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シンポジウム４

HBIG製剤の国内自給を目指したHBワクチンプロジェクト

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目　的

「安全な血液製剤の安定供給の確保等に関する法律」では，国内で使用される血液製剤が原則として国内の献血により得られた血液を原料として製造される体制の構築を目指すとされている。これに基づいて出された「血液製剤の安全性の向上及び安定供給の確保を図るための基本的な方針」（平成20年厚生労働省告示第326号）では，「アルブミン製剤及び免疫グロブリン製剤については，平成25年を目途に国内自給の達成を目指し，とくに，特殊免疫グロブリン製剤については，「国内自給の方策を具体的に検討していく必要がある」並びに「国内での原料血漿確保の実現可能性を考慮しながら，国内製造の方策を引き続き検討していく」ことが示されている。

現在，我が国で使用されている特殊免疫グロブリンは３種で，うち抗破傷風および抗Rh（D）人免疫グロブリンの２種は原料血漿のすべてを海外からの輸入に依存しているが，抗HBs人免疫グロブリン（HBIG）の一部は国内献血血漿を原料に製造されている。日本赤十字社では全献血者を対象にHBs抗体価を測定し，うち原料血漿基準を満たす高力価の血漿を選別する方法が採られているが，この受動的収集方法では限界があり，国内自給率は３％にも満たない。今後，HBIG自給に必要な量の原料血漿を国内献血により確保するためには，より積極的，能動的収集法を樹立する必要がある。

能動的血漿収集法の一つに，同意が得られた献血者にB型肝炎ワクチン（HBワクチン）を接種して抗体価を上昇させた後に供血いただく方法が考えられる。しかし，HBワクチン接種はB型肝炎ウイルスの感染予防を目的になされるため，初回の接種者ではHBIG原料血漿基準を満たす高力価の抗体（EIA法：10,000mIU以上）を獲得する人の割合は極めて低い事が既に分っている。そこで，現在もしくは過去にHBs 抗体を保有する事が確認されている者（感作者）を対象にワクチンを接種した場合，より効率的に高力価抗体保有者を見出し得ると期待されるが，これまでこの種の成績は報告されていない。

本研究では，HBワクチン既投与者を対象として，HBワクチンの追加投与をおこない，投与前後のHBs抗体価を評価することで，HBIG原料血漿収集の国内自給を目指した能動的血漿収集法の基礎的検討データを作成することを目的とする。

なお，本研究は，平成22年度厚生労働科学研究費補助金（医薬品・医療機器等レギュラトリーサイエンス総合研究事業）研究課題名（課題番号）：抗HBs人免疫グロブリンの国内製造用原料血漿収集におけるB型肝炎ワクチン接種の有効性に係わる基礎的検討（指定型研究）の中で実施した。

方　法

本プロジェクトの主旨に賛同したHBs抗体価３mIU/mL以上を示した当院の468名の医療職員（平均年齢33.6歳：21―63歳，看護師，検査技師，医師）が対象である。HBワクチン10 μgを投与し，投与前後のHBs抗体価を測定した。なおHBIGの原料血漿基準の高力価HBs抗体価は１万mIU/mL以上であることから，１万mIU/mL以上のHBs抗体価を示した対象の特徴を検討した。なお本研究計画は院内倫理委員会の承認をえて，書面にて本研究参加の同意を取得できた者を対象として実施した。

結　果

HBワクチン投与前後の468名でのHBs抗体価は，算術平均では380.9±1319.9mIU/mLから12,227.8±17,951.9mIU/mLに，幾何平均では1.985±0.665mIU/mLから3.708±0.669mIU/mLと共に有

意に上昇した。(P＜0.0001)。

投与前の時点からHBs抗体価1万mIU/mL以上を示した者は468名中2名(0.4%)だけであったが，HBワクチン投与後は164名(35%)へと増加した(**表1**)。

HBワクチン1回投与で，HBs抗体価(AxSYM EIA法)10,000mIU以上を示した者の特徴を，性別，年齢別，投与前のHBs抗体価別，HBc抗体別に検討したところ，その特徴は，以下の3点であった。

1．若年であること(長崎医療センターデータ：30歳未満：42.3% vs 50歳以上：12.5%)(**図1**)
2．投与前のHBs抗体価が100mIU以上であること。(長崎医療センターデータ：100mIU未満：22.5% vs 100mIU以上：48.2%)(**図2**)。
3．HBc抗体陰性であること。(長崎医療センターデータ：HBc抗体陰性者：36.8% vs 陽性者12.1%)

考　察

欧州では抗体価の高い献血者を登録し，必要に応じてワクチンを追加接種することで，抗体価の高い血漿を安定的に確保し，国内自給を維持しているが，わが国では初めての試みである本プロジェクトの妥当性，実現性をパイロット的に検討し，十分実現可能であることを示した。現状のままではHBIG製剤の国内自給は不可能に近く，今後も輸入血漿に依存せざるをえない。HBIG製剤国内自給の実現のためには，医療従事者を中心とするボランティアにより本プロジェクトを実施する必要がある。

なお2010年1月から9月末までの期間，献血所に行った者　36名/386名(9.3%)であった。

結　論

本プロジェクトの妥当性，実現性をパイロット的に検討し，十分実現可能であることを明らかにした。

表1　HBワクチン投与前後のHBs抗体価(AxSYM EIA)の分布(N=468)

HBs抗体価	投与前	投与後1カ月目	
2.0-9.9	27 (5.8%)	0	
10-99.9	213 (45.5%)	6 (1.3%)	
100-999.9	196 (41.9%)	66 (14.1%)	
1,000-9,999.9	30 (6.4%)	232 (49.6%)	
10,000-99,999.9	2 (0.4%)	160 (34.1%)	164 (35.0%)
100,000-	0	4 (0.9%)	
	468 (100%)	468 (100%)	

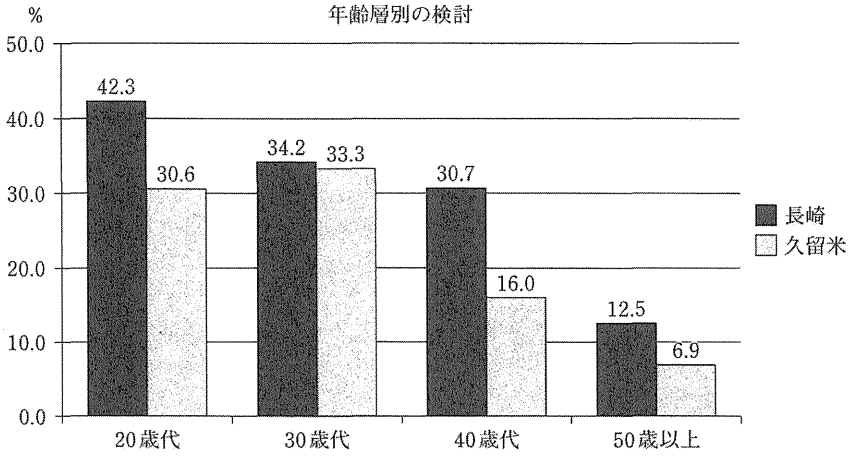

図1　HBワクチン投与後高力価(1万mIU以上)のHBs抗体価獲得者の頻度

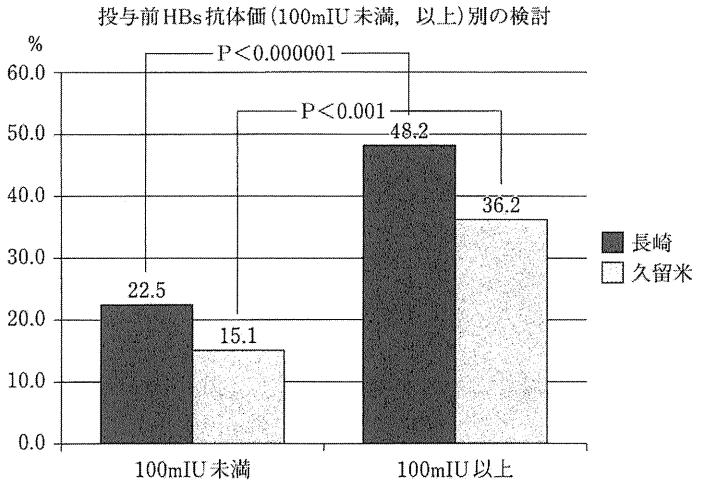

図２　HBワクチン投与後高力価（１万mIU以上）のHBs抗体価獲得者の頻度

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Case Report

Sequential occurrence of acute hepatitis B among members of a high school Sumo wrestling club

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A 17-year-old male was admitted to our hospital and diagnosed with acute hepatitis B. Six weeks later, a 15-year-old male was admitted with acute hepatitis B as well. They were Sumo wrestling players in the same club. A detailed survey in the club revealed that a 28-year-old male coach was a hepatitis B surface antigen carrier with high-level viremia. The consistency of hepatitis B virus (HBV) DNA in the infected players was revealed by analyzing the complete HBV genome sequences. Sumo players are more likely to get injured, including cuts and bleeding, compared with players of other sports because of the characteristic wrestling style. Several past reports have suggested that highly viremic HBV carriers have high HBV DNA titers in both their blood and other body fluids such as sweat. In our cases, percutaneous HBV transmission through the bleeding wounds was the most probable infection route. We conclude that a universal HBV immunization program should be introduced urgently in Japan, similar to those implemented in other countries worldwide.

Key words: hepatitis B virus, horizontal transmission, Sumo, universal vaccination

INTRODUCTION

THE HORIZONTAL TRANSMISSION of hepatitis B virus (HBV) occurs in limited situations such as sexual intercourse with HBV positive partners, the transfusion of HBV-contaminated blood, and the re-use of needles and syringes used for the i.v. administration of drugs.[1–3] In addition, there are several reports of horizontal HBV transmission in elementary schools and day-care centers due to bites and scratches or exposure to blood or blood-contaminated fluids among children.[4–7] Although it is rare, HBV horizontal transmission has been reported in various sports as well, including Sumo wrestling and American football, because of contact with open wounds during training.[8,9]

In this paper, we report a sequential occurrence of acute hepatitis B in members of a high school Sumo wrestling club. After a detailed field survey, a 28-year-old male coach was determined to be a hepatitis B surface antigen (HBsAg) carrier with a high-level of viremia. This individual was identified as the source of transmission by analyzing the complete HBV genome sequences.

CASE REPORT

A 17-YEAR-OLD MALE (case 1) was admitted to our hospital with a 1-week history of jaundice and itching. He had no past medical history, except pediatric asthma, and was not taking any medications currently. There were no HBV carriers in his family. He reported no alcohol consumption, recent travel or sexual contact. He was a member of a high school Sumo wrestling club. On examination, the patient was slightly icteric with stable vital signs. Blood test results (Table 1) revealed the following: total bilirubin (T-Bil), 3.9 mg/dL; aspartate aminotransferase (AST), 1152 IU/L; alanine aminotransferase (ALT), 2856 IU/L; HBsAg, 12 229.87 IU/mL; hepatitis B e-antigen (HBeAg), 473.29 S/CO; anti-hepatitis B core (anti-HBc), 4.0 S/CO; immunoglobulin

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Table 1 Laboratory findings at the initial visit

	Case 1	Case 2	Case 3	Reference range
White blood cells (10^3/μL)	5.8	4.0	4.2	3.9–9.8
Red blood cells (10^6/μL)	5.38	5.18	5.11	4.10–5.30
Hemoglobin (g/dL)	15.8	14.7	16.4	13.5–17.6
Platelet (10^3/μL)	293	232	198	131–362
Prothrombin time (%)	100.6	89.7	106.0	72.0–130.0
APTT (s)	38.7	36.6	38.7	24.8–40.4
Total bilirubin (mg/dL)	3.9	3.2	0.9	0.3–1.2
Direct bilirubin (mg/dL)	2.5	2.0	0.1	0.0–0.2
AST (IU/L)	1152	1567	42	13–33
ALT (IU/L)	2856	2526	76	8–42
ALP (IU/L)	729	1167	237	115–359
γ-GT (IU/L)	176	170	46	10–47
Albumin (g/dL)	4.9	4.1	4.9	4.0–5.0
Immunoglobulin G (mg/dL)	1600	1730	1080	870–1700
Immunoglobulin A (mg/dL)	220	297	281	110–410
Immunoglobulin M (mg/dL)	120	107	114	33–190
HBsAg (IU/mL)	12 229.87	12 381.98	62 276.59	<0.05
HBeAg (S/CO)	473.29	553.41	1394.20	<1.00
Anti-HBe (INH%)	0.0	0.0	0.0	<50
Anti-HBc (S/CO)	4.00	7.88	7.34	<1.00
IgM anti-HBc (S/CO)	24.10	19.30	0.78	<1.00
HBV DNA (log copies/mL)	6.1	6.1	>9.1	Non-detectable
HBV genotype	C	C	C	–
Precore mutations	Wild	Wild	Wild	–
Core promoter mutations	Wild	Wild	Wild	–
HCV RNA (log IU/mL)	Non-detectable	Non-detectable	Not tested	Non-detectable
IgM anti-HAV (S/CO)	<0.40	<0.40	Not tested	<0.40
EBV-VCA IgG	0.8	3.3	Not tested	<0.5
EBV-VCA IgM	0.0	0.0	Not tested	<0.5

ALP, alkaline phosphatase; ALT, alanine aminotransferase; anti-HBc, anti-hepatitis B core; anti-HBeAg, hepatitis B e-antibody; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; EBV-VCA, Epstein–Barr virus viral capsid antigen; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IgM anti-HAV, immunoglobulin M anti-hepatitis A virus; IgM anti-HBc, immunoglobulin M anti-hepatitis B core; γ-GT, γ-glutamyl transferase.

M anti-hepatitis B core (IgM anti-HBc), 24.1 S/CO; HBV DNA, 6.1 log copies/mL; and HBV genotype, C. On the basis of these results, a diagnosis of acute hepatitis B was confirmed, although the exact route and source of infection could not be identified. The patient recovered naturally and was discharged 12 days after admission. The clinical course was uneventful, and HBsAg clearance was achieved 157 days after admission.

Six weeks after discharge of case 1, a 15-year-old male (case 2) from the same high school Sumo wrestling club was admitted to our hospital with elevated transaminases. He had no past medical history, except atopic dermatitis, and was not taking any medications currently. There were no HBV carriers in his family, except that his father was an inactive HBsAg carrier. He reported no alcohol consumption, recent travel or sexual contact. On examination, the patient was slightly icteric with stable vital signs. Blood test results (Table 1) revealed the following: T-Bil, 3.2 mg/dL; AST, 1567 IU/L; ALT, 2526 IU/L; HBsAg, 12 381.98 IU/mL; HBeAg, 553.41 S/CO; anti-HBc, 7.88 S/CO; IgM anti-HBc, 19.30 S/CO; HBV DNA, 6.1 log copies/mL; and HBV genotype, C. On the basis of these results, this individual was diagnosed with acute hepatitis B as well. However, as in the first case, we could not identify the precise route or source of infection. The patient recovered naturally and was discharged 30 days after admission. The clinical course was uneventful, and HBsAg clearance was achieved 96 days after admission.

Because acute hepatitis B was observed to occur successively in the same high school Sumo wrestling club in a relatively short time period, we suspected the presence

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of an infection route and source within the club. After obtaining informed consent from all the club members and coaches, they were tested for HBsAg and hepatitis B surface antibody (anti-HBs) by the school health service. Consequently, a 28-year-old male coach (case 3) was observed to be HBsAg and HBeAg positive with a high level of viremia. There were no HBV carriers in his family. His blood test results (Table 1) revealed the following: T-Bil, 0.9 mg/dL; AST, 42 IU/L; ALT, 76 IU/L; HBsAg, 62 276.59 IU/mL; HBeAg, 1394.20 S/CO; anti-HBc, 7.34 S/CO; IgM anti-HBc, 0.78 S/CO; HBV DNA, more than 9.1 log copies/mL; and HBV genotype, C. To identify the infection source, we performed an analysis of the complete HBV genome sequences in the two patients with acute hepatitis B as well as in the coach suspected to be the source of HBV transmission. Three isolates obtained from the two patients (cases 1 and 2) and the coach (case 3) had the same genomic length of 3215. Between case 1 and case 3, one base (nt1272) had mutated from T to G, with 99.97% (3214/3215) HBV DNA being consistent. Further, between case 2 and case 3, the HBV DNA sequence was 100% (3215/3215) consistent. Using Basic Local Alignment Search Tool (BLAST) analysis, which is a sequence similarity search program to compare a query to a database of sequences, we found that the sample from case 1 was most genetically similar to samples from cases 2 and 3 among other pooled samples. A phylogenetic tree of full-length HBV, obtained using a neighbor-joining method, revealed that the three isolates in this study (cases 1, 2 and 3) were most closely related to each other, and classified into subgenotype C2 (Fig. 1). On the basis of these results, the coach was determined to be the infection source for the successive occurrence of acute hepatitis B in this Sumo wrestling club.

DISCUSSION

ALTHOUGH SEXUAL INTERCOURSE is known as the major route for the horizontal transmission of HBV, several other routes have been reported in the past as well. Iatrogenic routes, including dental or oral surgery,[10] sharing of needles,[11] fingerstick blood-sampling devices,[12] surgical procedures[13] and acupuncture,[14] have been revealed as possible routes of horizontal HBV transmission. On the other hand, non-iatrogenic routes for horizontal HBV transmission include bites and scratches in children's day-care centers or institutions for the mentally retarded,[4–7] household contact,[15–19] tattooing,[20] sharing knives among butchers,[21] and needle pricks or scissor cuts in barbers.[22]

With regard to the field of sports, Kashiwagi *et al.* reported an acute hepatitis B outbreak in a high school Sumo wrestling club in 1982.[8] They confirmed five cases of acute hepatitis B among 10 club members within a 1-year period. Investigations identified an asymptomatic carrier who was judged to be the source of transmission for the hepatitis infection that occurred during the training sessions. Thereafter, in 2000, Tobe *et al.* reported an outbreak of acute hepatitis B in an American university football team.[9] During a period of 19 months, they confirmed five cases of acute hepatitis B among 65 team members and detected a single HBeAg carrier in the same training group. Consequently, they concluded that the carrier was the source of the hepatitis infection that occurred during the training sessions. They performed HBsAg analysis (subtype adr) and suggested that horizontal HBV transmission can occur in sports, probably because of contact with open wounds during training.

We also experienced successive occurrence of acute hepatitis B in a high school Sumo wrestling club similar to that reported by Kashiwagi *et al.*[8] We initiated an investigation in the club after confirming the diagnosis in the second patient. Sumo players wrestle on hard soil in an almost naked style, except for the Sumo belt, which is referred to as "Mawashi" in Japanese. Therefore, they are more likely to be injured and incur cuts and bleeding compared with athletes in other sports. Several recent reports have suggested that HBV carriers may exhibit high HBV DNA titers in other body fluids such as sweat, saliva, tears, nasopharyngeal fluid and urine.[23–27] In our cases, we could not determine whether the intermediate for HBV was blood or other body fluids. However, during their daily training, the players take turns wrestling with one another and continue even when injured or while bleeding from wounds. The nature of this training and our test results suggested that HBV was transmitted through cuts and bleeding wounds sustained during training. We eventually identified the carrier as the source of transmission by analyzing the complete HBV genome sequences in the infected patients. Several cases of horizontal HBV transmission have been reported previously; however, in the field of sports, this is the first report that confirmed the consistency of HBV DNA in the infected patients. Meanwhile, identification of the exact route of HBV transmission was difficult in the three patients in this outbreak. The mean incubation period for acute hepatitis B is 2–3 months after exposure but can range 1–6 months after exposure.[28] This implies that it is possible for one of the two patients with acute hepatitis B to have

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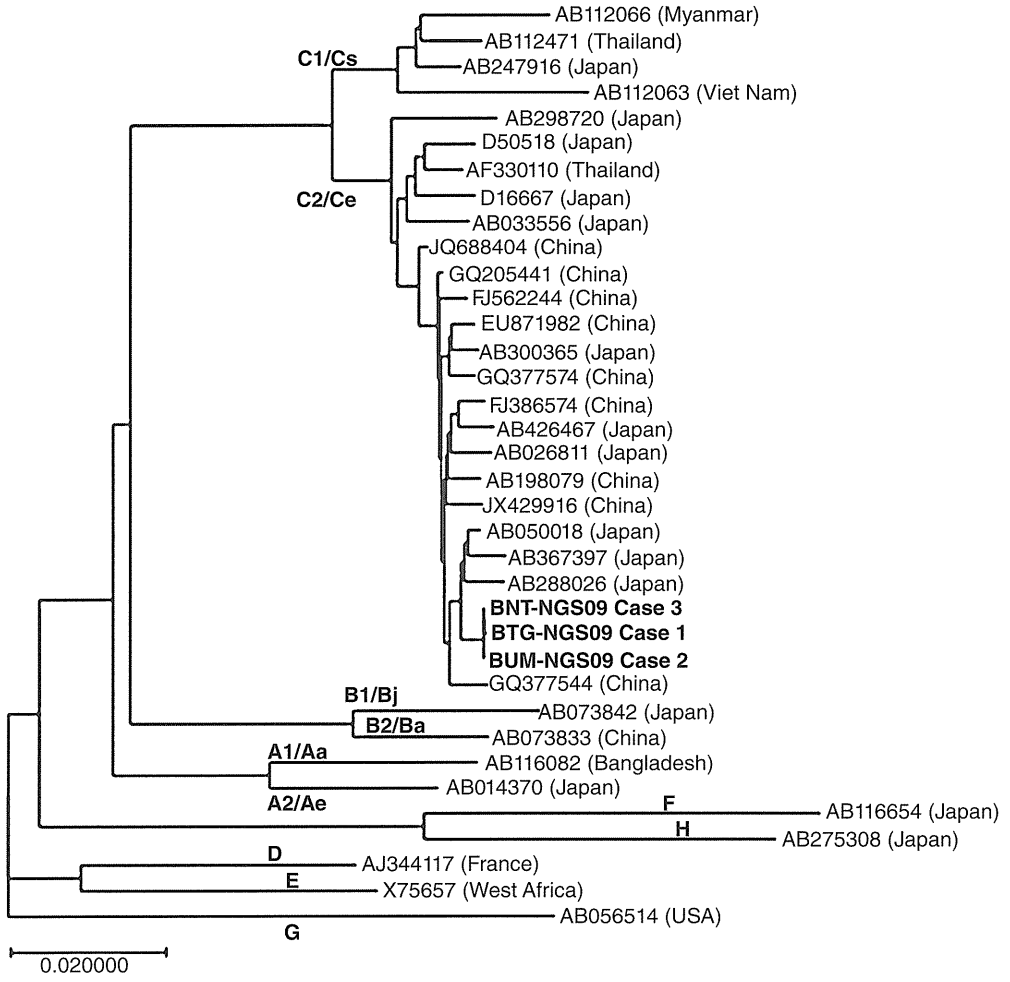

Figure 1 Phylogenetic tree of full-length hepatitis B virus by the neighbor-joining method. Isolates obtained in this study (cases 1, 2 and 3) are shown in bold.

infected the other during the incubation period. In our cases, the coach could have been the origin of transmission and could have infected at least one player, although we could not determine whether or not he infected the other player.

It is remarkable that all three reports of horizontal HBV transmission in the field of sports were from Japan. In 1992, the World Health Organization recommended that all countries should integrate hepatitis B vaccination into their national immunization programs by 1997. By the end of 2009, 177 countries had implemented a universal HBV immunization program for newborns, infants and/or adolescents. However, at the time of drafting of this manuscript (2013), Japan had not introduced this universal HBV immunization program yet. In 1986, Japan initiated a national prevention program comprising selective vaccination for newborns delivered by HBV carrier females. However, this does not aim at preventing horizontal HBV transmission but prevents vertical transmission alone.

Although the number of professional Sumo wrestling players in Japan is very few, the Japanese Ministry of Education revised the guidelines for junior high school education to include compulsory "Budo" (Japanese martial arts) education in 2008. Nowadays, all the students in Japanese junior high schools are taking martial arts classes such as Sumo and Judo. This means that they have a certain risk of exposure to HBV through body fluids or blood during the classes, even though most of them are negative for anti-HBs. In addition, recently

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8 million foreign tourists visit Japan and 18 million Japanese nationals travel abroad each year. This has resulted in the rapid development of Japan's internationalization. Consequently, HBV genotype A infections as a sexually-transmitted disease have increased in urban areas of Japan, and then spread to other areas.[29] Thus, this might have increased the risk of horizontal HBV transmission in Japan, particularly in young individuals without HBs antibodies. Therefore, there is an urgent need to prevent horizontal HBV transmission in Japan, and thus the introduction of a universal HBV immunization program is both needed and desirable.

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