unknown, but such studies could provide information on the zoonotic potential of these porcine NoVs.

The RdRp-capsid junction region of NoVs contains a highly conserved 18-nt motif in genomic and subgenomic RNA that is believed to be a transcription start signal (1,20). All 18 nt were identical within each genogroup except for the Hu/GII/J23, Po/GII/QW101, and Po/GII/QW125 strains (Figure 3B, sequence alignments on other GI and GIII strains are not shown). This finding suggests that homologous recombination may occur within this motif between NoVs of different genotypes within the same genogroup. Recombinant human GII NoVs have been reported previously (20–24). To our knowledge, this study is the first identification of a potential recombinant between pig NoVs. At present, NoV recombinants have been detected exclusively between viruses within the same genogroup and within the same host species, but few animal NoVs have been sequenced (RdRp and capsid) for comparative analysis, especially those from animals in developing countries, where humans and animals may be in close contact.

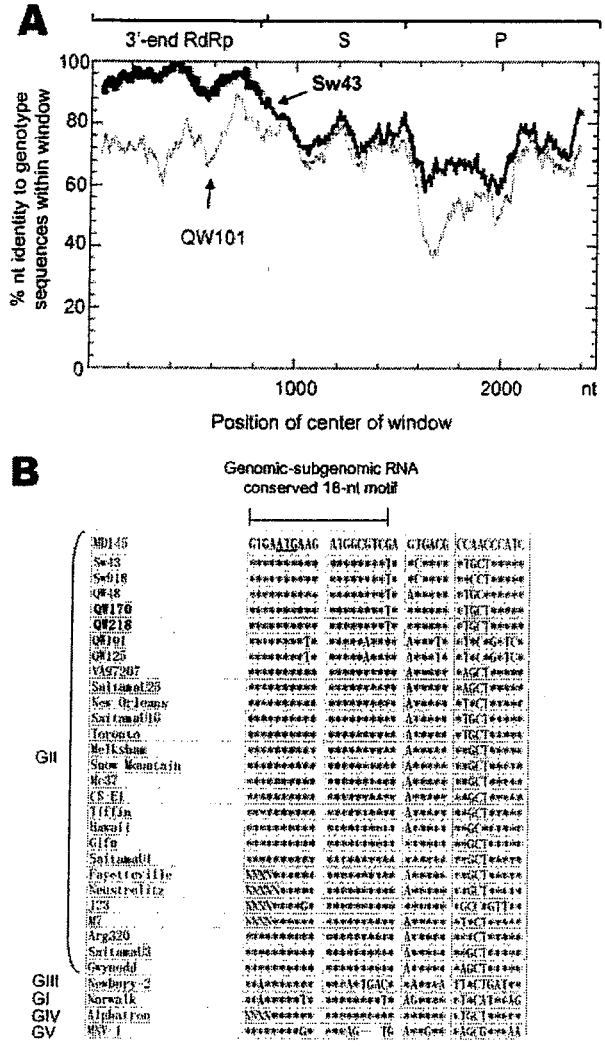

Figure 3. Identification of a potential recombination event between QW170 and Sw43 strains. A) Recombination Identification Program analysis of QW170 strain. At each position of the window, the query sequence (QW170) was compared to each of the background genotype representatives (GII-11/Sw43 and GII-18/QW101). When the query sequence is similar to the background sequences, the homologous regions are indicated as thick lines on the plot. Analysis parameters were window size of 100 and significance of 90%. The nucleotide positions of the 3'-end RNA-dependent RNA polymerase (RdRp) and the shell (S) and protruding (P) domains of the capsid protein are indicated. B) Sequence alignments of the RdRp-capsid junction region of noroviruses (NoVs). The genomic and subgenomic conserved 18-nucleotide (nt) motif is indicated by a horizontal line with 2 vertical bars. Asterisks indicate the identical residues to the sequence of the first line. Dashes represent gaps. The letter N indicates missing data on the residue. The start codon of open reading frame ORF 2 is underlined. Five NoV genogroups are indicated.

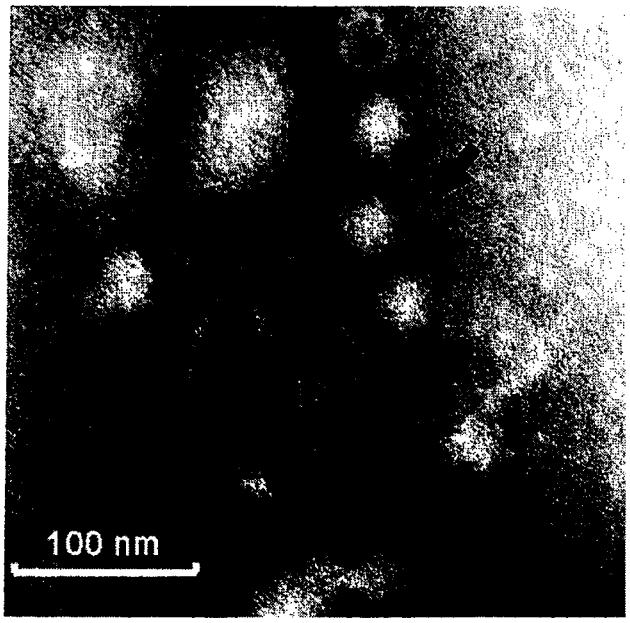

Figure 4. Immune electron micrograph of porcine noroviruses (NoVs). The diluted intestinal contents of a gnotobiotic pig euthanized on postinoculation day 5 to QW101-like porcine NoVs (QW144) were incubated with convalescent-phase serum LL616 from another gnotobiotic pig inoculated with QW101-like porcine NoVs (QW126) and visualized by negative staining with 3% phosphotungstic acid. The arrow indicates a small clump of NoV-like particles.

The QW101-like porcine NoVs replicated in gnotobiotic pigs with fecal shedding, documented by quantitative RT-PCR and IEM. No cell culture system or animal disease models are available for human NoVs, which impedes the study of their pathogenesis, replication strategies, host immune responses, and preventive approaches. The infection of pigs with porcine NoVs may provide a new infection or disease model to study NoV infections.

Table 4. Antigenic cross-reactivity between human GII NoV antigens (VLPs) and a pig convalescent-phase antiserum against porcine GII NoVs, as determined by ELISA*

Antiserum	ELISA antibody titer with each VLP antigen (genogroup-genotype)					
	Hawaii (GII-1)	Toronto (GII-3)	MD145 (GII-4)	HS66 (GII-4)	Florida (GII-6)	Desert Shield (GI-3)
HS66CS (positive control): human convalescent-phase antiserum to human HS66 (GII-4)	1:25,600	1:6,400	1:25,600	1:25,600	1:6,400	1:6,400
LL616: pig convalescent-phase antiserum to porcine QW126 (QW101-like, GII-18)†	1:100	1:800	1:400	1:400	1:400	1:10
LL368 (negative control): preinoculation serum‡	<1:10	<1:10	<1:10	<1:10	<1:10	<1:10
MM982 (negative control): preinoculation serum‡	<1:10	<1:10	<1:10	<1:10	<1:10	<1:10

*NoV, norovirus; VLP, viruslike particle; ELISA, enzyme-linked immunosorbent assay.
†The QW126 shared 99% and 100% amino acid identities to the QW101 strain (GII-18) for a 169-bp segment in the RNA-dependent RNA polymerase region and a 363-bp segment in the capsid region, respectively.
‡LL368 and MM982 were sera from 2 gnotobiotic pigs before inoculation with porcine NoVs.

In this study, 1-way antigenic cross-reactivity occurred between antiserum to QW101-like porcine NoVs and the capsid proteins of human NoVs, with highest cross-reactivity to GII-3, 4, and 6 NoVs. This finding coincides with the finding that the QW101 strain shares high amino acid identity with GII-3 (71%), GII-6 (71%), and GII-4 (63%) NoVs.

In summary, 3 genotypes of porcine NoVs were detected in US swine. One genotype (QW101-like, GII-18) was genetically and antigenically most closely related to human GII NoVs. Potential recombinant porcine NoV strains were identified. The QW101-like NoVs infected gnotobiotic pigs, and NoV particles were evident in intestinal contents. These results raise questions of whether pigs may be reservoirs for emergence of new human NoVs or if porcine/human GII recombinants could emerge.

Acknowledgments

We thank Kim Green and Steve Monroe for providing human NoV VLPs for ELISA, except for VLPs of GII-4/HS66/01/US, and Duping Zheng for assistance in recombination analysis.

This work was supported by grants from the National Institute of Allergy and Infectious Diseases, National Institutes of Health (Grant R01 AI 49742); National Research Initiative, US Department of Agriculture (CGP Grant 1999 02009); and the Ohio Agricultural Research and Development Center (OARDC), Ohio State University (Graduate Student Research Enhancement Grant project 2002-114).

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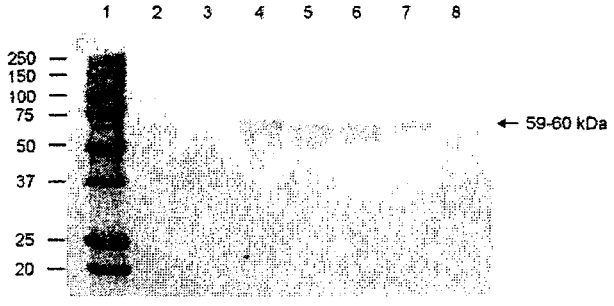

Figure 5. Antigenic cross-reactivity between human genogroup (G) II norovirus (NoV) capsid proteins and a pig convalescent-phase antiserum (LL616) against porcine QW101-like (GII-18) NoV was determined by Western blot. The CsCl-gradient purified viruslike particles (1,250 ng) were separated by sodium dodecyl sulfate 10% polyacrylamide gel electrophoresis, blotted onto nitrocellulose membranes, and tested with LL616. The sucrose-cushion (40%, wt/vol) purified Sf9 insect cell proteins acted as a negative control (lane 8). Lane 1, molecular weight marker (kDa); lanes 2–7, Hu/GI-3/Desert Shield, Hu/GII-1/Hawaii, Hu/GII-3/Toronto, Hu/GII-4/MD145, Hu/GII-4/HS66, and Hu/GII-6/Florida, respectively.

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別紙様式第2-1

No. 19

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	機構処理欄
				2006. 4. 26	該当なし	

一般的名称	人全血液	研究報告の公表状況		公表国
販売名(企業名)	人全血液CPD「日赤」(日本赤十字社) 照射人全血液CPD「日赤」(日本赤十字社)		H Cordel, I Quatresous, C Paquet, E Couturier. Eurosurveillance weekly release: 20 April 2006	フランス

研究報告の概要

○フランス本土におけるチクングンヤの輸入例 2005年4月～2006年2月

導入:2006年4月9日時点で、241,000のチクングンヤの症例がレユニオン島から、5,339例がマヨット島から報告されている。レユニオンから本土への渡航者は毎年30万人に上り、媒介蚊のヒトスジシマカがフランス及びイタリア北西部でも発見されているため、本土での流行が懸念される。

方法:チクングンヤの血清学検査を行っているフランス本土の検査施設のデータを分析した。患者と施設の郵便番号、患者の年齢、性別、検体採取の日付を分析に使用した。患者の渡航日と発症日は得られなかった。輸入例は以下のように定義された。

・チクングンヤIgM抗体陽性及び/あるいはPCR陽性及び/あるいはウイルス培養陽性

・患者がフランス本土在住か否かを問わず、本土で検体が採取された

結果:輸入例307例が検出された。平均年齢は47歳(7歳～81歳)で、男女比は0.8:1だった。2005年4月～7月の輸入例数は毎月平均20例で、コモロ諸島での流行およびレユニオンでの流行の最初のピークと一致している。8月から11月にかけて症例数は減少したが、12月、特に最終週には著しく多くなり、2006年2月には131例が検出された。この傾向は、同時期のレユニオンでの流行とよく似ている。患者のほとんどはフランス南東部およびパリ在住だった。フランス本土内での感染が2006年3月に1例発生した。海外で感染した患者を担当した看護師が、3日後にチクングンヤの症状を発症した。看護師はインド洋への渡航歴はなく、血液の暴露による感染が疑われた。

考察:輸入例の患者は、ほとんどがフランス南東部のプロヴァンス・アルプ・コートダジュール地方の住民である。この地方、特にマルセイユ市にはコモロ系移民のコミュニティがあり、メンバーはよくコモロに渡航している。チクングンヤ感染は無症候あるいは軽症のことが多いため、診察や検査を受けておらず、感染が確認されていない患者も多いと考えられる。輸入例に重篤なものはなかったが、治療のために本土に移送されたレユニオンの患者には一部重症となったものもあり、劇症肝炎(急性肝不全)のために肝臓移植が必要となった症例もあった。

使用上の注意記載状況・その他参考事項等

人全血液CPD「日赤」
照射人全血液CPD「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	今後の対応
フランス領レユニオン島においてチクングンヤウイルス感染症が大流行しており、フランス本土においても患者を担当した看護師がチクングンヤの症状を発症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問診時に海外渡航歴の有無を確認し、帰国後4週間は献血不適としている。今後も引き続き、新たなウイルス等による感染症の発生状況等に関する情報の収集に努める。

⑥

Imported cases of chikungunya in metropolitan France, April 2005 - February 2006

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Introduction

By 9 April 2006, 241 000 cases of chikungunya had been reported on the island of Reunion, and 5339 cases on the island of Mayotte. The islands of Mauritius, Seychelles, Madagascar, and Comoros are also affected. Imported cases have been reported from a number of European countries [1].

Each year, about 300 000 people travel to Reunion from metropolitan France (mainland France and Corsica), and therefore the risk of an outbreak in metropolitan France must be considered, especially since the vector, the *Aedes albopictus* mosquito, has been detected in metropolitan France and in northwest Italy, near the borders with France, Spain and Switzerland. Its role in transmission of the virus depends on vectorial competence (intrinsic to the mosquito) and vectorial capacity (dependent on the environment).

In addition to mosquito surveillance, the number of imported human cases must be reported as accurately as possible, in order to assess the risk of transmission within mainland Europe.

Methods

Recent infection is likely if chikungunya IgM antibodies are detected in the five days after symptom onset, but the presence of antibodies does not necessarily mean that the patient is viraemic. In metropolitan France, serology is carried out by two private laboratories and the two national reference laboratories, which also perform PCR and viral culture. Data from laboratories from April 2005 to the end of February 2006 have now been analysed. Variables used were patient and laboratory postcodes, patient age, patient sex, and date of the blood sample. Data on the patients' dates of travel and illness onset were not available from the laboratory database.

An imported case was defined as:
- detection of IgM antibodies against chikungunya virus and/or positive PCR, and/or positive viral culture,
- sampled in metropolitan France, whether or not the patient lives in metropolitan France.

Results

From 1 April 2005 to 28 February 2006, 307 imported cases of chikungunya were identified in France. The mean patient age was 47 years (range: 7-81 years), and the male-female sex ratio was 0.8:1.

Between April and July 2005, an average of 20 imported cases was observed each month. These cases correspond to the outbreak in Comoros (over 5000 cases), and to the first peak of the Reunion outbreak (during week 19 of 2005). Incidence then decreased between August and November. The number of cases greatly increased in December 2005, particularly in the final week of that month, and 131 imported cases were identified in February 2006. This trend is similar to the epidemic curve of the Reunion outbreak where weekly incidence greatly increased at the end of December 2005 (Figures 1 and 2). Most of the cases imported to France have been in patients living in southeast France and the Paris region (Figure 3).

Figure 1. Temporal evolution of imported chikungunya infections into metropolitan France, by date of blood sample, April 2005 - February 2006

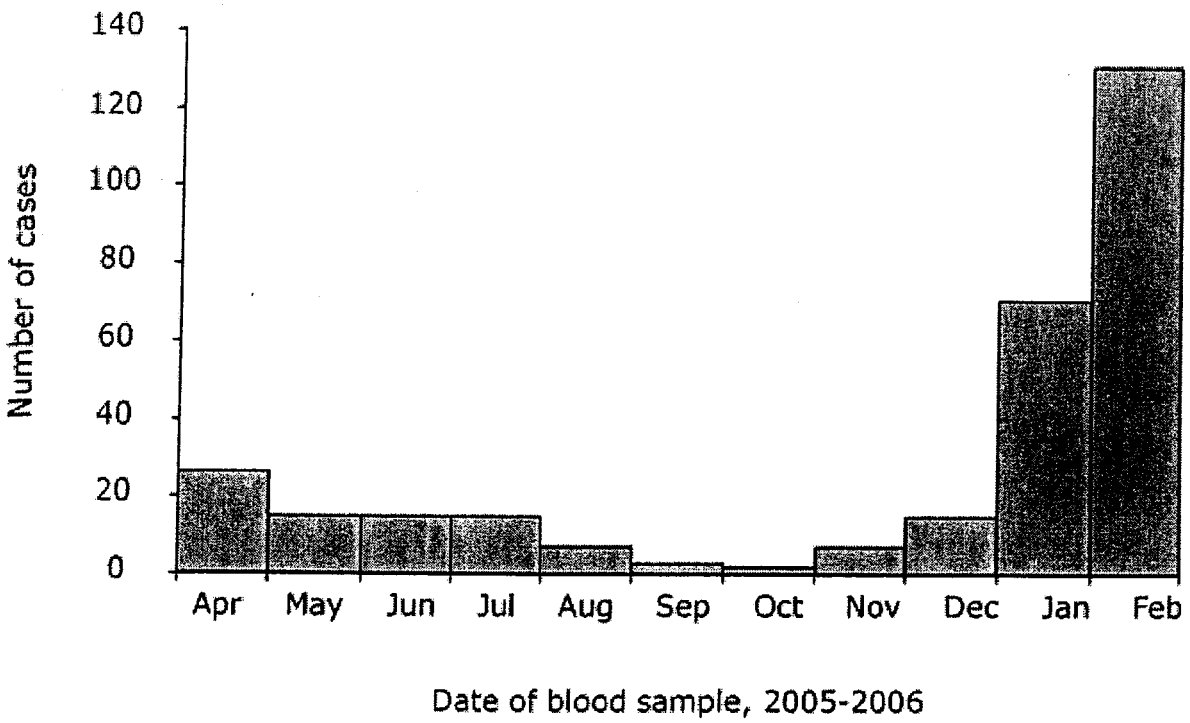


Figure 2. Chikungunya infections reported in Reunion, by date of illness onset, March 2005 – April 2006

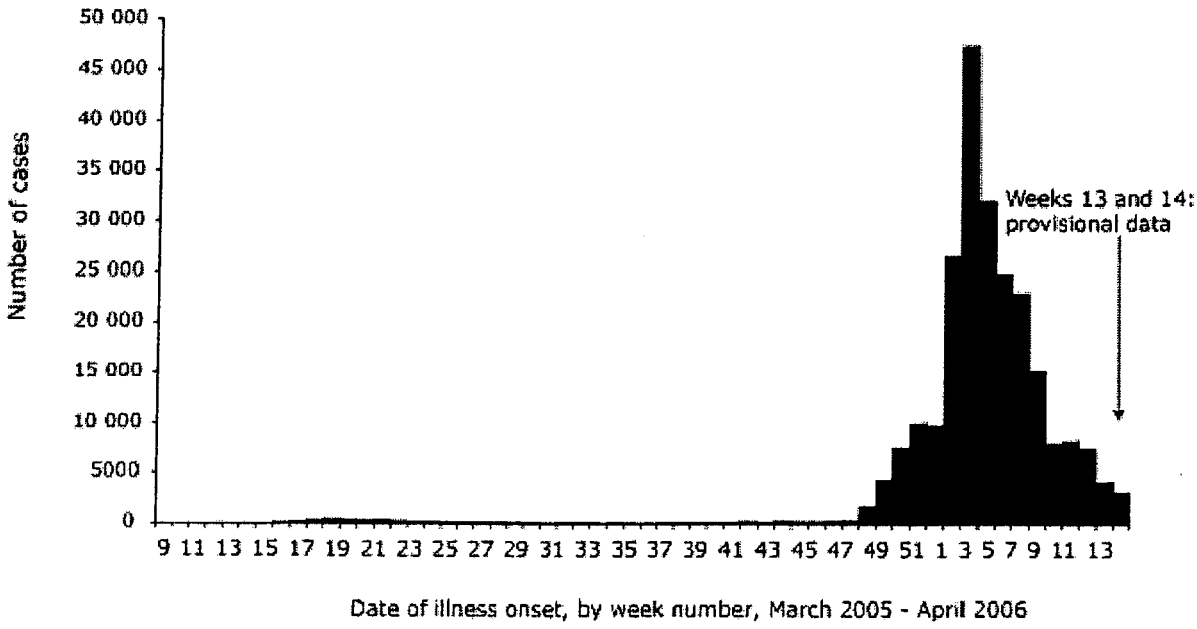
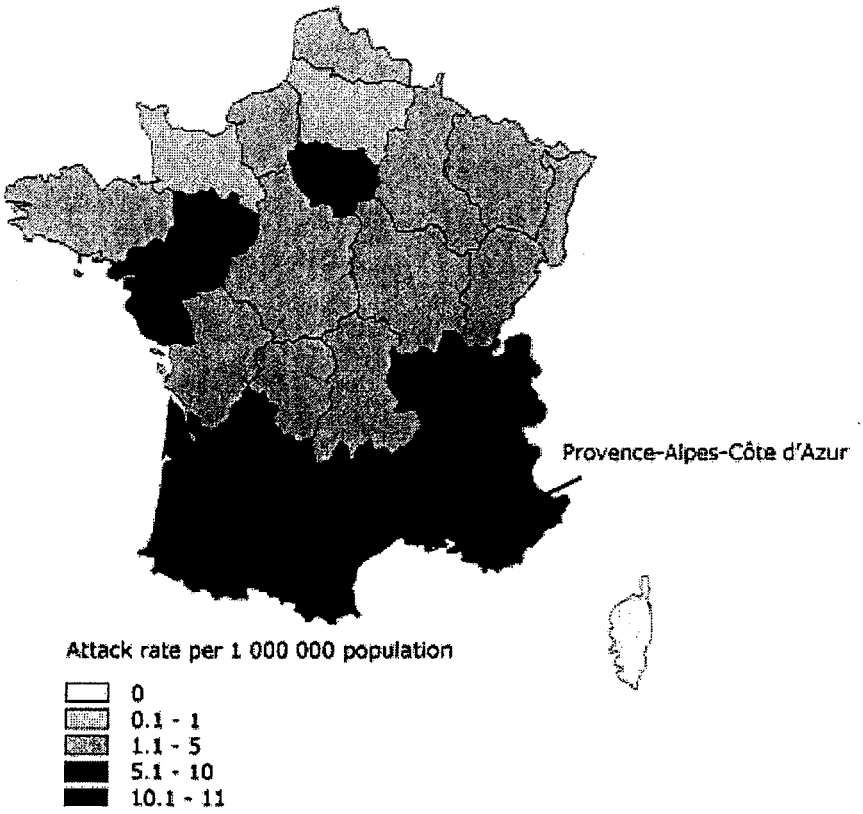


Figure 3. Attack rate per 1 000 000 population, by region, of imported chikungunya infections in metropolitan France, April 2005 – February 2006



An autochthonous case was reported in metropolitan France in March 2006. A nurse developed chikungunya fever (laboratory confirmed) three days after caring for a patient with an imported infection. The nurse had never travelled to the Indian Ocean, and investigation of this case has concluded that there was a probable blood exposure incident. Previous incidents involving transmission of chikungunya virus during laboratory procedures have been described [2,3,4].

Discussion

Most of the imported cases are in patients living in the Provence-Alpes-Côte d'Azur region in southeast France, which is home to a large Comorian community, particularly in the city of Marseille. Members of the community frequently travel to Comoros.

The imported cases reported here have been collated from laboratory data. Because chikungunya infections may be asymptomatic or have only mild clinical symptoms, it is likely that many or most of the people who have been ill with chikungunya in metropolitan France have not visited a doctor, and have not had their infections laboratory confirmed. Information on date of illness onset in relation to date of return to France would be a better indication of whether any of these patients had been viraemic when in metropolitan France, and thus present a risk for autochthonous transmission.

While none of the imported cases have been reported to be serious, some residents of Reunion who have become seriously ill with chikungunya on the island have been transferred to hospitals in metropolitan France for care. These patients include, for example, those who needed liver transplants to treat fulminant hepatitis (acute liver failure)

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医薬品
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				2006年4月13日	該当なし	

一般的名称	①ポリエチレングリコール処理抗破傷風人免疫グロブリン ②乾燥抗破傷風人免疫グロブリン	研究報告の公表状況	Journal of Medical Primatology 2005; 34(5-6 Iss. S1): 333	公表国 アメリカ	
販売名（企業名）	①テタノブリンーIH（ベネシス） ②テタノブリン（ベネシス）				

研究報告の概要

サル泡沫状ウイルス（Simian foamy virus ；以下SFV）は、ヒト以外の様々な霊長動物に蔓延している。感染の様式は十分に研究されていないが、感染率が高いのは唾液によって感染が起こるためである。ヒトへの種の壁を超えての感染が中央アフリカのハンターに見つかり、感染した動物との職業上の偶発的接触による感染の可能性がある。感染すると長期間ウイルスが持続する。自然宿主での感染に比較して、SFVのヒトからヒトへの感染の証拠はこれまでない。しかし、かつてAIDSが流行したことに鑑み、たとえ自然宿主に疾患が無かったとしても、レトロウイルスの人獣共通感染症を防ぐための警戒を欠かないようにしなければならない。加えて、ヒトへの感染によってウイルスがさらに順応することは断固避けなければならない。最近、ヒトでのSFV感染が報告されたことから、血液ドナーによるSFV感染の可能性について懸念されている。SFVが血液によって感染するか否かを調査するため我々は、SFV陰性のアカゲザルに対して、生物学的且つ遺伝的に異なるSFVに自然感染した2匹の大人のサルの血液を輸血した。レシピエントアニマルのウイルス感染並びに持続、抗体反応及び臨床的変化を観察した。接種1年後の結果は、SFVが全血によって感染する場合があることを示した。これらの事実は、血液ドナーについてのスクリーニングが必要なことを暗示させるものであった。

報告企業の意見	今後の対応
SFVが輸血により伝播する可能性を示唆する報告である。 血漿分画製剤からのSFV伝播の事例は報告されていない。また、万一原料血漿にSFVが混入したとしても、HIV-1をモデルウイルスとしたウイルスバリデーション試験成績から、本剤の製造工程において十分に不活化・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。

使用上の注意記載状況・その他参考事項等

代表としてテタノブリンーIH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血液については、HBs抗原、抗HCV抗体、抗HIV-1抗体、抗HIV-2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高力価の破傷風抗毒素を含有する血漿を原料として、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抗破傷風人免疫グロブリンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において60℃、10時間の液状加熱処理及び濾過膜処理（ナノフィルトレーション）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。

the island state of Singapore. Additionally, in 2003–2004, we screened 140 whole blood samples from newly quarantined *M. nemestrina* from Indonesia. Of the 37 Singaporean *M. fascicularis*, an overall seroprevalence of 86.5% (32/37) was found in five different troops and 70% (26/37) were found to contain detectable levels of SRV DNA. Among the 140 Indonesian *M. nemestrina*, the seroprevalence was 12% (17/140) and 8% (11/140) were PCR positive. Nine of the Indonesian *M. nemestrina* were identified as PCR positive when using primers targeting a conserved region of the envelope transmembrane region (gp20) but only two animals were positive when using primers to a more variable region of the envelope outer membrane (gp70). All Singapore PCR positive animals reacted to both gp20 and gp70 primers. Upon amplification and sequencing of the SRV envelope gene from the positive Indonesian *M. nemestrina*, all contained a new SRV isolate that is only 70–78% related to the other SRV serotypes one through six. The new SRV can be propagated on Raji cells but does not produce severe CPE. SRV-2 Western blots of the antibody positive Indonesian *M. nemestrina* appear weaker and less specific for the gp70 outer membrane glycoprotein than antibody positive *M. fascicularis* from Singapore. Phylogenetic analysis indicates that the Singaporean *M. fascicularis* SRV isolates are very closely related to other reported SRV-2 isolates (95–98% identity) while the new *M. nemestrina* Indonesian isolates are unique (70–80% identity) and may represent a new serotype. As we and others have not been able to isolate SRV-2 from other macaque species in wild settings, and SRV-2 is clearly prevalent in wild *M. fascicularis* and is considerably different than SRV in wild *M. nemestrina*, it is possible that *M. fascicularis* is the natural reservoir for SRV-2 and cross-species transmissions from *M. fascicularis* to other species may be responsible for the isolation of SRV-2 during outbreaks at primate centers.

ABSTRACT #56

CROSS-SPECIES TRANSMISSION OF SIMIAN FOAMY VIRUS FROM FERAL ASIAN MACAQUES TO HUMANS

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Feral populations of Asian macaques come in frequent contact with humans in settings ideal for transmission of simian retroviruses. Simian foamy viruses (SFV) are considered non-pathogenic infections of non-human primates (NHP) and recent studies have shown infrequent transmission to humans at primate research facilities, zoos, and in bushmeat hunters in Africa. No data have been published concerning cross-species infection of humans by Asian macaques. The significance of SFV infection in humans is unknown, however, studies to date have not identified any disease associated with long-term infection. In this study of 81 humans with frequent contact with macaques at Buddhist Temples in Bali, Indonesia, we identified one person with antibodies to SFV. Nested PCR assessment of whole blood from this individual confirmed infection. PCR products were cloned and sequenced and compared with SFVs from monkeys in the same geographic region as well as other Macaca species. Alignment and phylogenetic analysis of SFVhu-BH66 with Asian monkey SFVs indicated that SFVhu-BH66 was most closely related to an SFV-infected monkey from the area. The human origin of the BH66 blood sample was confirmed by PCR cloning, sequencing of the 12S RNA subunit of mitochondrial DNA, and phylogenetic analysis. These data further illustrate the potential for simian retroviral transmission to humans in enzootic areas and point to the risk for development of a new emerging infectious disease.

06. 4. 27

ABSTRACT #57

STUDIES OF SIMIAN FOAMY VIRUS TRANSMISSION BY BLOOD

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Simian foamy viruses (SFVs) are widespread in various non-human primate species. Although the mode of transmission has not been well studied, the high prevalence is thought to be due to transmission via saliva. Cross-species infection in humans has been found in Central African hunters, and can occur due to accidental, occupational exposure to infected animals. The infection results in long-term virus persistence. In contrast to the infection in its natural host, there has been no evidence of SFV human-to-human transmission. However, due to the AIDS epidemic, it is cautionary to prevent retroviral zoonosis, even in the absence of disease in its natural host. Additionally, it is imperative to avoid further virus adaptation by human passage. Recently, due to reports of SFV infections in humans, there has been a concern regarding potential SFV transmission by blood donors. To investigate whether SFV can be transmitted by blood, we transfused SFV-negative rhesus macaques with blood from two adult macaque donors that were naturally infected with biologically and genetically distinct SFVs. The recipient animals were monitored for virus infection and persistence, humoral antibody response and clinical changes. The results at 1-year post-inoculation indicate that SFV can be transmitted by whole blood, in some cases. These findings could have implications for blood donor screening.

ABSTRACT #58

REAL-TIME TAQMAN PCR AS A TOOL FOR SIMIAN RETROVIRAL DIAGNOSTICS

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Retroviral diagnostic testing is a critical tool for accurately assessing infection status of non-human primates (NHP). Determining simian retroviral infection presents unique challenges associated with the individual characteristics of each virus. We developed quantitative qTaqMan PCR to screen Asian and African NHPs for SRV, SIV, and STLV, the major exogenous retroviruses found in Old World Primates. Sensitivity and specificity correlated well with nested PCR in most instances. For SRV testing, comparison of antibody-based Western blotting with TaqMan PCR suggests that both assays are necessary to conclusively identify positive animals. Strain-specific SRV TaqMan assays were required to eliminate false positives due to endogenous SRV of macaques. SRV-1, -3, and SRV-2 assays have been developed with sensitivities of < 10 DNA copies/10^5 lymphocytes. Viral loads were examined for 54 SRV-2+ cynomolgus macaques by TaqMan DNA PCR. Copy numbers varied from < 10 copies to as high as 1.4×10^6 copies/10^5 cells with a median of 22 DNA copies. Similar sensitivities were found for to screen blood samples for retroviral infections with the added advantage in minimizing false positive sampling commonly seen with nested PCR.