center and during his transfer to the general hospital at Boma. All 6 individuals, including Patient 3, tested negative for BASV viremia by specific RT-PCR (data not shown).

Epidemiological Screening for BASV in the DRC

BASV was not detected by PCR in 43 serum samples from other unknown cases or outbreaks of hemorrhagic fever reported in the DRC from 2008–2010 (Fig. 7A, pink). Five of these 43 samples originated from the Bas-Congo outside of Mangala village and the Boma Bungu Health Zone. In total, the unknown hemorrhagic cases/outbreaks spanned 9 of the 11 provinces in the DRC, and all 43 samples also tested negative by PCR for the known hemorrhagic fever viruses circulating in Africa (data not shown). Fifty plasma samples collected from randomly selected blood donors in the Kasai-Oriental province of DRC (Fig. 7A, star; Table S2) were also screened and found to be negative for BASV-neutralizing antibodies (Fig. 7B).

Discussion

Among more than 160 species of rhabdoviruses identified to date, fewer than 10 have been isolated from humans [24]. In addition, while human infection by rhabdoviruses has previously been associated with encephalitis, vesicular stomatitis, or "flu-like" illness, the discovery of BASV is the first time that a member of the *Rhabdovirus* family has been associated with hemorrhagic fever in humans with a fulminant disease course and high fatality rate. To our knowledge, this is also the first successful demonstration of

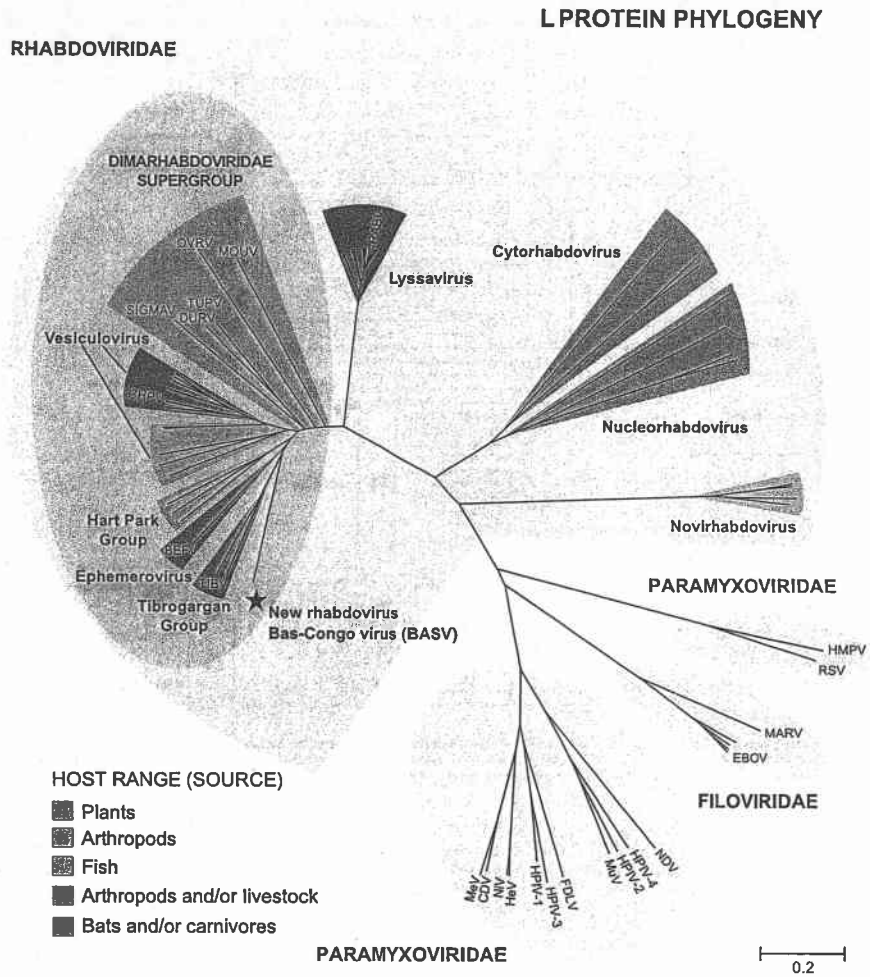

Figure 3. Phylogenetic analysis of the L proteins of BASV and other viruses in the order *Mononegavirales*. The host from which each virus was isolated is represented by a specific color. To generate the *Mononegavirales* (*Rhabdoviridae*, *Filoviridae* and *Paramyxoviridae*) phylogeny trees, all complete sequences of the large (L) protein, or RNA-dependent RNA polymerase (2000–2300 amino acids in length) were downloaded from GenBank. Abbreviations and accession numbers used for the phylogenetic analysis are provided in Methods.
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de novo assembly of a novel, highly divergent viral genome in the absence of a reference sequence and directly from a primary clinical sample by unbiased deep sequencing.

Several lines of evidence implicate BASV in the hemorrhagic fever outbreak among the 3 patients in Mangala. First, this virus was the only credible viral pathogen detected in the blood of the lone survivor during his acute hemorrhagic illness by exhaustive deep sequencing of over 140 million reads. Analysis of the Illumina deep sequencing reads for the presence of other viral pathogens yielded only endogenous flora or confirmed laboratory contaminants (Table

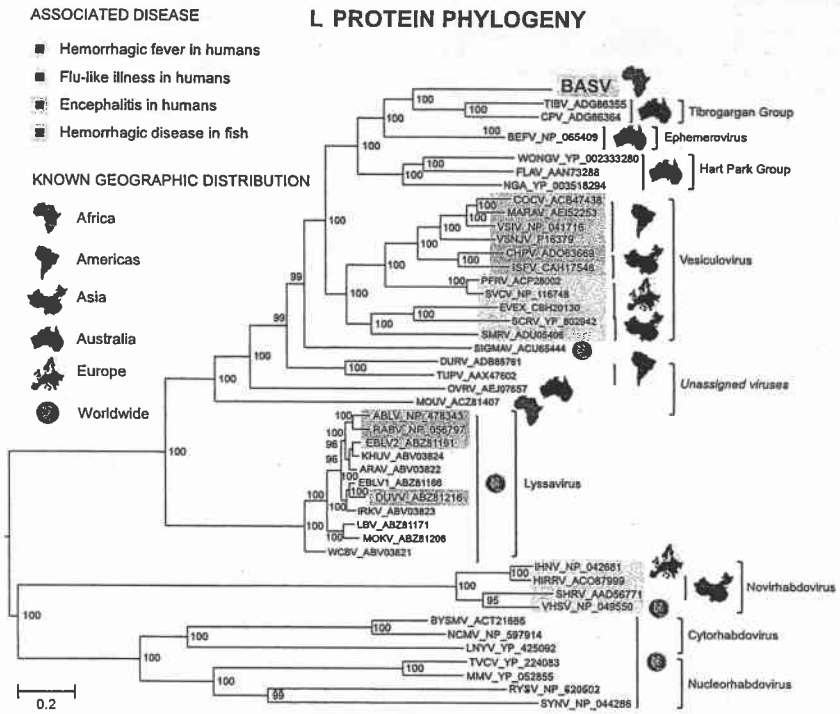

Figure 4. Phylogenetic analysis of the L proteins of BASV and other rhabdoviruses. The geographic distribution for each virus or group of viruses is indicated with a specific icon, while diseases associated with infection by certain rhabdoviruses are indicated by specific colors. Abbreviations and accession numbers used for the phylogenetic analysis are provided in Methods.
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S1 and Fig. S2). Some enteric pathogens, such as E. coli O157:H7, Campylobacter, Shigella, and Salmonella, are diagnosed through fecal laboratory testing and not blood, and have been associated with hemorrhagic diarrhea [25]. However, these outbreaks are typically foodborne and associated with larger clusters and much greater numbers of clinical cases than reported here [26,27,28]. Furthermore, enteric diarrheal cases rarely present with systemic symptoms such as fever or generalized mucosal hemorrhage, with bleeding most often limited to the gastrointestinal tract, and overall mortality rates are generally low [26]. Thus, the clinical syndrome observed in 3 patients with hemorrhagic fever in the DRC, a region endemic for viral hemorrhagic fevers, is much more consistent with infection by a VHF disease agent. BASV is a plausible hemorrhagic fever candidate because it is a novel, highly divergent infectious virus, thus of unknown pathogenicity, and was detected at a titer of >1 million copies/mL in blood from an acutely ill individual. In addition, there is ample precedent for hemorrhagic disease from rhabdoviruses, as members of the genus *Novirhabdovirus* cause severe hemorrhagic septicemia in fresh and saltwater fish worldwide [29] (Fig. 4). The detection of BASV seropositivity in an asymptomatic close contact (Fig. 6) is not surprising given that up to 80% of patients infected with Lassa virus do not exhibit any hemorrhagic fever symptoms [30,31].

Prior to the BASV outbreak, no hemorrhagic disease cases had been reported in Boma Bungu Health Zone. BASV was also not detected in 43 serum samples from unknown, filovirus-negative cases or outbreaks of hemorrhagic fever from 2008–2010 spanning 9 of the 11 provinces in the DRC (Fig. 7A). In addition, a serosurvey of 50 random blood donors from Kasai-Oriental province in central DRC was negative for prior exposure to BASV (Fig. 7B). Taken together, these data suggest that the virus may have emerged recently and locally from Boma Bungu in Bas-Congo, DRC.

We were unable to isolate BASV despite culturing the RNA-positive serum in a number of cell cultures and inoculation into suckling mice. One explanation for these negative findings may be that the virus inoculation titers of <50 µL were insufficient, although this is surprising given the concentration of >1 million copies per mL of BASV in blood from the lone survivor. A more likely explanation is viral inactivation resulting from the lack of

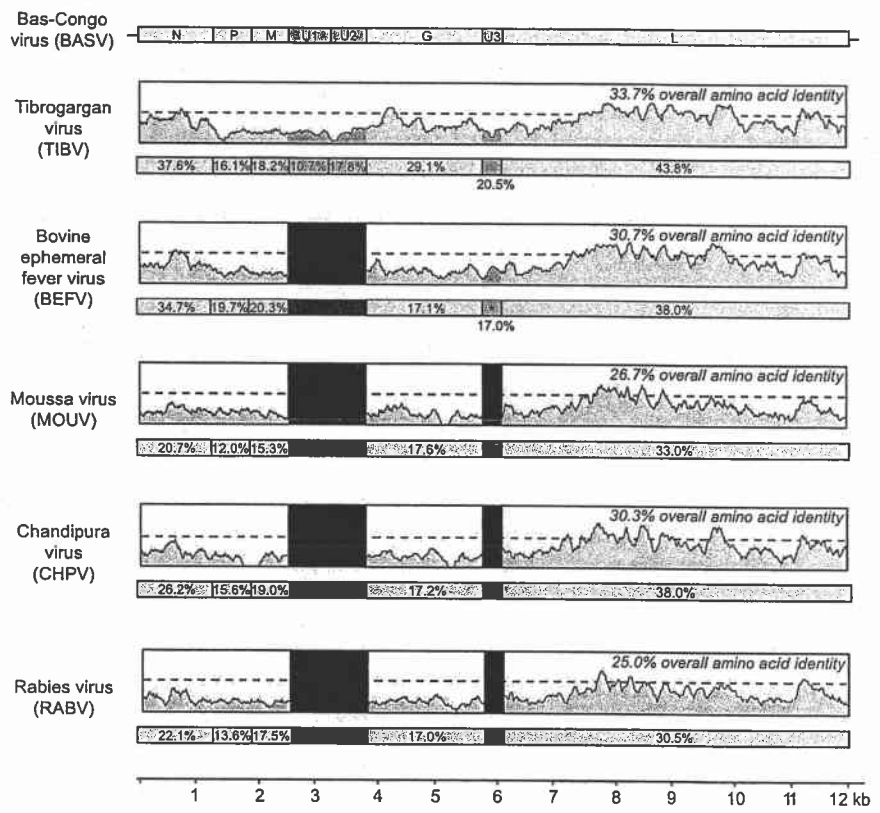

Figure 5. Schematic representation of the genome organization of BASV and its protein similarity plot compared to representative rhabdoviruses. The similarity plots are generated by aligning the concatenated rhabdovirus proteins and calculating scanning amino acid pairwise identities using a window size of 50 bp. The horizontal bar under each similarity plot shows the percent identity of the rhabdovirus protein relative to its corresponding protein in BASV. Genes coding for the 5 core rhabdovirus proteins are shown in green, while the accessory U1, U2, or U3 genes are shown in blue. Black bars correspond to accessory proteins which are not present in the genome. Note that BEFV contains 3 genes between G and L; only the alignment between the alpha-1 protein of BEFV and the U3 protein of BASV is shown (asterisk). The x-axis refers to the nucleotide position along the ~12 kb genome of BASV.
doi:10.1371/journal.ppat.1002924.g005

adequate cold chain facilities in remote Boma Bungu. Viral RNA can often still be detected by RT-PCR in sera that is culture-negative [32]. In support of this premise, we have observed that the BASV-G/VSVΔG-GFP pseudotyped virus efficiently infects and replicates in a variety of insect and mammalian (including human) cell lines (Steffen, *et al.*, manuscript in preparation). In the absence of a positive culture, a "reverse genetics" approach to produce recombinant BASV particles, if successful, would greatly facilitate further study of the virus, as established previously for other rhabdoviruses such as VSV [33].

Based on our findings, some speculations on the origin of and routes of transmission for BASV can be made. All 3 patients became ill with acute hemorrhagic fever over a 3-week period within the same 2500-m^2 area of Mangala village, suggesting that all 3 cases were infected with the same pathogen. Waterborne or airborne transmission would be expected to result in more numerous cases than the 3 reported. There were no reports of animal die-offs that would suggest potential exposures to infected wild animals or livestock. Taken together, these observations suggest that an unknown arthropod vector could be a plausible source of infection by BASV. This hypothesis is consistent with the phylogenetic and structural relationship of BASV to rhabdoviruses in the Tibrogargan group and *Ephemerovirus* genus, which are transmitted to cattle and buffalo by *Culicoides* biting midges [9]. In

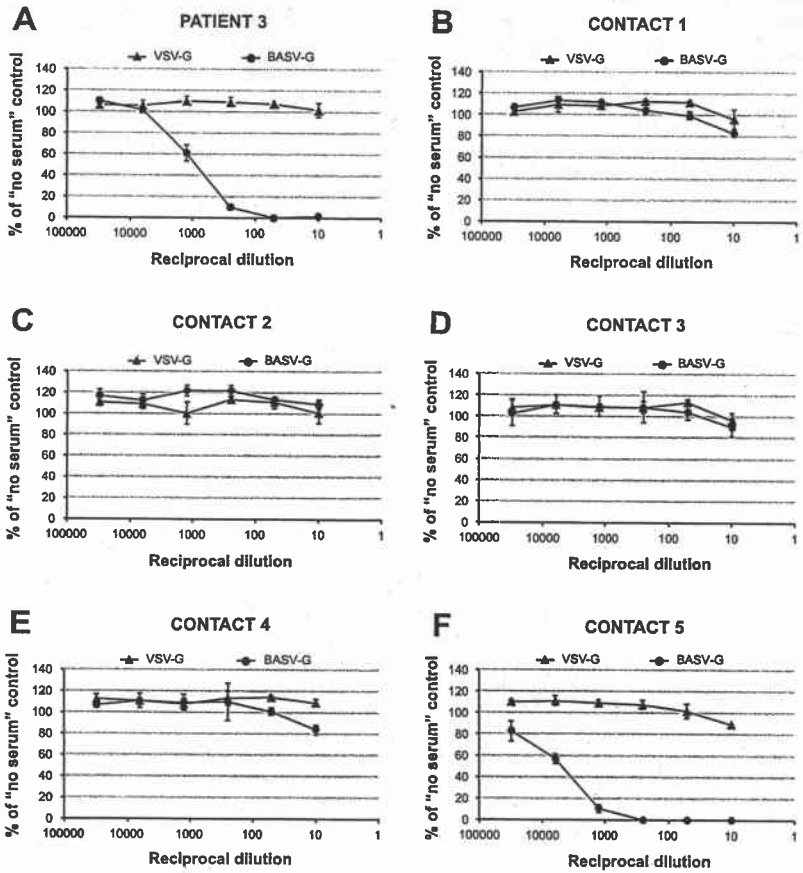

Figure 6. Detection of antibodies to BASV by serum neutralization of VSVΔG-GFP pseudotypes. Infectivities of VSVΔGFP pseudotypes bearing the glycoproteins of VSV or BASV, respectively, after incubation with 5-fold serial dilutions (1:10, 1:50, 1:250, 1:1,250, 1:6,250, 1:31,250) of sera from six individuals are depicted as percent of infectivity in the absence of serum. The six individuals tested include a patient with hemorrhagic fever (panel A, "Patient 3"), the nurse directly caring for him (panel F, "Contact 5"), and other health care workers in Mangala village (panels B–E). All data points represent the average of triplicate assays; error bars indicate standard deviations. Similar results were obtained in an independent experiment using murine leukemia virus (MLV)-based pseudotypes (data not shown).
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addition, the recent discovery of Moussa virus (MOUV), isolated from *Culex* mosquitoes in Cote d'Ivoire, Africa [23], implies the presence of hitherto unknown arthropod vectors for rhabdoviruses on the continent. Nevertheless, at present, we cannot exclude the possibility of other zoonotic sources for the virus or even nosocomial bloodborne transmission (as Patients 1 and 2 have not clearly been established to be BASV cases by serology or direct detection), and the natural reservoir and precise mode of transmission for BASV remain unknown. A community-based serosurvey in Boma Bungu and an investigation to track down potential arthropod or mammalian (e.g. rodents and bats) sources for BASV are currently underway.

Although we cannot exclude the possibility of independent arthropod-borne transmission events, our epidemiologic and serologic data do suggest the potential for limited human-to-human transmission of BASV. Patient 3, a nurse, had directly taken care of Patients 1 and 2 at the health center, and another nurse (Contact 5), who had taken care of Patient 3 (but not

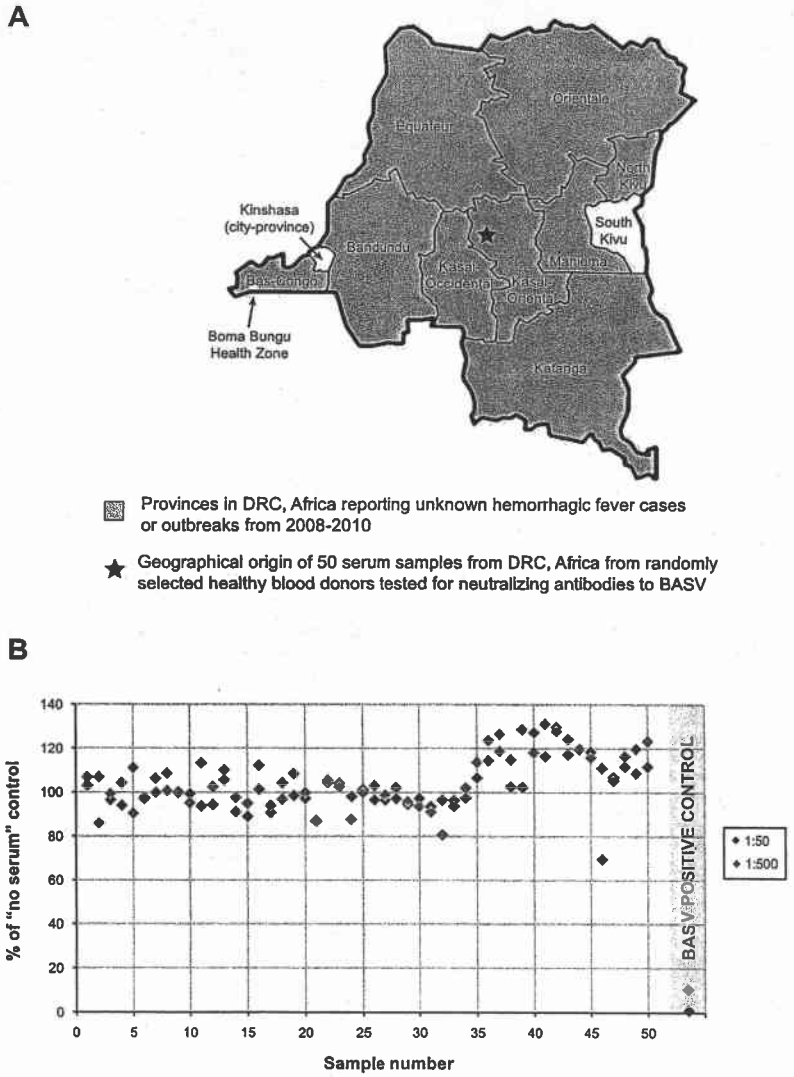

Figure 7. BASV Screening in DRC, Africa. (A) All 43 serum samples corresponding to unknown hemorrhagic fever cases or outbreaks in 2008–2010 from 9 provinces in DRC (pink) tested negative for BASV by PCR. (B) Sera from 50 donors in Kasai-Oriental province, DRC (Panel A, star) were tested for BASV-neutralizing antibodies. Sera at 1:50 (dark blue) or 1:500 dilution (light blue) were tested. Serum from the surviving Patient 3 was included as a positive control (grey shaded area). Data points represent an average of duplicate assays.
doi:10.1371/journal.ppat.1002924.g007

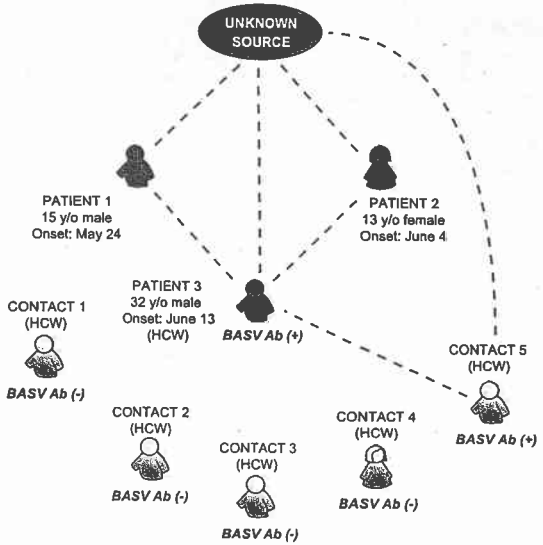

Figure 8. Proposed model for BASV transmission during the hemorrhagic fever outbreak in Mangala. Patients presenting with symptoms of acute hemorrhagic fever are depicted in red. Dashed red lines represent potential routes of BASV transmission. Contacts 1 through 5 are health care workers at the local health center in Mangala village. Abbreviations: HCW, health care worker; y/o, year-old; Ab, antibody.
doi:10.1371/journal.ppat.1002924.g008

Patients 1 or 2) had serologic evidence of asymptomatic BASV infection. We present a hypothetical model for BASV transmission during the hemorrhagic fever outbreak in which the initial infection of two children in Mangala (Patients 1 and 2) was followed by successive human-to-human transmission events involving two healthcare workers (Patient 3 and Contact 5) (Fig. 8). This pattern of transmission from the community to health care workers is also commonly seen in association with outbreaks of Ebola and Crimean-Congo hemorrhagic fever [6,34].

While rhabdoviruses are distributed worldwide, some authors have suggested that the *Rhabdoviridae* family probably originated from tropical regions of the Old or New World [9]. The discovery of BASV in Central Africa suggests that additional rhabdoviruses of clinical and public health importance likely await identification, especially in these poorly investigated geographic regions. Active epidemiological investigation and disease surveillance will be needed to fully ascertain the clinical and public health significance of BASV infection in humans, as well as to prepare for potentially larger human outbreaks from this newly discovered pathogen.

Methods

Ethics Statement

Written informed consent for publication of their case reports was obtained from the sole survivor of the hemorrhagic fever outbreak and the parents of the two deceased children. Written informed consent was obtained from the surviving patient and 5 of his close contacts for analysis of the serum samples reported in this study. Samples were analyzed under protocols approved by the institutional review boards of University of California, San Francisco, the University of Texas Medical Branch, and the National Institute of Biomedical Research (INRB) and CIRMF in Gabon, and the Institutional Animal Care and Use Committee (IACUC) of the University of Texas Medical Branch.

Diagnostic Samples

No diagnostic samples were available from Patient 1 or Patient 2. Blood was collected in a red top serum tube from Patient 3 on June 16, during the acute phase, three days after hemorrhagic onset. The sample was transported at 4°C to the BSL-4 facility at CIRMF. Serum was obtained by centrifugation at 2300 rpm for 10 min. No other acute samples from Patient 3 were available. In January of 2012 (~2.5 years after the outbreak), convalescent sera were collected from Patient 3 and close contacts (other workers at the health center) for BASV neutralization testing. Forty-three serum samples from other unknown hemorrhagic fever cases or outbreaks representing 9 of 11 provinces in the DRC were available for BASV PCR testing (Fig. 7A). Fifty available plasma samples from random blood donors (median age 27.5 years; age range 1–76 years) in Kasai Oriental province, DRC, were also tested for antibodies to BASV (Fig. 7A and B; Table S2).

Nucleic Acid Extraction and Viral PCR Testing

RNA was extracted from 140 µl of serum using the QIAamp viral RNA mini kit (Qiagen). Taqman real-time reverse-transcription-PCR (RT-PCR) testing for known hemorrhagic fever viruses was performed using primers and probes specific for Marburg virus (MARV), all four species of Ebola virus (Zaire, ZEBOV; Sudan, SEBOV; Côte d'Ivoire, CIEBOV, and Bundibugyo, BEBOV), Crimean-Congo hemorrhagic fever virus (CCHFV), Yellow fever virus (YFV), Dengue virus (DENV), Rift Valley fever virus (RVFV) and Chikungunya virus (CHIKV) (available upon request).

Discovery of the BASV Rhabdovirus by 454 Pyrosequencing

200 µL of serum sample were inactivated in 1 mL of TRIzol (Invitrogen), and nucleic acid extraction and purification were performed according to the manufacturer's instructions. Roche 454 pyrosequencing using randomly amplified cDNA libraries was performed as described previously [35]. Viral sequences were identified using BLASTn or BLASTx by comparison to the GenBank nonredundant nucleotide or protein database, respectively (E-score cutoff = 10^{-5}).

De novo Assembly of the BASV Genome by Illumina Sequencing

To recover additional BASV sequence, two sets of cDNA libraries were prepared from DNase-treated extracted RNA using a random PCR amplification method as described previously [36], or random hexamer priming according to the manufacturer's protocol (Illumina). The libraries were then pooled and sequenced on two lanes of an Illumina HiSeq 2000. Raw Illumina sequences consisting of 100 base pair (bp) paired-end reads were filtered to exclude low-complexity, homopolymeric, and low-quality sequences, and directly compared using BLASTn or BLASTx alignments to a library consisting of all rhabdovirus sequences in GenBank. The initial read obtained by 454 pyrosequencing as well as other reads aligning to rhabdoviruses were then inputted as "seeds" into the PRICE *de novo* assembler [37] (Fig. 2), with a criterion of at least 85% identity over 25-bp to merge two fragments. *De novo* assembly of the BASV genome was performed iteratively using PRICE and the Geneious software package (Biomatters) [38]. The near-complete whole genome sequence of the novel rhabdovirus (~98.2% based on protein homology to other rhabdoviruses) was determined to at least 3× redundancy by *de novo* assembly as well as PCR and Sanger sequencing of low-coverage regions. Sanger sequencing was also performed to verify the accuracy of the assembly and confirm the genomic organization of BASV (Fig. 2).

Deep Sequencing Analysis of the BASV Serum Sample for Other Pathogens

Rapid classification of the ~140 million 100-bp paired-end Illumina reads was performed using a modified cloud computing-based computational analysis pipeline [17] (Veeraraghavan, Sittler, and Chiu, manuscript in preparation). Briefly, reads corresponding to human sequences were taxonomically classified using SOAP and BLAT software [39,40]. Other reads were then identified using BLASTn or BLASTx by comparison to GenBank-derived reference databases (E-score cutoff = 10^{-5}).

PCR Quantitation of BASV Burden

To estimate the viral load in the patient's serum, we first designed a set of specific PCR primers for detection of BASV targeting the L protein, BASV-F (5'- CGCTGATGGTTTTTGACATGGAAGTCC-3')/BASV-R (5'-TAAACTTCCTCTCTCCTCTAG-3'), for use in a SYBR-Green real-time quantitative RT-PCR assay. A standard curve for the assay was constructed as described previously [36]. The viral load in the patient's serum was determined by comparison to the standard curve.

Structural Features and Phylogenetic Analysis

Predicted open reading frames (ORFs) in the BASV genome were identified with Geneious [38]. Multiple sequence (Figs. 3 and 4; Fig. S1) and pairwise (Fig. 5) alignments of BASV proteins relative to corresponding proteins from other rhabdoviruses were calculated using MAFFT (v6.0) with the E-INS-i option and at default settings [41]. To generate the phylogeny trees, all rhabdoviruses in GenBank were included as well as representative members of other families within the order *Mononegavirales*. Bayesian tree topologies were assessed with MrBayes V.32 software (20,000 sampled trees; 5,000 trees discarded as burn-in) [42]. Convergence was confirmed by the PSRF statistic in MrBayes, as well as by visual inspection of individual traces using TRACER from the BEAST software package [43]. Trees were visualized after midpoint rooting with FigTree V1.31 [43].

Virus Cultivation in Cell Cultures or Suckling Mice

Initial attempts were made to culture the virus using a total of 200 µL of BASV-positive serum inoculated onto confluent monolayers of Vero E6 and C6/36 (*Aedes albopictus* mosquito) cells in 6-well plastic tissue culture plates at 37°C and 28°C, respectively, in a 5% CO_2 environment as previously described [44]. From 20–50 µL of serum were used to inoculate the cells, which were examined daily for cytopathic effect (CPE) at days 5, 7, and 14. Supernatants were harvested and two additional blind passages were performed, each passage followed by 14 days of observation for CPE. Cell culture supernatants were also monitored for evidence of viral replication by quantitative RT-PCR.

Using the remaining 100 uL of BASV-positive serum, further attempts were made to culture the virus in 5 cell lines and in suckling mice. The serum sample was split in half and diluted 1:20 or 1:10 in phosphate-buffered saline with 20% fetal bovine serum (FBS) to allow sufficient volume to inoculate cell cultures or mice, respectively. The first diluted sample was inoculated intracerebrally into a litter (n = 12) of 1 day old mice. Pups were observed daily for 14 days for lethality or signs of clinical illness. The second diluted sample was inoculated into 12.5 cm^2 tissue culture flasks of Vero, BHK, LLC-MK_2 (rhesus monkey kidney), CCL-106 (rabbit kidney) and C6/36 cells. Vertebrate cells were held at 37°C for 14 days and observed for evidence of CPE. Mosquito cells were maintained at 28°C for 10 days. Since no CPE was observed in any of the cultures, cells were subsequently fixed for transmission electron microscopy to see if viral particles could be visualized [45].

Construction of VSVΔG-GFP Pseudotypes and BASV Serum Neutralization Testing

A pseudotype system based on a vesicular stomatitis virus (VSV) construct carrying a reporter gene for green fluorescent protein (VSVΔG-GFP) and bearing the predicted synthesized BASV glycoprotein (BASV-G) was used to generate a serum neutralization assay for BASV. Briefly, the predicted BASV glycoprotein (BASV-G) was synthesized (Genscript) and subcloned into the pCAGGS expression plasmid. Human embryonic kidney 293T cells were seeded (DMEM + 10% FBS + penicillin/streptomycin + Glutamax (Gibco) + non-essential amino acids (Gibco)) in 10 cm culture dishes 24 hours prior to transfection. Cells were transfected with 20 µg BASV-G, VSV-G, or empty pCAGGS DNA per dish following a calcium phosphate transfection protocol [46]. The culture medium was replaced 15 hours post-transfection and cells were stimulated with 6.2 mM valproic acid for 4 hours before the medium was replaced again. At 36 hours post-transfection the transfected cells were infected with VSVΔG-GFP/VSV-G pseu-

dotypes at a multiplicity of 0.1–0.3. The inoculum was removed after 4 hours and replaced by fresh culture medium. At 24 hours post-infection, infectious supernatants were harvested, filtered through 0.45 µm filters, and concentrated 10-fold by centrifugation through a 100-kDA filter (Millipore). Concentrated viruses were aliquoted and stored at −80°C.

For serum neutralization testing, human hepatoma Huh-7 cells were seeded (DMEM +10% FBS + penicillin/streptomycin + Glutamax (Gibco) + non-essential amino acids (Gibco)) in 48-well plates 24 hours prior to infection. Per well 10 µl of pseudovirus harboring either BASV-G or VSV-G (adjusted to obtain 25–50% infection of target cells) was mixed with 10 µl of the respective serum dilution and incubated for 45 minutes at 37°C. Subsequently, the mix was added to the target cells (performed in triplicate) and cells were incubated for 24 hours at 37°C. The infected cells were detached with trypsin and washed with PBS before fixing with 2% paraformaldehyde for 1 hour at room temperature. GFP expression in infected cells was quantified by flow cytometry using a LSR II (BD Biosciences) and the collected data was analyzed with FlowJo software (TreeStar).

Abbreviations and Nucleotide Sequence Accession Numbers

The annotated, nearly complete sequence of BASV has been submitted to GenBank (accession number JX297815). Deep sequencing reads have been submitted to the NCBI Sequence Read Archive (accession number SRA056894). Accession numbers used for the phylogenetic analyses in Figs 3, 4, and S1 are listed as follows, in alphabetical order: ABLV, Australian bat lyssavirus (NP_478343); ARAV, Aravan virus (ABV03822), BEFV, Bovine ephemeral fever virus (NP_065409); BYSMV, Barley yellow striate mosaic virus (BYSMV); CDV, Canine distemper virus (AAR32274); CHPV, Chandipura virus (ADO63669); CPV, Coastal Plains virus (ADG86364); COCV, Cocal virus (ACB47438); DURV, Durham virus (ADB88761); DUVV, Duvenhage virus (ABZ81216); EBLV1, European bat lyssavirus 1 (ABZ81166), EBLV2, European bat lyssavirus 2 (ABZ81191); EBOV, Ebola virus (AAG40171, AAA79970, BAB69010); EVEX, Eel virus European X virus (CBH20130); FDLV, Fer-de-lance virus (NP_899661); FLAV, Flanders virus (AAN73288); HeV, Hendra virus (NP_047113); HIRRV, Hirame rhabdovirus (ACO87999); HMPV, Human metapneumovirus (L_HMPVC); HPIV-1, Human parainfluenza virus type 1 (AA A69579); HPIV-2, Human parainfluenza virus type 2 (CAA 40788); HPIV-3, Human parainfluenza virus type 3 (AAA46854); HPIV-4, Human parainfluenza virus type 4 (BAJ11747); INHV, Infectious hematopoietic necrosis virus (NP_042681); IRKV, Irkut virus (ABV03823); ISFV, Isfahan virus (CAH17548); KHUV, Khujand virus (ABV03824); LBV, Lagos bat virus (ABZ81171); LNYV, Lettuce necrotic yellows virus (YP_425092); MARAV, Maraba virus (AEI52253); MARV, Marburg virus (YP_001531159); MeV, Measles virus (AF266288); MMV, Maize mosaic virus (YP_052855); MOKV, Mokala virus (ABZ81206); MOUV, Moussa virus (ACZ81407); MUV, Mumps virus (AF 201473); NCMV, Northern cereal mosaic virus (NP_597914); NDV, Newcastle disease virus (ADH10207); NGAV, Ngaingan virus (YP_003518294); NiV, Nipah virus (AAY43917); OVRV, Oak Vale rhabdovirus (AEJ07657); PFRV, Pike fry rhabdovirus (ACP28002); RABV, Rabies virus (NP_056797); RSV, Respiratory syncytial virus (NP_056866); RYSV, Rice yellow stunt rhabdovirus (NP_620502); SIGMAV, Sigma virus (ACU65444); SCRV, Siniperca chuatsi rhabdovirus (YP_802942); SHRV, Snakehead virus (AAD56771); SMRV, Scophthalmus maximus rhadovirus (ADU05406); SVCV, Spring viremia of carp virus (NP_116748); SYNV, Sonchus yellow net virus (NP_044286); TIBV, Tibrogargan virus (ADG86355); TUPV, Tupaia virus (AAX47602); TVCV, Tomato vein clearing virus (YP_224083); VHSV, Viral hemorrhagic septicemia virus (NP_049550); VSIV, Vesicular stomatitis virus, Indiana (NP_041716); VSNJV, Vesicular stomatitis virus, New Jersey (P16379); WCBV, West Caucasian bat virus (ABV03821); WONGV, Wongabel virus (YP_002333280).

Supporting Information

Figure S1 Phylogenetic analysis of the N, P, M, and G proteins of BASV and other rhabdoviruses. Each phylogenetic tree is rooted by using the corresponding protein from human parainfluenza virus type 1 (HPIV-1), a paramyxovirus, as an outgroup. Abbreviations and accession numbers used for the phylogenetic analysis are provided in Methods.
(TIF)

Figure S2 Confirmation of laboratory contamination by rotavirus and absence of rotavirus in BASV serum by specific PCR. An RT-PCR assay for detection of Group A rotaviruses was performed using primers NSP3F (5′-ACCATCTWCACRTRACCCTCTATGAG-3′) and NSP3R (5′-GGTCACATAACGCCCCTATAGC-3′), which generate an 87-bp amplicon (Freeman, et al., (2008) J Med Virol 80: 1489–1496). PCR conditions for the assay were 30 min at 50°C, 15 min at 95°C for the reverse transcription step followed by 40 cycles of 95°C, 30 s/55°C, 30 s/72°C, 30 s and 72°C/7 min for the final extension. PCR products are visualized by gel electrophoresis, using a 2% agarose gel and 1 kB ladder. Rotavirus is readily detected in extracted RNA from a stool sample taken from an ongoing study of viral diarrhea in the laboratory (lane 1), but not in two separate aliquots of extracted nucleic acid from the BASV serum sample (lanes 2 and 3).
(TIF)

Table S1 Viral reads in the deep sequencing data corresponding to the BASV-positive serum sample.
(DOCX)

Table S2 Demographics of 50 blood donors from Kasai-Oriental province, DRC, randomly selected for BASV antibody screening.
(DOCX)

Acknowledgments

The authors thank the national and international teams involved in the control of suspected hemorrhagic fever cases that occurred in 2009 in Democratic Republic of the Congo (DRC). The national teams are members of the DRC Ministry of Health and the National Institute of Biomedical Research (INRB). The international teams are epidemiological and medical experts of the World Health Organization (WHO) and the NGO 'Médecins Sans Frontières'. We thank all those involved in sample collection and case reporting, especially Etienne Mukendi at the Cellule de Surveillance Epidemiologique, Bas-Congo, DRC. We are also grateful to A Délicat and P Engandja from Centre International de Recherches de Franceville (CIRMF), Gabon, Matthew LeBreton at Global Viral Forecasting, Incorporated, Nicole A. Hoff at University of California, Los Angeles, Thomas Geisbert at University of Texas Medical Branch, as well as Samia Naccache, Rick Hsu and Yasamin Mohammadi at University of California, San Francisco (UCSF), for technical assistance during this work.

Author Contributions

Conceived and designed the experiments: GG JNF DL GS ED NDW CYC EML. Performed the experiments: GG DL ES IS RBT. Analyzed the data: GG JNF DL J-JM NV MM PM GS ED NDW CYC EML. Contributed reagents/materials/analysis tools: TS JGR CW RBT JM AWR TT BSS GS ED NDW CYC EML. Wrote the paper: GG JNF DL IS RBT GS ED NDW CYC EML. Obtained consents from patients and their families: PM.

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Novel Rhabdovirus in Acute Hemorrhagic Fever

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
				2012. 10. 20	該当なし	
一般的名称	新鮮凍結人血漿		研究報告の公表状況		公表国	
販売名(企業名)	新鮮凍結血漿-LR「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」成分採血(日本赤十字社) 新鮮凍結血漿-LR「日赤」120(日本赤十字社) 新鮮凍結血漿-LR「日赤」240(日本赤十字社) 新鮮凍結血漿-LR「日赤」480(日本赤十字社)			ProMED 20120929.1315179	オーストラリア	

研究報告の概要

○ロスリバーウイルスーオーストラリア(西オーストラリア州)
今年(2012年)西オーストラリア州で重大な蚊媒介性疾患が流行しており、ロスリバーウイルス感染者については3年前の5倍に増加している。生涯継続する後遺症を遺すこともあるこのウイルスに、2011年から2012年にかけて州全域で1,570人が感染した。マンジュラの衛生官は、2011年ー2012年の蚊のシーズンは史上最悪であるとした。西オーストラリア州のロスリバーウイルス感染者は2009年ー2010年の332人から2010年ー2011年には2倍以上の770人になった。過去2年間、ラニーニャ現象によって蚊が多く発生したことが原因であるとのこと。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿-LR「日赤」
新鮮凍結血漿-LR「日赤」成分採血
新鮮凍結血漿-LR「日赤」120
新鮮凍結血漿-LR「日赤」240
新鮮凍結血漿-LR「日赤」480

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

23

報告企業の意見	今後の対応
西オーストラリア州においてロスリバーウイルス感染者が3年前の5倍に増加しているとの報告である。	日本赤十字社では、輸血感染症対策として問診時に海外滞在歴の有無を確認し、帰国(入国)後4週間は献血不適としている。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。

MedDRA/J Ver.15.1J

ProMED-mail |

INTERNATIONAL SOCIETY FOR INFECTIOUS DISEASES

ProMED mail

Published Date: 2012-09-29 11:34:14
Subject: PRO/AH/EDR> Ross River virus - Australia (05): (WA)
Archive Number: 20120929.1315179

ROSS RIVER VIRUS - AUSTRALIA (05): (WESTERN AUSTRALIA)
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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: Sat 29 Sep 2012

Source: The West [edited]
http://au.news.yahoo.com/thewest/a/-/breaking/14991504/huge-rise-in-ross-river-cases/

Outbreaks of a serious mosquito-borne disease have exploded in WA [Western Australia state] this year [2012], with 5 times more people contracting Ross River virus than 3 years ago. The virus, which can leave victims with a lifetime of debilitating symptoms and side-effects, infected 1570 people across the State in 2011-2012.

Public health officials in Mandurah branded the 2011-2012 mosquito season the worst on record.

WA cases of Ross River virus reached 332 in 2009-2010 and the number more than doubled to 770 in 2010-2011.

Department of Health entomologist Peter Neville said there had been more mosquitoes over the past 2 years. "It's largely to do with weather events," he said. "Over the last 2 years we have been under La Nina weather conditions." Those conditions meant more rain and higher minimum temperatures, leading to more mosquitoes. He said there was a spike in Ross River virus cases every 3-4 years.

Infected people get a fever, headaches, rashes and painful, swollen joints. "In some cases it can last up to 12 months," Dr Neville said. "In some people, it can be quite devastating. The virus can reduce people's capacity to work. It's quite debilitating."

A report to the City of Mandurah this week revealed the council has struggled against mosquitoes. "The continuation of the La Nina weather event resulted in local weather and tide behaviour that made mosquito management very difficult due to consistent inundation of breeding sites and the frequent hatching of salt-marsh mosquito larvae," environmental health officer Brendan Ingle wrote.

Ross River virus cases in the Peel region soared from 68 in 2009-2010 to 206 in 2011-2012.

Mandurah residents complained this week that swarms of mosquitoes make it impossible for them to go outside and warned the city's reputation was being harmed.

Mandurah mayor Paddi Creevey said the council had quadrupled the amount of insecticide sprayed to kill mosquito larvae. "What we can't control is the

El Nino/La Nina effect, and when those tides stay up and they inundate the breeding areas, no amount of spraying will kill them," she said.

People are urged to be especially vigilant about mosquitoes at dawn and dusk. [They are advised to] wear long, loose clothing and apply insect repellent.

[Byline: Angela Pownall]

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Communicated by:

ProMED-mail Rapporteur Kunihiko Iizuka

[Ross River virus infections in Western Australia have increased significantly in 2012. In the 1st 2 months of 2012, there were 511 cases state-wide. The above report indicates that there have been 1570 cases in the 2011-2012 transmission season. Ross River virus is a zoonotic alphavirus transmitted by a wide range of mosquitoes including _Aedes_ and _Culex_ species, and causes acute polyarthritis in humans. - Mod.TY

A HealthMap/ProMED-mail map can be accessed at: http://healthmap.org/r/21Bk.]

See Also

Ross River virus - Australia (04) (VI) 20120421.1109313
Ross River virus - Australia (03): (VI) 20120419.1107581
Ross River virus - Australia (WA, TA) 20120325.1079824
Ross River virus - Australia (WA) 20120302.1059212
.....jw/ty/mj/ejp/jw

別紙様式第2-1

No. 8

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
				2013. 2. 20	該当なし	
一般的名称	新鮮凍結人血漿		研究報告の公表状況		公表国	
販売名(企業名)	新鮮凍結血漿-LR「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」成分採血(日本赤十字社) 新鮮凍結血漿-LR「日赤」120(日本赤十字社) 新鮮凍結血漿-LR「日赤」240(日本赤十字社) 新鮮凍結血漿-LR「日赤」480(日本赤十字社)			ProMED 20130215.1544648	オーストラリア	

研究報告の概要

○オーストラリアコウモリリッサウイルス－オーストラリア
クイーンズランド州北部在住の8歳の男児が、恐らくオーストラリアコウモリリッサウイルスを保有しているコウモリまたはオオコウモリにより咬傷あるいは擦過傷を受け、ウイルスに感染し、現在危篤状態である。これは狂犬病様のオーストラリアコウモリリッサウイルスに感染した3人目の確定症例である。過去(1996年と1998年)に感染した2人は死亡した。
ウイルスへの暴露から発症までの期間は様々であり、ヒトにおける既知の2症例のうち、1例はコウモリに咬まれてから数週間後、もう1例は2年以上経過してから発症している。このウイルスは麻痺、せん妄、痙攣をもたらし、通常呼吸麻痺により死亡する。ヒト－ヒト感染は理論上可能であるが、極めて起こりにくいと考えられる。男児の家族は現時点で症状は見られていないが、予防措置を受けた。
クイーンズランド州の保健担当官は、全てのオーストラリアのコウモリがこのウイルスを保有している可能性があり、ウイルスからの最良の防護策はコウモリやオオコウモリとの接触を避けることであると述べた。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿-LR「日赤」
新鮮凍結血漿-LR「日赤」成分採血
新鮮凍結血漿-LR「日赤」120
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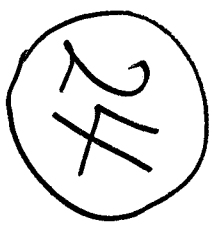
新鮮凍結血漿-LR「日赤」480

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
オーストラリアのクイーンズランド州在住の男児がオーストラリアコウモリリッサウイルスに感染し重篤となっており、これはこのウイルスへの感染が確認された3例目であるとの報告である。	日本赤十字社では、輸血感染症対策として受付時に海外滞在歴の有無を確認し、帰国(入国)後4週間は献血不適としているほか、発熱などの体調不良者を献血不適としている。また、動物に噛まれた場合は傷が治癒してから3カ月間献血不適としている。今後も情報の収集に努める。



Published Date: 2013-02-15 17:55:17
Subject: PRO/AH/EDR> Australian bat lyssavirus - Australia: (QL) 3rd victim
Archive Number: 20130215.1544648

AUSTRALIAN BAT LYSSAVIRUS - AUSTRALIA: (QUEENSLAND) THIRD VICTIM
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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: Fri 15 Feb 2013
Source: World News, AAP report [edited]
http://www.sbs.com.au/news/article/1737424/Qld-boy-ill-with-rabies-like-bat-virus

Queensland boy ill with rabid-like virus

A north Queensland boy was likely bitten or scratched by a bat or a flying fox carrying Australian bat lyssavirus, and he's now critically ill in hospital. An 8-year-old Queensland boy is critically ill with the bat-borne virus that causes fits [seizures], paralysis and death. It's only the 3rd confirmed case of the rabies-like Australian bat lyssavirus recorded in the country. The other 2 victims, both infected in Queensland, died.

It's assumed the north Queensland boy was bitten or scratched by a bat or a flying fox carrying the deadly virus. It's believed he was infected about 2 months ago and a few weeks ago developed a brain infection that led to fits [seizures]. He's now so unwell he cannot give doctors any clues about how he came to be infected. "We're not sure of the circumstances because the child is now too sick to tell us," Queensland Chief Health Officer Jeannette Young told reporters on Friday [15 Feb 2013].

"He's critically unwell. The previous 2 cases did not survive and the vast majority of people who contract rabies [rabies virus and Australian bat lyssavirus are distinct virus species - Mod.CP] overseas die, unfortunately. "The other 2 cases were recorded in 1996 and 1998.

Dr Young said the family was incredibly distressed given the prognosis for the boy. The time from exposure to the virus to the development of symptoms is variable. Of the 2 known human cases, one became ill several weeks after being bitten by a bat while the other became ill more than 2 years after a bat bite. The virus causes paralysis, delirium and convulsions. Death is usually caused by respiratory paralysis. It's theoretically possible that the virus could be passed from human to human but that is considered very unlikely. And so far the boy's family has not shown any signs of symptoms but they've been given post-exposure drugs [rabies virus vaccine?] as a safeguard.

Dr Young said it's assumed any bat in Australia could carry the disease, and bat behaviour is not an accurate guide to infection. She said the best protection against the virus was to avoid handling any bat or flying fox. "Only people who have been trained in the care of bats, and who have been vaccinated against rabies, should ever handle bats or flying foxes," she said. "It is important to also encourage young children to never handle bats, particularly if they should come across a sick or injured one."

Federal MP Bob Katter, who holds the north Queensland seat of Kennedy, says it's time to revisit the idea of culling bats. The independent MP has long supported culling because bats spread disease, ruin farmers' crops and are a pest. He says Premier Campbell Newman has broken a pre-election promise to do something about bat colonies that have invaded some Queensland towns. "Clearly the Liberal National Party puts the welfare of bats over the lives of human beings," Mr Katter told reporters on Friday. He said bat populations were out of control thanks to laws preventing farmers and others from killing them.

--
Communicated by:
Gert van der Hoek
Senior Moderator
FluTrackers.com
http://www.flutrackers.com/forum/index.php

[Gert van der Hoek is thanked for drawing attention to this report.

Australian bat lyssavirus [ABLV} is classified as a district species in the genus _Lyssavirus_ of the family _Rhabdoviridae_. It is closely related to rabies virus, but restricted to bats. It is antigenically similar enough to be neutralised by standard anti-rabies virus vaccine which can be used for post-exposure prophylaxis if administered before the onset of symptoms of disease. However in the present case in view of the lapse of time between exposure and appearance of symptoms it is unlikely that post-exposure prophylaxis could be successful.

According to Queensland Health
(http://access.health.qld.gov.au/hid/InfectionsandParasites/ViralInfections/australianBatLyssavirus_fs.asp):
Australian bat lyssavirus (ABLV) is a virus that can be transmitted from bats to humans, causing serious illness.
e virus was 1st identified in 1996 and has been found in 4 kinds of flying foxes/fruit bats and one species of insect-eating microbat. Evidence of previous infection has been found in blood tests from a number of other bat species. It is therefore assumed that any bat in Australia could potentially carry the virus.

Since November 1996, 2 people have died as a result of ABLV infection after being bitten by bats. ABLV is one of 12 types of lyssavirus which are found around the world. ABLV is the only one of these known to occur in Australia. ABLV infection in humans causes a serious illness which results in paralysis, delirium, convulsions and death. Death is usually due to respiratory paralysis. Transmission of the virus from bats to humans is thought to usually be by a scratch or bite, but also potentially by being exposed to bat saliva through the eyes, nose or mouth (mucous membrane exposure). ABLV is unlikely to survive outside the bat for more than a few hours, especially in dry environments that are exposed to sunlight. The time from exposure to the virus to the development of symptoms is variable; of the 2 other known human cases of ABLV infection, one became ill several weeks after being bitten by a bat while the other became ill more than 2 years after a bat bite.

There is no available treatment for ABLV. In all potential exposures to ABLV (bites, scratches, mucous membrane exposures), seek medical advice immediately, even if you have been vaccinated. Proper cleansing of the wound is the single most effective measure for reducing transmission. If bitten or scratched, immediately wash the wound thoroughly with soap and water for at least 5 minutes. If available, an antiseptic with anti-virus action such as ovidone-iodine, iodine tincture, aqueous iodine solution or alcohol (ethanol) should be applied after washing. If bat saliva contacts the eyes, nose or mouth, it is necessary to flush the area thoroughly with water. Seek medical attention as soon as possible. The best protection against being exposed to the virus is for members of the community to avoid handling any bat or flying fox.

Anyone who has been potentially exposed to ABLV, and has never received pre-exposure vaccination, will require an injection of rabies immunoglobulin and a series of 4 rabies vaccine injections over one month (on days zero, 3, 7, and 14). *Queensland Health will fund these injections, which are called 'post-exposure prophylaxis,' and your* local public health unit will arrange for these injections to be delivered to your GP or hospital. These injections are recommended for anyone who has been exposed to ABLV, regardless of how long ago the exposure occurred. *People with a weakened immune system will require a further (5th) dose of vaccine given at day 28 and follow up* blood tests to confirm their immunity. Post-exposure vaccination may be delayed for up to 48 hours if the bat is available for testing, without placing other people at risk of exposure.

A map of Australia, shooing the location of Queensland can be accessed at: http://mapsof.net/map/australia-states-rs01#.UR6fsaXEIac. - Mod.CP
A HealthMap/ProMED-mail map can be accessed at: http://healthmap.org/r/1z *.]

See Also

2011

別紙様式第2-1

No. 12

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
				2012. 11. 19	該当なし	

一般的名称	新鮮凍結人血漿	研究報告の公表状況	公表国
販売名(企業名)	新鮮凍結血漿-LR「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」成分採血(日本赤十字社) 新鮮凍結血漿-LR「日赤」120(日本赤十字社) 新鮮凍結血漿-LR「日赤」240(日本赤十字社) 新鮮凍結血漿-LR「日赤」480(日本赤十字社)	WHO Global Alert and Response (GAR); 8 October 2012	WHO

研究報告の概要

○コンゴ民主共和国におけるエボラアウトブレイク－最新情報
2012年10月7日現在、49人(確定患者は31人、可能性の高い患者は18人)のエボラ出血熱患者がコンゴ民主共和国で報告されている。うち24人(確定患者は10人、可能性の高い患者は14人)が死亡した。これらは同国のOrientale州、Haut Uélé地区のIsiroとViadanaから報告された。コンゴ民主共和国保健省は引き続き国の対策本部下で関係機関と連携して、感染連鎖のあらゆる可能性を調査し、アウトブレイクを止めるための適切な対策を講じている。最初の検体はウガンダウイルス研究所で検査され、ウイルスが確認された。CDCはアウトブレイクの早期にIsiroに検査施設を設置し、カナダ公衆衛生局は移動検査施設を用いて、現場での迅速な診断の支援を継続している。

使用上の注意記載状況・その他参考事項等

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新鮮凍結血漿-LR「日赤」成分採血
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新鮮凍結血漿-LR「日赤」480

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
コンゴ民主共和国でエボラ出血熱のアウトブレイクがあり、2012年10月7日現在49人の患者が報告され、そのうち24人が死亡したとの報告である。	日本赤十字社では、輸血感染症対策として受付時に海外滞在歴の有無を確認し、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。今後も引き続き情報の収集に努める。

25

World Health Organization

Global Alert and Response (GAR)

Ebola outbreak in Democratic Republic of Congo – update

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Related links

Ebola haemorrhagic fever
Fact sheet

Interim infection control recommendations for care of patients with suspected or confirmed filovirus (Ebola, Marburg) haemorrhagic fever

8 OCTOBER 2012 - As of 7 October 2012, 49 cases (31 laboratory confirmed, 18 probable) with Ebola haemorrhagic fever (EHF) have been reported in the Democratic Republic of Congo (DRC). Of these, 24 have been fatal (10 confirmed, 14 probable).

The cases reported are from Isiro and Viadana health zones in Haut-Uélé district in Province Orientale.

Ministry of Health (MoH) continues to work with partners, under the National Task Force to identify all possible chains of transmission of the illness and ensure that appropriate measures are taken to interrupt transmission and stop the outbreak. The task force includes Médecins Sans Frontières (MSF); the International Federation of Red Cross and Red Crescent Societies (IFRC); US Agency for International Development (USAID); US Centers for Disease Control and Prevention (CDC); and the United Nations Children's Fund (UNICEF) and WHO.

Response operations continue in the areas of coordination; Infection Prevention and Control (IPC); surveillance and epidemiology; case management; public information and social mobilization; psychosocial support; anthropological analysis; and logistics.

WHO and the Global Outbreak Alert and Response Network (GOARN) have deployed experts to support operational response, including establishment of a field laboratory and in the area of infection prevention and control in health care settings.

Initial samples were tested and confirmed by Uganda Virus Research Institute (UVRI). CDC established a field laboratory in Isiro in the beginning of the outbreak and Public Health Agency of Canada (PHAC) is continuing to provide support on rapid diagnosis in the field with their mobile laboratory facilities in Isiro.

Ongoing activities in Isiro and neighbouring areas include: training of health care workers on IPC in health care facilities, provision of support on case management, strengthening surveillance, working with traditional healers in raising awareness about EHF, providing psychosocial support to affected families, and conducting outreach to schools.

With respect to this event, WHO does not recommend any travel or trade restrictions to be applied to the DRC.

General information on controlling infection of EHF in health-care settings

Human-to-human transmission of the Ebola virus is primarily associated with direct contact with blood and body fluids. Transmission to healthcare workers has been reported when appropriate infection control measures have not been observed.

http://www.who.int/csr/don/2012_10_08a/en/index.html

Health-care workers caring for patients with suspected or confirmed Ebola virus need to apply infection control measures to avoid any exposure to the patient's blood and body fluids and/or direct unprotected contact with the possibly contaminated environment. In addition, it is important that Standard Precautions, particularly hand hygiene, the use of gloves and other personal protective equipment, safe injection practices and other measures are applied to all patients in all health care settings at all times.

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
				2013. 2. 6	該当なし	
一般的名称	新鮮凍結人血漿				公表国	
販売名(企業名)	新鮮凍結血漿-LR「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」成分採血(日本赤十字社) 新鮮凍結血漿-LR「日赤」120(日本赤十字社) 新鮮凍結血漿-LR「日赤」240(日本赤十字社) 新鮮凍結血漿-LR「日赤」480(日本赤十字社)		研究報告の公表状況	ProMED 20130205.1530748	バングラデシュ	

研究報告の概要

○ニパウイルス脳炎－バングラデシュ
2012－13年の冬、バングラデシュで再流行した致死性のニパウイルスによって、2013年2月3日現在、感染者12人中10人(首都の2人を含む)が死亡した。バングラデシュの疫学疾病対策研究所(IEDCR)によると、死亡者はダッカ県、パブナ県、ナトール県から各2名、ラジバリ県、ジェナイダ県、ナオガオン県、ラジシャヒ県から各1名が報告されている。ダッカ県の死亡者2名は、ミメシング県バールカでナツメヤシの生ジュースを飲んだと報告している。IEDCRの担当官は、感染したコウモリの尿や唾液で汚染された生のナツメヤシジュースや果物を飲食しないように警告した。患者を介護する者も予防策をとる必要がある。
バングラデシュでのアウトブレイクではこれまでに感染者180人中139人が死亡している。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿-LR「日赤」
新鮮凍結血漿-LR「日赤」成分採血
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新鮮凍結血漿-LR「日赤」480

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

26

報告企業の意見	今後の対応
2012－13年の冬にバングラデシュで再流行したニパウイルスにより、2013年2月3日現在、感染者12人中10人が死亡したとの報告である。	日本赤十字社では、輸血感染症対策として受付時に海外滞在歴の有無を確認し、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。今後も引き続き情報の収集に努める。

MedDRA/J Ver.15.1J

JRC2013T-006

Published Date: 2013-02-05 17:56:11
Subject: PRO/AH/EDR> Nipah encephalitis, human - Bangladesh (03)
Archive Number: 20130205.1530748

NIPAH ENCEPHALITIS, HUMAN - BANGLADESH (03)
****
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: Tue 5 Feb 2013
Source: Financial Express [edited]
http://www.thefinancialexpress-bd.com/index.php?ref=MjBfMDJfMDVfMTNfMV84OF8xNTkxODg=

After staging a comeback in the country this winter, deadly Nipah virus has so far claimed the lives of 10 people, including 2 in the capital, out of 12 infected as of 3 Feb [2013], reports UNB (United News of Bangladesh). Among the casualties, there have been 2 from each of Dhaka, Pabna, and Natore and one from each of Rajbari, Jhenaidah, Naogaon, and Rajshahi, according to Bangladesh's Institute of Epidemiology Diseases Control and Research (IEDCR). It says 2 of the victims of Dhaka consumed raw date palm juice from Bhaluka, Mymensingh.
Dr Mushtuq Hossain, the principal scientific officer (medical sociology) of IEDCR, told UNB on Monday [4 Feb 2013] that those died and who have been affected by the deadly Nipah virus consumed raw date palm juice. Mushtuq cautioned that no one should drink raw date palm juice and fruits that were partly eaten by animals earlier. "One should drink date juice after its proper boiling and eat raw fruit after washing it properly."
Asked about the symptoms of the disease, Mushtuq said high fever, senseless talking, acute chest pain, respiratory problems, and severe headache are the symptoms of the disease. "If any patient has those symptoms he or she should be admitted to nearby hospital for treatment." Mushtuq added that the attendants of the Nipah virus affected patients should take precautionary steps while taking care of the patients as the virus is contagious.
Human Nipah virus (NiV) infection, an emerging zoonotic disease, was 1st recognised in a large outbreak of 276 reported cases in Malaysia and Singapore from September 1998 through May 1999.
NiV is a highly pathogenic paramyxovirus belonging to genus Henipavirus. It is an enveloped RNA virus.
But now, according to Mushtuq, the disease is only found in Bangladesh. Some 139 patients out of 180 infected people so far died in the outbreak of the disease in Bangladesh.
-- communicated by: ProMED-mail from HealthMap alerts <promed@promedmail.org>

[The number of Nipah virus infections and deaths continues to slowly rise so far this year (2013). Curiously, the above report makes no mention of the source of palm sap or fruit contamination. The reservoir hosts of Nipah virus are giant fruit bats (_Pteropus_ species). They shed virus, particularly during the breeding season when pregnant or lactating. Because these sporadic cases occur in geographically scattered areas, increasing the degree of public awareness, and need for either boiling the sap or preventing access to sap collection vessels by the bats by placing barriers around the jars, is a major public health education challenge. - Mod.TY
An image of a _Pteropus_ fruit bat can be found at http://promedmail.ask.com/ts?u=/wikipedia/commons/thumb/3/3d/Pteropus_giganteus_fg01.JPG/180px-Pteropus_giganteus_fg01.JPG.
A HealthMap/ProMED-mail map can be accessed at http://healthmap.org/r/1ywE.]

See Also

Nipah encephalitis - Bangladesh (02) 20130128.1518442
Nipah encephalitis - Bangladesh: 20130124.1513132
2012

Nipah encephalitis, human - Bangladesh (03): (JI): 20120212.1040138
Nipah encephalitis, human - Bangladesh (JI) (02), Susp.: 20120128.1024955

別紙様式第2-1

No. 25

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
				2013. 2. 15	該当なし	
一般的名称	新鮮凍結人血漿		研究報告の公表状況	Krause PJ, Narasimhan S, Wormser GP, Rollend L, Fikrig E, Lepore T, Barbour A, Fish D. N Engl J Med. 2013 Jan 17;368(3):291-3. doi: 10.1056/NEJMc1215469.	公表国	
販売名(企業名)	新鮮凍結血漿-LR「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」成分採血(日本赤十字社) 新鮮凍結血漿-LR「日赤」120(日本赤十字社) 新鮮凍結血漿-LR「日赤」240(日本赤十字社) 新鮮凍結血漿-LR「日赤」480(日本赤十字社)				米国	

研究報告の概要

○米国におけるヒト*Borrelia miyamotoi*感染

回帰熱を引き起こすスピロヘータの一種である*Borrelia miyamotoi*は、ライム病を媒介する全ダニ種から検出されている。2001年にコネチカット州でシカダニから検出されて以来、米国のライム病が浸淫している全地域で検出されるようになった。ヒトにおける初めての*B.miyamotoi*感染は2011年ロシアで報告された。現在、米国にも*B.miyamotoi*感染が存在する証拠及び感染率について報告する。

1990年～2010年、ライム病浸淫地域在住者の3群(第1群;ロードアイランド州及びマサチューセッツ州でダニ媒介性感染症の血清検査を受けた584人、第2群;ニューイングランド州南部でライム病が疑われた277人、第3群;ニューヨーク州南部でウイルス感染様症状を呈しライム病検査を行った14人)から採取した血清保管検体について、ELISA法とウエスタンブロット法を用いて*B.miyamotoi*のGlpQタンパク質抗体の検出を行った。

結果、抗体陽性率は第1群で1.0%、第2群で3.2%、第3群で21.0%であった(3群間の比較でP<0.001)。第2群の1人及び第3群の2人の回復期抗体価は、急性期の抗体価と比べて4倍以上であった。この所見から、これらの患者は最近*B.miyamotoi*に感染したと考えられる。この3人はいずれも免疫不全ではない。ウイルス感染様症状を呈していた症候性患者は全員、ドキシサイクリンまたはアモキシシリンが投与された。

今回、18人から*B.miyamotoi*抗体が検出された。これは米国のライム病浸淫地域で*B.miyamotoi*感染が広がっている可能性を示唆している。

使用上の注意記載状況・その他参考事項等

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血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
米国のライム病が浸淫している地域の在住者における血清検体から、回帰熱を引き起こす*Borrelia miyamotoi*の抗体が検出され、*B.miyamotoi*感染がこれらの地域で広がっている可能性が示唆されるとの報告である。	国内外のダニ媒介性感染症について、今後も引き続き情報の収集に努める。

12

tory tract infections cautioning against their misuse.[3] Linezolid may become subject to similar misuse by physicians who prescribe it for the treatment of undiagnosed infections, as has been reported.[4] This observation is consistent with our own at a tertiary care hospital in India. In the recent guidelines on pneumonia from India, we have called for restrictions on the use of linezolid.[5] It is desirable that future guidelines on respiratory and other infections advise against its use early in the course of an infection.

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1214183

TO THE EDITOR: Lee et al. report that 82% of the patients with XDR tuberculosis who were treated with linezolid had drug-related toxicity. This prompted the authors to ask for careful drug monitoring by means of conventional blood analysis. Can we do more? Preliminary evidence[1-4] has suggested the potential relation between the pharmacokinetics of linezolid and its tolerability, providing the rationale for targeting linezolid dosage on the basis of its plasma concentrations — that is, therapeutic drug monitoring. Further study is warranted to determine whether therapeutic drug monitoring can serve as a predictive tool to improve the safety of patients requiring long-term therapy with linezolid.

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No potential conflict of interest relevant to this letter was reported.

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4. Pea F, Viale P, Cojutti P, Del Pin B, Zamparini E, Furlanut M. Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients. J Antimicrob Chemother 2012;67:2034-42.

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Human *Borrelia miyamotoi* Infection in the United States

TO THE EDITOR: *Borrelia miyamotoi*, a spirochete that is genetically related to the species of borrelia that cause relapsing fever, has been detected in all tick species that are vectors of Lyme disease.[1,2] It was detected in *Ixodes scapularis* ticks from Connecticut in 2001 and subsequently has been detected in all areas of the United States where Lyme disease is endemic. The first human cases of *B. miyamotoi* infection were reported in Russia in 2011.[3] We now provide evidence of *B. miyamotoi* infection and the prevalence of this infection among people in the United States.

Enzyme-linked immunosorbent assays and confirmatory Western blot assays of archived serum samples obtained from three groups of patients who were living in areas where Lyme disease was endemic between 1990 and 2010 were used to detect antibody against *B. miyamotoi* GlpQ protein (an antigen that is nonreactive to *B. burgdorferi* antibody).[4] Group 1 consisted of 584 patients who participated in serologic surveys for tickborne infections on Block Island and Prudence Island, Rhode Island, and Brimfield, Massachusetts. Patients in the serologic survey were healthy at the time of blood sampling and were enrolled during the spring and autumn of each year. Group 2 included 277 patients from southern New England who were evaluated for suspected Lyme disease. Group 3 consisted of 14 patients from southern New York who were evaluated at a Lyme disease clinic with a viral-like illness in the late spring or summer; these patients did not have symptoms or signs suggestive of an upper respiratory tract infection or gastroenteritis.

The seroprevalence was 1.0% in group 1, 3.2% in group 2, and 21.0% in group 3 (P<0.001 for comparisons among the three groups). In one patient in group 2 and two patients in group 3, the antibody titer was at least four times as high in the convalescent serum samples as in the acute serum samples; these findings suggest that these patients were recently infected with *B. miyamotoi* (Table 1). All symptomatic patients presented with a viral-like illness and were treated with doxycycline or amoxicillin. Unlike

Table 1. Serologic and Clinical Characteristics of *Borrelia miyamotoi* Infection in Study Patients.*

Group, Patient No., and Serum Phase†	Assay Method			Coinfection‡	No. of Symptoms
	ELISA	Western Blot			
		IgM	*IgG*		
Group 1					
Patient 1	Positive at 1:320 dilution	Positive	Positive	None	None
Patient 2	Positive at 1:320 dilution	Positive	Negative	None	None
Patient 3	Positive at 1:320 dilution	Positive	Positive	None	None
Patient 4	Positive at ≥1:320 dilution§	Not done	Positive	None	None
Patient 5	Positive at ≥1:320 dilution§	Not done	Positive	None	None
Patient 6	Positive at 1:320 dilution	Positive	Positive	None	None
Group 2					
Patient 7	Positive at ≥1:320 dilution§	Not done	Positive	None	5
Patient 8	Positive at 1:320 dilution	Negative	Positive	None	9
Patient 9	Positive at 1:320 dilution	Negative	Positive	None	8
Patient 10	Positive at ≥1:320 dilution§	Not done	Positive	None	6
Patient 11	Positive at ≥1:320 dilution§	Not done	Positive	None	3
Patient 12	Positive at 1:1280 dilution	Negative	Positive	Lyme disease	4
Patient 13	Positive at 1:320 dilution	Negative	Positive	Lyme disease	Uncertain
Patient 14	Positive at 1:320 dilution	Positive	Positive	Lyme disease	Uncertain
Patient 15					
Acute	Negative at 1:160 dilution	Negative	Negative	Babesiosis	12
Convalescent	Positive at 1:1280 dilution	Positive	Positive		
Group 3					
Patient 16	Positive at 1:1280 dilution	Positive	Positive	None	5
Patient 17					
Acute	Negative at 1:80 dilution	Positive	Negative	None	10
Convalescent	Positive at 1:320 dilution	Positive	Positive		
Patient 18					
Acute	Negative at 1:80 dilution	Positive	Positive	Lyme disease	12
Convalescent	Positive at 1:320 dilution	Negative	Positive		

* ELISA denotes enzyme-linked immunosorbent assay.
† See the text for the definition of the various groups.
‡ The diagnosis of Lyme disease was based on a typical erythema migrans skin lesion in Patients 12, 13, 14, and 18. Patients 8 and 16 had an atypical erythema migrans skin lesion (<5 cm in diameter).
§ Tests to determine the presence of antibody in serum dilutions greater than 1:320 were not performed.

the patient with well-documented *B. miyamotoi* infection described by Gagliotta et al.[5] elsewhere in this issue of the *Journal*, none of the three patients with evidence of recent *B. miyamotoi* infection in our study were immunocompromised. One patient had *B. miyamotoi* seroconversion and no erythema migrans skin lesion or laboratory evidence of human granulocytic anaplasmosis coinfection (Patient 17). This patient had a temperature of 39.4°C, chills, sweats, a headache, neck stiffness, fatigue, myalgias, arthralgias, abdominal pain, a cough, a sore throat, and right inguinal lymphadenopathy. He was treated successfully with 14 days of doxycycline. The identification of *B. miyamotoi* antibody in 18 of our study patients, including seroconversion associated with symptoms in 3 patients, suggests that *B. miyamotoi* infection may be prevalent in areas where Lyme disease is endemic in the United States.

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Checklists for Invasive Procedures

TO THE EDITOR: In recent years, the World Health Organization (WHO) has undertaken a number of global and regional initiatives to improve the safety of surgical care. Its 2008 Safe Surgery Saves Lives campaign introduced the concept of a checklist, which was intended to identify and control risk during each of the three phases of an operation: before induction of anesthesia ("sign-in"), before incision of the skin ("time-out"), and before the patient leaves the operating room ("sign-out"). It has been well received by the spectrum of health care professionals in the operating room[1] and has been shown to reduce mortality and morbidity.[2]

However, the concept has faltered in moving beyond the operating room, despite the rapidly expanding list of invasive procedures now taking place in nonsurgical, interventional specialties. The same sign-in, time-out, and sign-out phases are eminently applicable to procedures performed in the endoscopy suite, the cardiac catheter laboratory, and interventional radiology rooms. These patients are deserving of the same safety considerations that are being afforded to those undergoing an operation; the essential objectives listed by the WHO include appropriate consent, appropriate personnel and equipment, correct procedural site, avoidance of known al-

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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
				2012. 10. 20	該当なし	
一般的名称	新鮮凍結人血漿					
販売名（企業名）	新鮮凍結血漿-LR「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」成分採血（日本赤十字社） 新鮮凍結血漿-LR「日赤」120（日本赤十字社） 新鮮凍結血漿-LR「日赤」240（日本赤十字社） 新鮮凍結血漿-LR「日赤」480（日本赤十字社）		研究報告の公表状況	Bautista G, Ramos A, Forés R, Regidor C, Ruiz E, de Laiglesia A, Navarro B, Bravo J, Portero F, Sanjuan I, Fernández MN, Cabrera R. Transpl Infect Dis. 2012 Oct;14(5):496-501. doi: 10.1111/j.1399-3062.2012.00735.x. Epub 2012 May 1.	公表国 スペイン	使用上の注意記載状況・その他参考事項等 新鮮凍結血漿-LR「日赤」 新鮮凍結血漿-LR「日赤」成分採血 新鮮凍結血漿-LR「日赤」120 新鮮凍結血漿-LR「日赤」240 新鮮凍結血漿-LR「日赤」480 血液を介するウイルス、細菌、原虫等の感染 vCJD等の伝播のリスク
研究報告の概要	○臍帯血移植レシピエントにおけるトキソプラズマ症 トキソプラズマ症は臍帯血移植（CBT）レシピエントのような免疫不全患者に影響を及ぼす重篤な日和見感染症である。この病院で治療された4人及び文献から収集した5人（計9人）のトキソプラズマ症CBT患者について再評価した。 この病院におけるトキソプラズマ症の割合はCBTレシピエントで6%、同種造血幹細胞移植レシピエントで0.2%であった（P<0.001）。5人（56%）は播種性トキソプラズマ症、4人（44%）は中枢神経系への限局性感染であった。9人のうち5人（56%）において、トキソプラズマ症の発症の前にサイトメガロウイルスの複製が確認された。7人（78%）は以前、移植片対宿主病を発症した。播種性疾患を呈した患者は全てトキソプラズマ感染症により死亡した。彼らの移植前の血清学検査結果は、陽性1人、陰性3人、不明1人であった。播種性患者5人のうち1人のみ、トキソプラズマ予防薬コトリモキサゾールを受けていた。CBTレシピエントにおける播種性トキソプラズマ症の死亡率は容認出来ないほどに高いことが示された。これらの患者の多くは血清学的検査で陰性となり、臨床症状が明確ではないため診断が難しい。CBTレシピエントにおいて、より良い診断検査と予防戦略が必要とされる。					
報告企業の意見	臍帯血移植では同種造血幹細胞移植に比べてトキソプラズマ症の発症率が非常に高いことが示されたとの報告である。					
今後の対応	日本赤十字社では輸血感染症対策として、トキソプラズマ症の既往がある場合は完全に治癒して一定期間が経過するまで献血不適としている。今後も情報の収集に努める。					

28

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Toxoplasmosis in cord blood transplantation recipients

G. Bautista, A. Ramos, R. Forés, C. Regidor, E. Ruiz, A. de Laiglesia, B. Navarro, J. Bravo, F. Portero, I. Sanjuan, M.N. Fernández, R. Cabrera. Toxoplasmosis in cord blood transplantation recipients.
Transpl Infect Dis 2012: 14: 496–501. All rights reserved

Abstract: Toxoplasmosis is a devastating opportunistic infection that can affect immunocompromised patients such as cord blood transplantation (CBT) recipients. The clinical characteristics of 4 toxoplasmosis CBT patients treated at our institution are reviewed, together with 5 cases collected from the literature. The rate of toxoplasmosis in our hospital was 6% in CBT recipients and 0.2% in other types of allogeneic hematopoietic stem cell transplantation ($P < 0.001$). Five patients (56%) presented disseminated toxoplasmosis and 4 patients (44%) had localized infection in the central nervous system. In 5 of the 9 patients considered (56%), cytomegalovirus viral replication had been detected before the clinical onset of toxoplasmosis. Seven patients (78%) had previously developed graft-versus-host disease. All patients who exhibited disseminated disease died due to *Toxoplasma* infection. Pre-transplant serology was positive in 1 patient, negative in 3 patients, and not performed in another. Only 1 of these 5 patients with disseminated disease had received *Toxoplasma* prophylaxis with cotrimoxazole. It could be concluded that mortality in CBT patients with disseminated toxoplasmosis is unacceptably high. The negative results of serology in the majority of these cases, and its unspecific clinical presentation, makes diagnosis exceedingly difficult. Better diagnostic tests and prophylaxis strategy are needed in CBT recipients.

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Key words: toxoplasmosis; cord blood stem cell transplantation; sulfadiazine; pyrimethamine; cytomegalovirus; graft-versus-host disease

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Toxoplasmosis is a devastating opportunistic infection in hematopoietic stem cell transplant (HSCT) patients that is caused by the protozoan *Toxoplasma gondii,* and is associated with high mortality (1). It can induce symptoms limited to the central nervous system, lung, heart, and eyes, or cause disseminated infection (2). Its incidence shows marked geographical variations, being higher in Southern Europe in comparison with other developed regions (3). Primary infection in immunocompetent hosts leads to latency of the parasite as cysts in muscle and other tissues (4). Toxoplasmosis in HSCT recipients usually results from the reactivation of latent infection rather than being due to primary infection. A few cases have been reported in HSCT recipients with negative *Toxoplasma* antibody titers, suggesting transmission of infection via marrow or blood products (5).

Cord blood transplantation (CBT) is associated with prolonged and severe impairment of cellular immunity and is considered an important risk factor for *Toxoplasma* infection and other opportunistic infections (1, 6–8). The experience of toxoplasmosis in CBT patients communicated in the literature up to now has consisted of reports of isolated cases (1, 6, 9, 10).

We report 4 cases of toxoplasmosis in CBT recipients treated in our institution and review similar previously reported cases in HSCT patients.

Methods

In our institution, some eligible patients have received a single unit of CBT following myeloablative conditioning, supported by the co-infusion of a relatively low number of T-cell-depleted, mobilized hematopoietic stem cells (MHSC) from a third-party donor ("dual" CBT). This strategy results in early recovery of circulating granulocytes and high rates of CB engraftment and full chimerism, making CBT with single units of relatively low content feasible in adults (11). A minimum of 1.5×10^7 total nucleated cells, and 0.1×10^6 CD34+ cells/kg recipient body weight before freezing, were infused. Third-party donors were selected based on their suitability to donate and undergo an MHSC collection procedure with granulocyte colony-stimulating factor mobilization, negative serological cross-match with the patient, cytomegalovirus (CMV) serology, age, and gender. For most patients, the preparative regimen consisted of fractionated total body irradiation to a total of 10 Gy in 5 doses over 3 days (−8 to −6) with lungs shielded at 8 Gy; fludarabine, total dose of 120 mg/m^2 (30 mg/m^2/day intravenous [IV], days −5 to −2); cyclophosphamide 120 mg/kg total dose (60 mg/kg/day IV over 1 h, days −3 and −2); and equine antithymocyte globulin (Lymphoglobuline, Imtix-Sangstat, Lyon, France) 30 mg/kg on day −1, versus Thymoglobulin (Genzyme, Cambridge, Massachusetts, USA) 0.5 mg/kg day −3 and 2 mg/kg/d days −2 and −1. Busulfan at a total oral dose of 8 mg/kg (6.4 mg/kg IV after 2004) substituted for total body irradiation when the latter was contraindicated. Patients were nursed in positive pressure air-filtered rooms. Gut decontamination using ciprofloxacin was initiated on day −8 and continued until the absolute neutrophil count (ANC) dropped below 0.5×10^9/L, when patients were switched to IV meropenem. Patients also received daily cotrimoxazole (1200/240 mg/12 h IV from day −8 to −1), and 3 times per week from CB engraftment until day +180. After May 2004 (when the third case was diagnosed) chemoprophylaxis against toxoplasmosis was changed to pre-transplant cotrimoxazole, oral azithromycin 1 g twice a week until CB engraftment, and then pyrimethamine/sulfadoxine (Fansidar®; Roche Pharmaceuticals, Nutley, New Jersey, USA) and folinic acid, continued until day +180. Patients also received fluconazole from day −8 until ANC recovery, immunoglobulin (400 mg/kg weekly from day −3 to +60), and acyclovir (200 mg/8h from day −8 to +35, when it was switched to the oral route. The enzyme-linked fluorescence assay (VIDAS®, bioMérieux Inc., Marcy l'Etoile, France) technique was employed for *Toxoplasma* IgG antibody determination.

A definition of possible, probable, and definite toxoplasmosis had previously been proposed (12). Patients who had clinical and radiological evidence suggestive of brain *Toxoplasma* disease plus a positive polymerase chain reaction (PCR) test from cerebrospinal fluid (CSF) (or other biological specimen), but who had no histological confirmation, were classified as having probable *Toxoplasma* disease. Disseminated toxoplasmosis was defined as clinical, radiological, or histological evidence of disease affecting >1 organ. Samples of CSF (0.5 mL) were concentrated by centrifuging at 1800 3 *g* for 10 min. The samples were incubated and shaken in 100-mL portions of lysis buffer (10 mM Tris-HCl [pH 8.3], 1.5 mM $MgCl_2$, 50 mM KCl, 0.1 mg of gelatin per mL, 0.5% Tween 20, 20 mg of proteinase K) at 55°C for 90 min. After inactivating the proteinase K at 94°C for 10 min, the suspension was centrifuged at 12,000 rpm for 5 min, and the supernatant, which contained the DNA, was moved to a new tube. *T. gondii* infections were initially confirmed by nested PCR amplification of the repetitive and conserved gene B1 (13).

Toxoplasma disease was considered the main cause of death when no other relevant complication occurred prior to death. Patients were considered to have died from another cause if they had responded to therapy before death from an unrelated complication. Patients were considered evaluable for response to anti-*Toxoplasma* therapy if they completed at least 4 days of treatment. Response to therapy was defined as an improvement of clinical signs and symptoms attributable to *Toxoplasma* disease despite residual findings in physical examinations or imaging studies.

A search of literature was conducted in MEDLINE to find documented cases of toxoplasmosis in CBT recipients between 1980 and March 2011. The key words used were "cord blood stem cell transplantation," "hematopoietic stem cell transplantation," "toxoplasmosis," and "*Toxoplasma*." Care was taken to exclude cases likely to reflect duplicate reporting. Six cases were detected. One case was not included in the study owing to paucity of clinical information (8).

A comparison was undertaken of the clinical characteristics of patients who developed toxoplasmosis with those without the disease in our cohort. In the case of patients who received >1 transplant, only the clinical features of the first transplant were considered.

Continuous variables were compared with the Student *t*-test or the Mann–Whitney test when a normal distribution could not be assumed. Categorical data were compared with the chi-square, chi-square for trends, or Fisher's exact test when appropriate.

Results

Since our institution began the CBT program, 75 transplants have been performed in 70 patients

(5 patients received a second transplant due to failure of the first CBT which, in all cases, occurred during the first 3 months). Four cases of toxoplasmosis were diagnosed in these patients between 1993 and 2007 (6%). This rate was higher than that observed in patients receiving other types of allogeneic HSCT treated in the same institution (0.2%, 1 case in 2008 out of 401 transplanted patients, $P < 0.001$). Hematological diseases that gave rise to CBT were acute lymphoblastic leukemia (2 patients), acute myeloid leukemia (1 patient), and accelerated phase-chronic myeloid leukemia (1 patient). Three patients suffered graft-versus-host disease (GvHD) before toxoplasmosis. CMV replication was demonstrated before the onset of the disease in all 4 cases. In 2 of them, there was also CMV disease (viral syndrome and esophagitis, 1 patient each). In our institution, there were no significant differences in age, gender, underlying disease, proportion of uncontrolled disease at transplantation or engraftment day in CBT between patients with and without toxoplasmosis. There were more cases of CMV replication during the first 6 weeks in patients who suffered from toxoplasmosis ($P = 0.148$). After May 2004 (when azithromycin prior to engraftment was added to the toxoplasmosis prophylaxis), the incidence of toxoplasmosis decreased from 15% (3 cases in 20 CBT patients) to 2% (1 case in 50 CBT, $P = 0.067$). Three patients (75%) had positive pre-transplant recipient serology and 1 patient had negative. Two third-party donors had positive serology, in another patient it was negative and, in the last one, the result was unknown. None of these patients who developed toxoplasmosis and had a positive (or unknown) pre-transplant or third-party donor serology received prophylaxis with trimethoprim/sulfamethoxazole or pyrimethamine/sulfadoxine ($P = 0.062$). Administration of these drugs was not commenced owing to their potential hematological toxicity in patients that did not achieve adequate CBT engraftment.

The clinical characteristics of these 4 patients, together with the other 5 patients included from the literature review, are shown in Table 1 (1, 6, 10, 11). The mean age was 29 years (range 7–53 years) and 5 patients (56%) were male. The underlying disease was acute leukemia in 7 patients (78%). A total of 5 patients (56%) presented disseminated toxoplasmosis and 4 (44%) with localized infection in the central nervous system. Of the 5 patients (56%) who presented with disseminated disease, only 1 had positive donor serology (they were negative in 3, and not reported in 1). All of them died due to *Toxoplasma* infection. One patient developed disseminated toxoplasmosis despite having had negative pre-transplant serology, negative third-party donor transplant serology, and having been infused seronegative hemotherapeutic products. In 5 of 9 patients (56%), CMV viral replication was detected before the clinical onset of toxoplasmosis. In all, 7 patients (78%) developed GvHD. Those patients who received adequate treatment for >4 days survived.

Discussion

The high incidence of toxoplasmosis in CBT patients in our institution is consistent with that reported in relation to other infections (6–8, 14–16). The high seroprevalence of toxoplasmosis in southern Europe, together with the increasing number of CBTs to be performed in the coming years, could lead to a significant rise in toxoplasmosis in these patients (3, 12, 15–17).

The timing of disease onset (+48 day) in CBT recipients was earlier than that observed in patients with other types of allogenic HSCT (10, 12). This finding could be related to distinctive features of CBT, such as the severe impairment of cellular immunity and the absence of specific immunity in the donor (10, 16, 17).

As observed in other HSCT patients, the development of GvHD seems related to the risk of toxoplasmosis (12). The intensification of immunosuppression for GvHD control could induce the reactivation of latent *Toxoplasma* infection (18–20). However, the difference in the frequency of occurrence of this complication between patients with and without toxoplasmosis in our institution was not significant. Antithymocyte globulin in the conditioning regimen and lymphocytopenia early after HSCT could increase the risk of developing toxoplasmosis (21, 22). Another interesting point is the analysis of the relationship between CMV replication and the subsequent development of toxoplasmosis. All 4 patients treated in our hospital showed viral replication before the onset of toxoplasmosis, which is compatible with the immunomodulatory effect of CMV replication in *Toxoplasma* reactivation, as has been seen in other opportunistic infections (23–26).

The proportion of disseminated disease in the 9 CBT cases described was similar to that detected in patients with other types of HSCT (1). The majority of "probable" CBT cases were diagnosed with PCR amplification of specific *T. gondii* antigens or DNA sequences in CSF (22, 27). This technique can be used in blood, CSF, and bronchoalveolar lavage fluid (22, 23, 27, 28). However, results in published studies

Summary of reported toxoplasmosis cases in cord blood transplantation (CBT) patients

Case	Reference	Age/gender	Underlying disease	Conditioning regimen	Previous CMV replication	Previous GvHD (grade)	Pre-transplant recipient serology	Third-party donor serology[2]	Post-transplant prophylaxis	Time presentation (days)	Diagnosis certainty[3]	Disease location	Toxoplasmosis treatment >4 days	Diagnosis	Infection outcome	Patient status (cause of death)
	Martino et al. (6)	30/M	ALL	NR	NR	Acute (2)	NR	–	TMP-SMZ	59	Probable	Brain	P-S	PCR	Recovery	Unknown
	Martino et al. (6)	21/M	ALL	NR	NR	Acute (0)	NR	–	Atovaquone	45	Definite	Disseminated	No	PCR, autopsy	Failure	Death (toxo)
	Goebel et al. (1)	7/M	ALL	TBI, CFM, ATG	No	Acute (2)	No		No	48	Definite	Disseminated	No	Autopsy	Failure	Death (toxo)
	Dehaas et al. (10)	42/F	AML	BU, FLU	No	Acute (NR)	No		No	48	Definite	Disseminated	No	Bone marrow smear	Failure	Death (toxo)
	Bautista et al. (11)	15/F	MDS	BU, CFM, ATG	Yes	No	Yes		No	35	Definite	Disseminated	P-S[4]	PCR in blood and BAL	Failure	Death (toxo)
Case 1 (PR)		21/M	ALL	FLU, BU, CTX, ATG	Yes	Acute (3)	Yes	Unknown	No	37	Probable	Brain	P-S	PCR in CSF	Recovery	Death (GvHD)
Case 2 (PR)		53/M	AML	FLU, BU, CTX, ATG	Yes	Acute (1)	No	No	No	70	Definite	Disseminated	No	Autopsy	Failure	Death (toxo)
Case 3 (PR)		29/F	AP-CML	FLU, TBI, CTX, ATG	Yes	Acute (1)	Yes	Yes	No	43	Probable	Brain	P-S	PCR in CSF	Recovery	Alive
Case 4 (PR)		45/F	ALL	FLU, TBI, CTX, ATG	Yes	No	Yes	Yes	Azithromycin	50	Probable	Brain	P-S	PCR in CSF	Recovery	Death (MOF)

[1]TBI: total body irradiation (10 Gy with 8 in the lung).
[2]Auxiliary mini-allogeneic transplantation (*dual CBT).
[3]Probable: positive result of PCR of a blood sample and/or another sample from the organ involved with clinical signs and symptoms and radiological evidence of active disease. Definite: histological evidence of active toxoplasmosis.
[4]P-S treatment was stopped 12 days before death because of liver toxicity.
CMV, cytomegalovirus; GvHD, graft-versus-host disease; M, male; ALL, acute lymphoid leukemia; NR, not reported; TMP-SMZ, trimethoprim/sulfamethoxazole; BAL, bronchoalveolar lavage; P-S, pyrimethamine/sulfadoxine; PCR, polymerase chain reaction; toxo, toxoplasmosis; TBI, total body irradiation; CFM, cyclophosphamide; ATG, antithymocyte globulin; F, female; CSF, cerebrospinal fluid; AML, acute myeloid leukemia; BU, busulfan; FLU, fludarabine; MDS, myelodysplastic syndrome; CTX, cytoxan; AP-CML, accelerated phase-chronic myeloid leukemia; PR, present report; MOF, multiorgan failure.

Table 1

are difficult to judge because PCR techniques are not standardized clinical tests (29).

As could be expected, in our institution, a tendency to a more positive pre-transplant serological status was seen in recipients who developed toxoplasmosis than in the other patients. However, a significant proportion of these patients had previous negative *Toxoplasma* serology. This fact, also observed in other toxoplasmosis studies in HSCT patients, has been mainly attributed to primary infection suffered a few days after transplantation and to the fact that, in heavily pre-treated patients, the titers may drop just below the level of positivity (5, 30). However, this fact is intriguing because some patients had not left the hospital, had not eaten uncooked food, and had not received transfusions from seropositive donors, thereby putting the reliability of *Toxoplasma* serology results into question.

Altogether, 3 of the 9 cases presented (33%) developed the disease despite prophylaxis (31, 32). Some prophylaxis failures have been attributed to underdosing cotrimoxazole (double-strength, 2 or 3 times a week). One of the most remarkable results of this study was the finding of increased risk of toxoplasmosis in patients who should have received prophylaxis as recommended in the ASBMT guidelines (i.e., trimethoprim/sulfamethoxazole or pyrimethamine/sulfadoxine), but in whom it was not administered because of poor or delayed engraftment (5). In most cases, the rationale for not using these drugs is their bone marrow toxicity (5). Although little information is available about the role of azithromycin in the treatment and prevention of toxoplasmosis, we thought it could be effective in CBT (33). For this reason, in our institution, it was decided to prescribe post-transplant prophylaxis with azithromycin in seropositive recipients before the transplant engraftment, and a significant decrease in the incidence was noted (15% versus 2%) (34, 35).

The mortality from toxoplasmosis in the 9 CBT patients studied was quite high (56%); however, this was similar to that reported in other types of HSCT (36). Interestingly, all patients with disease located in the central nervous system survived, whereas all patients with disseminated forms died (12). The majority of patients who suffered from disseminated infection had a negative pre-transplant serology. In many of these patients, the diagnosis was achieved very late because of a lack of clinical suspicion due to negative serology and a non-specific clinical presentation. None of these patients received *Toxoplasma*-specific treatment for >4 days. Therefore, one of the biggest challenges in this field is to consider disseminated toxoplasmosis as a possible diagnosis, even when the serology is negative.

One strategy to improve this dramatic situation could be to perform periodic *Toxoplasma* genome determinations in blood using PCR amplification of *T. gondii* DNA in patients who, despite negative serology, are considered to have a higher risk of developing toxoplasmosis, such as those with GvHD or reactivation of an immunomodulating infection (1, 4, 10). However, the use of prophylaxis and/or preemptive therapy based on PCR presents several problems. This technique is not available in many hospitals and could produce false-positive and -negative results. In addition, preemptive therapy based on PCR did not prevent the development of 6 cases of toxoplasmosis among 16 patients with positive blood PCRs (6). Finally, the clinical meaning and prognosis of a positive *Toxoplasma* PCR in an asymptomatic patient is unknown (6).

One limitation of this study is that not all the relevant data were available in some of the cases, such as pre-transplantation *Toxoplasma* serology, prophylaxis administered, conditioning regimen, engraftment day, or previous CMV replication.

In summary, toxoplasmosis is an important infection in HSCT patients. A high mortality has been shown in the cases of disseminated toxoplasmosis in CBT studied. The negative results of serology in the majority of these cases and its unspecific clinical presentation make diagnosis exceedingly difficult. Better diagnostic tests are needed to identify recipients at risk of *Toxoplasma* disease in CBT. An improvement in *Toxoplasma* prophylaxis protocols is desirable in CBT recipients. The possible role of azithromycin in the prevention of toxoplasmosis in these patients should be analyzed in future studies.

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Conflict of interest: The authors declare no conflict of interest.

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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
				2012. 11. 16	該当なし	
一般的名称	新鮮凍結人血漿		研究報告の公表状況		公表国	
販売名(企業名)	新鮮凍結血漿-LR「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」成分採血(日本赤十字社) 新鮮凍結血漿-LR「日赤」120(日本赤十字社) 新鮮凍結血漿-LR「日赤」240(日本赤十字社) 新鮮凍結血漿-LR「日赤」480(日本赤十字社)			ProMED 20121114.1409214	メキシコ	

研究報告の概要

○ロッキー山紅斑熱ーメキシコ
メキシコ保健省はダニ媒介性のリケッチア感染症であるロッキー山紅斑熱の4症例を確定し、別の4症例を疑いありとした。Coahuila州Saltilloの4集落で既に防疫線が設けられた。確定した4症例のうち1例がSaltillo、1例がParras de la Fuente、2例がTorreonからで、疑い例は全てSaltilloでの発生であった。Valle de las Aves集落において少なくとも2人の女児が死亡するというこの緊急事態に直面し、当該集落及びLomas de Zapaliname、Pedregal、Nueva Imagenでは2012年11月10日・11日から予防措置が実施された。これらの地域は上下水道、舗装などが未整備で、河川がゴミで溢れ、犬などの繁殖地となり、これらの動物がヒトへの感染原因となるという。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿-LR「日赤」
新鮮凍結血漿-LR「日赤」成分採血
新鮮凍結血漿-LR「日赤」120
新鮮凍結血漿-LR「日赤」240
新鮮凍結血漿-LR「日赤」480

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
メキシコのCoahuila州でダニ媒介性のリケッチア感染症であるロッキー山紅斑熱が発生しているとの報告である。	日本赤十字社では、輸血感染症対策として受付時に海外滞在歴の有無を確認し、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ほか、リケッチア感染症の既往がある場合は完全に治癒して一定期間が経過するまで献血不適としている。今後も引き続き情報の収集に努める。

29

MedDRA/J Ver.15.1J

http://www.promedmail.org/direct.php?id=20121114.1409214

JRC2012T-045

Published Date: 2012-11-14 14:58:38
Subject: PRO/EDR> Rocky Mountain spotted fever - Mexico (02): (CA)
Archive Number: 20121114.1409214

ROCKY MOUNTAIN SPOTTED FEVER - MEXICO (02): (COAHUILA)
****
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: Mon 12 Nov 2012

Source: Zocalo [in Spanish, machine trans., summ. & edited]
http://www.zocalo.com.mx/seccion/articulo/van-4-casos-de-infeccion-por-garrapatas-sospechan-otros-4

The Health Ministry has confirmed 4 cases of people with tickborne spotted fever and 4 more that are likely, so a sanitary cordon has already been implemented in 4 colonies of Saltillo [Coahuila]. Of the 4 confirmed cases, one is located in Saltillo, another in Parras de la Fuente, and 2 in Torreon, while the 4 probable cases are of the state capital [Saltillo].

Faced with this emergency, which has killed at least 2 girls in the Valle de las Aves colony in this sector and in the colonies of Lomas de Zapalinname, Pedregal, and Nueva Imagen, preventive measures were undertaken since last weekend [10-11 Nov 2012].

Luis Armando Hernandez Perez, head of Sanitary District no 8 of the Ministry of Health, said that these areas lack services such as water, sewage, pavement, and that nearby there is a stream full of garbage, which becomes a breeding ground so that dogs that inhabit the area fill with these animals and transmit them to humans.

To receive adequate treatment the patient must be attended within the 1st 7 days of when symptoms first appeared. Treatment is mainly based on antibiotics and in some cases the patient must remain hospitalized.

[byline: Aracely Gallegos]

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[_Rickettsia rickettsii_, the cause of Rocky Mountain spotted fever, has been identified in southern Canada, the USA, northern Mexico, Costa Rica, Panama, Brazil, and Argentina (1-6). Some synonyms for Rocky Mountain spotted fever in other countries include tick typhus, Tobia fever (Colombia), Sao Paulo fever and febre maculosa (Brazil), and fiebre manchada (Mexico).

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A HealthMap/ProMED-mail map can be accessed at: http://healthmap.org/r/45rQ.]

See Also

Rocky Mountain spotted fever - Brazil (03): (SP) 20121001.1318074
Rocky Mountain spotted fever - Mexico: (BN) 20120828.1268087
Rocky Mountain spotted fever - Brazil (02): (SP) 20120816.1247445
Rocky Mountain spotted fever - USA (05): (TN) increase 20120802.1225293
Rocky Mountain spotted fever - Brazil: (SP) 20120724.1213447
Rocky Mountain spotted fever - USA (04): (KS, IL, AR) 20120719.1206256
Rocky Mountain spotted fever - USA (03): (TN) 20120606.1157629
Rocky Mountain spotted fever - USA (02): (AZ) 20120411.1097210
Rocky Mountain spotted fever - USA: (MO), early susp. cases 20120404.1090349
Rickettsiosis - Mexico: comments 20120102.0008
2011

Rickettsiosis - Mexico: (Michoacan) 20111231.3724
Rocky Mountain spotted fever - USA: (OH) 20110811.2436
2010

Rickettsiosis - Mexico: (SO) 20100729.2547
2009

Rickettsiosis - Mexico: (BN) 20090821.2959
2003

Rickettsiosis - Mexico: background 20030810.1977
Rickettsiosis - Mexico (Durango): RFI 20030808.1958
Rocky Mountain spotted fever - Latin America 20030726.1828
Rocky Mountain spotted fever - Brazil (Sao Paolo) 20030725.1814
1997

Rocky Mountain spotted fever - Brazil (Minas Gerais) 19970903.1886
.....sb/ll/mj/sh

資料３－１

供血者からの遡及調査の進捗状況について
（目次）

事　務　連　絡
平成２５年４月４日

日本赤十字社血液事業本部　御中

薬事・食品衛生審議会血液事業部会事務局
厚生労働省医薬食品局血液対策課

供血者からの遡及調査の進捗状況について

日頃より血液事業の推進に御努力いただき、厚く御礼申し上げます。
さて、標記につきましては、平成２５年２月２１日付け血安第７６号にて貴社血液事業本部長より資料の提出があり、これを平成２４年度第４回血液事業部会運営委員会に提出したところです。今般、平成２５年６月１２日に平成２５年度第１回血液事業部会運営委員会を開催することといたしますので、下記の事項について改めて資料を作成いただき、平成２５年５月１５日（水）までに当事務局あて御提出いただきますようお願いいたします。

記

１．「供血者の供血歴の確認等の徹底について」（平成１５年６月１２日付け医薬血発第 0612001 号）に基づく遡及調査に係る以下の事項
（１）遡及調査実施内容
①　調査の対象とした献血件数
②　上記①のうち、調査の対象とした輸血用血液製剤の本数
③　上記②のうち、医療機関に情報提供を行った本数
（２）個別 NAT 関連情報
①　（１）①のうち、個別 NAT の結果が陽性となった献血件数
②　上記①のうち、医療機関へ供給された製剤に関する報告件数
③　上記②のうち、受血者情報が判明した件数
④　上記③のうち、医薬品副作用感染症報告を行った件数

２．資料の作成に当たっての留意事項
①　本数又は件数については、病原体別及びその合計を明らかにすること。また、上記（１）の③及び（２）の①～③については、対象期間ごとに本数又は件数を記載すること。
②　本数又は件数については、平成２５年２月２１日付け血安第７６号の提出時において判明したものに、その後の遡及調査の進展状況を反映させて記載すること。

血安第１８０号
平成 25 年５月 13 日

厚生労働省
医薬食品局血液対策課長 様

日本赤十字社
血液事業本部長

供血者からの遡及調査の進捗状況について（回答）

平成 25 年４月４日付事務連絡によりご連絡のありました標記の件について、別紙により報告いたします。

別紙

供血者から始まる遡及調査実施状況

平成25年3月31日現在

	平成21年4月1日 ～ 平成22年3月31日			平成22年4月1日 ～ 平成23年3月31日			平成23年4月1日 ～ 平成24年3月31日			平成24年4月1日 ～ 平成25年3月31日		
	HBV	HCV	HIV	HBV	HCV	HIV	HBV	HCV	HIV	HBV	HCV	HIV
(1)遡及調査実施内容												
① 調査の対象とした献血件数(個別NAT実施件数)												
1)総数	1,806			1,852			2,491			9,983		
2)個別件数	1,688	69	49	1,730	74	48	2,407	59	25	9,889	56	38
② 上記①のうち、調査の対象とした輸血用血液製剤の本数												
1)総数	2,014			2,072			2,749			10,334		
2)個別本数	1,877	84	53	1,934	82	56	2,659	67	23	10,231	58	45
③ 上記②のうち、医療機関に情報提供を行った本数												
1)総数	2,014			2,072			2,749			9,013		
2)個別本数	1,877	84	53	1,934	82	56	2,659	67	23	8,914	54	45
(2)個別NAT関連情報												
① 遡及調査実施対象〔(1)①〕のうち、個別NATの結果が陽性となった献血件数												
1)総数	144			100			116			149		
2)個別件数	144	0	0	100	0	0	116	0	0	149	0	0
② 上記①のうち、医療機関へ供給された製剤に関する報告件数												
1)使用された本数	140	0	0	98	0	0	119	0	0	146	0	0
2)医療機関調査中	0	0	0	0	0	0	0	0	0	0	0	0
3)院内で廃棄	6	0	0	5	0	0	3	0	0	6	0	0
4)不明	6	0	0	3	0	0	0	0	0	0	0	0
計	152	0	0	106	0	0	122	0	0	152	0	0
③ 上記②のうち、受血者情報が判明した件数												
1)陽転事例	1	0	0	5	0	0	6*	0	0	5	0	0
2)非陽転事例	55	0	0	28	0	0	46	0	0	54	0	0
3)死亡	55	0	0	44	0	0	56	0	0	55	0	0
4)退院・未検査	19	0	0	15	0	0	7	0	0	29	0	0
5)陽性だが輸血前不明	10	0	0	6	0	0	4	0	0	3	0	0
計	140	0	0	98	0	0	119	0	0	146	0	0
④ 上記③のうち、医薬品副作用感染症報告を行った件数												
報告件数	1	0	0	5	0	0	4	0	0	5	0	0

＊6例中2例はHBs抗体のみの陽転であり、輸血血液からの移行抗体等と医療機関において判断された事例である。

※血液製剤等に係る遡及調査ガイドライン(平成24年3月6日一部改正)に基づく遡及調査対応基準を適用。

HBV ：HBs抗原CLEIA法確認試験（中和試験）又は個別NAT陽性の場合は遡及調査を行う。
：HBc抗体CLEIA法陽転の場合は遡及調査を行う。
HCV ：HCV抗体CLEIA法陽転の血液及び前回の血液について個別NATを実施し、いずれかが陽性の場合は遡及調査を行う。
HIV ：HIV抗体CLEIA法で陽転し、確認試験（WB法）又は個別NAT陽性の場合は遡及調査を行う。
共通 ：スクリーニングNAT陽転の場合は遡及調査を行う。

〈参考〉

供血者から始まる遡及調査実施状況

対象期間	平成11年4月1日～平成18年3月31日			平成18年4月1日～平成19年3月31日			平成19年4月1日～平成20年3月31日			平成20年4月1日～平成21年3月31日		
	HBV	HCV	HIV	HBV	HCV	HIV	HBV	HCV	HIV	HBV	HCV	HIV
① 調査の対象とした献血件数												
1)遡及調査の対象件数	23,104			2,193			2,694			5,219		
② 上記①のうち、個別NAT検査を実施した本数(検体数)												
1)本数(検体数)	23,104			2,193			2,694			5,219		
2)実施率	100%			100%			100%			100%		
③ 上記②のうち陽性が判明した本数												
本数	311	3	1	60	1	0	25	0	0	118	0	0
④ 上記①のうち医療機関に情報提供を行った件数												
1)血液製剤数(総数)	33,114			2,408			2,867			4,034		
個別本数				2,062	288	58	2,444	345	78	3,552	417	65
2)情報提供数	33,114			2,408			2,708			3,469		
個別件数				2,062	288	58	2,319	317	72	3,150	254	65
＊平成11年4月1日～平成17年3月31日までの情報提供数には、医療機関の廃院等による追跡不能数930件を含む												
⑤ 上記③のうち医療機関へ供給された製剤に関する報告件数												
1)使用された本数	326	3	1	51	2	0	26	0	0	94	0	0
2)医療機関調査中	0	0	0	0	0	0	0	0	0	0	0	0
3)院内で廃棄	16	0	0	2	0	0	2	0	0	5	0	0
4)不明	7	1	0	0	0	0	0	0	0	0	0	0
計	349	4	1	53	2	0	28	0	0	99	0	0
⑥ 上記⑤のうち、受血者情報が判明した件数												
1)陽転事例	17	1	1	4	1	0	4	0	0	3	0	0
2)非陽転事例	69	0	0	11	0	0	9	0	0	30	0	0
3)死亡	118	2	0	31	1	0	10	0	0	42	0	0
4)退院・未検査	15	0	0	0	0	0	0	0	0	0	0	0
5)陽性だが輸血前不明	7	0	0	1	0	0	0	0	0	0	0	0
計	226	3	1	47	2	0	23	0	0	75	0	0
＊個別NAT陰性(NATウインドウピリオド)の遡及調査対象血液の輸血により、受血者が陽転した例を含む												
⑦ 上記⑥のうち、医薬品副作用感染症報告を行った件数												
報告件数	16*	1	1	5	1	0	4	0	0	3	0	0
ウイルス別合計	HBV:28 HCV:2 HIV:1											

＊受血者情報の陽転事例のうち医薬品感染症報告が行われていない平成12年3月の事例は、献血血液が遡及調査の対象(個別HBV-NAT陽性)となり、受血者の陽転化情報が得られたが、患者は原疾患により死亡した事例である。

＊平成20年度は、遡及調査対応基準を改定した。(同年10月29日開催「薬事・食品衛生審議会血液事業部会運営委員会」にて了承済)

薬事法第７７条の４の３に基づく回収報告状況

○平成２５年２月～平成２５年４月

報告日	回収開始年月日	回収対象製品	製造番号	対象本数
平成25年4月26日	平成25年4月24日	照射赤血球濃厚液-LR「日赤」400mL由来	55-5021-1280	1
平成25年4月23日	平成25年4月19日	照射赤血球濃厚液-LR「日赤」400mL由来	55-1027-6308	1
平成25年4月9日	平成25年4月9日	新鮮凍結血漿-LR「日赤」200mL由来	72-4317-0218	1
平成25年4月9日	平成25年4月5日	照射赤血球濃厚液-LR「日赤」200mL由来	29-1224-2104	1
平成25年4月2日	平成25年4月1日	新鮮凍結血漿-LR「日赤」400mL由来	03-0325-5269	1
平成25年3月21日	平成25年3月18日	赤血球濃厚液-LR「日赤」400mL由来	01-0527-5718	1
平成25年3月18日	平成25年3月14日	赤血球濃厚液-LR「日赤」400mL由来	70-1727-1700	1
平成25年2月13日	平成25年2月12日	照射赤血球濃厚液-LR「日赤」400mL由来	52-2228-2660	1
平成25年2月13日	平成25年2月9日	赤血球濃厚液-LR「日赤」400mL由来	13-1120-0605	1

資料３－２

血液製剤に関する医療機関からの感染症報告事例等について

輸血用血液製剤で感染が疑われる事例について

（平成２５年５月１３日時点。過去５年間分）

【ＨＢＶ感染が疑われた事例】

報告日	輸血された血液製剤	供血者数	供血者検査結果等	同一血液由来の他製剤等について	新規報告
H21.11.20	新鮮凍結血漿 血小板製剤 赤血球製剤	45 人	保管検体個別 NAT 全て陰性 感染が疑われる輸血時の製剤の供血者 45 人中 43 人来訪 （43 人の個別 NAT は全て陰性。うち 2 人は HBs 抗体のみ陽性で、その当該献血時については、1 人は HBs 抗体のみ陽性、もう 1 人は HBs 抗体及び HBc 抗体が陽性）	原料血漿：20 本中 2 本確保。18 本使用済み。 新鮮凍結血漿：3 本全て供給済み。 赤血球製剤：22 本全て供給済み。	平成 25 年 2 月 21 日以降、残る 2 人の来訪なし。
H24.10.15	血小板製剤 赤血球製剤	15 人	保管検体個別 NAT 全て陰性 供血者 15 人中 11 人来訪 HBV 関連検査陰性：11 人	原料血漿：14 本中 6 本確保。1 本廃棄。7 本使用済み。 新鮮凍結血漿：1 本全て確保。	平成 25 年 2 月 21 日以降、1 人が新たに来訪したが、残る 4 人の来訪なし。

【ＨＣＶ感染が疑われた事例】

報告日	輸血された血液製剤	供血者数	供血者検査結果等	同一血液由来の他製剤等について	新規報告
H24.2.8	新鮮凍結血漿 赤血球製剤	11 人	保管検体個別 NAT 全て陰性 供血者 11 人中 9 人来訪 HCV 関連検査陰性：9 人	原料血漿：7 本全て確保。 新鮮凍結血漿：1 本全て確保。 赤血球製剤：3 本全て使用済み。	平成 25 年 2 月 21 日以降、残る 2 人の来訪なし。

感染症報告事例のまとめについて

（平成 25 年 2 月～平成 25 年 4 月報告分）

1　平成 25 年 2 月～平成 25 年 4 月に報告（新規及び追加）があった感染症報告（疑い事例を含む。供血者からの情報により開始した遡及調査によるものを除く）は、輸血用血液製剤 24 件である。

輸血用血液製剤の内訳は、

（１）HBV 感染報告事例：　15 件
（２）HCV 感染報告事例：　4 件
（３）HIV 感染報告事例：　0 件
（４）その他の感染症報告例：　5 件（細菌 5 件）

2　HBV 感染報告事例

（１）輸血前後に感染症検査で HBV-DNA、HBs 抗原等が陽転した事例は 15 件。
輸血後 NAT で陰性又は輸血前後で陽性は 0 件。

（２）使用された輸血用血液製剤を提供した献血者の保管検体の個別 NAT 陽性の事例は 4 件。

（３）劇症化又は輸血後に死亡（原疾患又は他の原因による死亡を除く）したとの報告を受けた事例は 0 件。

3　HCV 感染報告事例

（１）輸血前後に HCV-RNA、抗体検査等が陽転した事例は 4 件。輸血後 NAT で陰性又は輸血前後で陽性は 0 件。

（２）使用された輸血用血液製剤を提供した献血者の保管検体の個別 NAT 陽性事例は 0 件。

（３）劇症化又は輸血後に死亡（原疾患又は他の原因による死亡を除く）したとの報告を受けた事例は 0 件。

4　HIV 感染報告事例

（１）輸血前後に抗体検査等が陽転した事例は 0 件。

（２）使用された輸血用血液製剤を提供した献血者の保管検体の個別 NAT 陽性事例は 0 件。

（３）輸血後に死亡（原疾患又は他の原因による死亡を除く）したとの報告を受けた事例は 0 件。

5　その他の感染症報告事例

（１）B 型肝炎及び C 型肝炎以外の肝障害報告事例は 0 件。

（２）細菌等感染報告事例において、使用された輸血用血液製剤を提供した献血者の保管検体の無菌試験陽性事例は 0 件。

（３）輸血後に死亡（原疾患又は他の原因による死亡を除く）したとの報告を受けた事例は 0 件。

【国内輸血用血液製剤例】

日赤番号	識別番号	FAX受付日	報告受領日	販売名（一般名）	患者性別	年代	原疾患（簡略名）	感染症名	投与年月	投与前検査(年月)	投与後検査(年月)	日赤投与前検査	日赤投与後検査	受血者個別NAT	献血者個別NAT	併用血液製剤等	備考	使用単位数	供血者再献血※	同一供血者製剤確保※	同一供血者製剤使用※	感染症等転帰	転帰	供血者発遡及の場合の供血者保管検体(抗原、抗体、NAT)（投与時	供血者発遡及の場合の供血者の検査値
				輸血によるHBV感染報告例（疑い例を含む。）																					
供血者陽性事例																									
3-1300014	A-1200146	2013/2/7	2013/2/21	新鮮凍結血漿-LR(新鮮凍結人血漿)	女	70	外傷・整形外科的疾患	B型肝炎	11/4	HBsAg(－)(11/4)	HBV-DNA(+) HBsAg(＋) HBcAb(＋) (遡及調査による情報提供により実施した検査結果) (13/02)	HBV-DNA(－) HBsAg(－) HBsAb(－) HBcAb(－) (11/04)	HBV-DNA(＋) HBsAg(＋) HBsAb(－) HBcAb(＋) (13/02)	陰性(輸血前) 陽性(輸血後)	保管検体1本についてHBV-DNA(+)		同一採血番号製剤を使用した患者は死亡されていたが、HBsAg陰性を確認していた。【献血者陽転化情報】 当該　2010年8月2日 HBV関連検査　陰性 個別HBV-NAT　陽性 （遡及調査） 次回　2013年1月14日 HBc抗体陽性（陽転献血） 個別HBV-NAT　陰性	2単位	－	1本の赤血球濃厚液-LRを製造。	医療機関へ供給済み	重篤	軽快		当該保管検体と患者検体中のウイルスの塩基配列を比較したところ、両者は検査した範囲（献血者検体のウイルス量が少ないことから、S領域193bpで比較）で全て一致した。 献血者検体と患者検体のHBVはGenotype Cで、塩基配列からSubtypeはadrと推定した。
3-1300020	A-1200152	2013/2/18	2013/3/1	照射赤血球濃厚液－LR（人赤血球濃厚液（放射線照射））	女	50	腎・泌尿器系疾患	B型肝炎	12/6-12/9	HBsAg(－) HBsAb(－) (12/02) HBV-DNA(－) HBsAg(－) (12/06)	HBsAg(－) (12/08) HBsAg(＋)(13/02/04の検査結果を受けて保存検体にて検査実施) (12/10) HBsAg(＋) HBeAg(－) (13/02) HBeAb(＋) (13/02) 家族のHBV関連検査実施。 同居家族：全員HBsAg(－) 別居の息子：HBsAg(－)、HBcAb(＋) 院内での感染ルートを確認したが該当なし。 (13/02)	HBsAg(－) HBsAb(－) HBcAb(－) (12/06)	HBV-DNA(－) HBsAg(－) HBsAb(－) HBcAb(－) (12/07) HBV-DNA(＋) HBsAg(＋) HBsAb(－) HBcAb(－) (12/10) HBV-DNA(＋) HBsAg(＋) HBsAb(－) HBcAb(＋) (13/02)	陰性(輸血前) 陽性(輸血後)	保管検体7本HBV-DNA(-)、1本HBV-DNA(＋)		保管検体陽性血液についてその後の献血は確認されていない。1本の原料血漿を製造、使用済み。 可能な限り過去に遡り、保管検体個別NAT陰性と判定されるまで全ての輸血用血液、原料血漿を遡及する。	16単位	3/8(HBV関連検査陰性)	8本の原料血漿を製造。7本確保済み	1本使用済み。	重篤	回復		当該保管検体と患者検体中のウイルスの塩基配列を比較したところ、両者は検査した範囲（献血者検体のウイルス量が少ないことから、S領域193bpで比較）で全て一致した。 ※献血者検体と患者検体のHBVはGenotype Cで、塩基配列からSubtypeはad(r/w not determine)と推定した。

日赤番号	識別番号	FAX受付日	報告受領日	販売名（一般名）	患者性別	年代	原疾患（簡略名）	感染症名	投与年月	投与前検査(年月)	投与後検査(年月)	日赤投与前検査	日赤投与後検査	受血者個別NAT	献血者個別NAT	併用血液製剤等	備考	使用単位数	供血者再献血※	同一供血者製剤確保※	同一供血者製剤使用※	感染症等転帰	転帰	供血者発遡及の場合の供血者保管検体(抗原、抗体、NAT)（投与時	供血者発遡及の場合の供血者の検査値
3-1300033	A-1200169	2013/3/13	2013/3/28	赤血球濃厚液－LR（人赤血球濃厚液	女	30	その他の疾患	B型肝炎	08/03	HBsAg(－) (08/02)	HBsAg(－) (08/06) HBV-DNA(－) HBsAg(－) HBsAb(＋) HBcAb(＋) (13/03)（遡及調査による情報提供により実施した検査結果）	調査中	調査中	調査中	保管検体1本についてHBV-DNA(+)		【献血者陽転化情報】 当該献血　2008年2月28日　HBV関連検査 陰性 個別HBV-NAT 陽性（遡及調査） 次回献血　2013年2月14日　HBc抗体検査 陽性（陽転献血） 個別HBV-NAT 陰性	1単位	－	1本の原料血漿を製造。	原料血漿は使用済み。	調査中	調査中		
3-130040	A～1300005	2013/4/4	2013/4/16	照射赤血球濃厚液－LR(人赤血球濃厚液（放射線照射）)	女	90	外傷・整形外科的疾患	B型肝炎	12/03	HBsAg(－) (12/03)	他院にて、HBsAg(＋)(13/02)（遡及調査による情報提供により実施した検査結果） HBV-DNA(＋) HBsAg(＋) HBsAb(－) HBcAb(＋)(13/03)（情報提供により実施した検査結果）	－	HBV-DNA(＋) HBsAg(＋) HBsAb(－) HBcAb(＋) (13/03)	陽性(輸血後)	保管検体1本HBV-DNA(＋)			2単位	－	1本の原料血漿を製造。	原料血漿1本は使用済み。	非重篤	不明		献血者検体と患者検体のHBV塩基配列相同性について調査予定
陽転事例																									
3-1300022	A-1200155	2013/2/26	2013/3/12	照射赤血球濃厚液－LR(人赤血球濃厚液（放射線照射）） 照射濃厚血小板-LR(人血小板濃厚液（放射線照射）	女	50	血液腫瘍	B型肝炎	09/08-09/12	09/05/18 HBsAg(－) HBsAb(＋) （ワクチン接種後） HBcAb(－) (09/05)	HBV-DNA(＋)(13/02/18の検査結果を受けて調査実施) (10/03) HBsAg(－) HBsAb(－) HBcAb(－) (12/06) 肝障害あり（薬剤性や原疾患関連と考えた）。 (12/11) HBV-DNA(＋) (13/01) HBV-DNA(＋) HBsAg(＋) HBsAb(－) HBcAb(－) (13/02) 急変し、肝不全により死亡。（剖検なし、輸血と死亡との関連性なし） (13/02)	－	HBV-DNA(－) HBsAg(－) HBsAb(＋) HBcAb(－) (12/06) HBV-DNA(＋) HBsAg(＋) HBsAb(－) HBcAb(－) (13/01)	陽性(輸血後)	保管検体13本(全部)についてHBV-DNA(－)			12単位 75単位	13/13(HBV関連検査陰性)	12本の原料血漿、1本の新鮮凍結血漿-LRを製造。	原料血漿はすべて使用済み。新鮮凍結血漿-LRは医療機関へ供給済み	重篤（死亡）	未回復		

日赤番号	識別番号	FAX受付日	報告受領日	販売名(一般名)	患者性別	年代	原疾患(簡略名)	感染症名	投与年月	投与前検査(年月)	投与後検査(年月)	日赤投与前検査	日赤投与後検査	受血者個別NAT	献血者個別NAT	併用血液製剤等	備考	使用単位数	供血者再献血※	同一供血者製剤確保※	同一供血者製剤使用※	感染症等転帰	転帰	供血者発遡及の場合の供血者保管検体(抗原、抗体、NAT)(投与時	供血者発遡及の場合の供血者の検査値
3-1300025	A-12000159	2013/3/4	2013/3/14	照射赤血球M・A・P(人赤血球濃厚液(放射線照射))赤血球M・A・P(人赤血球濃厚液)照射濃厚血小板(人血小板濃厚液(放射線照射)濃厚血小板(人血小板濃厚液)	女	70	血液腫瘍	B型肝炎	05/11-06/01	HBsAg(−)(04/11)	HBsAg(−)HBcAb(−)(05/12)他院にてHBV-DNA(+)HBsAg(+)HBsAb(−)HBeAg(+)HBeAb(−)(13/01)HBV-DNA(+)HBsAg(+)HBeAg(+)(13/02)※家族(親戚含む)で肝炎を発症した者はいない。	−	HBV-DNA(+)HBsAg(+)HBsAb(−)HBcAb(+)(13/03)	陽性(輸血後)	保管検体15本はすべてHBV-DNA(−)			6単位6単位65単位30単位	15/15(13人はHBV関連検査陰性、2人はHBs抗体のみ陽性であり、当該献血時においても同様	16本の原料血漿、2本の新鮮凍結血漿を製造。	原料血漿はすべて使用済み。新鮮凍結血漿は全て医療機関へ供給済み。	非重篤	未回復		
3-1300027	A-12000161	2013/3/5	2013/3/14	新鮮凍結血漿-LR(新鮮凍結人血漿)照射濃厚血小板-LR(人血小板濃厚液(放射線照射))照射赤血球濃厚液−LR(人赤血球濃厚液(放射線照射))	女	80	血液腫瘍	B型肝炎	12/06-07	HBsAg(−)HBsAb(−)HBcAb(−)(12/06)	HBV-DNA(+)(13/01)HBsAg(−)HBsAb(+)IgM-HBcAb(+)HBeAb(+)(13/02)	HBV-DNA(−)HBsAg(−)HBsAb(−)HBcAb(−)(12/06)	HBV-DNA(−)HBsAg(−)HBsAb(+)HBcAb(+)(13/03)	陰性(輸血前)陰性(輸血後)	保管検体10本すべてHBV-DNA(−)			12単位30単位2単位	6/10(HBV関連検査異常なし)	4本の原料血漿、6本の赤血球濃厚液-LRを製造。	原料血漿はすべて使用済み。赤血球濃厚液-LRは全て医療機関へ供給済み。	非重篤	軽快		
3-1300028	A-12000162	2013/3/5	2013/3/14	照射赤血球濃厚液−LR(人赤血球濃厚液(放射線照射))	女	60	腎・泌尿器系疾患	B型肝炎	12/06	HBsAg(−)(12/08)HBsAg(−)HBsAb(−)HBcAb(−)(12/06)	HBsAg(+)HBsAb(−)HBcAb(+)(13/02)	−	HBV-DNA(−)HBsAg(−)HBsAb(−)HBcAb(+)(12/06)(輸血期間中)HBV-DNA(−)HBsAg(−)HBsAb(−)HBcAb(+)(13/03)	陰性(輸血後)	保管検体2本全てHBV-DNA(−)			4単位	2/2(HBV関連検査陰性)	2本の原料血漿を製造。	原料血漿はすべて使用済み。	非重篤	未回復		
3-1300029	A-12000163	2013/3/7	2013/3/14	照射赤血球濃厚液−LR(人赤血球濃厚液(放射線照射))	男	40	腎・泌尿器系腫瘍	B型肝炎	12/11	HBsAg(−)(12/10)HBsAb(−)HBcAb(−)(12/11)	HBV-DNA(+)(13/02)	HBV−DNA(−)HBsAg(−)HBsAb(−)HBcAb(−)(12/11)	HBV−DNA(−)HBsAg(−)HBsAb(+)HBcAb(+)(13/03)	陰性(輸血前)陰性(輸血後)	保管検体4本全てHBV-DNA(−)			8単位	0/4	3本の原料血漿、1本の新鮮凍結血漿-LRを製造。原料血漿はすべて確保済み。新鮮凍結血漿-LRは確保済み。	−	非重篤	不明		

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3-1300030	A-12000164	2013/3/7	2013/3/14	照射赤血球濃厚液−LR(人赤血球濃厚液(放射線照射))照射濃厚血小板-LR(人血小板濃厚液(放射線照射))	男	30	血液腫瘍	B型肝炎	12/06-09	HBV-DNA(−)HBsAg(−)HBsAb(+)HBcAb(−)(11/03)HBsAg(−)HBsAb(+)HBcAb(−)(11/09)膵帯血移植施行。(11/09)HBV-DNA(−)HBsAg(−)HBsAb(+)HBcAb(−)(12/01)	HBsAg(−)HBsAb(+)HBcAb(−)(12/07)骨髄移植施行。(12/08)HBV-DNA(+)HBsAg(+)HBsAb(−)HBcAb(−)(13/02)※患者にHBワクチン接種歴なし。	HBV-DNA(−)HBsAg(−)HBsAb(+)HBcAb(−)(12/06)	HBV-DNA(+)HBsAg(+)HBsAb(−)HBcAb(−)(13/02)	陰性(輸血前)陽性(輸血後)	保管検体8本全てHBV-DNA(−)			8単位40単位	4/8(HBV関連検査陰性)	7本の原料血漿、1本の新鮮凍結血漿-LRを製造。原料血漿は3本廃棄済み、3本確保済み。新鮮凍結血漿-LRは確保済み。	原料血漿は1本使用済み。	非重篤	軽快		
3-1300035	A-12000171	2013/3/15	2013/3/28	照射赤血球濃厚液−LR(人赤血球濃厚液(放射線照射))	女	90	外傷・整形外科的疾患	B型肝炎	12/07	HBsAg(−)(12/07)	HBV-DNA(+)(12/11)HBV-DNA(+)HBsAg(−)HBsAb(+)HBcAb(+)HBeAg(−)HBeAb(+)(13/03)	−	HBV-DNA(−)HBsAg(−)HBsAb(−)HBcAb(+)(13/03)	陰性(輸血後)	保管検体1本HBV-DNA(−)			2単位	0/1	1本の原料血漿を製造	使用済み	重篤	不明		
3-130036	A-13000001	2013/3/27	2013/4/9	照射赤血球濃厚液−LR(人赤血球濃厚液(放射線照射))	男	80	腎・泌尿器系疾患	B型肝炎	12/07	HBsAg(−)(12/05)	HBsAg(+)(13/02)HBsAg(+)(13/02)	調査中	調査中	調査中	保管検体2本についてHBV-NAT実施予定			4単位	調査中	調査中	調査中	重篤	未回復		
3-130037	A-13000002	2013/3/29	2013/4/10	照射赤血球濃厚液−LR(人赤血球濃厚液(放射線照射))	男	70	血液腫瘍	B型肝炎	11/08-10	−	HBV-DNA(−)HBsAg(−)HBsAb(−)HBcAb(−)(11/09)HBV-DNA(+)(13/03)	HBV-DNA(−)HBsAg(−)HBsAb(+)HBcAb(−)(11/08)	HBV-DNA(−)HBsAg(−)HBsAb(−)HBcAb(−)(11/10)HBV-DNA(+)HBsAg(+)HBsAb(−)HBcAb(+)(13/03)	陰性(輸血前)陽性(輸血後)	保管検体2本(全部)HBV-DNA(−)			4単位	1/2(HBV関連検査陰性)	2本の原料血漿を製造。	2本とも使用済み。	非重篤	不明		

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3-130039	A-13000004	2013/4/3	2013/4/16	照射赤血球濃厚液-LR(人赤血球濃厚液(放射線照射))	女	80	腎・泌尿器系疾患	B型肝炎	12/01	HBsAg(-)(12/01)A院にて、輸血施行。	B院に転院し、輸血施行。(12/01)HBsAg(+)(13/01)(13/03/14の検査結果を受けて、A院に確認)HBsAg(+)(13/03)HBsAb(+)HBcAb(+)IgM-HBcAb(+)HBeAg(+)HBeAb(-)(13/03)HBV-DNA(+)(13/03)	調査中	調査中	調査中	保管検体2本についてHBV-DNA(-)			4単位	1/2(HBV関連検査陰性)	2本の原料血漿を製造。使用の有無を調査中	調査中	重篤	調査中		
3-130041	A-13000006	2013/4/4	2013/4/16	新鮮凍結血漿-LR(新鮮凍結人血漿)照射赤血球濃厚液-LR(人赤血球濃厚液(放射線照射))	女	～10	先天性疾患	B型肝炎	12/02 12/10	HBsAg(-)HBsAb(+)HBcAb(-)HBeAg(-)(12/01)生体部分肝移植(12/02)	HBsAg(+)HBsAb(-)HBcAb(+)IgM-HBcAb(+)HBeAg(+)HBeAb(-)(13/03)HBV-DNA(+)(13/03)	-	HBV-DNA(+)HBsAg(+)HBsAb(-)HBcAb(+)(13/04)	陽性(輸血後)	保管検体5本(全部)HBV-DNA(-)			2単位5単位	0/5	3本の原料血漿、1本の新鮮凍結血漿-LR、1本の赤血球濃厚液-LRを製造。原料血漿2本は確保済み。	原料血漿1本は使用済み。新鮮凍結血漿-LR、赤血球濃厚液-LRは医療機関へ供給済み。	重篤	未回復		
輸血後NATで陰性又は輸血前後で陽性																									
(該当例なし)																									

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				輸血によるHCV感染報告例(疑い例を含む。)																					
供血者陽性事例																									
(該当例なし)																									
陽転事例																									
3-1300026	A-12000160	2013/3/5	2013/3/14	照射赤血球濃厚液-LR(人赤血球濃厚液(放射線照射))	男	60	消化器疾患	C型肝炎	12/03	10/09/19HCV-Ab(-)(12/07)HCV-Ab(+)(13/02)刺青なし。HCV-RNA(-)HCVコア抗原(-)(13/03)	他院にて輸血施行。HCV-Ab(-)(12/07)HCV-Ab(+)(13/02)刺青なし。HCV-RNA(-)HCVコア抗原(-)(13/03)	HCV-RNA(-)HCV-Ab(-)(12/03)	HCV-RNA(-)HCV-Ab(-)(12/03)HCV-RNA(-)HCV-Ab(+)(12/03)	陰性(輸血前)陰性(輸血後)	保管検体3本すべてHCV-RNA(-)			6単位	0/3	2本の原料血漿、1本の新鮮凍結血漿-LRを製造。	原料血漿はすべて使用済み。新鮮凍結血漿-LRは医療機関へ供給済み。	非重篤	不明		
3-1300031	A-12000166	2013/3/8	2013/3/21	照射赤血球濃厚液-LR(人赤血球濃厚液(放射線照射))	女	70	肝・胆・膵腫瘍	C型肝炎	12/08	HCV-RNA(-)HCVコア抗原(-)HCV-Ab(-)(12/08)	HCV-Ab(+)(13/02/13の検査結果を受けて保存検体にて検査実施)(12/11)HCV-Ab(+)(13/02)HCV-RNA(-)(13/02)HCVコア抗原(-)(13/02)	HCV-Ab(-)(12/08)	HCV-RNA(+)HCV-Ab(+)(12/11)HCV-RNA(-)HCV-Ab(+)(13/02)	陽性(輸血後)	保管検体2本全てHCV-RNA(-)			4単位	0/2	1本の原料血漿、1本の新鮮凍結血漿-LRを製造。原料血漿は確保済み。新鮮凍結血漿-LRは確保済み。	-	非重篤	未回復		
3-1300034	A-12000170	2013/3/14	2013/3/28	照射赤血球濃厚液-LR(人赤血球濃厚液(放射線照射))	女	80	その他の疾患	C型肝炎	12/12	HCVコア抗原(-)HCV-Ab(-)(12/12)	HCVコア抗原(+)HCV-Ab(-)(13/01)HCV-RNA(-)HCVコア抗原(-)HCV-Ab(+)(13/03)	HCV-RNA(-)HCV-Ab(-)(12/12)	HCV-RNA(-)HCV-Ab(+)(13/02)HCV-RNA(-)HCV-Ab(+)(13/03)	陰性(輸血前)陰性(輸血後)	保管検体1本HCV-RNA(-)			2単位	0/1	1本の原料血漿を製造、確保済み。	-	重篤	回復		
3-130038	A-13000003	2013/3/29	2013/4/10	赤血球濃厚液-LR(人赤血球濃厚液)	男	80	腎・泌尿器系疾患	C型肝炎	12/10	HCV-Ab(-)(12/10)	HCV-Ab(-)(12/11)HCV-Ab(+)(13/03)HCVコア抗原(+)(13/03)	HCV-RNA(-)HCV-Ab(-)(12/10)	HCV-Ab(+)(13/03)HCV-RNA(+)HCV-Ab(+)(13/04)	陰性(輸血前)陽性(輸血後)	保管検体3本についてHCV-RNA(-)			6単位	1/3(HCV関連検査陰性)	3本の原料血漿を製造、すべて確保済み。	-	重篤	不明		
輸血後NATで陰性又は輸血前後で陽性																									
(該当例なし)																									

日赤番号	識別番号	FAX受付日	報告受領日	販売名(一般名)	患者性別	年代	原疾患(簡略名)	感染症名	投与年月	投与前検査(年月)	投与後検査(年月)	日赤投与前検査	日赤投与後検査	受血者個別NAT	献血者個別NAT	併用血液製剤等	備考	使用単位数	供血者再献血※	同一供血者製剤確保※	同一供血者製剤使用※	感染症等転帰	転帰	供血者発遡及の場合の供血者保管検体(抗原、抗体、NAT)(投与時	供血者発遡及の場合の供血者の検査値
				輸血によるHEV,CMV等感染報告例(疑い例を含む。)																					
(該当例なし)																									
				輸血による細菌等感染報告例(疑い例を含む。)																					
陽性等事例																									
3-1300023	A-12000156	2013/2/26	2013/3/12	新鮮凍結血漿-LR(新鮮凍結人血漿)	女	80	肝・胆・膵腫瘍	細菌感染	13/02	輸血前 BT 36℃台	輸血開始約20分後、振戦と不快感出現。 輸血中止。 その後、振戦おさまり、BT 37.5℃の発熱。気分不快もおさまる。 蕁麻疹やかゆみなし。 5時間後、BT 39.9℃まで上昇。 血培採取。 抗生剤とγ-グロブリン製剤投与。 院内にて実施の患者血液培養よりBacillus cereusを同定した。	当該製剤のセグメントチューブ(1本)で細菌培養試験を実施、陰性。 非溶血性副作用関連検査実施 抗血漿タンパク質抗体検査:抗C9抗体弱陽性 血漿タンパク質欠損検査:欠損なし	-	-	-		被疑薬:採血256日目の新鮮凍結血漿-LR(1本)	2単位	-	1本の赤血球濃厚液-LRを製造。	医療機関へ供給済み。	非重篤	回復		
3-1300032	A-12000167	2013/3/12	2013/3/26	照射濃厚血小板-LR(人血小板濃厚液(放射線照射))	女	80	血液腫瘍	細菌感染	13/03	BT 36.8℃、BP 100/58、HR 70 前投薬後、輸血施行。	輸血開始後1時間25分 震えが出現。BP 37.1℃、BP 148/93、HR 91 輸血投与中止。 ステロイド投与にて、震え消失。 2時間40分後 BT 38.5℃、SBP 80台 院内にて実施の患者血液培養は陰性。 患者は肺炎にて死亡。 剖検なし。死亡と本剤の因果関係無し(担当医の見解) ※HLA適合血小板対応の患者だが、今回は通常の血小板製剤を使用した。	投与中止の当該製剤(1本)で細菌培養試験を実施、陰性 非溶血性副作用関連検査実施 抗血漿タンパク質抗体検査:抗IgA抗体陽性 血漿タンパク質欠損検査 :欠損なし	-	-	-			10単位	-	1本の原料血漿を製造、確保済み。	-	重篤	軽快		

日赤番号	識別番号	FAX受付日	報告受領日	販売名(一般名)	患者性別	年代	原疾患(簡略名)	感染症名	投与年月	投与前検査(年月)	投与後検査(年月)	日赤投与前検査	日赤投与後検査	受血者個別NAT	献血者個別NAT	併用血液製剤等	備考	使用単位数	供血者再献血※	同一供血者製剤確保※	同一供血者製剤使用※	感染症等転帰	転帰	供血者発遡及の場合の供血者保管検体(抗原、抗体、NAT)(投与時	供血者発遡及の場合の供血者の検査値
3-130043	A-13000007	2013/4/10	2013/4/23	照射濃厚血小板-LR(人血小板濃厚液(放射線照射))	男	60	血液腫瘍	敗血症性ショック	13/04	-	輸血開始40分後 ふらつき・悪寒戦慄あり。呼吸荒く、顔面蒼白。体幹部体熱感あるが、末梢冷感。 BT 40.9℃、SpO2 88%。輸血中止。 45分後 ヒドロコルチゾン100mg 静注。O2 5Lマスク投与開始。BP 118/52。採血、血培実施。 1時間後 ヒドロコルチゾン500mg + 生食100mL 点滴静注。BP 122/58、HR 150～160台頻拍。SpO2 96%(O2 5L)。反応鈍い。 胸部聴診にて、湿性ラ音あり。 1時間5分後 O2 3Lに減量。BT 42.0℃。 1時間40分後 BT 41.9℃、BP 80/44、HR 163/min。 1時間45分後 胸部X線検査にて、浸潤影なし、心拡大なし。 院内にて実施の患者血液培養は陰性。	投与中止の当該製剤(1本)で細菌培養試験を実施する予定。 非溶血性副作用関連検査実施予定	-	-	-		被疑薬:採血3日目の照射濃厚血小板-LR(1本)	10単位	-	調査中	調査中	重篤	不明		
3-130042	A-13000008	2013/4/9	2013/4/23	照射赤血球濃厚液-LR(人赤血球濃厚液(放射線照射))	男	80	消化器腫瘍	細菌感染	13/04	BT 37.0℃、BP 132/60、P 78	輸血開始15分後 BT 37.4℃、SBP 148、P 86 輸血2本目施行。 BT 37.9℃、BP 140/62 輸血終了時 BT 38.0℃、BP 138/70、P 74 輸血終了後30分 悪寒。 2時間30分 BT 38.7℃、BP 130/64 翌日 朝 BT 37.5℃、BP 80/40 昼 BT 38.9℃、BP 132/70 2日後 夜 BT 38.1℃、 院内にて実施の患者血液培養よりグラム陽性球菌を検出。その後、MSSAと同定された。	同一採血番号の血漿(2本)で無菌試験実施予定	-	-	-		被疑薬:採血3日目の照射赤血球濃厚液-LR(2本)	4単位	-	調査中	調査中	非重篤	軽快		
3-130044	A-13000009	2013/4/10	2013/4/23	照射赤血球濃厚液-LR(人赤血球濃厚液(放射線照射))	男	70	調査中	細菌感染		BT 37.1℃、BP 136/56、P 88、SpO2 100、CRT 3秒 WBC 10300/μL、CRP 2.3 全身造影CT施行。	輸血開始。BP 116/60、P 72、SpO2 100 10分後 悪寒の訴えあり、つづいてシバリング。BP 113/55、SpO2 100 13分後 BT 37.3℃、SpO2 85～91 輸血中止。O2投与開始。 消炎鎮痛剤の挿肛、生食 500mLを投与。 悪寒、シバリング軽快。 30分後 BT 39.2℃、BP 148/122、P 108、SpO2 98(O2 2L継続) 1時間30分後BT 38.5℃、BP 102/51、P 90、SpO2 100(O2 2L継続) 全経過中、GCS 15点を維持、アナフィラキシーの身体所見は皆無。	投与中止の当該製剤(1本)で細菌培養試験を実施する予定。	-	-	-		被疑薬:採血12日目の照射赤血球濃厚液-LR(1本)	1単位	-	調査中	調査中	調査中	調査中		

【国内血漿分画製剤例】

識別番号	FAX受付日	報告受領日	販売名(一般名)	患者性別	年代	原疾患(簡略名)	感染症名	投与年月	投与前検査(年月)	投与後検査(年月)	患者検体確保状況	受血者個別NAT	原料血漿・製品NAT検査(再検査・製造時検査の別)	併用血液製剤等	備考	使用単位数	ロット番号	同一製剤ロット使用状況	感染症転帰	転帰
A-1200-0168	2013/3/18	2013/3/26	献血ヴェノグロブリンIH(ポリエチレングリコール処理人免疫グロブリン)	女性	30	その他	伝染性紅斑	2013/1		2013/01 流産予防のため本剤投与開始(20g/日)。 2013/01 発熱・皮疹・血球減少・B19感染疑い。 2013/02/13 転帰は回復。 患者はB19 IgM(-)										
A-1300-0010	2013/4/16	2013/4/23	コンコエイトーHT(乾燥濃縮人血液凝固第8因子)	男性	40	血液疾患	HIV C型肝炎			血友病Aのため使用した非加熱血液製剤でHIV, HCVに感染した。 1996年6月からHIV感染症の治療目的で当院に紹介された。 種々の薬剤を用いて抗HIV治療を行い、HIV-RNA量は検出限界未満になったが、CD4陽性細胞数は100/μL前後で推移した。 2000年3月, 肝細胞癌と診断し、肝動脈塞栓術を施行した。 2006年5月に右膝痛を自覚し、CTで右腸骨転移を認めた。 7月には右骨盤に腫瘤が出現し、CTで右腸腰筋→大腿四頭筋への転移が疑われた。 12月下旬から全身倦怠感、黒色便、貧血を認めたため、緊急入院。 入院後に明らかな出血源は見いだせなかったが、輸血と第VIII因子補充で病状は安定した。入院3日目に右上肢筋力低下が出現し、頭部MRIでC3-5レベルの髄椎転移巣による脳髄圧迫所見を認めた。入院11日目から呼吸筋麻痺も出現し、その3日後に永眠。								

平成25年6月12日開催
薬事・食品衛生審議会
血液事業部会運営委員会
提　出　資　料

別紙

日本赤十字社血液事業本部

試行的HEV20プールNAT実施状況について
(輸血後HEV感染の予防対策)

北海道ブロック血液センター管内

調査期間:平成17年1月1日～平成25年3月31日

	HEV-RNA陽性者数(男:女)	献血者数(検査総数)	陽性率	年齢平均±標準偏差(範囲)	Genotype G3:G4	抗HEV抗体 IgM/IgG
平成17年	30 (17:13)	295,444	0.010% (1/9,848)	38.0±12.2 (20～65)	29:1	
平成18年	39 (27:12)	273,688	0.014% (1/7,018)	42.9±13.2 (17～68)	36:3	
平成19年	31 (28:3)	265,660	0.012% (1/8,570)	41.3±11.0 (19～59)	27:3 同定不能1	
平成20年	42 (33:9)	264,193	0.016% (1/6,290)	40.4±10.8 (19～62)	42:0	-/-:205 +/-: 3
平成21年	26 (18:8)	275,998	0.009% (1/10,615)	43.4±12.4 (20～65)	22:4	+/+: 34 -/+: 12
平成22年	28 (24:4)	277,025	0.010% (1/9,894)	43.0±11.4 (25～67)	26:2	
平成23年	35 (25:10)	279,841	0.013% (1/7,995)	39.1±10.7 (20～60)	30:4 同定不能1	
平成24年	23 (18:5)	275,923	0.008% (1/11,997)	43.5±10.0 (21～64)	21:2	
平成25年1-3月	6 (5:1)	69,490	0.009% (1/11,582)	39.0±10.8 (21～51)	6:0	-/-: 6 +/-: 0 +/+: 0 -/+: 0
合計	260 (195:65)	2,277,262	0.011% (1/8,759)	41.3±11.7 (17～68)	239:19 同定不能2	-/-: 211 +/-: 3 +/+: 34 -/+: 12

註:平成17年1月～平成18年2月は、HEV-NATにALT高値、検査不合格検体が含まれているが、
平成18年3月以降は、HEV-NATにALT高値、検査不合格検体は含まれていない。

事　務　連　絡
平成２５年４月４日

日本赤十字社血液事業本部　御中

薬事・食品衛生審議会血液事業部会事務局
厚生労働省医薬食品局血液対策課

血液製剤に関する報告事項について

日頃より血液事業の推進に御努力いただき、厚く御礼申し上げます。

さて、標記につきましては、平成２５年２月２１日付け血安第７７号にて貴社血液事業本部長より資料の提出があり、これを平成２４年度第４回血液事業部会運営委員会に提出したところです。今般、平成２５年６月１２日に平成２５年度第１回血液事業部会運営委員会を開催することといたしますので、下記の事項について資料を作成いただき、平成２５年５月１５日（水）までに当事務局あて御提出いただきますようお願いします。

なお、資料の作成に当たっては、供血者、患者及び医療機関の名称並びにこれらの所在地又はこれらの事項が特定できる情報を記載しないよう、個人情報及び法人情報の保護に特段の御配慮をお願いします。

記

１．平成２１年１１月２０日付けで報告された輸血用血液製剤でＨＢＶ（Ｂ型肝炎ウイルス）感染が疑われる事例について、残る２人の供血者のその後の検査結果。来訪がなければ、その旨。

２．平成２４年２月８日付けで報告された輸血用血液製剤でＨＣＶ（Ｃ型肝炎ウイルス）感染が疑われる事例について、残る２人の供血者のその後の検査結果。来訪がなければ、その旨。

３．平成２４年１０月１５日付けで報告された輸血用血液製剤でＨＢＶ感染が疑われる事例について、残る５人の供血者のその後の検査結果。来訪がなければ、その旨。

４．試行的ＨＥＶ２０プールＮＡＴについて、その後の調査実施状況。
　なお、検査総数、陽性者数、陽性率、年齢、性別、ジェノタイプ、抗ＨＥＶ抗体について、全調査期間での合計に加え、年ごとの結果も含めた表を作成してください。

血安第１８１号
平成25年5月13日

厚生労働省
医薬食品局血液対策課長 様

日本赤十字社
血液事業本部長

血液製剤に関する報告事項について（回答）

平成 25 年４月４日付事務連絡によりご依頼のありました標記の件について、下記のとおり報告いたします。

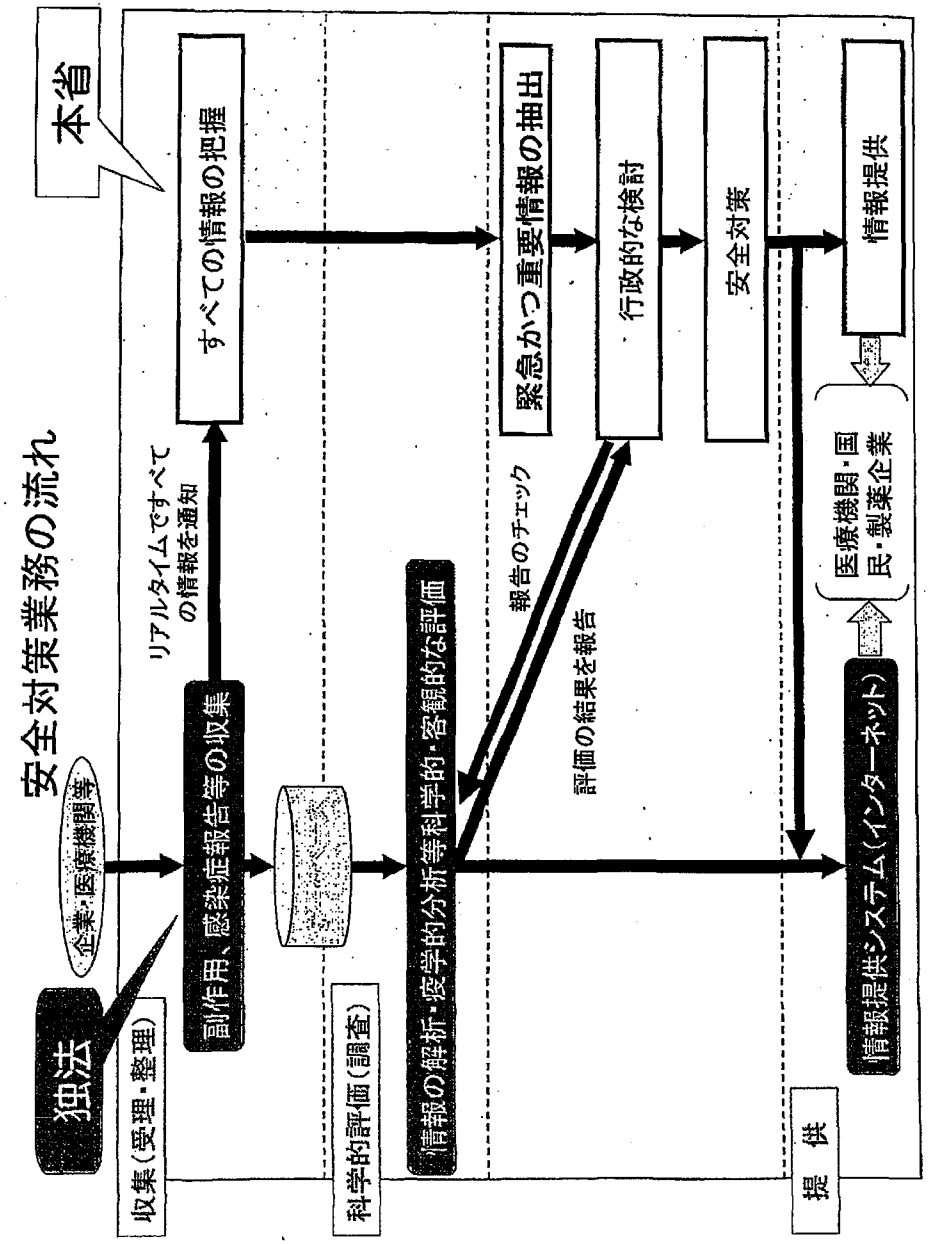
記

１．平成21年11月20日付けで報告した輸血用血液製剤でＨＢＶ（Ｂ型肝炎ウイルス）感染が疑われる事例について、供血者45人のうち、43人が来所しＨＢＶ関連検査を実施したが、残る２人については依然として来訪なし。

２．平成24年２月８日付けで報告した輸血用血液製剤でＨＣＶ（Ｃ型肝炎ウイルス）感染が疑われる事例について、供血者11人のうち、９人が来所しＨＣＶ関連検査を実施したが、残る２人については依然として来訪なし。

３．平成24年10月15日付けで報告した輸血用血液製剤でＨＢＶ（Ｂ型肝炎ウイルス）感染が疑われる事例について、供血者15人のうち、10人が来所しＨＢＶ関連検査を実施した。残る５人のうち、１人が献血に来訪し、検査は陰性であった。

４．試行的ＨＥＶ20 プールＮＡＴについて、その後の調査実施状況については別紙のとおり。



献血件数及びＨＩＶ抗体・核酸増幅検査陽性件数

年	献血件数（検査実施数）	陽性件数 ( ) 内女性 [ ] 内核酸増幅検査のみ陽性	10万件当たり
	件	件	件
１９８７年 （昭和62年）	8,217,340	11(1)	0.134
１９８８年 （昭和63年）	7,974,147	9(1)	0.113
１９８９年 （平成 元年）	7,876,682	13(1)	0.165
１９９０年 （平成 2年）	7,743,475	26(6)	0.336
１９９１年 （平成 3年）	8,071,937	29(4)	0.359
１９９２年 （平成 4年）	7,710,693	34(7)	0.441
１９９３年 （平成 5年）	7,205,514	35(5)	0.486
１９９４年 （平成 6年）	6,610,484	36(5)	0.545
１９９５年 （平成 7年）	6,298,706	46(9)	0.730
１９９６年 （平成 8年）	6,039,394	46(5)	0.762
１９９７年 （平成 9年）	5,998,760	54(5)	0.900
１９９８年 （平成10年）	6,137,378	56(4)	0.912
１９９９年 （平成11年）	6,139,205	64(6)	1.042
２０００年 （平成12年）	5,877,971	67(4) [3]	1.140
２００１年 （平成13年）	5,774,269	79(1) [1]	1.368
２００２年 （平成14年）	5,784,101	82(5) [2]	1.418
２００３年 （平成15年）	5,621,096	87(8) [2]	1.548
２００４年 （平成16年）	5,473,140	92(4) [2]	1.681
２００５年 （平成17年）	5,320,602	78(3) [2]	1.466
２００６年 （平成18年）	4,987,857	87(5) [1]	1.744
２００７年 （平成19年）	4,939,550	102(3) [6]	2.065
２００８年 （平成20年）	5,077,238	107(3) [0]	2.107
２００９年 （平成21年）	5,287,101	102(6) [2]	1.929
２０１０年 （平成22年）	5,318,586	86(3) [1]	1.617
２０１１年 （平成23年）	5,252,182	89(8) [3]	1.695
２０１２年 （平成24年）	5,271,103	68(6) [1]	1.290
２０１３年 （平成25年） （１～３月）	1，304，418 （速報値）	23(1) [1]	1.763

（注１）・ 昭和６１年は、年中途から実施したことなどから、3,146,940件、
うち、陽性件数１１件（女性０）となっている。
（注２）・ 抗体検査及び核酸増幅検査陽性の血液は廃棄され、製剤には使用されない。
・ 核酸増幅検査については、平成１１年１０月より全国的に実施している。
（注３）・ 平成２５年は、１月～３月の速報値で集計している。

ＨＩＶ抗体・核酸増幅検査陽性献血者数内訳

1. 性別・年齢区分・国別

	男性			女性			合計		
	日本人	外国人	計	日本人	外国人	計	日本人	外国人	計
	人	人	人	人	人	人	人	人	人
16～19歳	39	1	40	12	0	12	51	1	52
20～29歳	572	31	603	52	4	56	624	35	659
30～39歳	548	14	562	27	2	29	575	16	591
40～49歳	204	1	205	12	1	13	216	2	218
50～69歳	90	0	90	9	0	9	99	0	99
合　計	1453	47	1500	112	7	119	1565	54	1619

※ 昭和61年～平成25年3月（昭和61年については年途中から集計）

2. 都道府県別（献血地別）

県別	61年	62年	63年	元年	2年	3年	4年	5年	6年	7年	8年	9年	10年	11年	12年	13年	14年	15年	16年	17年	18年	19年	20年	21年	22年	23年	24年	25年	合計	構成割合	ブロック別 献血件数	ブロック別 構成割合
	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(件)	(%)	(件)	(%)
1.北海道			1			1	2	1	1	1		1	1	3	2	2	3	2	2	3	2	3	3	2	2	2	2		42	2.6		
2.青森			2				1					1				1	1	2	1	1	1			1	2				13	0.8		
3.岩手										1				1										3		1			6	0.4		
4.宮城							1	1				1	1	1		1	1	1	1	2				2					13	0.8	北海道	
5.秋田																1			1				1		1				4	0.2	・東北	
6.山形													1				1							1	1				4	0.2		
7.福島							1					2		1	1			1					1		1	2	1		11	0.7	93	5.7
8.茨城					1	1	4	2			1	2		1	2	1	1				1	1	1	5	1	1	2		28	1.7		
9.栃木					3	1			2	1	1		1			3		1		1	4	2	1	1	1	3	2		28	1.7		
10.群馬					1	1		1			1		1	3	1			2		3		2	1	3		1		1	22	1.4		
11.埼玉		1				1	1	2	1	2	3	3	3	3	3	3	3	3	5	2	1	3	2	8	3	1	3		60	3.7		
12.千葉						1	6	2	2	3	7	2	4	5	4	5	3	3	2	2	2	6	9	5	6	8	6	2	93	5.7	関東	
13.東京	10	6	4	10	10	11	12	11	14	21	18	18	19	27	26	29	23	25	24	22	24	17	21	19	25	18	23	7	494	30.5		
14.神奈川		1		1	1	4	1	3	4	2	5	3	4	3	5	3	5	5	8	4	5	5	5	1	2	4	4	1	89	5.5	814	50.3
15.新潟				1		1		1						1		2			1		2			2			1		12	0.7		
16.富山					2						1				1		1				1								6	0.4		
17.石川																2				1		3		1					7	0.4	北陸・	
18.福井			1							2							1	1											5	0.3	甲信越	
19.山梨					1	1					1					1													4	0.2		
20.長野							1	1			2						1				1	1					2	1	10	0.6	44	2.7
21.岐阜							1									1			1				1	2	1	2			9	0.6		
22.静岡						1	3		1					1	1			1	1			4		2	1	2		1	19	1.2	東海	
23.愛知		1			3	2		3	1	1			4	3	2	3	2	2	4	4	5	4	10	4	2	3	2	1	66	4.1		
24.三重											1	1	1		1			1		2				1					8	0.5	102	6.3
25.滋賀																1	3							1	2				7	0.4		
26.京都								2		2	1	1				2	5	2		4	5	1			2	5			32	2.0		
27.大阪	1	1	1	1	3		1		4	2	1	8	14	6	8	10	10	15	17	19	17	26	26	13	18	16	7	2	247	15.3		
28.兵庫						2			1	2				2	1	1	4	5	3		3	3	4	3	2		3	1	40	2.5	近畿	
29.奈良										1	2	3	1		1		1	1	1				1	1				1	14	0.9		
30.和歌山																			2				1	1		2			6	0.4	346	21.4
31.鳥取									1							1				1			1		1				5	0.3		
32.島根						1															1				3	1			6	0.4		
33.岡山									2									2	1	2	2	3	1			1		1	15	0.9	中国	
34.広島							2	1	1				1				1	2	6		2	2	1	4		1	1		25	1.5		
35.山口					1						2											1		1		1			5	0.3	56	3.5
36.徳島										1				1						1		1	1	1		1			7	0.4		
37.香川							1												1			1	2	2	1			1	9	0.6	四国	
38.愛媛												1	1	2	3	2	2			1	1	2		1		2			18	1.1		
39.高知																		1	1		1		1	1					6	0.4	40	2.5
40.福岡							1		2	2	2	1	1	1	1	2	4	2	2		3	1	3	2	4	4	2	1	41	2.5		
41.佐賀																											2		2	0.1		
42.長崎																	2					1	1	2		2			8	0.5		
43.熊本						1				2	1			1	2		1	2		1	1	2	2	2	1	3	1		23	1.4		
44.大分									1									2	1										4	0.2	九州	
45.宮崎														2						2		1	1	1		1	1		9	0.6	・沖縄	
46.鹿児島							1						2			1	1		1		1	1	2		2	1		1	14	0.9		
47.沖縄		1									1							2	3		1	5	1	3	1	1	3	1	23	1.4	124	7.7
合計	11	11	9	13	26	29	34	35	36	46	48	54	56	64	67	79	82	87	92	78	87	102	107	102	86	89	68	23	1619	100	1619	100

※ 「構成割合」は端数処理しているため、合計が必ずしも１００％にはならない

※ 平成25年については、1月～3月の速報値で集計

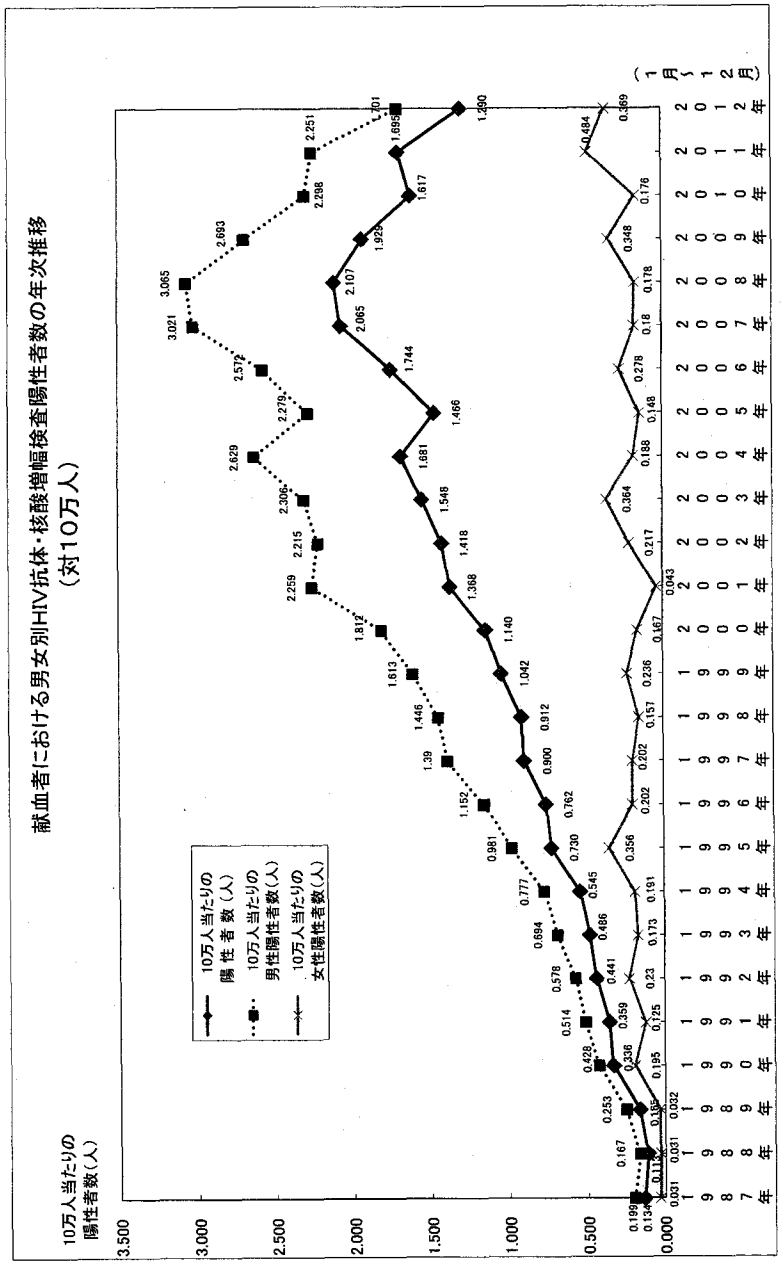
ブロック別ＨＩＶ抗体・核酸増幅検査陽性献血者

	平成21年			平成22年			平成23年			平成24年			平成25年（1月～3月）（速報値）		
	献血者	陽性	10万人当たり	献血者	陽性	10万人当たり	献血者	陽性	10万人当たり	献血者	陽性	10万人当たり	献血者	陽性	10万人当たり
	人	件	件	人	件	件	人	件	件	人	件	件	人	件	件
北海道・東北	677,073	9	1.329	690,050	7	1.014	645,896	5	0.774	675,676	3	0.444	168,529	[illegible]	0.000
関東	1,705,070	42	2.463	1,698,561	38	2.237	1,649,186	36	2.183	1,685,544	40	2.373	417,339	11	2.636
北陸・甲信越	340,901	3	0.880	340,203	0	0.000	349,241	0	0.000	340,542	3	0.881	86,273	[illegible]	1.159
東海	584,495	9	1.540	589,557	4	0.678	586,872	7	1.193	575,228	2	0.348	142,764	[illegible]	1.401
近畿	863,744	20	2.316	876,750	22	2.509	873,048	23	2.634	869,738	10	1.150	213,767	[illegible]	1.871
中国	329,443	4	1.214	330,284	5	1.514	324,416	3	0.925	323,135	1	0.309	79,679	[illegible]	1.255
四国	173,914	5	2.875	176,923	2	1.130	176,841	3	1.696	166,492	0	0.000	39,584	[illegible]	2.526
九州・沖縄	612,461	10	1.633	616,258	8	1.298	646,682	12	1.856	634,748	9	1.418	156,483	[illegible]	1.917
合計	5,287,101	102	1.929	5,318,586	86	1.617	5,252,182	89	1.695	5,271,103	68	1.290	1,304,418	23	1.763

年齢別HIV抗体・核酸増幅検査陽性献血者

	平成20年			平成21年			平成22年			平成23年			平成24年（1月～12月）（確定値）		
	献血者	陽性	10万人当たり	献血者	陽性	10万人当たり	献血者	陽性	10万人当たり	献血者	陽性	10万人当たり	献血者	陽性	10万人当たり
	人	件		人	件		人	件		人	件		人	件	
16才～19才	308,019	2	0.649	295,811	3	1.014	292,853	5	1.707	286,534	2	0.698	295,683	4	1.353
														(1)	
20才～29才	1,141,746	41	3.591	1,139,991	37	3.246	1,080,385	21	1.944	1,037,257	41	3.953	1,000,086	20	2.000
					(1)			(1)			(4)			(3)	
30才～39才	1,391,141	50	3.594	1,414,747	42	2.969	1,376,596	43	3.124	1,317,138	31	2.354	1,243,040	23	1.850
		(1)			(3)			(1)			(2)			(1)	
40才～49才	1,171,449	11	0.939	1,272,397	17	1.336	1,350,490	10	0.740	1,379,078	8	0.580	1,442,101	14	0.971
		(1)			(2)						(1)				
50才～59才	785,280	3	0.382	841,168	3	0.357	872,113	6	0.688	878,562	6	0.683	926,865	6	0.647
		(1)						(1)			(1)			(1)	
60才～	279,603	0	0.000	322,987	0	0.000	346,149	1	0.289	353,613	1	0.283	363,328	1	0.275
合計	5,077,238	107	2.107	5,287,101	102	1.929	5,318,586	86	1.617	5,252,182	89	1.695	5,271,103	68	1.290
		(3)			(6)			(3)			(8)			(6)	

（注）陽性件数の（）内女性



資料4

ひと、くらし、みらいのために
厚生労働省
Ministry of Health, Labour and Welfare

Press Release

平成25年5月31日
医薬食品局血液対策課
（担当・内線）課長補佐　笠松（2905）
血液安全係長　松本（2908）
（代表電話）03(5253)1111
（直通電話）03(3595)2395

報道関係者　各位

フィブリノゲン製剤納入先医療機関の追加調査について

平成16年12月9日に公表したフィブリノゲン製剤納入先医療機関を対象として、平成19年11月7日付で実施した追加調査の結果について、前回の報告から平成25年5月31日までに、医療機関から新たに届いた回答はありませんでしたので、平成24年12月27日に公表した調査結果からの変更はありません。

（参考）C型肝炎ウイルス検査受診の呼びかけ（下記の厚生労働省ホームページにリンク）
http://www.mhlw.go.jp/houdou/2008/01/h0117-2/index.html