(b) Imported case(s).

(c) Canada – Data as of 26 February 2008.
Ireland – Data as of 31 March 2008. Cases detected by the passive surveillance programme = 1. Cases detected by the active surveillance programme = 5.

(d) France year 2000 – Clinical cases = 101. Cases detected within the framework of the research programme launched on 8 June 2000 = 60.
Ireland year 2000 – Clinical cases = 138. Cases identified by active surveillance of at risk cattle populations = 7. Cases identified by examination of depopulated BSE positive herds, birth cohorts and progeny animals = 4.
Switzerland year 2000 – Clinical cases = 17. Cases detected within the framework of the investigation programme = 16.

(e) France year 2001 – Clinical cases = 91. Cases detected at rendering (bovines at risk) = 100 (out of 139,500 bovines tested). Cases detected as result of routine screening at the abattoir = 83 (out of 2,373,000 bovines tested).
Ireland year 2001 – Clinical cases = 123. Cases identified by systematic active surveillance of all adult bovines = 119. Cases identified by examination of depopulated BSE positive herds, birth cohorts and progeny animals = 4.
Japan year 2001 – Clinical cases = 1. Cases detected as result of screening at the abattoir = 2.

(f) France year 2002 – Clinical cases = 41. Cases detected at rendering (bovines at risk) = 124 (out of 274,143 bovines tested). Cases detected as result of systematic screening at the abattoir = 74 (out of 2,915,103 bovines tested). The active BSE surveillance programmes implemented in France in 2002 led to routine examination of cattle aged over 24 months, which were slaughtered for consumption purposes, were euthanised or died due to other reasons.
Ireland year 2002 – Clinical cases = 108. Cases detected by the active surveillance programme = 221. Cases identified by examination of depopulated BSE positive herds, birth cohorts and progeny animals = 4.
Poland year 2002 – Clinical cases = 1. Cases detected as result of routine screening at the abattoir (cattle over 30 months) = 3.

(g) France year 2003 – Clinical cases = 13. Cases detected at rendering (bovines at risk) = 87. Cases detected as result of systematic screening at the abattoir = 37.
Japan year 2003 – The 9th case was a bullock aged 21 months.
Ireland year 2003 – Clinical cases = 41. Cases detected by the active surveillance programme = 140.
Switzerland year 2003 – Clinical cases: 8. Cases detected within the framework of the official surveillance programme: 11. Cases detected through voluntary testing following routine slaughter: 2.

(h) France year 2004 – Clinical cases = 8. Cases detected at rendering (bovines at risk) = 29. Cases detected as result of systematic screening at the abattoir = 17.
Ireland year 2004 – Clinical cases = 31. Cases detected by the active surveillance programme = 94. Cases identified by examination of depopulated BSE positive herds, birth cohorts and progeny animals = 1.

(i)
Ireland year 2005 – Cases detected by the passive surveillance programme = 13. Cases detected by the active surveillance programme = 56.
Switzerland year 2005 – Cases detected by the passive surveillance programme = 1. Cases detected

within the framework of the official surveillance programme: 1. Cases detected through voluntary testing following routine slaughter = 1.

(j) Ireland year 2006 – Cases detected by the passive surveillance programme = 5. Cases detected by the active surveillance programme = 36.

(k) Greece – Data as of 30 June 2007.

Ireland year 2007 – Cases detected by the passive surveillance programme = 5. Cases detected by the active surveillance programme = 20.

Italy – Data as of 30 June 2007.

Japan – Data as of 21 December 2007.

Luxembourg – Data as of 30 June 2007.

Poland – Data as of 20 December 2007.

Slovenia– Data as of 30 June 2007.

Spain– Data as of 30 June 2007.

United States of America – Data as of 30 June 2007.

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別紙様式第2-1

No. 24

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
				2008. 3. 5	該当なし	

一般的名称	解凍人赤血球濃厚液	研究報告の公表状況	OIE - World Organisation for Animal Health. Available from: URL: http://oie.int/eng/info/en_esbru.htm	公表国
販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社) 解凍赤血球-LR「日赤」(日本赤十字社) 照射解凍赤血球-LR「日赤」(日本赤十字社)			OIE

研究報告の概要

○英国の畜牛におけるウシ海綿状脳症(BSE)症例の報告数
1987年以前から2008年(3月現在)までに、英国から国際獣疫事務局(OIE)に報告されたウシ海綿状脳症の報告数である。2007年にはグレートブリテン島で53頭、北アイルランドで14頭の計67頭が報告された。2008年には、これまでにグレートブリテン島で10頭の症例が報告されている。

報告企業の意見	今後の対応
1987年以前から2008年(3月現在)までに、英国から国際獣疫事務局(OIE)に報告されたウシ海綿状脳症の報告数である。英国では、1992年の37,280例をピークに流行は収束しつつある。	日本赤十字社は、vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴(旅行及び居住)を確認し、欧州36ヶ国に一定期間滞在したドナーを無期限に献血延期としている。また、英国滞在歴を有するvCJD患者が国内で発生したことから、平成17年6月1日より1980～96年に1日以上の英国滞在歴のある方からの献血を制限している。今後もCJD等プリオン病に関する新たな知見及び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

解凍赤血球濃厚液「日赤」
照射解凍赤血球濃厚液「日赤」
解凍赤血球-LR「日赤」
照射解凍赤血球-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

(N)

idefined JRC2008T-019

■ Number of cases in the United Kingdom ■ Number of reported cases worldwide (excluding the United Kingdom)
■ Cases in imported animals only ■ Annual incidence rate

Number of cases of bovine spongiform encephalopathy (BSE) reported in the United Kingdom [1]

	Alderney	Great Britain	Guernsey [3]	Isle of Man [2]	Jersey	Northern Ireland	Total United Kingdom
1987 and before[4]	0	442	4	0	0	0	446
1988[4]	0	2 469	34	6	1	4	2 514
1989	0	7 137	52	6	4	29	7 228
1990	0	14 181	83	22	8	113	14 407
1991	0	25 032	75	67	15	170	25 359
1992	0	36 682	92	109	23	374	37 280
1993	0	34 370	115	111	35	459	35 090
1994	2	23 945	69	55	22	345	24 438
1995	0	14 302	44	33	10	173	14 562
1996	0	8 016	36	11	12	74	8 149
1997	0	4 312	44	9	5	23	4 393
1998	0	3 179	25	5	8	18	3 235
1999	0	2 274	11	3	6	7	2 301
2000	0	1 355	13	0	0	75	1 443
2001	0	1,113	2	0	0	87	1,202
2002	0	1,044	1	0	1	98	1,144
2003	0	549	0	0	0	62	611
2004	0	309	0	0	0	34	343
2005	0	203	0	0	0	22	225
2006	0	104	0	0	0	10	114
2007	0	53	0	0	0	14	67
2008[5]	0	10	0	0	0	0	10

(1) Cases are shown by year of restriction.

(2) In the isle of Man BSE is confirmed on the basis of a laboratory examination of tissues for the first case on a farm and thereafter by clinical signs only. However, all cases in animals born after the introduction of the feed ban have been subjected to histopathological/scrapie-associated fibrils analysis. To date, a total of 277 animals have been confirmed on clinical grounds only.

(3) In Guernsey BSE is generally confirmed on the basis of clinical signs only. To date, a total of 600 animals have been confirmed without laboratory examination.

(4) Cases prior to BSE being made notifiable are shown by year of report, apart from cases in Great Britain which are shown by year of clinical onset of disease.

(5) Data as of 31 March 2008.

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番号7

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 2008年2月18日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称	①乾燥抗HBs人免疫グロブリン ②ポリエチレングリコール処理抗HBs人免疫グロブリン		研究報告の公表状況	Transfusion 2008; 48(2): 286-294	公表国 日本	
販売名 (企業名)	①ヘブスブリン（ベネシス） ②静注用ヘブスブリンーIH（ベネシス）					

研究報告の概要

【背景】
HBV血液スクリーニングの最適な戦略を計画するには、最小感染価とHBVの初期動態を測定し、HBs抗原に加えてHBV DNAについてのウインドウ期間を明確にすることが必要である。
【研究デザイン及び方法】
最小感染価を求めるために、遺伝型A、または遺伝型CのHBVを含む急性期前の接種株をそれぞれチンパンジー1対に接種するとともに、遺伝型Aと遺伝型CのHBVの最小感染価を接種した2対のチンパンジーについてHBVマーカーを追跡調査した。
【結果】
遺伝型Aおよび遺伝型Cの50%チンパンジー感染価（CID50）は、約10コピーであると推定された。最小感染価を接種された2頭のチンパンジーにおいて、HBV DNAのウインドウ期は、遺伝型Aおよび遺伝型Cでそれぞれ55-76日及び35-50日であった。HBsAgのウインドウ期は、遺伝型A及び遺伝型Cでそれぞれ69-97日及び50-64日であった。HBV DNAのダブリングタイムは、遺伝型A及び遺伝型Cでそれぞれ3.4日及び1.9日であった。この2つの遺伝型の間でのHBV DNAの複製速度を比較すると、遺伝型Cのダブリングタイムは遺伝型Aよりも著しく短かった。
【結論】
CID50は約10コピーで2つの遺伝型で類似していたが、ダブリングタイムおよび最小感染価に感染したチンパンジーにおけるHBV NATウインドウ期間（<100コピー/mL）は、遺伝型Aよりも遺伝型Cが短いようであった。

報告企業の意見	今後の対応
チンパンジーにおけるHBVの遺伝型Aと遺伝型Cの最小感染価、初期動態(ダブリングタイム、ウインドウ期)に関する報告である。 万一、原料血漿にHBVが混入したとしても、BVD及びBHV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

代表として静注用ヘブスブリンー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抗HBs抗体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HBs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ろ過膜処理（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。

(3)

Minimum infectious dose of hepatitis B virus in chimpanzees and difference in the dynamics of viremia between genotype A and genotype C

Yutaka Komiya, Keiko Katayama, Hisao Yugi, Masaaki Mizui, Harumichi Matsukura, Tetsushi Tomoguri, Yuzo Miyakawa, Ayako Tabuchi, Junko Tanaka, and Hiroshi Yoshizawa

BACKGROUND: In planning optimal hepatitis B virus (HBV) blood screening strategies, the minimum infectious dose and early dynamics of HBV need to be determined for defining the window period for HBV DNA as well as for hepatitis B surface antigen (HBsAg).

STUDY DESIGN AND METHODS: Pairs of chimpanzees were inoculated with preacute-phase inocula containing HBV of genotype A or genotype C to determine the minimum infectious dose, and two pairs of chimps infected with the lowest infectious dose of genotypes A and C were followed for HBV markers.

RESULTS: The minimum 50 percent chimpanzee infectious dose (CID_{50}) was estimated to be approximately 10 copies for genotype A and for genotype C. In the two chimps inoculated with the lowest infectious dose, the HBV DNA window was 55 to 76 days for genotype A and 35 to 50 days for genotype C, respectively. The HBsAg window was 69 to 97 days for genotype A and 50 to 64 days for genotype C, respectively. The doubling times of HBV DNA were 3.4 days (95% confidence interval [CI], 2.6-4.9 days) for genotype A and 1.9 days (95% CI, 1.6-2.3 days) for genotype C. When comparing the replication velocity of HBV DNA between the two genotypes, the doubling time of genotype C was significantly shorter than that of HBV genotype A ($p < 0.01$).

CONCLUSION: Although the CID_{50} of approximately 10 copies was similar for the two HBV genotypes, the doubling time and pre-HBV nucleic acid amplification technology (<100 copies/mL) window period in chimps infected with the lowest infectious dose seemed to be shorter for genotype C than for genotype A.

Posttransfusion infection with hepatitis B virus (HBV) has decreased dramatically since screening for hepatitis B surface antigen (HBsAg) was introduced in the early 1970s. The number of reported posttransfusion hepatitis B cases has been further reduced after screening for antibody to HBV core (anti-HBc) was implemented in the late 1980s in the United States and Japan.[1,2] Japan introduced HBV DNA screening by nucleic acid amplification technology (NAT) in minipools (MPs) in 1999. Since introduction of MP-NAT, more than 500 seronegative donations with detectable HBV DNA have been interdicted, although there are still units of blood in an early or late phase of HBV infection

ABBREVIATIONS: CID_{50} = 50 percent chimpanzee infectious dose; CLIA = chemiluminescent immunoassay; JRC = Japanese Red Cross; MP(s) = minipool(s).

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TRANSFUSION 2008;48:286-294.

with low viral load that can escape detection by NAT.[3] Interestingly, the lookback program of the Japanese Red Cross (JRC) demonstrated that low viral load donations in the window phase were more than 10-fold more often implicated in HBV transmission reports than were occult carriers with anti-HBc titers below the exclusion limit of the anti-HBc hemagglutination inhibition screening assay.[3] Bearing in mind the relatively high infectivity of HBV in the window phase, exact knowledge on early dynamics of HBV replication is important for residual risk estimations.[4-7] It will determine the threshold of NAT in identifying blood donors during the preacute phase of HBV infection, which is important for planning and executing evidence-based hepatitis B blood screening strategies.[7,8] In this context, the relative infectivity of HBV in the early window phase is an important factor for measuring the effect of NAT screening systems on the residual risk of HBV transmission by blood transfusion.[7-9]

Chimpanzees are the only experimental animals susceptible to human hepatitis viruses and have been very useful in transmission studies.[10] As early as the mid-1970s, it was demonstrated that blood units from HBV carriers, especially those positive for the presence of hepatitis B e antigen (HBeAg), have a tremendously high infectious potential and can transmit infection to chimps by intravenous inoculation with 1 mL of plasma diluted to $1:10^8$.[11] Now that NAT enables detection of HBV DNA in blood donors even in individual-donation format, it can be estimated by mathematical modeling what the residual risk would be depending on the minimum copy number required for infection.[9] More conservative risk modeling assumes that a single copy of HBV, if it successfully reaches a hepatocyte in susceptible hosts, may be enough to establish infection.[5] To pursue strategies for preventing HBV infections by blood transfusions, additional information on the infectivity of HBV is crucially required. It is imperative to define not only the minimum copy number of HBV DNA or number of virions required for transmission of HBV, but also the early dynamics of HBV replication in the circulation of infected hosts. This can be established more accurately in chimpanzee experiments. In this report on experimental transmission of hepatitis B in chimps, the minimum infectious dose was determined separately for HBV of genotypes A and C, and the copy number of HBV DNA for establishing infection was defined for each of them. Moreover, the doubling time and logarithmic time of HBV DNA were determined by following the viral dynamics in the preacute phase of chimpanzees who had received the minimum infectious dose of HBV.

MATERIALS AND METHODS

Chimpanzees

Six chimps entered this study. Their age, sex, and weight, as well as the HBV inocula that they received are listed in Table 1 along with the infection outcome. Every chimp was kept in an individual cage and received humane care in accordance with all relevant requirements for the use of primates in an approved institution. None of the six chimps had serologic or molecular biologic evidence of past or present HBV infection prior to the inoculation. They were also not infected with hepatitis C virus (HCV) and human immunodeficiency virus type-1. Chimps were inoculated intravenously while they were under anesthesia by intramuscular injection with ketamine hydrochloride. After the inoculation, serum samples were obtained once a week or more frequently as required, until 16 weeks or longer. They were tested for HBV DNA, HBsAg, anti-HBc, anti-HBs, and alanine aminotransferase as well as aspartate aminotransferase.

Inocula containing HBV

The chimpanzees received four kinds of inocula (Table 1). Inocula I and III were fresh-frozen plasma (FFP) units from blood donors acutely infected with HBV genotypes A and C, respectively. Inocula II and IV were plasma samples from chimps infected with inoculum I of genotype A and inoculum III of genotype C, respectively (see Figs. 1A and 1B). Inocula II and IV were: 1) recovered in the preacute phase of HBV infection before immune responses of the host had developed; 2) positive for the presence of HBV DNA in the highest titer before anti-HBc developed; and 3) taken with utmost care to maintain the infectious activity and avoid attenuation during serial processing from blood collection until storage. Immediately after blood drawing

TABLE 1. Six chimpanzees and HBV inocula and HBV infection outcomes

Chimpanzee	Age, sex, weight	HBV DNA copies	Outcome
Inoculum I: FFP from a human donor in the preacute phase of HBV infection of genotype A			
1 Chimp 246	13 years, male, 60.7 kg	1 mL (6.9×10^4 copies/mL)	Infected
Inoculum II: Preacute-phase plasma of Chimp 246 containing HBV (2.6×10^6 copies/mL)			
2 Chimp 272	9 years, male, 58.7 kg	1 mL ($1:10^6$ dilution)	Not infected
3 Chimp 279	8 years, male, 51.4 kg	1 mL ($1:10^6$ dilution)	Not infected
3 Chimp 279	Reinoculation	1 mL ($1:10^5$ dilution)	Infected
4 Chimp 280	8 years, male, 39.4 kg	1 mL ($1:10^5$ dilution)	Infected
Inoculum III: FFP from a human donor in the preacute phase of HBV infection of genotype C			
2 Chimp 272	Reinoculation	5 mL (5.3×10^5 copies/mL)	Infected
Inoculum IV: Preacute-phase plasma of Chimp-272 containing HBV (3.0×10^6 copies/mL)			
5 Chimp 269	11 years, male, 62.5 kg	1 mL ($1:10^6$ dilution)	Not infected
6 Chimp 285	7 years, male, 41.1 kg	1 mL ($1:10^6$ dilution)	Not infected
5 Chimp 269	Reinoculation	1 mL ($1:10^5$ dilution)	Infected
6 Chimp 285	Reinoculation	1 mL ($1:10^5$ dilution)	Infected

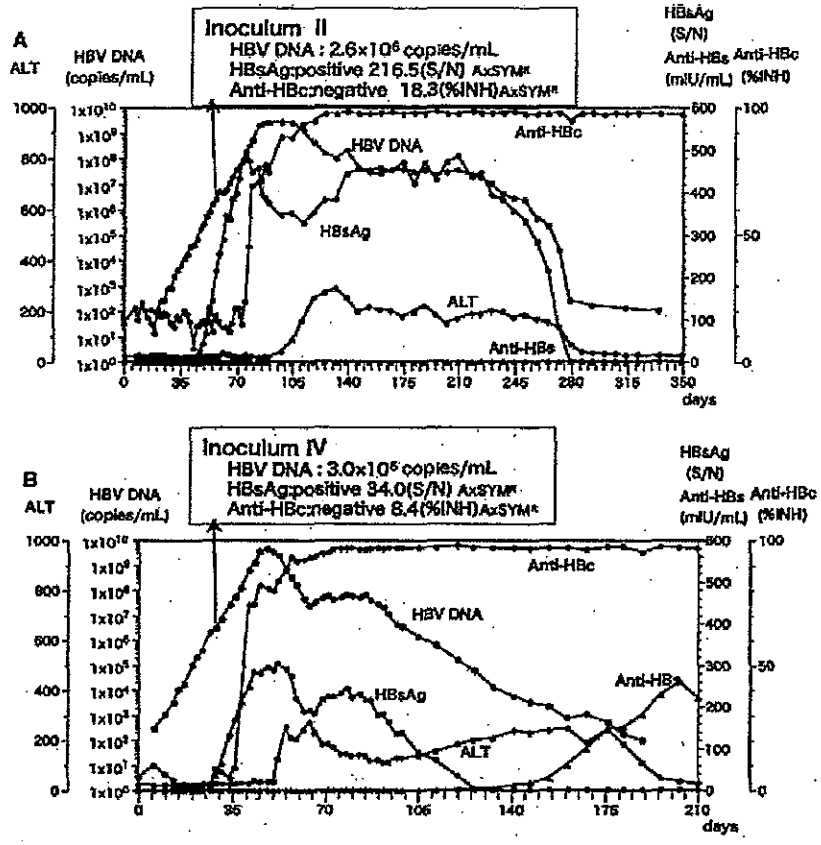

Fig. 1. Time course of HBV serum markers in chimps used as a source of inoculation of HBV genotype A and genotype C. (A) Chimp 246 was inoculated with human plasma of HBV genotype A. Inoculum II for chimp infectivity studies was harvested in the ramp-up phase of viremia before anti-HBc seroconversion at the time HBV DNA had reached a concentration of 2.6×10^6 copies per mL and the HBsAg response had increased to a signal-to-noise (S/N) ratio of 216.5 (cutoff S/N = 2.0). (B) Chimp 272 was inoculated with human plasma of HBV genotype C. Inoculum IV was harvested in the ramp-up phase of viremia before anti-HBc seroconversion at the time HBV DNA had reached a concentration of 3.0×10^6 copies per mL and HBsAg had increased to an S/N ratio of 34.0.

from chimps, plasma samples were separated. They were divided into 15 tubes in 1-mL aliquots, snap-frozen in liquid nitrogen, and kept in a deep freezer at –80°C until used for transmission experiments. For each experiment, the plasma in one tube was thawed gently by immersing it in a water bath at 37°C, and the required amounts were used.

Laboratory tests

HBsAg, anti-HBc, and antibody to HBsAg (anti-HBs) were determined by chemiluminescent immunoassay (CLIA) with commercially available kits (AxSYM, Abbott Japan, KK, Tokyo, Japan), with the index of 2.0 (signal-to-noise [S/N]), 50 percent inhibition, and 5.0 mIU per mL as cutoff values, respectively. Qualitative assay for HBV DNA was performed by polymerase chain reaction (PCR) with primers deduced from the S region of HBV DNA.[12] HBV DNA was quantitated by the PCR (TaqMan, Roche Diagnostics KK, Tokyo, Japan) with a sensitivity of 100 copies per mL. Quantitative assays for HBV DNA were performed simultaneously for an accurate comparison of data.

Calculation for doubling time and logarithmic time of HBV DNA

To calculate the doubling time and the logarithmic time (time for reaching 10 times the amount) of HBV DNA at ramp-up after the infection, HBV DNA copy numbers were evaluated statistically by log linear regression analysis. The comparison of regression slope (the doubling time and the logarithmic time) between HBV genotypes was evaluated by growth curve analysis (Vonesh-Carter-Ohtaki method).[13,14]

RESULTS

Inocula and copy numbers of HBV genotype A or genotype C recovered from chimpanzees in the preacute phase of infection

Chimp 246 was injected intravenously with 1 mL of FFP from a blood donor in the preacute phase of HBV infection (Table 1); the donor had been screened by NAT at a JRC Blood Center. His plasma sample contained 6.9×10^4 copies per mL of HBV DNA genotype A and was positive for the presence of HBsAg but negative for the presence of anti-HBc (inoculum I). Plasma was harvested from Chimp 246, in the preacute phase of HBV infection 57 days after inoculation (inoculum II). It contained 2.6×10^6 copies per mL HBV DNA and was positive for the presence of HBsAg but still negative for the presence of anti-HBc and anti-HBs (Fig. 1A).

Likewise, Chimp 272 was injected intravenously with 5 mL of FFP from a blood donor in the preacute phase of HBV infection who had been screened by NAT at JRC (Table 1). It contained 5.3×10^5 copies per mL of HBV DNA genotype C and was positive for the presence of HBsAg but negative for the presence of anti-HBc and anti-HBs (inoculum III). Thus, Chimp 272 was inoculated with