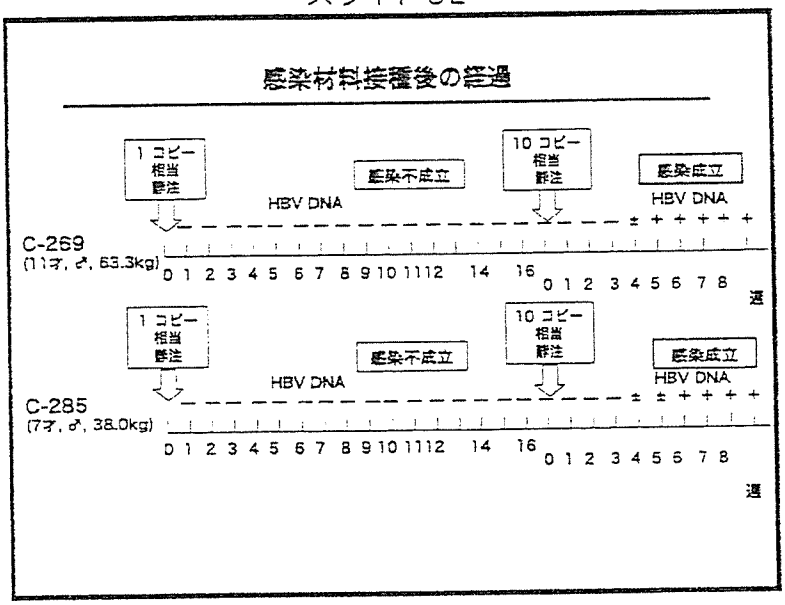
スライド32

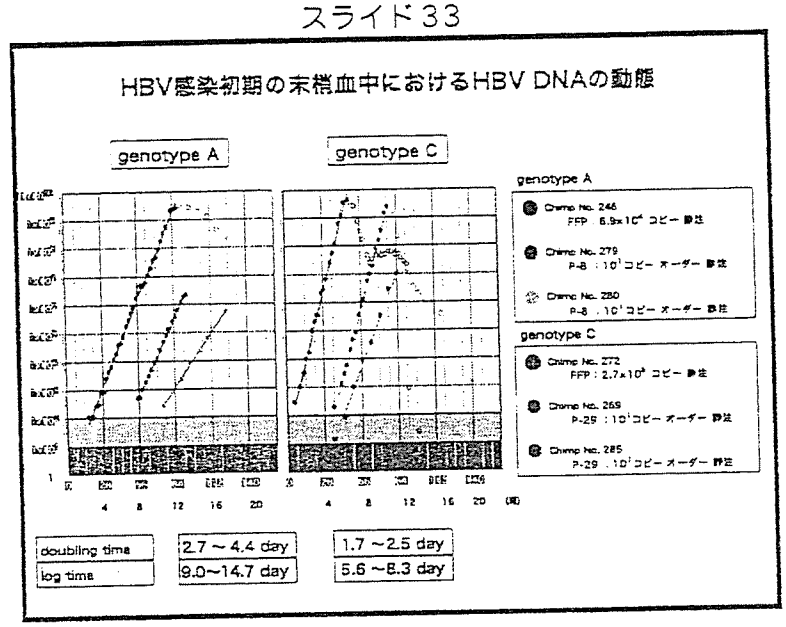


感染成立後の末梢血中における HBV DNA が２倍量に増えるために必要な時間（doubling time）を求めるとジェノタイプＡの HBV の場合は 2.7 日～4.4 日、ジェノタイプＣの HBV の場合は 1.7 日～2.5 日となりました。同様に 10 倍量に増えるために必要な時間（log time）を求めると、ジェノタイプＡの HBV の場合は 9.0 日～14.7 日、ジェノタイプＣの HBV の場合は 5.6 日～8.3 日となることがわかりました。

また、感染成立に必要な最少 HBV 量（10 コピー相当）を接種した場合の核酸増幅検査（NAT）のウインドウ期間（末梢血中の HBV 量が 10^2 コピー/ml に達するまでの期間）は、ジェノタイプＡの HBV の場合は８週～11 週、ジェノタイプＣの HBV の場合は５週～７週であることが明らかとなりました。

一方、検出感度の高い酵素抗体法（EIA 法）で検出した場合の HBs 抗原のウインドウ期間は、ジェノタイプＡの HBV の場合は 10 週～14 週、ジェノタイプＣの HBV の場合は７週～９週であることが明らかとなりました。

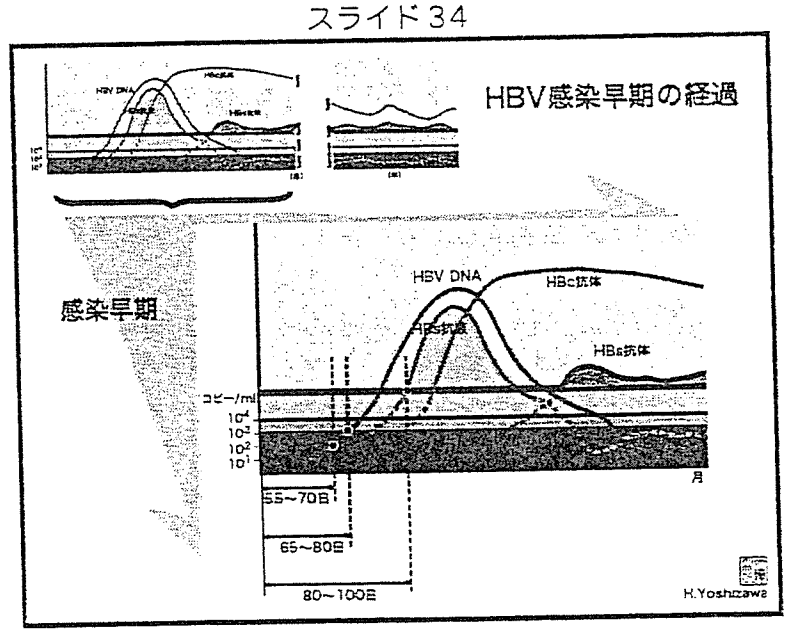
スライド33



感染実験によって得られた結果をもとに、「HBV感染早期」の経過をまとめるにあたっては、安全を見込むために増殖速度が遅いジェノタイプAのHBVを感染させて得られたデータをもとに作図することが望ましいと考えられます。

そうしますと、HBVに感染してから、日赤血液センターにおいて日常検査として行われている核酸増幅検査（ミニプールNAT）によるHBV DNAのウインドウ期間は65日～80日を、最も検出感度が高いEIA法によるHBs抗原のウインドウ期間は80日～100日を見込む必要があるということになります。

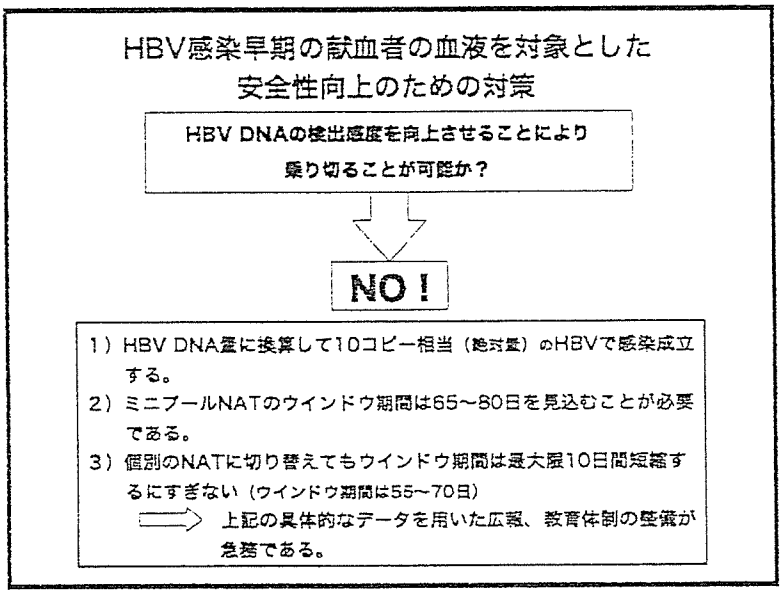
スライド34



つまり、結論はこういうことになります。すなわち、「HBV感染早期」の血液を対象とした場合、核酸増幅検査（NAT）によるHBV DNA検査も含めて、検査によって血液の完璧な安全性を確保することは、そもそも不可能であるということです。

従って、残された方法は、感染実験によって得られたデータも含めて、これまでに話した具体的なデータを用いた広報と教育を徹底して行うことに尽きると言うことになります。

スライド35



これまでの話をまとめるとこうなります。

日赤血液センターが自主的に行った調査から、以下のようなことがわかりました。すなわち、わが国では年間約100万人が輸血を受け、このうちの約50万人が輸血後1年以上にわたって生存することができている。この約50万人の中で、最大限に見積もっても年平均20人前後の輸血後B型肝炎が発生しているにすぎず、その感染源のほとんどは「HBV感染早期」に献血された血液であるということです。

このわずかに残っている輸血後肝炎の発生数を1例でも減らすためには、3つのHBV感染の態様を十分に理解した上でそれぞれの態様に則した合理的な対策を立て、実施に移す必要があるということになると思います。

そして、検査によってはどうしても捉えることができないHBV感染早期の献血者の血液に対する対応としては、HBV感染早期の自然経過を基とした具体的なデータを用いた広報、教育を徹底して行う以外に方法は無いということになると思います。

スライド36

まとめ

1）輸血後B型肝炎の現状

HBs抗原検査、HBc抗体検査、NATによるHBV DNA検査を組み合わせたスクリーニングの導入により、わが国における輸血後B型肝炎の発生数は最大限に見積もっても年間20例前後にまで減少したと推定される。

2）輸血後B型肝炎の更なる減少のために

HBV感染の特性に基づいた合理的な対策の樹立

（1）（定型的な）HBV持続感染者（HBVキャリア）

現行のHBs抗原検査のみで充分対応が可能

（2）（非定型的な）HBV持続感染者（HBV感染既往/感染時期）

HBc抗体価の測定とHBV DNA検査（NAT）を合理的に組み合わせたスクリーニングの実施

（3）HBV感染の新規発生（HBV感染の早期）

現行のHBs抗原とHBV DNA検査（NAT）を組み合わせたスクリーニングの実施

献血者を対象とした安全教育の実施

・HBV感染の回避、検査を目的とした献血の停止など

3）今後の目標

輸血後B型肝炎の発生ゼロは関係者の共通の到達目標である。

最後に、今回用いたデータは、スライドに示す３つの研究グループに所属する人々を始めとする多くの共同研究者の10年以上にわたる献身的な努力によって得られたものであることを付け加えておきたいと思います。

長時間にわたり、御清聴ありがとうございました。

スライド37

謝　辞

本研究を共に推進した下記の方々に深く感謝いたします。

1．日本赤十字社　NAT研究グループ

Yuji Hoshi BS	JRC Tokyo NAT center
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Hiroyuki Murokawa BS	JRC Tokyo NAT center
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Hidetaka Minagawa PhD	Fujirebio Inc. Japan
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Yutaka Komiya MD	Hiroshima University
Junko Tanaka PhD	Hiroshima University
Hiroshi Yoshizawa MD	Hiroshima University : chairman

【飯野】どうもありがとうございました。会場のほうから，どなたかご質問はありませんか。

実際，以前は健康保険の制約がいろいろあって，輸血後 virus marker の検査ができないということがありましたが，実際的にはＢ型肝炎というのは，感染して，トランスアミラーゼが 1,000 程度上がっても，自覚症状がない感染者，そしてそのまま治っていく。あるいは最近の例ですと，ジェノタイプＡだとそのままキャリア化するのが現実にはいるので，輸血後で発生するＢ型肝炎は，つかまらないのがもう少し多いのかもしれませんね。

ですから，保険のほうで制約があったから，輸血後でも臨床の先生は，そうでなくても検査しないのですが，それを徹底するようなことも，輸血後肝炎の実態をはっきり知るためには必要ですね。

【吉澤】その通りだと思います。

輸血前、後のウイルスマーカーの検査については、平成 17 年（2005 年）3 月に厚生労働省から「血液製剤等に係る遡及調査ガイドライン」が出され、HBV、HCV、HIV の検査については、（原則として）保険で認められることになりました。

ただ、モデル地区を選んで、pilot 的に全数調査をやってみると、受血者の 2.2%（22/1,021）は輸血前から HBV DNA が陽性、すなわちキャリアであること、また、8.6%（86/1,000）は輸血前から HCV RNA が陽性、すなわち HCV キャリアであることがわかりました。

ですから、受血者の検査をする際には、必ず輸血前の血清を保存しておくことが必要です。ちなみに、輸血後に HBV が陽転したのは 9 例（0.9%）、HCV が陽転したのは 2 例（0.2%）でしたが、このうち輸血に用いた血液が感染源になったことが立証されたのは HBV が陽転した 1 例だけでした。

輸血が原因で、HBV、HCV 又は HIV に感染したとの因果関係が立証された場合には、救済制度が設けられています。

【飯野】キャリアというか，非常に幅の広い意味のキャリアですね。既感染者のウイルスの動態は，常に増えたり減ったりしているわけですね。免疫状態，ＨＢｓ抗体の状態と思いますが，抗体が減ってくればウイルスが表に出てくるという状態は，ある意味では始終起こっている現象かもしれませんね。

ですから，そこのところの問題ですが，先生がちょっとおっしゃいましたが，日赤が 50 本プールから 25 本プールにしましたね。個別ＮＡＴでも無理な話で，それはお金が倍かかっているわけで，そこで得られるメリットは微々たるものですね。

【吉澤】メリットと言える程のものは得られないと思います。

HBV DNA の検出は桁の問題ですので…。

【飯野】「微々たる」と言ったのは，吉澤先生と同じ意味ですが。

【吉澤】はい。

【飯野】そのお金の分で，もう少し有効に使うべきで，50 本に戻したほうが……。500 本から 50 本というのは，そこの領域は意味があるのだけれども，そのあとは 2 倍しか上がらないので，ほとんどナンセンスですよね。そこに属する集団は，ほとんどない

わけですから。50本に真そうという話はないのですか。こんなばかばかしいことはやめようと。

【吉澤】今のところはないようです。

今日のような話を聞いていただいて、多くの方々に理解してもらうしか方法はないのかも知れません。そんなことを考えて、今日、この時間をいただいたわけです。

【飯野】会場のほうからどなたかありませんか。いろいろな方には，感覚的にわかっても，すべてクリアにはなかなかわかってもらえない。特に行政の方にはそうだろうと思いますが，どなたかいかがでしょうか。

【会場】HBc抗体陽性（HBs抗原は陰性）の血液の輸血によりHBVに感染した場合、受血者が劇症肝炎になる頻度は高いのでしょうか。

【吉澤】日赤血液センターが行なった遡及調査により見出された輸血後B型肝炎例でみる限り、必ずしも全ての例が劇症化するとは限らないようです。

一方、HBc抗体測定によるスクリーニングが導入された1989年11月以前にB型劇症肝炎と診断された患者では、輸血が原因となっていたことを推定させる例が比較的多くみられたと言われています。

ですから、ご質問の件については、まだはっきりした答は得られていないというのが実際だろうと思います。

【飯野】ＨＢｃ抗体の200倍というのは頭から一切除いて，ＨＢｃ抗体というものをもう少し広く測定をして，ＨＢｃ抗体陽性者については，特にステロイドホルモンを含む免疫抑制剤を使う。これは極端な場合だけはいま注目されていますが，悪性腫瘍などで免疫抑制剤，抗腫瘍剤を使うとき，一般的な他の人たちでも結局同じことですよね。

【吉澤】そうです。

【飯野】そういうときに，ウイルスのreactivationを引き起こしているということを，みんなが認識しなければいけない時代だと思うのですが，どうでしょうか。

【吉澤】その通りだと思います。

occult infectionとか、低濃度キャリアとか、非定型的なキャリア状態とか、これまで様々な名前で呼ばれてきましたが、ウイルス学的には「HBV感染晩期」の状態という名前で1つにくくることができるのではないかと思います。この状態にある人は、HBc抗体の力価にかかわらず、肝細胞の中にHBVが存在し続けているわけですから、どのような原因であれ、生体側の免疫が低下すればreactivationを引きおこすということを認識した上で経過を見ていただくことが大事だと思います。結核の石灰化巣とreactivationとの関係を思いうかべるとわかりやすいのではないでしょうか。

ただし、一般には急性B型肝炎あるいは定型的なキャリア状態から離脱して臨床的に治癒した後は、ほとんどの人はそのまま健康な状態で生涯を全するわけですから、いたずらに不安をあおることは必要のないことだろうと思います。

【飯野】吉澤先生，長時間ありがとうございました。

Reprinted from

Congenital and Other Related Infectious Diseases of the Newborn

Editor

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Abbott Park, IL 60064, USA

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Amsterdam – Boston – Heidelberg – London – New York – Oxford – Paris
San Diego – San Francisco – Singapore – Sydney – Tokyo

Congenital and Other Related Infectious
Diseases of the Newborn
Isa K. Mushahwar (Editor)

DOI 10.1016/S0168-7069(06)13008-6

Perinatal Hepatitis B Virus Infection in Japan

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Introduction

In areas where infection by hepatitis B virus (HBV) is prevalent and persistent, perinatal transmission from HBV-infected mothers is an essential route for establishing a persistent carrier state.

These babies carrying HBV can transmit it via a secondary horizontal route to infants of the same generation, who frequently acquire persistent HBV infections. Approximately 30% of the infants exposed to HBV when under 3 years of age become HBV carriers. Together, they serve as a reservoir of HBV throughout their lives in the community, and may therefore cause, or contribute to, a continuous spread of the infection.

Perinatal HBV infections resulting in the persistent carrier state occur in approximately 90% of babies born to mothers who are positive for hepatitis B surface antigen (HBsAg) as well as hepatitis B e antigen (HBeAg) in the serum (Okada et al., 1976; Stevens et al., 1979). Persistent infections rarely occur in babies born to mothers who carry HBsAg, but are negative for HBeAg or are positive for the antibody to HBeAg (anti-HBe). Only around 10–15% of babies contract transient HBV infections (Shiraki et al., 1980).

In countries where the prevalence of HBsAg is less than 0.2–1.0% in children, the perinatal HBV transmission is the major route where the HBV carrier state is established. In these countries, a selective vaccination program, i.e., combined passive–active immunoprophylaxis of babies born to mothers with HBsAg and HBeAg by anti-HBs hyper-immune globulin (HBIG) and hepatitis B vaccine (HB vaccine), is a rational approach to the control of HBV infection.

In contrast, in countries where the prevalence of HBsAg exceeds 8%, perinatal transmission accounts for only 10–20% of infants who are persistently infected with HBV (Yao, 1996; Lee, 1997). Since horizontal transmission to children younger than 5 years old is the major route by which the HBV carrier state becomes established in these hyperendemic countries, universal vaccination of babies is recommended.

It is important to realize that universal vaccination prevents mainly horizontal HBV transmission, but not perinatal HBV infection. In addition, the fact that universal vaccination has the potential for inducing HBV mutants remains a serious problem of this particular approach (Zanetti et al., 1988; Brunetto et al., 1999).

In two model areas in Japan, Shizuoka and Iwate prefectures, the immunoprophylaxis of babies born to HBV carrier mothers with HBeAg, by means of combined hepatitis B HBIG and HB vaccine, was started as a clinical trial in the early 1980s and became a national project in 1986. This chapter presents an account of the experience gained in the prevention of perinatal HBV transmission from the 1980s into the 1990s in Shizuoka and Iwate prefectures.

Carrier rates of hepatitis B virus in Japan

To understand the sero-epidemiological background of HBV infection in Japan, the age-specific HBV carrier rates were estimated on a national basis (Tanaka et al., 2004). To avoid selection bias, only the data of first-time blood donors aged 16–64 years in the Japanese Red Cross Blood Center were collected and analyzed.

During the 6 years from January 1995 to December 2000, 3,485,648 individuals visited their local Japanese Red Cross Blood Centers for the first time to donate blood. The proportion of HBsAg-positive subjects, determined by reversed-passive hemagglutination (R-PHA) reagents made in-house by the Japanese Red Cross Blood Center, was calculated. To ascertain the influence of age on the proportion of HBsAg-positives, the ages of all first-time blood donors were adjusted, taking the year 2000 as the current year. The sex- and age-specific HBsAg-positive rates are shown in Table 1. Overall, HBsAg was detected in 22,018 (0.63%) of 3,485,648 blood donors. The prevalence of HBsAg was significantly higher in men (0.73%) than in women (0.53%, $p<0.001$), and increased in both with time until the age of 60 years. The HBsAg-positive rates were lowest in the age group under 20: 0.26 and 0.20% in men and women, respectively.

These data suggest that the improvement of sanitary conditions in Japan has helped to decrease the horizontal transmission of HBV and the HBV carrier state in the age groups born before the prevention of perinatal HBV transmission was started in the 1980s.

Prevention of perinatal transmission of hepatitis B virus in Japan

The prevention of perinatal HBV infections has been followed up in two model areas of Japan, namely, Shizuoka and Iwate prefectures.

Table 1

Age-specific HBsAg positive rates in first-time male and female blood donors in Japanese Red Cross Blood Center from 1995 to 2000

Age groups in 2000 (year of birth)	Total number of first-time donors	HBsAg positives (%)	Men		Women	
			Number	HBsAg positives (%)	Number	HBsAg positives (%)
16–19 (1981–1984)	582,415	1327 (0.23)	273,842	709 (0.26)	308,573	618 (0.20)
20–29 (1971–1980)	1,929,147	10,054 (0.52)	1,004,986	5955 (0.59)	924,161	4099 (0.44)
30–39 (1961–1970)	472,447	3988 (0.84)	277,627	2828 (1.02)	194,820	1160 (0.60)
40–49 (1951–1960)	247,020	2950 (1.19)	120,576	1796 (1.49)	126,444	1154 (0.91)
50–59 (1941–1950)	198,477	2984 (1.50)	80,336	1388 (1.73)	118,141	1596 (1.35)
60–69 (1931–1940)	56,142	715 (1.27)	22,782	314 (1.38)	33,360	401 (1.20)
Total	3,485,648	22,018 (0.63)	1,780,149	12,990 (0.73)	1,705,499	9028 (0.53)

In Shizuoka prefecture, immunoprophylaxis of perinatal HBV infection was initiated in 1980 as a clinical trial and became a national project in April 1986 (Noto et al., 2003). In a similar way in Iwate prefecture, following the clinical trial that began in 1981, prophylaxis of perinatal HBV infection in all babies was started in 1986 (Koyama et al., 2003).

The same protocol was used in both prefectures, and was executed as follows: babies born to HBV carrier mothers who were HBeAg reactive (high-risk babies) received HBIG at birth (within a maximum of 48 h after delivery) and the second injection was given 2 months thereafter. The babies were inoculated with HB vaccine 2, 3 and 5 months after birth and were followed until the baby reached 12 months of age (arrows, Fig. 1). In cases in which the antibody titer fell to less than 22–23 PHA, inoculation was repeated as necessary at months 9 and 12 (arrows in parentheses).

Immunoprophylaxis of perinatal HBV transmission in Shizuoka prefecture and its effectiveness in decreasing the transmission of the HBV carrier state

Shizuoka prefecture is located near the center of the main island of Japan, at the foot of Mt. Fuji, and has 3.6 million residents. In this prefecture, the first clinical trial was started in 1980 (Tanaka et al., 2004).

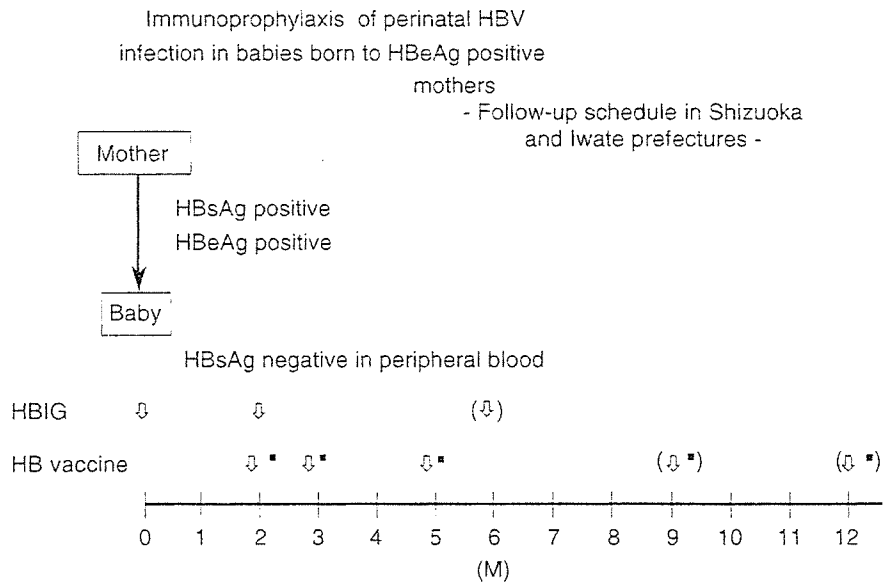

Fig. 1 Prevention of perinatal transmission of HBV: follow-up schedule in Shizuoka and Iwate prefectures. Babies born to HBsAg and HBeAg-positive mothers received two injections of HBIG ⇩ and three inoculations of HB vaccines ↓ at indicated time points. Serological tests for HBsAg and anti-HBs were performed monthly. During the follow-up period, anti-HBs titer was maintained at more than 2^3 PHA titer (equivalent to 200 mIU/ml) with appropriate use of HBIG or HB vaccine, or both. (⇩), and (↓), until 12 months after birth. During the follow-up period, when HBsAg became positive, all the prevention programs were stopped.

During the 5 years from 1980 to 1985, a total of 172 high-risk babies received immunophylaxis in a clinical trial. Of them, 166 (96.5%) were protected successfully so that they did not become HBV carriers, but this outcome could not be prevented in the remaining 6 babies (3.5%).

In 1985, the year of transition of the clinical trial to a national program status, out of 94 high-risk babies receiving immunoprophylaxis, 85 (90.4%) were protected, while the treatment failed in 9 (9.6%). During the first 9 years of the national project from 1986 to 1994, 764 high-risk babies received immunoprophylaxis. A total of 729 (95.4%) were protected, but the HBV carrier state developed in the remaining 35 (4.6%).

Overall, passive–active immunoprophylaxis following the protocol shown in Fig. 1 was effective in preventing persistent HBV infection in 980 (95.1%) of the 1030 babies born to HBeAg-positive HBV carrier mothers, but the HBV carrier state developed in the remaining 50 babies (4.9%) (Noto et al., 2003).

To estimate the efficacy of immunoprophylaxis of HBV infection, changes in the prevalence of HBsAg and anti-HBs in elementary school children (7–12 years of age) were compared in groups divided according to their birth year (Table 2). The children in group I were born before 1980 the year when the immunoprophylaxis of HBV was initiated. Those in group III were born after 1985, when the national

Table 2

Prevalence of HBsAg and anti-HBs among elementary school children in Shizuoka prefecture, divided into 3 groups according to birth year

Group	Number tested	HBsAg positives (%)	Anti-HBs positives (%)
I. Born before 1980	3446	7 (0.20)	33 (0.96)
II. Born in 1980–1985	46,993	77 (0.16)	260 (0.55)
III. Born after 1985	23,792	2 (0.01)	51 (0.21)
Total	74,231	86 (0.21)	344 (0.46)

program to prevent perinatal HBV infection commenced. The group II children were born in the period sandwiched between the clinical trial and the national program.

The prevalence of HBsAg gradually decreased from group I (0.20%), to group II (0.16%) to group III (0.01%). Likewise, the prevalence of anti-HBs decreased in a similar manner from group I (0.96%), to group II (0.55%) and group III (0.21%).

These results indicate that, in Japan, preventive measures taken against perinatal HBV infection were largely effective in decreasing the transmission of the HBV carrier state including that due to horizontal infection.

Prevention of perinatal HBV transmission in Iwate from 1981–1992 and sero-epidemiological evidence for its effectiveness

In Iwate prefecture, which has a population of 1.4 million, the clinical trial of prevention of perinatal HBV transmission was started in 1981. In 1985, the year of transition from clinical trial to national program, almost all babies born to HBeAg-positive HBV carrier mothers were given immunoprophylactic treatment (Koyama et al., 2003).

During that year, 39 (86.7%) of 45 babies who received immunoprophylaxis were protected against HBV. During the 7 years from 1986 to 1992, 100,286 (96.0%) of 104,493 pregnant women received tests for HBsAg, and it was detected in 1242 (1.2%) of them. Of those HBsAg-positives, 257 (20.7%) were positive also for HBeAg and all of their babies received immunoprophylaxis (Table 3).

The effectiveness of the immunoprophylaxis of perinatal HBV infection was clearly reflected in the changes in prevalence of HBsAg among elementary school children aged 7–12 years (Table 4). They were divided into three groups according to their birth year. In the group born between 1978 and 1980, before the start of the clinical trial of immunoprophylaxis, the prevalence of HBsAg was 0.75% (78/10,437). The prevalence of HBsAg was already decreasing among those who were born from 1981 to 1985, during the period of the clinical trial on prevention. In this group of subjects, the prevalence of HBsAg was 0.22% (46/20,812). The decrease was more prominent in children born after 1985, since the national program of

Table 3

Babies who were treated to prevent perinatal HBV transmission from 1981 to 1992 in Iwate, Japan

Year	Number of deliveries	HBsAg tested (% of deliveries)	HBsAg (+) (% of tested)	HBeAg (+) (% in HBsAg)	Prevention (% of HBeAg (+))
Before national program (1981–1985)					
1981	18,600	ND	ND	ND	1
1982	18,581	ND	ND	ND	12
1983	19,582	ND	ND	ND	18
1984	18,043	ND	ND	ND	29
1985	17,232	10,628 (61.7)	ND	45	39 (86.7%)
After start of national program (1986–1992)					
1986	16,536	15,872 (96.0)	244 (1.4)	47 (19.3)	47 (100.0)
1987	15,567	15,205 (97.7)	241 (1.6)	60 (24.9)	60 (100.0)
1988	15,410	14,282 (92.7)	166 (1.2)	40 (24.1)	40 (100.0)
1989	14,548	14,541 (99.9)	179 (1.2)	25 (14.0)	25 (100.0)
1990	14,254	13,997 (98.2)	161 (1.2)	42 (26.1)	42 (100.0)
1991	14,270	13,245 (92.8)	136 (1.0)	21 (15.4)	21 (100.0)
1992	13,908	13,144 (94.5)	115 (0.9)	22 (19.1)	22 (100.0)
Total	104,493	100,286 (96.0)	1242 (1.2)	257 (20.7)	257 (100.0)

Note: ND, no data available.

immunoprophylaxis was set in motion. HBsAg was detected in only 12 (0.04%) of 32,049 children born between 1986 and 1990 ($p<0.001$ against the prevalence in t he children born between 1981 and 1985). Likewise, the prevalence of anti-HBs decreased from 1.52% (159/10,437) in those born from 1978 to 1980, to 0.79% (165/20,812) in those born from 1981 to 1985, and 0.85% (274/32,049) in the children born between 1986 and 1990 ($p<0.001$).

The rate of anti-HBc-positives among the children with anti-HBs decreased from 81.9% (127/155) among those who were born in the years 1978–1980 to 43.3% (68/157) in those born in 1981–1985, and finally to 11.0% (59/536) in those born in 1986–1994 (Table 5). These results indicate that preventive measures against perinatal HBV infection could eventually result in the prevention of horizontal transmission among children in the same age groups.

Prevalence of surface antigen mutants

Serum HBV DNA from 15 infants and 11 mothers with chronic hepatitis acquired by either intra-uterine infection or post-vaccination prophylaxis were cloned then followed by direct sequencing of the HBV genome encoding the major antigenic

Table 4

Changes in prevalence of HBsAg and anti-HBs in 3 groups of elementary school children devided according to birth year

Year of birth	Number tested	HBsAg positives (%)	Anti-HBs positives (%)
Before immunoprophylaxis (1978–1980)			
1978	2666	26 (0.94)	52 (1.95)
1979	4212	27 (0.64)	72 (1.71)
1980	3559	25 (0.70)	35 (0.98)
Subtotal	10,437	78 (0.75)	159 (1.52)
During clinical trials of immunoprophylaxis (1981–1985)			
1981	2541	12 (0.47)	30 (1.18)
1982	1594	4 (0.25)	12 (0.75)
1983	3847	6 (0.16)	17 (0.44)
1984	6206	11 (0.18)	58 (0.93)
1985	6624	13 (0.20)	48 (0.72)
Subtotal	20,812	46 (0.22)	165 (0.79)
After start of national immunoprophylaxis program (1986–1990)			
1986	6775	3 (0.04)	41 (0.61)
1987	6505	4 (0.06)	62 (0.95)
1988	6310	2 (0.03)	58 (0.92)
1989	6436	2 (0.03)	64 (0.71)
1990	6023	1 (0.02)	67 (1.11)
Subtotal	32,049	12 (0.04)	292 (0.91)

epitopes of HBsAg (amino acids 100–200). The results of this analysis are listed in Table 6, and the following observations are listed as noted below:

1. Three novel HBV variants were detected in babies and their mothers, namely, I126T and S114T (Cases 1/I and 5/I) that were acquired by intrauterine infection. Also variant P127T in both mother and baby (Case 5/L) indicating vertical transmission. To our knowledge, these variants have not been reported previously.
2. Another novel variant, namely, G145A (Case 4/L) was detected in the baby but not his mother. This variant has been reported to occur naturally in sera of HBV chronic carriers in Korea (Song et al., 2005).
3. Analysis of all other remaining cases revealed that mixed populations of wild type and mutant viruses are found in all the tested infants and their mothers.
4. Many of the surface antigen mutants that were identified in the babies were not found in their mothers. This finding is similar to previously reported work (Nainan et al., 2002).
5. A surprising finding was the absence of supposedly the most predominant HBsAg variant, namely, G145R from the sera of the babies and their mothers.

Table 5

Prevalence of anti-HBc among elementary school children positive for anti-HBs, divided by birth year

Year of birth	Anti-HBs positive children	Anti-HBc positives (%)
Before immunoprophylaxis (1978–1980)		
1978	49	40 (81.6)
1979	72	64 (88.9)
1980	34	23 (76.7)
Subtotal	155	127 (81.9)
During clinical trials of immunoprophylaxis (1981–1985)		
1981	30	23 (76.7)
1982	12	9 (75.0)
1983	14	6 (42.9)
1984	58	18 (31.0)
1985	43	12 (27.9)
Subtotal	157	68 (43.3)
After start of national immunoprophylaxis program (1986–1994)		
1986	41	10 (24.4)
1987	61	11 (18.0)
1988	58	9 (15.5)
1989	46	6 (13.0)
1990	67	6 (9.0)
1991	62	7 (11.3)
1992	72	2 (2.8)
1993	63	5 (7.9)
1994	66	3 (4.6)
Subtotal	536	59 (11.0)

Instead, variant G145A was idetified (Cases 5/I, 2/L and 4/L). This variant has already been reported to occur naturally in sera of HBV chronic carriers in Korea (Song et al., 2005).

6. Another novel HBV variant, namely, K141E was found in a baby (Case 4/I). This is the second report of such a finding. Originally, this unique variant was identified in the sera of two Gambian children (Karthigesu et al., 1994).
7. Of interest is the presence of the novel mutant T118K (Case 2/L). This mutant has been reported once in the literature (Kfoury et al., 2001), and it is found outside the HBsAg "a" determinatnt region (amino acids 124–147) just as the case with mutant S114T (Cases 1/I and 5/I). HBsAg mutations outside the "a" determinant have been reported to damage the immunodominant region structure and thus alter the group specific dominant antigenicity (Kfoury et al., 2001). Hence, the reason we are reporting in Table 6 a variety of HBsAg mutants outside the "a" determinant itself. Current studies show that the HBsAg loop extends much further than initially believed, because other

Table 6

Mutation in the S gene of HBV DNA clones from 15 HBV positive babies and some of their mothers

Babies			Mothers		
Case/ group	Clones tested	Variant[a]	Case/ group	Clones tested	Variant[a]
1/I	21	I126T[b]	1/I	23	I126T[b]
2/I	22	Q101R, Q129R, W156R, W172R	2/I	23	P105L, T116I, K122E, C137R, L162P
3/I	6	M133T, S174G	3/I	20	A157T, L162P
4/I	12	P135S, K141E, F158S, F161S, L176P	4/I	17	Y100H, S132P, S154P, F158S, F161S
5/I	14	S114T[b], G145A[b]	5/I	16	S114T[b], G145A[b]
6/I	24	L109P, S136P, S155Y	6/I	23	T113A, G119R, S136P, T148A
7/I	22	S113A, S117C, T118P, C139Y N146D, L176P	7/I	24	G112E, S117N, Q129H, S132L, C149Y, R160G, F170L
8/I	23	P142L	8/I	23	L109P, S114P, C124R, T131A, C138R, S171F, W172C, W172R
9/I	24	G130E, T148A, C149R, S171F	9/I	24	S117R, C121G, Q129P, M133I, P135L, S171P
10/I	17	C121S, T115A	10/I	0	NT
1/L	10	T116A[b]	1/L	0	NT
2/L	10	T118K, G145A	2/L	0	NT
3/L	10	I126T, T131A	3/L	0	NT
4/L	16	G145A[b]	4/L	14	C124R, C137R
5/L	19	P127T[b]	5/L	20	P127T[b]

Note: I, intrauterine infection; L, late-phase infection; NT, Not Tested.

[a]Amino acid substitution in "a" determinant (124–147) and outside "a" determinant (100–123 and 148–176).

[b]Novel variants, no wild-type virus present.

conserved epitopes have been found also between amino acids 100 and 200 (Kfoury et al., 2001; Gerlich, 2004).

The data shown in Table 6 illustrate that changes in either the major hydrophilic loop of HBsAg or outside it are common and do play an important role in transfusion safety, HBV vaccine efficacy and diagnostic accuracy and reliability.

Acknowledgments

This work was executed under the guidance of the Special Committee for Preventing Hepatitis B both in Iwate and Shizuoka, supported by the Department of Public Health of Iwate and Shizuoka Prefecture Government, respectively. We are very appreciative of all medical and co-medical staff members in departments of obstetrics and pediatrics in Iwate and Shizuoka who participated actively and practically in this project.

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最新医学・別冊　新しい診断と治療のABC 44　(別刷)

消化器 6　肝 硬 変

我が国における肝硬変の疫学

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第1章　概念・定義と疫学

我が国における肝硬変の疫学

要旨

肝硬変を含む肝疾患および肝癌の大半は肝炎ウイルス（B型肝炎ウイルス：HBV，C型肝炎ウイルス：HCV）の持続感染に起因すること，また現在の我が国における肝癌の 80％以上は HCV の持続感染に起因することが明らかとなっている．年齢階級別にみた HCV キャリア率と肝発癌の好発年齢とから，現在の我が国における肝癌死亡数は頭打ちの状態を迎えており，今後 5 ～ 10 年以内に我が国における肝硬変を含む肝疾患および肝癌による死亡数は自然減少に転じると推測された．

●キーワード

肝硬変
肝癌
C型肝炎ウイルス キャリア
B型肝炎ウイルス キャリア

はじめに

肝硬変は，種々の原因により長期間に持続する肝細胞障害（慢性の肝障害）の修復機転としての肝臓の線維化が進行した結果，肝小葉が線維によって囲まれた再生結節によって置換・改変された状態を示すと定義されている．

我が国では，肝硬変は肝癌を終末病変とする肝炎ウイルスの持続感染の中途病態と考えられることから，必ずしも厳密に診断し，集計されているわけではないこと，また画像診断などの診断技術の進歩により肝硬変，肝癌の診断基準が時代ごとに異なることなどから，“肝硬変”のみを取り上げてその疫学的実態について述べることは困難であると言える．

したがって，本稿では主として肝炎ウイルスの持続感染の終末像としての肝癌に焦点を当てて述べることにより，与えられた任務を全うしたい．

我が国の肝疾患，肝癌による死亡の推移

図 1 は，1950 年から 2004 年までの我が国における肝疾患，肝癌に