20. Emerson SU, Arankalle VA, Purcell RH. Thermal stability of hepatitis E virus. J Infect Dis 2005;192:930-3.
21. Feagins AR, Opriessnig T, Guenette DK, Halbur PG, Meng XJ. Detection and characterization of infectious hepatitis E virus from commercial pig livers sold in local grocery stores in the USA. J Gen Virol 2007;88:912-7.
22. Mansuy JM, Peron JM, Abravanel F, Poirson H, Dubois M, Miedouge M, Vischi F, Alric L, Vinel JP, Izopet J. Hepatitis E in the south west of France in individuals who have never visited an endemic area. J Med Virol 2004;74:419-24.
23. Waar K, Herremans MM, Ventema H, Koopmans MP, Benne CA. Hepatitis E is a cause of unexplained hepatitis in The Netherlands. J Clin Virol 2005;33:145-9.
24. Chauhan A, Jameel S, Dilawari JB, Chawla YK, Kaur U, Ganguly NK. Hepatitis E virus transmission to a volunteer. Lancet 1993;341:149-50.
25. Li TC, Zhang J, Shunzawa H, Ishibashi M, Sata M, Mast EE, Kim K, Miyamura T, Takeda N. Empty virus-like particle-based enzyme-linked immunosorbent assay for antibodies to hepatitis E virus. J Med Virol 2000;62:327-33.
26. Tanaka E, Takeda N, Tian-Chen L, Orii K, Ichijo T, Matsumoto A, Yoshizawa K, Iijima T, Takayama T, Miyamura T, Kiyosawa K. Seroepidemiological study of hepatitis E virus infection in Japan using a newly developed antibody assay. J Gastroenterol 2001;36:317-21.
27. Ijaz S, Arnold E, Banks M, Bendall RP, Cramp ME, Cunningham R, Dalton HR, Harrison TJ, Hill SF, Macfarlane L, Meigh RE, Shafi S, Sheppard MJ, Smithson J, Wilson MP. Non-travel-associated hepatitis E in England and Wales: demographic, clinical, and molecular epidemiological characteristics. J Infect Dis 2005;192:1166-72.
28. Lozano M, Cid J, Bedini JL, Mazzara R, Gimenez N, Mas E, Ballesta A, Ordinas A. Study of serum alanine-aminotransferase levels in blood donors in Spain. Haematologica 1998;83:237-9.
29. Grunenberg R, Banik N, Kruger J. Alanine aminotransferase (ALAT, GPT): a reevaluation of exclusion limits for blood donors. Infusionsther Transfusionsmed 1995;22:145-51. □

別紙様式第2-1

No. 2

医薬品 研究報告 調査報告書

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研究報告の概要

○米国の供血者におけるヘルペスウイルス8(HHV 8)ゲノム

背景:カポジ肉腫の原因となるヘルペスウイルス8(HHV 8)について、これまで供血者のウイルスゲノム陽性率は系統的に調査されたことがなかった。

方法:ランダムに選択された米国供血者から分離したCD19+Bのリンパ球DNA抽出物からHHV8ゲノムを検出するため、高感度定量RT-PCR法を用いた。血液採取から24時間以内にCD19+Bリンパ球を選択し、HHV8のPCR反応のDNAインプットを決定するため、GAPDH遺伝子の細胞標的を用いて、DNAの細胞相当量を定量した。

結果:950名の供血者から検体を入手し、684名から1 × 10^6 B細胞相当以上の精製DNAが得られた。RT-PCRにてGAPDH細胞標的を増幅させ、それぞれの供血者の細胞DNA量を測定した。HHV8 RT-PCR反応には、3 × 10^5 B細胞(全血1 mL中のB細胞の総量に当たる)に相当する細胞DNAを加えた。検出限界8コピーのRT-PCRで、3〜6 × 10^5 CD 19+ Bリンパ球相当のDNAからHHV8ゲノムは検出されなかった(95% CI : 0〜3/684)。

結論:PCR反応の検出限界が8コピーであるRT-PCRにおいてHHV8ゲノムが検出されなかったことから、健康な供血者中のHHV8ゲノム陽性率は極めて低い。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25

血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
米国の供血者のヘルペスウイルス8(HHV 8)ゲノム陽性率について、高感度定量RT-PCR法によりDNAの細胞相当量を定量した結果、684名の供血者からはHHV8ゲノムは検出されなかったとの報告である。 HHV-8は脂質膜を持つ大型DNAウイルスである。これまで、本剤によるHHV-8感染の報告はない。本剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれていることから、本剤の安全性は確保されていると考える。	本剤の安全性は確保されていると考えるが、今後も情報収集に努める。

⑧

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Groups for Comparison	Crude Prev (% Positive)	Adjusted Odds Ratio* (95% CI)
Southeast vs. Northeast US	49.0 vs. 28.2	2.25 (2.2, 2.3)
Age group ≥70 years vs. <20-29 years	60.6 vs. 27.9	5.20 (5.0, 5.4)
Female vs. male	35.9 vs. 28.9	1.52 (1.5, 1.5)
US vs. Non-US born	31.0 vs. 62.7	0.40 (0.4, 0.4)
Asian vs. white	65.3 vs. 30.0	3.20 (3.0, 3.4)
Black vs. white	60.0 vs. 30.0	2.99 (2.9, 3.1)
Hispanic vs. white	50.3 vs. 30.0	2.27 (2.2, 2.4)
Transfused vs. non-transfused	40.3 vs. 31.7	1.13 (1.1, 1.2)
Body mass index (BMI, kg/M²) <18.5 vs. ≥35	27.5 vs. 34.7	0.8 (0.8, 0.9)

* Adjusted for region, gender, age, race/ethnicity, country of birth, body mass index (BMI), transfusion, collection procedure, and first-time vs. repeat status.

Disclosure of Conflict of Interest

Ram Kakaiya, Darrell Triulzi, John D. Roback, Junyong Fang, Yongling Tu, Steven Kleinman, Michael P. Busch, Jorge A. Rios, Christopher Hillyer, Simone Glynn, George Schreiber, for the Retrovirus Epidemiology Donor Study-II: Nothing to Disclose
Jerome L. Gottschall: Not Specified

SP197

Control Charts for Monitoring Viral Incidence Rates: An Illustration

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Background: Monitoring of new and repeat donor incidence rates is a means to ensure control of transfusion related infectious disease transmission risks. In the Netherlands systematic evaluation of annual incidence rates is performed since the 1980s. Analysis of infection data allows identification of trends in incidence rates and of years with excessively deviating incidence rates. Analysis results can potentially pinpoint to areas for improvement of blood supply safety. **Methods:** HIV infection data from the years 1995 through 2006 were analyzed using a Shewhart Control Chart which is commonly applied in industrial statistics. The likelihood of the observed number of incidents in a particular year is calculated on basis of the mean incidence rate over the whole observation period and the population size in that particular year. The observed number of incidents is presumed to follow a Poisson distribution. **Results:** The results show that in the year 2002 there was an unusual increase in the HIV incidence rate. The likelihood of the observed 8 infections (or more) in that year on basis of the average HIV incidence rate (0.0000057) is less than 0.7% (1 in 138). **Conclusion:** Given the low exceedance probability it is unlikely that the observed 8 infections in 2002 were a chance finding. This conclusion holds even if the result is corrected for multiple testing (as there are 12 years of observation). Therefore other causes for the incidence rate increase in this particular year should be considered. Control Charts can be easily applied to monitor and control viral incidence rates. The graphical presentation of the Control Chart (not give here) provides an intuitive and easily interpretable result.

Disclosure of Conflict of Interest

Mart P. Janssen, Cees L. van der Poel: Nothing to Disclose

SP198

Cost-Utility of a Publicly Funded Hepatitis B Vaccination Program for Blood Donors in British Columbia, Canada

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Background: The current strategy for preventing transfusion-transmitted hepatitis B virus (TT-HBV) infection in Canada and the United States relies on donor behavioral risk and laboratory screening. The objective of this study, undertaken in British Columbia (BC) Canada in 2007, was to assess the cost-utility and benefits to transfusion safety, of offering a publicly funded HB vaccination program for previously unvaccinated blood donors. **Methods:** A "health care payer" perspective, using deterministic estimates, was taken. Fixed costs (e.g. space) and savings from prevented infections were not included. Direct and indirect program costs associated with vaccinating eligible donors through the existing regional, mixed, public health/physician vaccine delivery model in BC, were included in the analysis, along with relevant blood donor and recipient data, obtained from Canadian Blood Services (CBS) and the BC Ministry of Health. Ninety percent of donors under 25 years were estimated to have had prior HB vaccination. Sensitivity analyses were conducted around estimates for prevalence of prior HB vaccination among donors >25 years (10-30%) and HB vaccine uptake (80-100%). **Results:** As of May 2007 there were 52,758 active donors in BC and CBS attracts approximately 8000 new donors per year in the province. Assuming 100% vaccine uptake among eligible donors, total program cost over the first program year ranged between $CDN 2.55 M and $CDN 3.04 M. Program cost would drop to $CDN 0.38 M in the following year. Up to 2.46 TT-HBV infections might be averted in the first 2 program years, with a corresponding range of cost-utility based on scenarios of 30% and 10% prevalence of prior HB vaccination among donors >25 years, of $CDN 6.92-$8.09 M per Quality Adjusted Life Year (QALY) gained. An estimated one TT-HBV related death would be averted over 40-80 years. **Conclusions:** Although costing about $2.90 M in the first year (assuming 100% uptake), program cost would drop by 87% to about $0.38 M in the following year and likely continue to decrease in ensuing years, as the proportion of new donors previously HB vaccinated increases, as a result of existing public health HB immunization programs. The estimated cost-utility of the program in its first 2 years, approximately $7.77 M per QALY, would also improve over the longer term. Although not within the usual cost-utility range of many healthcare interventions, it is comparable to that of other safety measures implemented by many blood suppliers over the past decade, such as donor nucleic acid testing for HIV and hepatitis C virus. Conceptually, this program could expand the current means of enhancing blood safety, which focus on donor risk behavior screening and testing, to include donor primary disease prevention, that better integrates blood safety into a comprehensive public health disease-prevention strategy.

Disclosure of Conflict of Interest

Mark Bigham, Jane Buxton, Shannon Waters: Nothing to Disclose

SP199

Detection of Hepatitis C Virus in Brazilian Blood Donors – Age Group Study

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Background: Hepatitis C virus (HCV) is a public health problem worldwide; it is estimated that about 170 millions people are infected and 2.4 millions only in Brazil. Blood transfusion is one way of HCV transmission that fortunately has relative decreased after introduction of ELISA and genomic tests. The 3rd generation ELISA test (ELISA1) targeted to antibodies against HCV capsid and 4th generation ELISA test (ELISA2) directed to antibodies against the capsid and the core proteins allied to HCV genomic test provide most powerfull instruments of safe HCV detection. **Methods:** One year screening of 98,581 blood bank samples of healthy donors at COLSAN/UNIFESP using immunological and molecular HCV tests. It was studied 584 (0.59%) positive ELISA1 donors samples (ELISA Hepanostika HCV ultra – BioMerrieux); all these samples were submitted to ELISA2 (ELISA Ortho HCV – Ortho) and to genomic HCV amplification by Reverse Transcriptase Nested-Polimerase-Chain-Reaction (RT-NPCR). The blood donors were distributed in five age groups, to study the rate for HCV detection tests. **Results:** It was detected 333 samples (0.34%) positive to both ELISA tests and the presence of HCV genome in 208 samples (0.21%). The age groups rates were: 18-29 years – 0.41%/ELISA1 and 0.13%/RT-NPCR; 30-39 years – 0.62%/ELISA1 and 0.19%/RT-NPCR; 40-49 years – 0.75%/ELISA1 and 0.32%/RT-NPCR; 50-59 years – 0.96%/ELISA1 and 0.42%/RT-NPCR; 60-65 years – 1%/ELISA1 and 0.27%/RT-NPCR. **Conclusions:** Immunological and molecular tests comparison demonstrated that 65% HCV positive ELISA1 test do not correspond to positive viral genome detection in brazilian blood donors at COLSAN/UNIFESP. Despite been characterized as healthy donors 0.2% of the blood donators in our Institution have positive genomic HCV test, remarkably groups 40-49 and 50-59 years.

Disclosure of Conflict of Interest

Fabricio Carvalho, Jose Augusto Barreto, Madalena Pares, Italiana Rodart, Cleidenice Silva, Mittermeyer Reis: Nothing to Disclose

SP200

Herpesvirus 8 (HHV 8) Genomes in US Blood Donors

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Background: HHV-8 is a gamma-herpesvirus that causes Kaposi's sarcoma. The prevalence of viral genomes in blood donors has not been systemically studied. **Methods:** We employed a sensitive and quantitative real-time PCR

assay to detect HHV 8 genomes from DNA extracted from purified CD19+ B lymphocytes from randomly selected US whole blood donors. Blood specimens were stored at 4C overnight prior to processing. CD19+ B lymphocytes were selected within 24 hours of specimen collection. Cellular target for the GAPDH gene was used to quantify cell-equivalent DNA in order to determine the DNA input into the HHV 8 PCR reaction. Real-time HHV 8 PCR was run in duplicate for each donor specimen along with an HHV 8 genomic copy standard. Five-fold dilution series of a calibrated HHV8 DNA provided 200, 40, 8 and 1.6 copies for a standard curve. Two sets of standard DNA were run with each plate, the 8 copy HHV 8 genome standard was always detected; the 1.6 copy control was detected at greater than 50% of the time. **Results:** Specimens were obtained from 950 blood donors and purified DNA from greater than 1×10^6 B cell-equivalents was obtained from 684 donors. DNA of lesser amount was obtained from168 donors. The remaining 98 specimens did not produce sufficient DNA for HHV 8 PCR. The quantity of cellular DNA from each donor was measured with a real-time PCR target amplifying cellular GAPDH target. Cellular DNA equivalent to 3×10^6 B cells (which approximates total B cells from 1 ml whole blood) was used as input material for each real-time HHV8 PCR reaction. No HHV 8 DNA was detected from any of the blood donor specimens. For the 684 donors from whom sufficient DNA were obtained, HHV 8 genomes were not detected in the DNA equivalent of 3 to 6×10^5 CD19+ B lymphocytes with real time PCR which has a detection limit of 8 copies per PCR reaction (95% CI: 0-3/684). Negative results from the 168 donors were potentially confounded by insufficient input DNA into the PCR reactions. **Conclusions:** HHV8 genomes were not detected from 684 blood donors using DNA equivalent of 3 to 6×10^5 CD19+ B lymphocytes with a real-time PCR, which has a detection limit of 8 copies per PCR reaction. Therefore, the prevalence of detectable HHV8 genomes in healthy blood donors is very low.

Disclosure of Conflict of Interest

Lirong Qu, Darrell Triulzi: Nothing to Disclose

SP201

Identification of a Parvovirus B19 Genotype 3 Isolate in the United States

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Background: Parvovirus B19 (B19V) is a human pathogen frequently detected in plasma donations through the detection of nucleic acids. Three B19V genotypes have been defined based on isolates having greater than 10% divergence in overall DNA sequence. B19V genotype 3 is a rarely occurring genotype that has been detected primarily in Ghana with sporadic reports in Brazil and France. B19V genotype 3 has not been previously reported in North America. **Methods:** A multi-probe fluorogenic PCR assay has been developed to ensure broad specificity for the detection of B19V. A detection probe specific for genotype 1 contains the DNA sequence of the B19V Au prototype strain and a second probe contains a DNA consensus sequence derived from the A6 (genotype 2) prototype strain and the V9 and D91.1 (genotype 3) isolates. The assay was used to evaluate over 400,000 clinical samples. Determinations of the B19V virus titer and antibody concentration were performed on samples of interest. **Results:** This evaluation identified a series of 8 plasma donations spanning 28 days from a single donor in the United States. DNA sequence analysis of nucleic acids isolated from the index donation indicates significant homology with B19V genotype 3. The B19V titer of this series of donations showed virus titers that peaked at greater than 10^{11} International Units (IU)/mL. The virus titer decreased significantly over the next several donations coinciding with an increase in IgM levels. The IgG levels also increased but lagged approximately 7 days after the IgM levels. **Conclusions:** Recent reports surrounding the incidence of the B19V genotype 3 infection among blood and Source Plasma donors indicate that the prevalence of this genotype is quite low. Our data corroborate these reports since testing over 400,000 clinical samples yielded only one donor that tested positive for genotype 3. Analysis of the viral load through the course of infection for this donor suggests an infection cycle similar to that associated with B19V genotype 1 infection. The significance of detecting this rare B19V genotype 3 and its importance to public health is unclear.

Disclosure of Conflict of Interest

Michael Gray, Lori Rinckel, Todd Gierman, Douglas Lee: Nothing to Disclose

SP202

Methoxypoly (Ethylene Glycol) Modification of Viruses or Host Cells: A Broad Spectrum Antiviral Prophylactic

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Background: Nosocomial viral infections (both transfusion and non-transfusion associated) pose a risk to patients. Previously, we have demonstrated that covalent grafting of methoxypoly (ethylene glycol) (mPEG; pegylation) to the surface of RBC and WBC prevented cell-cell interaction, allorecognition, and cell activation. Thus, as a novel means of viral inactivation, we evaluated the efficacy of mPEG-modification of respiratory syncytial virus (RSV) or its host cells as a model system. **Methods:** Four mPEG linker chemistries (cyanuric chloride mPEG (CmPEG), benzotriazole carbonate mPEG (BTCmPEG), succinimidyl propionate mPEG (SPAmPEG) and succinimidyl carbonate mPEG (SCmPEG)) were tested. These mPEGs were assessed via syncytia formation and immunostaining using two polymer sizes (2 and 5 kDa) and at concentrations ranging from 0-15 mM mPEG. For direct viral modification, ~120 syncytia forming units of RSV were modified with mPEG, overlaid on Vero cells, and examinnd over 5 days. For host cell modification, Vero cells were similarly modified with mPEG, challenged with unmodified-RSV and followed for 5 days. **Results:** For all linker chemistries examined direct modification of RSV significantly reduced the number of syncytia. For example, modification with 15 mM, 5 kDa SCmPEG significantly reduced the number of syncytia from 12612 to 145 ($p < 0.001$) per well (1.9 cm). Furthermore, at the same concentration, modification with 2 kDa SCmPEG showed complete inhibition of viral infection. For host cell modification, 5 kDa CmPEG and 2 kDa SCmPEG grafting also inhibited infection, resulting in a 33 and 45% reduction in the number of syncytia, respectively ($p < 0.001$). Immunostaining over 96 hours further demonstrated the efficacy of pegylating either the virus or host cells. Pegylation of RSV with 15 mM SCmPEG (2 kDa) resulted in a >95% reduction in RSV infection at 24 hours ($p < 0.001$). **Conclusions:** Our findings demonstrate that mPEG modification of RSV or its host cell can effectively limit or prevent viral invasion. Application of this technology to blood products could prove to be a valuable method for inactivating known and unknown blood-borne viruses. Furthermore, additional studies demonstrate that pegylation of viruses, or their host cells provide, a broad spectrum anti-viral prophylaxis effective against both enveloped and non-enveloped viruses.

Disclosure of Conflict of Interest

Troy Sutton, Mark Scott: Nothing to Disclose

SP203

Prevalence of Transfusion Transmitted Infections in Brazilian Blood Donors as Determined by a Dual EIA Strategy

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Background: Representative data on prevalence of infection markers among Brazilian blood donors are scarce due to the lack of common informational systems infrastructure and because confirmatory assays are not routinely performed on reactive samples at the time of screening. Here we describe infectious marker prevalence results obtained in Brazil during the first year of the study. **Methods:** Donation data including supplemental testing results were collected and compiled from 3 Brazilian blood centers located in states of São Paulo, Minas Gerais and Pernambuco for 2007. Donation samples that tested EIA repeat reactive were tested with alternative EIA assays to confirm infection. Prevalence of transfusion transmissible infections (TTI) were calculated using the number of donors reactive on the confirmatory EIA at their index donation divided by the total number of donors screened for that disease in 2007. **Results:** There were 307,085 blood donations collected from 245,445 donors at these three blood centers. Thirty-five percent were first time (FT) donors (n = 85,954). HIV prevalence was 2x higher in FT compared to repeat donors. Whereas for the other markers prevalence was 10x or more higher in FT donors. Stratified prevalence in FT donors is reported in the lower portion of the table. Strong differences were noted by demographic characteristics for all agents. For example HIV prevalence in FT donors in Pernambuco is over 2x that of Sao Paulo. Patterns of the epidemic for each agent were dramatically different

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NO. 12

医薬品 研究報告 調査報告書

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研究報告の概要

○欧州のHIV/AIDS調査:2007年最新データ
ヒト免疫不全ウイルス(HIV)感染症はヨーロッパの公衆衛生にとって重要な問題であり、複数の国でHIV感染増加のエビデンスが示されている。本稿は、HIVおよび後天性免疫不全症候群(AIDS)の調査データの概要を提供し、ヨーロッパにおいて症例報告された人口100万人当たりの新規HIV感染率が、2000年以降にほぼ2倍となったことを示す。
2007年は、当該地域53カ国中49カ国から合計48,892例のHIV感染が報告され、エストニア、ウクライナ、ポルトガルとモルドバ共和国で感染率が最も高かった。欧州連合(EU)および欧州自由貿易連合(EFTA)諸国において、HIV感染の主要感染経路は男性間の性行為であり、次いで異性間接触である。WHO欧州地域東部では、現在も静注薬物使用が主な感染経路であるが、中部では異性接触が主要な感染経路である。2007年のAIDS診断症例の報告件数は、東部を除く全域で減少した。
HIV/AIDS調査データは、HIV流行の傾向をモニターし、公衆衛生の対応を評価するために不可欠である。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25

血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
ヨーロッパにおいて症例報告された人口100万人当たりの新規HIV感染率は、2000年以降ほぼ2倍となった。2007年は、当該地域53カ国中49カ国から合計48,892例のHIV感染が報告され、エストニア、ウクライナ、ポルトガルとモルドバ共和国で感染率が最も高かったとの報告である。 これまで、本剤によるHIV感染の報告はない。また本剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれている。さらに最終製品についてHIV-NAT陰性であることを確認している事から本剤の安全性は確保されていると考える。	本剤の安全性は確保されていると考えるが、今後も情報の収集に努める。なお、日本赤十字社ではHIV抗体検査にこれまでの凝集法と比べてより感度の高い化学発光酵素免疫測定法(CLEIA)を導入したことに加え、20プールNATについてもHIV-2及びHIVグループOの検出が可能な新NATシステムを導入し、陽性血液を排除している。また、輸血感染症対策として、男性と性的接触を持った男性は1年間献血不適としている。

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Rapid communications

HIV/AIDS SURVEILLANCE IN EUROPE: UPDATE 2007

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2. World Health Organization Regional Office for Europe, Copenhagen, Denmark

Human immunodeficiency virus (HIV) infection remains of major public health importance in Europe, with evidence of increasing transmission of HIV in several countries. This article provides an overview of HIV and acquired immunodeficiency syndrome (AIDS) surveillance data, and indicates that since 2000 the rate of newly reported cases of HIV per million population has almost doubled in Europe. In 2007, a total of 48,892 cases of HIV infection were reported from 49 of 53 countries in the Region, with the highest rates in Estonia, Ukraine, Portugal and the Republic of Moldova. In the European Union (EU) and European Free Trade Association (EFTA) countries, the predominant mode of transmission for HIV infection is sex between men followed by heterosexual contact. Injecting drug use is still the main mode of transmission in the eastern part of the WHO European region, while in the central part heterosexual contact is the predominant mode of transmission. In 2007, the reported number of AIDS cases diagnosed decreased in the Region overall, except in the eastern part. HIV/AIDS surveillance data are vital to monitor the trends of the HIV epidemic and evaluate public health responses.

Introduction

Since January 2008, the European Centre for Disease Prevention and Control (ECDC) and the World Health Organization Regional Office for Europe have been jointly carrying out the HIV/AIDS surveillance in Europe [1]. This article presents the main findings for the whole WHO European Region, the three geographical regions of the WHO European Region (West, Centre and East)* and the European Union (EU) and European Free Trade Association (EFTA)** countries.

TABLE 1
Characteristics of newly diagnosed cases of HIV infection reported in the WHO European Region and by geographical area, 2007

	WHO European Region*	West*	Centre*	East*
Number of HIV cases	48892	24202	1897	22793
Rate per million population	76.4	77.0	10.1	164.8
Percentage of cases:				
Age 15-29 years	33%	26%	41%	40%
Female	33%	31%	24%	36%
Transmission mode**				
Heterosexual***	35%	29%	53%	42%
Men who have sex with men	20%	40%	30%	0.4%
Injecting drug users	32%	8%	13%	57%

* Missing data: Austria, Italy, Monaco, Russian Federation.
** Transmission group unknown is excluded from the percentages.
*** Excludes persons originating from countries with generalised epidemics (4555 in total; 4540 in West).

HIV case reports in WHO European Region

In 2007, 48,892 newly diagnosed HIV cases (76 per million population) were reported from 49 of the 53 countries in the WHO European Region (no data from Austria, Italy, Monaco and the Russian Federation). In the three parts of the WHO European Region, the rate of newly reported cases of HIV per million population was highest in the East (Table 1), whereas among individual countries, the highest rates were reported in: Estonia (472 per million), Ukraine (285 per million), Portugal (217 per million) and the Republic of Moldova (204 per million). Between

TABLE 2
Characteristics of newly diagnosed cases of HIV infection reported in the EU/EFTA countries*, 2007

	EU/EFTA countries*
Number of HIV cases	25279
Rate per million population	64.1
Percentage of cases:	
Age 15-29 years	28%
Female	31%
Transmission mode**	
Men who have sex with men	29%
Heterosexual***	35%
Injecting drug users	9%

* Missing data: Italy, Austria.
** Transmission group unknown is excluded in the percentages.
*** Excludes persons originating from countries with generalised epidemics (4422 in total).

2000 and 2007, the annual rate of newly reported cases of HIV per million population has increased from 39 to 75 per million (90% increase) among the 44 countries that have consistently reported.

HIV case reports in the EU/EFTA

In 28 of the 30 EU/EFTA countries, 26,279 cases of HIV infection (64 per million) were reported in 2007 (Table 2), with the highest rates reported in Estonia (472 per million), Portugal (217 per million) and Latvia (149 per million). The predominant mode of transmission is sexual contact between men (39%), followed by heterosexual contact (29%), when persons originating from countries with generalised epidemics are excluded. Injecting drug use accounted for 9% of newly reported infections. Among the countries that have consistently reported, the rate has increased from 44 per million in 2000 to 58 per million in 2007. Rates of reported HIV infection have doubled in Bulgaria, Czech Republic, Hungary, the Netherlands, Slovakia, Slovenia, Sweden and the United Kingdom.

The number of HIV reports among men who have sex with men (MSM) has increased by 39% between 2003 and 2007 (Figure 1). The number of heterosexually acquired cases has remained fairly stable at around 6,000 cases (although higher numbers were reported in 2004-2006). Further, the number of cases originating from countries with generalised epidemics amongst heterosexually acquired cases varied between 5,000 in 2005 and 4,400 in 2007. The number of HIV reports among injecting drug users (IDUs) has declined by 30% between 2003 and 2007.

HIV case reports by geographical area

The HIV epidemics across the three geographical areas show remarkable differences (Figure 2).

The data suggest that the HIV epidemic in the western part of the WHO European Region is characterised by a continuing increase in sexual transmission of HIV infection. The distribution of transmission modes largely mirrors that described for the EU/EFTA countries. In 2007, 24,202 new cases of HIV infec¬tion (77/million) were reported from 20 countries (Table 1).

The HIV epidemic in the central part of the WHO European Region remains at low and stable levels (1,897 cases; 10 per million), although there is evidence of increasing sexual (both heterosexual and homosexual) transmission in many countries (Table 1). Heterosexual transmission accounted for 53% of all reported cases, followed by 30% cases reported among MSM and 13% cases among IDUs, data on transmission mode were missing for 33% of cases.

In the eastern part of the WHO European Region, in 2007, 14 countries reported 22,793 new HIV cases (165 per million), of which 58% were from Ukraine. The predominant mode of trans¬mission in this region is through IDUs, accounting for 57% of the reported cases. Between 2000 and 2007, the rate of newly reported HIV infections has in¬creased from 54 per million to 160 per million. However, the numbers in this region are greatly underestimated as no data were reported from the Russian Federation.

AIDS diagnoses

In 2007, 5,244 AIDS cases were reported as being diagnosed in 48 of the 53 countries (9 per million) in the WHO European Region (no data from Italy, Kazakhstan, Monaco, Russian Federation and Ukraine). Due to incomplete reporting and no adjustment for reporting delays the total number of AIDS cases is underestimated.

Trends in AIDS diagnoses per million population (Figure 3) have continued to decrease in the WHO European Region overall, from 16 per million in 2000 to 9 per million in 2007, mainly due to decrease in western and central regions probably due to a combination of reporting delay and the effect of highly active antiretroviral therapy (HAART) [2]. However, during the same period, the rate increased in 21 (mainly eastern) countries, with the largest increases in Belarus and the Republic of Moldova.

Discussion and conclusion

HIV infection remains of major public health importance in Europe with a continued increase in the number of HIV cases reported [1,3]. In contrast, the number of AIDS cases diagnosed (not adjusted for reporting delays) has continued to decline, except in the eastern part of the WHO European Region. The data suggest evidence of increased transmission of HIV in many countries. However, the predominant transmission group varies by country and geographical area and the data illustrate the wide diversity in the epidemiology of HIV in Europe.

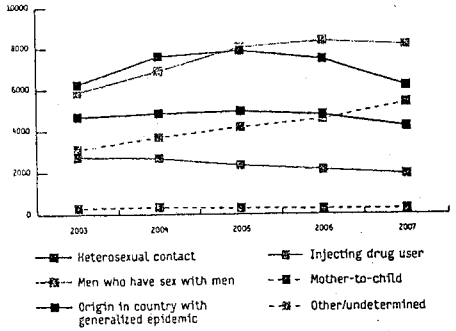
In 2007, in the EU/EFTA countries, also reflecting the western part of the WHO European Region, the highest proportion of HIV cases was reported among MSM. National prevention programmes aimed at reducing HIV transmission within Europe should have a strong focus on MSM [4]. Migrant populations should also be targeted in national prevention programmes and access to treatment and care services should be ensured. Although there seems to be a decline in the number of new diagnoses among IDUs, this is still the predominant transmission group in the Baltic States. In the central part of the WHO European Region, levels of HIV remain low and stable, al¬though there is evidence of increasing sexual transmission in many countries. In the eastern part, the number of HIV cases has increased substantially, mainly driven by an increase in cases acquired through IDU but also by an increase in heterosexually-acquired cases. Interventions to control HIV among IDUs should be the cornerstone of HIV prevention strategies in the eastern part but measures should also be strengthened to prevent heterosexual transmission, especially targeted at those with high-risk partners.

In interpreting the presented data, it should be taken into account that data are incomplete due to non-reporting from a few large countries. Therefore the findings and conclusions are limited to the surveillance data reported by these 49 countries. Had all data from all countries been available, the total number of reported HIV infections could have doubled to almost 100,000 cases in 2007.

Surveillance of HIV/AIDS is essential to monitor the epidemic and evaluate the public health response to control the transmission of infections. Countries in Europe need to ensure that surveillance data is of high quality by implementing case-based reporting systems for HIV and AIDS cases and ensuring its completeness, especially regarding the probable mode of transmission. Achieving full coverage of reporting from all countries in Europe is of utmost importance.

FIGURE 1

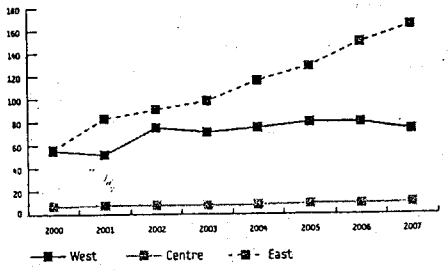
Number of reported HIV infections by transmission mode, origin and year of notification, EU/EFTA, 2003–2007



Data were not available for: Austria, Estonia (except for IDU), Italy, and Malta.

FIGURE 2

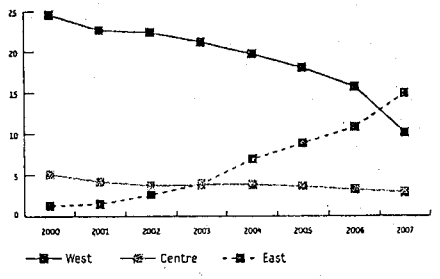
HIV cases per million population in geographic areas of the WHO European Region (West, Centre, East) by year of notification, 2000-2007



Data not included from: West: Andorra, Austria, France, Italy, Malta, Monaco, Spain; Centre: Serbia; East: Russian Federation.

FIGURE 3

Number of diagnosed AIDS cases per million population in the geographic areas of WHO European Region (West, Centre, East) by year of diagnosis, 2000-2007



Data not included from: West: Andorra, Italy, Monaco; East: Kazakhstan, Russian Federation, Ukraine

*The WHO European Region comprises:

The West, 23 countries: Andorra, Austria (EU), Belgium (EU), Denmark (EU), Finland (EU), France (EU), Germany (EU), Greece (EU), Iceland (EFTA), Ireland (EU), Israel, Italy (EU), Luxembourg (EU), Malta (EU), Monaco, the Netherlands (EU), Norway (EFTA), Portugal (EU), San Marino, Spain (EU), Sweden (EU), Switzerland (EFTA), United Kingdom (EU).

The Centre, 15 countries: Albania, Bosnia and Herzegovina, Bulgaria (EU), Croatia, Cyprus (EU), Czech Republic (EU), Hungary (EU), the Former Yugoslav Republic of Macedonia, Montenegro, Poland (EU), Romania (EU), Serbia, Slovakia (EU), Slovenia (EU), Turkey.

The East, 15 countries: Armenia, Azerbaijan, Belarus, Estonia (EU), Georgia, Kazakhstan, Kyrgyzstan, Latvia (EU), Lithuania (EU), Republic of Moldova, Russian Federation, Tajikistan, Turkmenistan, Ukraine, Uzbekistan.

Acknowledgements

We would like to thank all participating countries and national institutions of the European network for HIV/AIDS surveillance for their important contributions.

References

1. European Centre for Disease Prevention and Control / WHO Regional Office for Europe: HIV/AIDS Surveillance in Europe 2007. Stockholm: European Centre for Disease Prevention and Control; 2008. Available from: http://ecdc.europa.eu/en/files/pdf/Publications/20081201_Annual_HIV_Report.pdf
2. Sterne JAC, Hernán MA, Ledergerber B, Tilling K, Weber R, Sendi P, et al. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. Lancet 2005;366(9483):378–84.
3. EuroHIV. HIV/AIDS Surveillance in Europe. End-Year report 2006. Saint-Maurice: Institut de veille sanitaire, 2007. No. 75.
4. Likatavicius G, Klavs I, Devaux I, Alix J, Nardone A. An increase in newly diagnosed HIV cases reported among men who have sex with men in Europe, 2000-6: implications for a European public health strategy. Sex Transm Infect. 2008;84(6):499-505.

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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
				2008. 11. 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	Stramer S L, Foster G, Townsend R, Krysztof D, Notari E, Trouern-trend J, Brodsky J, Lenes B, Nguyen M, Proctor M, Bet A, Leiby D, Rouault C, Dodd R. AABB Annual Meeting and TXPO 2008; 2008 Oct 4-7; Montreal.	公表国 米国	
販売名(企業名)	新鮮凍結血漿「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」(日本赤十字社)					

研究報告の概要

○米国における供血者の *Trypanosoma Cruzi* 抗体スクリーニング：米国赤十字の1年間の経験

背景：*Trypanosoma Cruzi* (*T. cruzi*)により発症するシャーガス病は、ラテンアメリカ諸国の大半で流行しており、米国では2007年から供血者に対するスクリーニングを開始した。

方法：*T. cruzi* ELISA(Ortho社)を用いたスクリーニングで繰り返し陽性(RR)となった検体および最初の検査で10% negative gray zoneとなった検体について、RIPA(Quest社)を用いて再検査した。また、陽性供血者に対してリスク質問票に回答するよう依頼した。

結果：2007年1月29日～2008年1月28日までのARC供血者のRR率は0.009%(586/6,549,933; 1:11,117)であった。586例中129例(22%)が確定陽性で、うち2例は10% negative gray zoneであった。最も陽性率が高い地域はフロリダ南部で、RIPA(+)供血者が68名特定された(1:3,600)。RIPA(+)の供血者(75名)はRIPA(−)の供血者(169名)と比較して、既知のリスク因子を有する可能性が12～225倍高かった。米国内で生まれたRIPA(+)供血者18名はリスク因子が特定されなかったが、残りのRIPA(+)供血者は12の流行国とリンクされた。RIPA(+)供血者56名由来の輸血済268製剤から155名の受血者が追跡され、65名の受血者(血小板受血者7名を含む)から採取された68件の追跡検体の検査結果からは、輸血感染の可能性は示されなかった。

結論：供血者の有病率は1/30,000で、感染供血者のほとんどに明確なリスク因子があった。感染供血者では寄生虫血症が示される場合があったが、検査を実施した65名の受血者のうち、明白な感染症例はなかった。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿「日赤」
新鮮凍結血漿-LR「日赤」

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

米国赤十字で2007年から開始された供血者に対する *T. cruzi* スクリーニングの結果、陽性率は1/30,000であったが、受血者には明白な感染症例はなかったとの報告である。

今後の対応

日本赤十字社は、輸血感染症対策として献血時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、シャーガス病の既往がある場合には献血不適としている。日本在住の中南米出身献血者については、厚生労働科学研究「献血血の安全性確保と安定供給のための新興感染症等に対する検査スクリーニング法等の開発と献血制限に関する研究」班と共同して検討する予定である。今後も引き続き情報の収集に努める。

reported only a single episode of MSM activity; by contrast, 42% reported exposure that lasted 2 years or more. Of 1,652 whose date of last exposure was recorded, 64.6% had MSM contact within the last 1-year period, and 84% within the prior 5 years. Those donors reporting a single MSM exposure were 2-1/2 times more likely to have reported their last exposure more than 5 years ago compared to donors reporting multiple incidents (32% vs. 13%). One in seven blood donors with a single MSM exposure reported that the exposure was within the last 3 months. **Conclusions:** The epidemiology of HIV in the United States shows a strong association between MSM activity and risk for HIV infection, justifying the exclusion from blood donation of men with ongoing MSM exposures. Harmonizing the deferral period for MSM exposure to that of other TTVI risks (1-year) or to that of other tissue donations (5 years) is likely to lead to only modest increases in the proportion of MSM-deferred donors who regain eligibility; the deferral period for MSM exposure to that of other TTVI risks (1-year) or to that of other tissue donations (5 years) is likely to lead to only modest increases in the proportion of MSM-deferred donors who regain eligibility; barring significant changes in the presenting donor population. From our population, only a small minority appear to present a risk profile epidemiologically distinct from those MSM deferrals with ongoing or recent exposures.

Disclosure of Conflict of Interest

Bryan Spencer, Jorge A. Rios, Richard Cable: Nothing to Disclose

P4-020A

Selection, Expansion and Functional Restoration of NS3-Specific CD4 T Cells from HCV-Infected Patients

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Introduction: Tolerance of T cells to non-structural antigens of HCV virus may explain persistent infection. We hypothesize that this state can be reversed ex vivo in absence of the anergy-inducing antigens and in presence of homeostatic cytokines. **Aims:** To isolate HCV-specific CD4 T cells from chronic patients according to antigen-induced surface expression of CD154 and determine the degree of functional restoration after ex vivo expansion in absence of antigenic stimulus. **Patients and methods:** Lymphocytes from peripheral blood were obtained from 5 patients with persistent infection and 5 patients with spontaneous resolved infection. After stimulation with NS3-helicase recombinant protein, the CD4+/CD154+ lymphocytes were selected and expanded in complete medium supplemented with IL-7/IL-15 during 3 weeks. Cellular phenotype was determined by flow cytometry (CD4/CD45RO/CCR7/CD28/CL). HCV-specific cellular immune response was measured by IFN-gamma spot forming units (SFU-ELISPOT assay) and soluble cytokine production of IFN-gamma, IL-4 and IL-10 (CBA). Proliferation was determinate by CFSE. **Results:** In the group of chronic patients the mean yield of sorted CD4+/CD154+ was 0.076% while in the recovered patients was 0.81% of sorted CD4+ cells. After 21 days of culture, sorted patients had expanded 3 logarithms and, after ex vivo expansion, 96-98% of cells had effected memory phenotype. In patients with persistent infection, mean IFN-gamma production for expanded NS3-helicase specific cells was 785 SFU/10E5 CD4+, that is, 42 times higher than basal production (19 SFU/10E5 CD4+) by only three-fold increase in patients with resolved infection (752 vs. 252 IFN-gamma SFU/10E5 CD4+). CBA assay confirmed production of IFN-gamma (943.6 pg/ml for NS3-specific T cells vs. 7.65 pg/ml for basal CD4+) in individuals with persistent infection, and mean production of IL-10 and IL-4 for specific T cells was 327.7 pg/ml and 92.8 pg/ml, respectively and higher than basal CD4+ production (4.3 and 6.75 pg/ml). Proliferation capacity was not different between CD4+ specific and basal CD4 T cells. The expanded cells did not respond or proliferate when cultured with HCV core protein and therefore specificity of selection and expansion to NS3-helicase protein was confirmed. **Conclusions:** We were able to select NS3-specific T CD4 cells in patients with persistent infection and to expand them ex vivo with homeostatic interleukins. In absence of the anergy-inducing antigens, the capacity to produce IFN-gamma is restored thus confirming the presence of anergic T cells in chronic patients. This finding also raises the possibility of designing strategies for adoptive immunotherapy in non responders to standard antiviral therapy or difficult to treat subjects, such as liver transplant patients.

Disclosure of Conflict of Interest

Marta Bes, Silvia Sauleda: Nothing to Disclose
Lluis Puig, Josep Quer, Juan Esteban, Maria Cubero: Not Specified

P5-020A

Trypanosoma Cruzi Antibody Screening In US Blood Donors: One Year Experience at the American Red Cross

S L Stramer[1] (Dodd@usa.redcross.org), G Foster[2], R Townsend[3], D Krysztof[4], E Notari[4], J Trouern-Trend[4], J Brodsky[4], B Lenes[4], M Nguyen[4], M Proctor[4], A Bet[4], D Leiby[4], C Rouault[4], R Dodd[4]. [1]American Red Cross Biomedical Services, Gaithersburg, MD; [2]American Red Cross – Scientific Support Office, MD; [3]American Red Cross, Rockville, MD; [4]American Red Cross Blood Services, Holland Lab, Rockville, MD; [4]Quality Analytics, Inc, Glenview, IL; [4]Community Blood Centers of South Florida, Lauderhill, FL.

Background: *T. cruzi*, the blood-borne parasite that causes Chagas disease, is endemic in most of Latin America. The majority of infected individuals acquire infection outside the US; some autochthonous cases have been reported. Blood donor screening for most of the US was initiated during 2007 (75-80% of the US blood supply); we report the ARC experience. **Methods:** All donations collected on or after 1/29/07 were screened using the Ortho *T. cruzi* ELISA. All repeat reactive (RR) and initially reactive samples repeating with one or both retests in a 10% negative gray zone were tested by RIPA (Quest); in addition, all reactive donors were invited to participate in follow up (f/u) testing and the completion of a donor risk questionnaire. F/u samples from RIPA (+) donors at index were retested simultaneously by ELISA, RIPA (in-house), PCR (in-house) and Immunoblot (IHC). In-house) whereas f/u samples from RIPA (−) donors were tested by ELISA and the other tests only if ELISA RR. Recipients of prior components from RIPA (+) donors were traced and consenting recipients tested. **Results:** Prevalence by donor/donation for ARC donors is shown in the table for 1/29/07-1/28/08. The RR rate (586/6,549,933) was 0.009% or 1:11,177; 129/586 (22%) confirmed (+) of which 2 were in the 10% gray zone. An additional 68 RIPA (+) donor from South Florida were identified by the ARC; this was the highest prevalence area of the US (1:3600). An ELISA S/CO of 3.8 or greater had a 95% likelihood of being RIPA (+). RIPA (+) donors (75) as compared to RIPA (−) donors (169), who provided risk info, were 12-225 times more likely to have a known risk factor; nevertheless, 18 (24%) RIPA (+) donors born in the US had no identified risk factors. ELISA/RIPA false (+) must be considered as a possibility for some of these potential autochthonous cases. The remaining RIPA (+) donors were linked to 12 endemic countries. 268 transfused components from 56 RIPA (+) donors were traced to 155 recipients; 68 f/u samples were collected from 65 recipients including only 7 who received platelets. Of the 68 samples tested, 7 had isolated reactive test results: none ELISA RR but either RIPA or PCR (+) plus 1 ELISA/RIPA (+) recipient born in an endemic country. No recipient could be demonstrated to have been infected by transfusion. In contrast, PCR and IHC found that 3-15% of RIPA (+) donors may have circulating parasites. **Conclusions:** Donor prevalence is 1:30,000; most infected donors have established risk factors however 24% did not. Although parasitemia could be demonstrated in infected donors, there were no unequivocal cases of infection among the 65 recipients tested.

Donation Type	No. Screened	No. RIPA Pos	Prevalence
Total donors	3,872,957	129	1:30,023
Allogeneic	3,542,989	125	1:28,344
Autologous	41,618	3	1:13,873
Pheresis	288,250	1	1:288,350
Total donations	6,549,933	129	1:50,775
Allogeneic	5,789,336	125	1:46,356
Autologous	59,520	3	1:19,840
Pheresis	691,077	1	1:691,077

Disclosure of Conflict of Interest

Susan L. Stramer, Gregory Foster, Rebecca Townsend, David Krysztof, Edward Notari, Jonathan Trouern-Trend, Jaye Brodsky, Bruce Lenes, Megan Nguyen, Melanie Proctor, Anne Bet, Charles Rouault, Roger Dodd: Nothing to Disclose
David Leiby: Ortho Clinical Diagnostics – Consulting or Board of Director Fees

別紙様式第２－１

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日	第一報入手日 2009年2月2日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称	別紙のとおり		研究報告の公表状況	ProMED-mail, 20090129.0400	公表国 スウェーデン	
販売名(企業名)	別紙のとおり					

研究報告の概要

問題点：ユンガンウイルスがヒトにおける子宮内胎児死亡に関連していることが示唆された。

ユンガンウイルス（バレコウイルス属、ピコルナウイルス科）は、実験用マウスにおいて胎児の死亡や奇形を起こすことが知られている。研究データ及び疫学的データからこのウイルスがヒトにおける子宮内胎児死亡に関連していることが示唆された。
このウイルスは、スウェーデン中央部のユンガン川の近くに生息するハタネズミ（野生齧歯類宿主の一種）から分離された。ユンガンウイルスは、米国の野生の齧歯類においても確認されている。また、同様に齧歯類を主な宿主とするカルディオウイルス属やピコルナウイルス属と関係があるとされている。
実験用マウスでの研究では、妊娠中にユンガンウイルスに感染し、ストレスにさらされた母親の半数以上は周産期に死産した。その中には、水頭症や無脳症といった中枢神経系の奇形が認められた子マウスもいた。
スウェーデンでの最近の研究で、子宮内胎児死亡があったヒトの胎盤及び組織において、免疫組織化学的手法及びリアルタイム PCR によってユンガンウイルスが検出された。コントロールとした正常妊婦の胎盤からはウイルスは検出されなかった。子宮内胎児死亡の発生と周期的な齧歯類の密度との間に興味ある関連が認められている。米国の子宮内胎児死亡例においても、ユンガンウイルスが確認されている。

使用上の注意記載状況・その他参考事項等

記載なし

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

MedDRA/J ver.11.1

別紙

一般的名称	①人血清アルブミン、②人血清アルブミン、③人血清アルブミン*、④人免役グロブリン、⑤乾燥ペプシン処理人免疫グロブリン、⑥乾燥スルホ化人免疫グロブリン、⑦乾燥スルホ化人免疫グロブリン*、⑧乾燥濃縮人活性化プロテインC、⑨乾燥濃縮人血液凝固第Ⅷ因子、⑩乾燥濃縮人血液凝固第Ⅸ因子、⑪乾燥抗破傷風人免疫グロブリン、⑫抗 HBs 人免疫グロブリン、⑬トロンビン、⑭フィブリノゲン加第ⅩⅢ因子、⑮乾燥濃縮人アンチトロンビンⅢ、⑯ヒスタミン加人免疫グロブリン製剤、⑰人血清アルブミン*、⑱人血清アルブミン*、⑲乾燥ペプシン処理人免役グロブリン*、⑳乾燥人血液凝固第Ⅸ因子複合体*、㉑乾燥濃縮人アンチトロンビンⅢ
販売名(企業名)	①献血アルブミン20“化血研”、②献血アルブミン25“化血研”、③人血清アルブミン“化血研”*、④“化血研”ガンマーグロブリン、⑤献血静注グロブリン“化血研”、⑥献血ベニロンーⅠ、⑦ベニロン*、⑧注射用アナクトC2,500単位、⑨コンファクトF、⑩ノバクトM、⑪テタノセーラ、⑫ヘパトセーラ、⑬トロンビン“化血研”、⑭ボルヒール、⑮アンスロビンP、⑯ヒスタグロビン、⑰アルブミン20%化血研*、⑱アルブミン5%化血研*、⑲静注グロブリン*、⑳ノバクトF*、㉑アンスロビンP1500注射用
報告企業の意見	ユンガンウイルスが属するバレコウイルス属は、9つあるピコルナウイルス科の属の1つで、他にヒトバレコウイルスが属している。ピコルナウイルス科ウイルスは、一本のプラス鎖 RNA を核酸として持ち、直径22～30nm でエンベロープを持たない。ヒトバレコウイルスは呼吸器官と消化器官で増殖する。幼児を中心として感染するが、ほとんどが無症候性と見られている。呼吸器感染や下痢症に加え、中枢神経系の感染症も報告されている。ユンガンウイルスは野ネズミから分離されているが、情報は少ない。 本研究報告はユンガンウイルスの垂直感染に関する報告であり、ヒト血液を原材料とする本剤に直ちに影響があるものではない。仮に、ウイルスが原材料に混入していたとしても、本剤の製造工程には冷エタノール分画工程、ウイルス除去膜ろ過工程あるいは加熱工程等の原理の異なるウイルス除去及び不活化工程が存在しているので、ウイルスクリアランスが期待される。各製造工程のウイルス除去・不活化効果は、「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）」に従い、ウシウイルス性下痢ウイルス（BVDV）、仮性狂犬病ウイルス（PRV）、ブタパルボウイルス（PPV）、A型肝炎ウイルス（HAV）または脳心筋炎ウイルス（EMCV）をモデルウイルスとして、ウイルスプロセスバリデーションを実施し、評価を行っている。今回報告したユンガンウイルスは、エンベロープの有無、核酸の種類等からモデルウイルスとしては HAV または EMCV が該当すると考えられるが、上記バリデーションの結果から、本剤の製造工程がこれらのウイルスの除去・不活化効果を有することを確認している。また、これまでに本剤によるユンガンウイルスの感染の報告例は無い。 以上の点から、本剤はユンガンウイルス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

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LJUNGAN VIRUS, INTRAUTERINE FETAL DEATH - SWEDEN
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A ProMED-mail post
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International Society for Infectious Diseases
<http://www.isid.org>

Date: Wed 28 Jan 2009
From: Bo Niklasson <bo.niklasson@medcellbiol.uu.se>

Ljungan virus associated with intrauterine fetal death in humans (Sweden)

Ljungan virus (genus _Parechovirus_, family _Picornaviridae_) has been shown to cause fetal death and malformations in laboratory mice. The virus now has been associated with intrauterine fetal deaths in humans based on both laboratory and epidemiological evidence. This virus was isolated from one of its wild rodent reservoirs, the bank vole (_Myodes glareolus_), near the Ljungan River in central Sweden (1, 2). Ljungan virus also has been identified in wild rodents in the USA (3, 4). Ljungan virus is related to cardioviruses, picornaviruses which also have rodents as their main reservoir hosts.

Cardioviruses and their role as potential human pathogens recently were discussed on ProMED — see ProMED archive refs. below.

Studies with laboratory mice showed that more than half of the dams infected with Ljungan virus during pregnancy and then exposed to stress gave birth to pups that died during the perinatal period (5). Malformations of the central nervous system, including hydrocephaly [water on the brain] and anencephaly [lack of brain], were seen in some of these offspring.

Recent studies in Sweden found Ljungan virus in placenta and tissue from human cases of intrauterine fetal death (IUFD) using both immunohistochemistry and real time RT-PCR (6, 7). Placentas from normal pregnancies have been used as controls and found to be Ljungan virus-negative. An intriguing association between the incidence of IUFD and cyclic rodent density has been observed. Ljungan virus also was found in one IUFD case in the United States.

References:

1. Niklasson B, Kinnunen L, Hornfeldt B, Horling J, Benemar C, Hedlund KO, et al. A new picornavirus isolated from bank voles (Clethrionomys glareolus). Virology 1999 Mar 1;255(1):86-93.
2. Niklasson B, Nyholm E, Feinstein RE, Samsioe A, Hornfeldt B. Diabetes and myocarditis in voles and lemmings at cyclic peak densities--induced by Ljungan virus? Oecologia 2006 Nov;150(1):1-7.
3. Main AJ, Shope RE, Wallis RC. Characterization of Whitney's Clethrionomys gapperi virus isolates from Massachusetts. J Wildl Dis 1976 Apr;12(2):154-64.
4. Whitney E, Roz AP, Rayner GA. Two viruses isolated from rodents (Clethrionomys gapperi and Microtus pennsylvanicus) trapped in St. Lawrence County, New York. J Wildl Dis 1970 Jan;6(1):48-55.
5. Samsioe A, Feinstein R, Saade G, Sjoholm A, Hornfeldt B, Fundele R, et al. Intrauterine death, fetal malformation, and delayed pregnancy in Ljungan virus-infected mice. Birth Defects Res B Dev Reprod Toxicol 2006 Aug;77(4):251-6.
6. Samsioe A, Papadogiannakis N, Hultman T, Sjoholm A, Klitz W, Niklasson B. Ljungan virus present in intrauterine fetal death diagnosed by both immunohistochemistry and PCR. Birth Defects Res A Clin Mol Teratol 2009 Jan 9.
7. Niklasson B, Samsioe A, Papadogiannakis N, Kawecki A, Hornfeldt B, Saade GR, et al. Association of zoonotic Ljungan virus with intrauterine fetal deaths. Birth Defects Res A Clin Mol Teratol 2007 Jun;79(6):488-93.

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[The genus _Parechovirus_ is one of the 9 genera comprising the family _Picornaviridae_ and includes 2 species, _Human parechovirus_ and _Ljungan virus_. According to Virus Taxonomy (The Eighth Report of the International Committee on Taxonomy of Viruses), the human parechoviruses replicate in the respiratory and gastrointestinal tracts. Infection is particularly prevalent in young children but is probably mostly asymptomatic. In addition to respiratory infections and diarrhea, infections of the central nervous system have been reported occasionally. The cytopathology may be unusual in including changes in granularity and chromatin distribution in the nucleus when viewed by the electron microscope. Isolates of Ljungan virus appear to infect predominantly rodents. The predicted protein sequences of parechoviruses are highly divergent, with no protein having a greater than 30 percent level of identity compared with corresponding proteins of any other member of the family _Picornaviridae_. The American and Swedish isolates of Ljungan virus show some divergence.

*****Professor Niklasson has indicated that he is seeking collaborators to pursue these observations in greater depth. Anyone with an interest or involvement in the field should contact Professor Niklasson directly.*****
- Mod.CP]

[see also:
2008

Cardioviruses, human (02): global presence 20080911.2845
Cardioviruses, human: 1st report 20080910.2824
1998

Myocarditis, rodent vector - Sweden 19980720.1371]
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