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Effectiveness of combined intramuscular and intravenous administration of hepatitis B immunoglobulin to newborns in preventing mother-to-child transmission of hepatitis B virus

Running title： combined intramuscular and intravenous administration

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Abstract:

Objective While achieving a good success rate of approximately 95% in preventing mother-to-child transmission of hepatitis B virus (HBV), 10-20% of infants born to HBeAg-positive or high-viral-load mothers still become infected.

Study Design To strengthen the prevention of HBV MTCT at birth, intravenous injection was added to the conventional regimen of intramuscular hepatitis B immune globulin (HBIG) administration immediately after delivery, thereby achieving a more rapid rise in blood antibody levels. Vaccination was initiated once antibody titers had declined to a certain level.

Results The study method maintained higher levels than existing methods for approximately 4 months post-delivery. No infection was detected at one year of age in the seven HBeAg-positive cases(including two involving in utero infection) and the five cases with high viral loads (≥5.3 log IU/mL).

Conclusions Designed to protect newborns from HBV infection by enhancing their defenses against infection immediately after birth, this offers a new option.

Keywords hepatitis B virus, mother-to-child transmission, hepatitis B immune globulin, immunoprophylaxis

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Introduction：

In Japan, from 1995 to 2013, two methods were used to prevent mother-to-child transmission (MTCT) of hepatitis B virus (HBV): the former Ministry of Health, Labour and Welfare (MHLW) method and the CDC method. Subsequently, the current MHLW method, based on the CDC method, became the new standard. Both methods have good preventive and therapeutic outcomes, achieving an MTCT prevention rate of approximately 95% for all births in mothers with persistent HBV infection. However, the remaining 5% of cases indicate that prevention is not yet complete [1–5].

In a study of 10,012 cases conducted at our center over seven years from March 2002 to March 2009, prior to the start of this research, the hepatitis B surface antigen (HBsAg) positivity rate was 0.56%, and MTCT prevention was performed using the former MHLW method. The MTCT prevention rate among HBsAg-positive cases was 96.0%, largely consistent with rates observed in other countries. However, when the evaluation was limited to hepatitis B e antigen (HBeAg)-positive cases, approximately 15% of infants acquired the infection from their mothers and developed persistent infection [6]. Internationally, many countries use the CDC method for MTCT prevention, and surveys of HBeAg-positive cases show that, similar to the results at our hospital, 10–20% of infants experienced MTCT and developed persistent infection [7–13]. The most effective way to prevent HBV MTCT is to prevent acute infection caused by the massive influx of the virus that can occur at birth, while simultaneously ensuring continuous prevention of transmission through close contact with the mother, such as breastfeeding. Intramuscular administration of HB immune globulin (HBIG), as practiced in both the former and current MHLW methods, takes time to raise blood antibody titers, raising concerns

that it may be insufficient when the viral load entering the body at birth is high [14,15]. Although some reports indicate that simultaneous administration of the vaccine and anti-HBs HBIG does not affect vaccine immunogenicity [2], there is a theoretical concern that HBIG binding to epitopes on the vaccine protein could reduce its immunogenicity. Based on these issues, we devised an improved method with the goal of achieving a 100% prevention rate for HBV MTCT. Our new method aimed to ensure that infants maintain sufficient antibody levels to protect against infection immediately after birth.

Materials and Methods

Study participants

This study included infants born to mothers with persistent HBV infection (HBsAg-positive) who visited the National Center for Child Health and Development between 2012 and 2025. For specific clinical trials, the study population was limited to individuals who were HBeAg-positive. We excluded infants born to mothers who were HBs antibody-positive and in whom viral DNA could not be identified by real-time PCR, and infants whose condition at birth required treatment other than HBV MTCT prevention. This study was approved by the Institutional Ethics Committee of our institution (No. 532; January 6, 2012) and subsequently approved under the Clinical Research Act of Japan on January 31, 2019 (CRB3180023). The study procedures encompassed participant enrollment, therapeutic interventions, trial

procedures, data collection, data analysis, monitoring, and auditing. This trial was registered in the Japan Registry of Clinical Trials (jRCTs031180137) and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent for participation in the trial was obtained from participants and their partners.

Implementation period

This trial was conducted from January 6, 2012, to February 18, 2026 (14 years and 1 month).

Protocols for each MTCT prevention method

This was a single-center interventional trial. Participants received a full explanation of the study details and consented to participate. MTCT prevention was performed using the former MHLW method, the current MHLW method, and the study method (Table 1). The former MHLW method is unique to Japan, and its protocol involves administering HBIG (Hebsbulin® I.M.; Japan Blood Products Organization, Tokyo, Japan) at 200 IU at birth and 2 months of age, followed by hepatitis B vaccination (Bimmugen Injection 0.25 mL, KM Biologics Co., Ltd., Kumamoto, Japan) at 2, 3, and 5 months of age (Figure 1). The current MHLW protocol involves intramuscular administration of HBIG (200 IU) at birth, followed by vaccination (0.25 mL) at birth and at 1 and 6 months of age. The study protocol involves the simultaneous intramuscular (200 IU) and intravenous (500 IU) administration of HBIG (Hebsbulin®

IH I.V.; Japan Blood Products Organization, Tokyo, Japan) at birth, followed by hepatitis B vaccination (0.25 mL) at 1, 2, and 4 months of age.

Evaluation of the MTCT prevention rate using a study-based approach

The primary endpoint was the prevention rate of HBV MTCT one year after birth using the study method. HBV MTCT prevention was considered successful if the infant's blood HBsAg test was negative at one year of age, and the prevention rate was evaluated. Secondary endpoints included periodic measurements of anti-HBs titers after birth. Changes in neonatal blood anti-HBs titers over one year after birth were compared among the study method group, the former MHLW method group, and the current MHLW method group, based on the anti-HBs titers at each measurement point. Furthermore, we examined whether the lower limit of the 95% confidence interval for antibody titers at each time point in the study method exceeded 100 IU/L.

Number of participants analyzed for each method

Preventive treatment was administered to seven HBeAg-positive and ten HBeAg-negative cases under the study protocol, five HBeAg-negative cases under the former MHLW protocol, and eleven HBeAg-negative cases under the current MHLW protocol.

Statistical analysis

Statistical differences between groups were evaluated using Welch's t-test, performed as a two-tailed test assuming unequal variances between groups. A *p*-value of less than 0.05 was considered statistically significant.

Results

MTCT prevention rate by study method

Prevention of MTCT was implemented under the study protocol for infants born to seven HBeAg-positive mothers and ten HBeAg-negative. Among the ten HBeAg-negative cases, five had viral loads of ≥5.3 $\log_{10}$ IU/mL, meaning there were a total of 12 high-risk cases for MTCT [16]. In all cases, the infants tested negative for serum HBs antigen at one year of age. Although the number of cases was small, the prevention rate for MTCT was 100% among infants born to HBeAg-positive mothers who completed the one-year follow-up (Table 2). Additionally, there were five cases of infants born to HBeAg-negative mothers with viral loads of ≥5.3 $\log_{10}$ IU/mL, but no MTCT was observed in any of these cases (Table 3). In two cases of infants born to HBeAg-positive mothers, the virus was already present in the umbilical cord blood at birth, indicating intrauterine infection. However, this study method reduced the viral load in the newborns without the need for antiviral drugs, and carrier status was prevented within one year of birth.

Maternal management

Unlike methods involving maternal administration of antiviral drugs such as nucleoside or nucleotide acid analogs prior to delivery, this treatment had absolutely no impact on the mother. Drug dosage control was therefore unnecessary during the perinatal period. In addition, maternal management was easy in all cases, and the perinatal course was stable. With tenofovir disoproxil fumarate, the decision to continue or discontinue breastfeeding must be considered, as its transfer into human milk has been reported [17]. However, this study method was highly favored by mothers because it allowed them to breastfeed with peace of mind. In one case, although MTCT prevention was successful, the mother experienced a postpartum hepatitis flare-up, resulting in severe hepatic dysfunction characterized by elevated total bilirubin levels (≥3.0 mg/dL) and reduced coagulation factors (PT% ≤70%); consequently, treatment with tenofovir disoproxil fumarate was initiated, and breastfeeding was discontinued.

Changes in antibody titers up to one year for each method

Because the efficiency of antibody induction by vaccination varies among individual cases and carries a large margin of error, antibody titers were evaluated for one year after infection prevention. Regarding the study method, because the scope initially included HBeAg-negative individuals prior to the launch of the clinical trial focused

solely on HBeAg-positive individuals, data were available for both groups, allowing comparisons of anti-HBs titer trends. Average antibody titers were higher among HBeAg-positive individuals after 4 months, but the difference was not statistically significant. Therefore, the results from both groups were combined for comparison with other prevention methods (Figure 2A).

Using the former MHLW method, antibody titers showed no significant increase until the third vaccination (at 5 months of age), after which they increased rapidly (Figure 2B). Using the current MHLW method, antibody titers remained approximately 200 mIU/mL after vaccination at birth and at 1 month, then tended to increase between 4 and 6 months, before the third vaccination (at 6 months of age). Using the study method, the lowest antibody titer was approximately 300 mIU/mL before the third vaccination (at 4 months of age), but the average value was more than 100 mIU/mL, higher than that of the other preventive methods. This higher mean value was sustained for roughly four months after birth. Following the third vaccination, the trend resembled that observed with the other methods.

As the timing of clinic visits differed by protocol, the number of patients tested at each month of age varied, reducing evaluation accuracy. Nonetheless, significant differences were observed with the study method compared with the former MHLW protocol during the 1- to 4-month period, while comparisons with the current MHLW

protocol showed a significant difference at 1 month of age but not thereafter. A common observation across all three methods was the sporadic occurrence of cases showing a marked antibody increase from six months of age onward.

Discussion

While existing methods for preventing MTCT are evaluated to achieve a 95% infection prevention rate among pregnant women positive for HBsAg (HBV carriers), MTCT still occurs in 10–20% of cases among those who are positive for HBeAg. Therefore, a new method was devised to improve the rate of infection prevention. Assuming that infectivity and pathogenicity are consistent across viral infections, the viral load at the time of infection significantly influences the post-onset prognosis. For prevention, the most critical factor is blocking the infection during the interval between the entry of viral particles into the body and their arrival at the target cells, where infection is established. The current method of administering HBIG, which is used to neutralize the virus, is intramuscular, and it takes 2–4 days for the blood antibody titer to reach its peak, which is estimated to be approximately 40% of the administered dose. This indicates a time lag between birth, when most virus particles enter the body, and when sufficient neutralizing antibodies necessary for infection defense reach the bloodstream. Consequently, if the viral load upon entry is high,

there is an increased risk of infection owing to insufficient neutralizing antibody titers in the blood. In this method, a rapid increase in blood antibody titers sufficient to withstand the rapid entry of a large number of viral particles at birth is ensured by intravenous administration, followed by intramuscular administration to maintain long-term blood antibody titer, and subsequent antibody induction with a vaccine. Regarding the timing of vaccination, although administering gamma globulin and the vaccine together from birth is generally considered the most efficient approach in terms of adherence, intravenous administration can cause the vaccine to lose its immunogenicity during periods of very high blood antibody titers. Therefore, the vaccine was not administered at the time of HBIG administration at birth; rather, the first dose was started at the check-up one month after birth, when antibody titers had decreased to a certain extent and the infant had the earliest opportunity to visit the clinic. Subsequent vaccine doses were administered at 2 and 4 months of age.

The combination of intravenous and intramuscular HBIG administration at birth is novel, adding intravenous administration to the method previously performed using intramuscular administration alone. We have previously reported the time course of antibody titers up to one month of age; theoretically, the peak occurs immediately after HBIG administration, reaching approximately 3,000 mIU/mL on day 1 of life. In contrast, with intramuscular injection alone, the peak occurred on day 3 at

227 approximately 400 mIU/mL [6]. While the number of vaccinations remains the same
228 as in the existing method (three doses), vaccination was started one month earlier
229 than in the former MHLW method and one month later than in the current MHLW
230 method (CDC method). Regarding safety, since this research method involves
231 adding intravenous injection to the usual intramuscular injection, raising concerns
232 about hyperviscosity syndrome due to increased blood antibody titer. However,
233 previous clinical trials have shown no significant changes in blood IgG levels [6]. For
234 other risks, including infections, standard intramuscular injections are also
235 administered concurrently, so there are no special considerations. Therefore, no
236 safety concerns were identified, and high blood antibody titers could be maintained
237 immediately after birth, achieving a 100% MTCT prevention rate among study
238 participants. Even in two cases in which in utero infection had occurred, no
239 persistent HBV infection was detected at one year of age, suggesting the efficacy of
240 this method.
241 During the research period, the MHLW method was changed, resulting in three
242 types of methods: the former MHLW method, the current MHLW method, and the
243 research method. A comparison of anti-HBs titer trends across these three methods
244 revealed that the study method maintained higher antibody titers immediately after
245 birth compared with the other methods [6]. Furthermore, as the lower limit of the 95%

246 confidence interval for antibody titers at each time point exceeded 100 IU/L, the
247 study method provided coverage extending from birth through breastfeeding. With
248 each method, sporadic cases were observed in which antibody levels increased
249 significantly after 6 months of age. In addition to induction by vaccines, direct
250 immunity induction from the virus in the mother's body through contact with the
251 mother, such as during breastfeeding, may have occurred. Even if the mother has
252 HBeAb and antibodies have been transferred, the risk of infection during
253 breastfeeding is high because the antibodies may have disappeared by this time.
254 However, regardless of the presence or absence of HBeAb or viral load, if the HbsAb
255 titer is sufficiently maintained, infection will not occur.
256 Internationally, antiviral agents are recommended as a countermeasure against
257 high viral loads in mothers, which are associated with increased rates of MTCT [18–
258 20], and their usefulness has been reported [21]. Studies have shown that
259 discontinuing treatment within one month postpartum does not result in problematic
260 liver dysfunction [22], and new guidelines were issued in 2020 [23]. However, options
261 for antiviral drugs are limited because of the emergence of drug-resistant strains
262 [24–26], and accumulated data regarding the safety of placental transfer and
263 breastfeeding are insufficient. If antiviral drugs are used, the first treatment of a
264 lifetime will begin during pregnancy, requiring careful control of maternal disease

progression. Recently, there have been reports of treatment being resumed owing to postpartum flare [27]. Therefore, even if the policy is to discontinue medication after childbirth to avoid impacts on the infant through breastfeeding, postpartum flare must also be taken into consideration. Furthermore, if medication is continued after delivery, the involvement of a specialist is essential to carefully evaluate its potential impact on nursing infants. A viral load of 5.3 $\log_{10}$ IU/mL has been identified as the threshold associated with high rates of MTCT [16], with an HBV DNA level of ≥200,000 IU/mL serving as the threshold for antiviral prophylaxis to prevent MTCT.

This prevention method for MTCT focuses primarily on the immediate postnatal period, when the risk of infection is greatest. It employs a combination of intramuscular and intravenous HBIG injections to rapidly achieve high antibody titers capable of protecting against substantial viral exposure. Subsequently, the lower limit of the 95% confidence interval for antibody titers remained above 100 IU/L throughout the first year of life. No cases of MTCT were observed among seven HBeAg-positive cases, including two cases with in utero infection and five HBeAg-negative cases with high maternal viral loads (5.3 $\log_{10}$ IU/mL). Although this study involved long-term enrollment, the limited number of eligible patients in Japan limits the generalizability of these findings and precludes a robust statistical evaluation of the method's efficacy. Further accumulation of data on cases and treatment

outcomes is needed through continued implementation of this prevention strategy to more conclusively establish its clinical utility.

Considering the safety of both mother and fetus, and with a view to providing long-term infection protection from birth to breastfeeding, this research method, devised from the perspective of "protecting newborns from HBV infection by raising the level of infection protection in newborns," is simple and effective, and we believe that it could be one option in addition to antiviral drug treatment.

Conflict of Interests

The authors declare that they have no competing interests.

Ethics approval and consent participate:

This study was approved by the Institutional Ethics Committee of our institution (No. 532; January 6, 2012) and subsequently approved under the Clinical Research Act of Japan on January 31, 2019 (CRB3180023). This trial was registered in the Japan Registry of Clinical Trials (jRCTs031180137). Written informed consent for participation in the trial was obtained from participants and their partners.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

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*Author Contributions: T*he authors confirm contribution to the paper as follows: study conception and design: K.Yamaguchi; data collection: K.Yamaguchi, K.Tsukamoto, R.Ito, M.Hisano, H Sago, M.Hanaoka; analysis and interpretation of results: K.Yamaguchi, M.Hanaoka; draft manuscript preparation: K.Yamaguchi. All authors reviewed the results and approved the final version of the manuscript.

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Figure Legends

Figure 1. Protocols for each MTCT prevention method

411 ▼indicates the timing of HBIG administration. ◆ indicates the timing of vaccination.

412 HBIG, hepatitis B immune globulin; MTCT, mother-to-child transmission.

413 **Figure 2.** Changes in anti-HBs titers during the first year of life and comparison with

414 other preventive methods

415 Comparison of changes in antibody titers between HBeAg-positive and HBeAg-

416 negative individuals who underwent mother-to-child transmission prevention under

417 the study protocol (A). Antibody titers were higher in HBeAg-positive individuals after

418 4 months of age; however, the difference was not statistically significant. HBeAg,

419 hepatitis B e antigen. Changes in antibody titers across the three prevention

420 methods and comparison with the study method (B)

421 Using the study method, antibody titers were the lowest immediately prior to the third

422 vaccination (at 4 months of age), at approximately 300 mIU/mL. The mean antibody

423 titer remained higher than those observed with the other two methods, exceeding

424 100 mIU/mL from immediately after birth through approximately 4 months of age.

425 Compared with the former MHLW method, significant differences were observed at 1

426 and 4 months of age; compared with the current MHLW method, a significant

427 difference was observed at 1 month of age but not from 2 months onwards. MHLW,

428 Ministry of Health, Labour and Welfare.

Table 1. Treatment methods and target populations

Methods	Applicable period	Patients eligible for treatment	Number of precipitants
Former MHLW method	Jan.1986-Nov.2013	HBs antigen positive	5
Current MHLW method	Dec.2013–Present	HBs antigen positive	11
Study method (clinical study)	Jan.2012–Jan.2019	HBs antigen positive	10
Study method (specified clinical trial)	Feb.2019 -Feb.2026	HBe antigen positive	7

Table 2. Background Characteristics of HBeAg-Positive Mothers and Outcomes of Mother-to-Child Transmission

Patient No.	Maternal						Neonatal					
	Age (years)	*Serum HBV-DNA (log IU/mL)	HBe antigen	Genotype	Liver function	Relevant family history	Gestational age at birth (wks)	Mode of delivery	Sex	Birth weight (g)	* Umbilical dord blood HBV-DNA (log IU/mL)	MTCT at 1 y.o.
1	33	＞9	positive	C	WNL	mother and brother infected	36	VD	female	2302	0	none
2	36	8.8	positive	C	WNL	mother infected, first child MTCT	38	CS	female	2948	0	none
3	39	7.3	positive	C	WNL	mother infected; died of liver cancer.	38	CS	female	2556	0	none
4	46	8.2	positive	C	WNL	father infected; died of liver cancer.	41	CS	male	3850	3.5	none
5	37	8.5	positive	C	exacerbation after delivery	mother and brother infected	36	VD	male	2166	0	none
6	38	8	positive	C	WNL	mother infected, first child MTCT	38	CS	female	2948	1.6	none
7	36	7.2	positive	C	WNL	none	38	CS	male	3899	0	none

*The viral DNA in serum was measured by real time PCR.

WNL, within normal limits; wk, week; CS, cesarean section; VD, vaginal delivery; HBIG, HBV immune globulin; IM, intramuscular; IV, intravenous; MTCT, mother-to-child transmission; mo, month.

Table 3. Background Characteristics of HBeAg-Negative Mothers and Outcomes of Mother-to-Child Transmission

Patient No.	Maternal						Neonatal					
	Age (years)	*Serum HBV-DNA (log IU/mL)	HBe antigen	Genotype	Liver function	Relevant family history	Gestational age at birth (wks)	Mode of delivery	Sex	Birth weight (g)	* Umbilical dord blood HBV-DNA (log IU/mL)	MTCT at 1 y.o.
1	40	6.7	negative	C	WNL	father infected; died of liver cancer. mother and sister infected	39	VD	female	3124	0	none
2	35	6.6	negative	C	WNL	none	38	VD	male	2394	0	none
3	36	6.6	negative	B	WNL	father infected; died of liver cancer.	40	CS	male	4220	0	none
4	38	4.4	negative	B	WNL	father infected; liver cancer.	41	VD	male	3440	0	none
5	39	2.8	negative	B	WNL	mother and sister infected	39	CS	male	2956	0	none
6	39	3	negative	B	WNL	none	40	VD	female	2962	0	none
7	39	3.7	negative	B	WNL	mother and brother infected	40	VD	female	2884	0	none
8	36	6.5	negative	B	WNL	mother and brother infected	39	VD	female	2830	0	none
9	39	5.8	negative	B	WNL	mother infected	38	CS	female	2826	0	none
10	24	4.2	negative	B	WNL	unknown	39	VD	male	2738	0	none

*The viral DNA in serum was measured by real time PCR.

WNL, within normal limits; wk, week; CS, cesarean section; VD, vaginal delivery; HBIG, HBV immune globulin; IM, intramuscular; IV, intravenous; MTCT, mother-to-child transmission; mo, month.

Figures

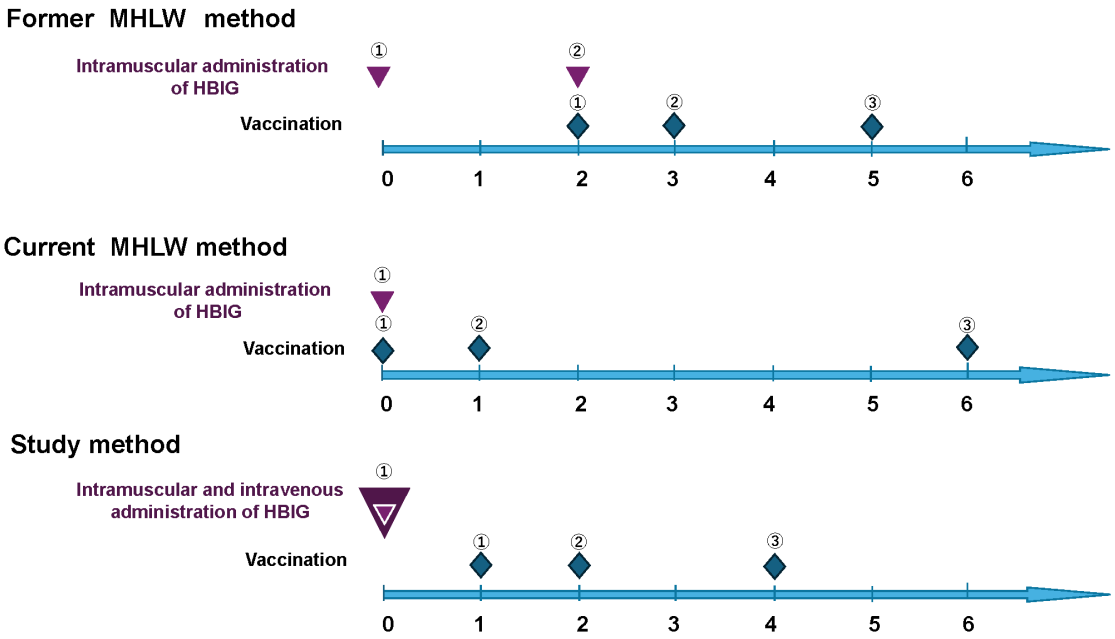
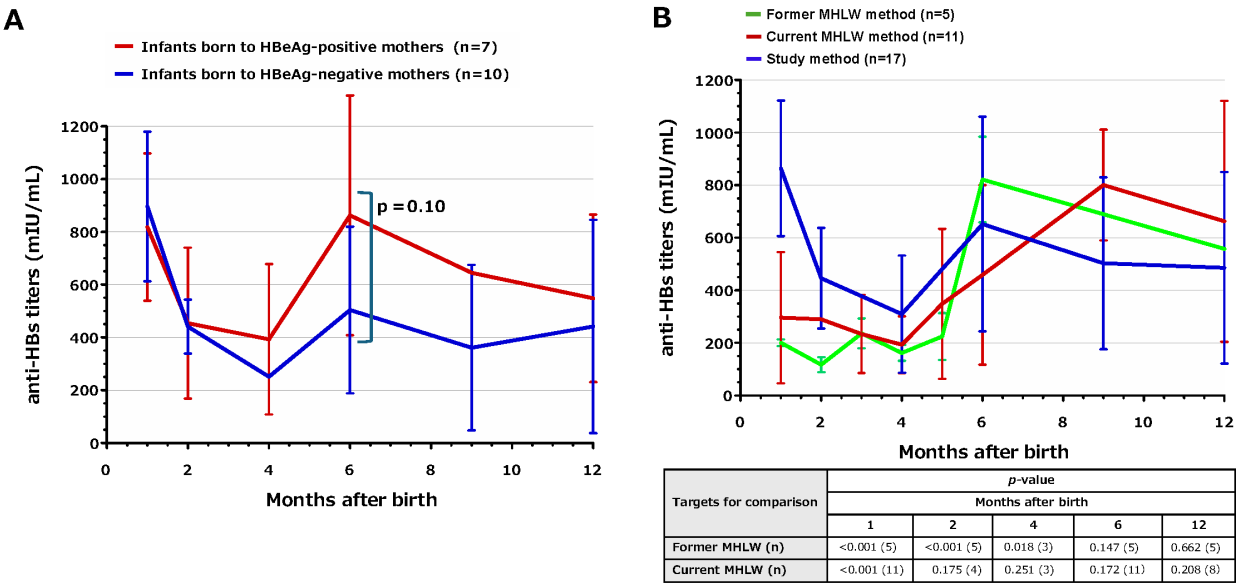


Figure 1

Protocols for each MTCT prevention method

24 ▼indicates the timing of HBIG administration. ▯ indicates the timing of vaccination. HBIG, hepatitis B immune globulin; MTCT, mother-to-child transmission.



Targets for comparison	*p*-value				
	Months after birth				
	1	2	4	6	12
Former MHLW (n)	<0.001 (5)	<0.001 (5)	0.018 (3)	0.147 (5)	0.662 (5)
Current MHLW (n)	<0.001 (11)	0.175 (4)	0.251 (3)	0.172 (11)	0.208 (8)

Figure 2

Changes in anti-HBs titers during the first year of life and comparison with other preventive methods

Comparison of changes in antibody titers between HBeAg-positive and HBeAg-negative individuals who underwent mother-to-child transmission prevention under the study protocol (A). Antibody titers were higher in HBeAg-positive individuals after 4 months of age; however, the difference was not statistically significant. HBeAg, hepatitis B e antigen. Changes in antibody titers across the three prevention methods and comparison with the study method (B)

Using the study method, antibody titers were the lowest immediately prior to the third vaccination (at 4 months of age), at approximately 300 mIU/mL. The mean antibody titer remained higher than those observed with the other two methods, exceeding 100 mIU/mL from immediately after birth through approximately 4 months of age. Compared with the former MHLW method, significant differences were observed at 1 and 4 months of age; compared with the current MHLW method, a significant difference was observed at 1 month of age but not from 2 months onwards. MHLW, Ministry of Health, Labour and Welfare.