Impact of the National Perinatal Hepatitis B Prevention Programme in the Republic of Korea: A retrospective registry-based cohort study

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Abstract

Introduction: Hepatitis B is a major preventable cause of morbidity and mortality from chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. We aimed to evaluate the performance and outcomes of the Korean Perinatal Hepatitis B Prevention Programme (PHBPP) and to investigate the impact of the current post-exposure immunoprophylaxis protocol.

Methods: A retrospective cohort study was performed based on electronic data registry of infants born to hepatitis B virus (HBV)-infected mothers between July 2002 and 2013.

Results: During the study period, 159,983 Korean infants were registered with the PHBPP, with an overall programme coverage of 92.8%. Despite receiving timely post-exposure immunoprophylaxis, 8.6% of infants born to mothers aged <25 years and hepatitis B e antigen (HBeAg)-positive, and 0.7% of infants born to mothers aged ≥25 years and HBeAg-negative were infected. An estimated 14,123 infants were directly protected from perinatal HBV transmission by the PHBPP during the 11.5-year period, at a cost of 1157 US dollars per case averted. The incidence of paediatric hepatocellular carcinoma declined dramatically during the period.

Conclusions: A substantial number of infants have been prevented from hepatitis B since the PHBPP was launched in the Republic of Korea. Continued efforts to promote the programme, an integrated approach to maximising its coverage, a risk-stratified strategy, and innovations in logistics could further reduce perinatal HBV transmission.

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The risk of perinatal transmission, which is the period during which most HBV MTCT occurs [8], can be effectively reduced by timely and complete post-exposure immunoprophylaxis (PEI). PEI involves administration of hepatitis B immune globulin (HBIg) and a hepatitis B vaccine birth dose (HepB-BD) to infants born to HBV-infected mothers within 12 or 24 h of birth, followed by two doses of HepB vaccine [9,10]. Overall, the effectiveness of PEI is 85–95%, varying by maternal HBsAg status and the level of maternal viremia [11,12]. Clinical trials have shown PEI to reduce the risk from 85–100% to 9.3% and from 10–30% to 0.3% in infants born to HBsAg-positive and HBsAg-negative HBV-infected mothers, respectively [6,13]. Thus, alongside the antenatal screening of all pregnant women for HBsAg, PEI is a key HepB prevention strategy for infants born to HBsAg-positive mothers. Several countries have successfully implemented national perinatal hepatitis B prevention programmes (PHBPPs) [10,14,15].

Healthcare in the ROK is accessible to the entire population through mandatory enrolment in the National Health Insurance (NHI) system, funded by employers and individual contributions. Most services require a co-payment. A large majority of healthcare providers are in the private sector, and compensation is provided through NHI based on a list of covered services and prices set by the government. Before 2002, the NHI did not cover a full course of PEI or a post-vaccination serologic test (PVST) for infants born to HBV-infected mothers. However, free HepB vaccination has been available at public health centres (PHCs) since 1985. In private clinics, patients paid for HepB vaccination out-of-pocket until 2008. The cost of hepatitis B vaccination was subsidised from 2009 to 2013, and has been fully funded by the national immunisation programme (NIP) since 2013. Administration of HBIg has been covered by the NHI since October 2000.

To increase access to perinatal HBV transmission prevention, the Korea Centres for Disease Control and Prevention (KCDC) launched the Korean PHBPP in July 2002. The programme set to achieve a sustained HBsAg seroprevalence <0.1% among children aged <10 years, and HBsAg seroprevalence <2% in the general population within 10 years. This target had been set at a time before the regional and global HBV elimination targets were introduced.

The Korean PHBPP is fully funded by the government and based on public-private partnerships between the government and five major medical societies. The PHBPP committee includes representatives from the government and collaborators, whose responsibilities include an annual review of the programme’s performance, as well as setting reimbursement thresholds and criteria for the following year. To promote the programme, the KCDC distributes information, education, and communication materials to health facilities, ensures the programme is covered by the mass media, and provides programme guidance and training to participating health professionals. Public and private hospitals, and private clinics are eligible to participate but participation is voluntary. Applications to participate are approved by the managers of the local PHCs. Screening for HepB—specifically, HBsAg and antibody to HBsAg (anti-HBs)—is offered to pregnant women attending antenatal services as part of standards of maternal care covered by the NHI. Infants born to HBsAg-positive mothers are eligible for free participation in the PHBPP. The programme consists of (1) HBIg and HepB-BD within 12 hours of birth; (2) a second dose of HepB vaccine at 1 month and a third dose at 6 months of age (4 doses of HepB vaccine are administered to infants with birthweight <2000 g at 0, 1, 2, and 6 months of age); and (3) a PVST for HBsAg and anti-HBs conducted between 9 and 15 months of age at participating health facilities. Additional serologic tests and HepB vaccine doses for non-responders to HepB vaccination series, which are determined by a separate protocol, are also covered. Infants not registered in the PHBPP remain eligible to receive HepB vaccination at any PHCs, private clinics, or hospitals covered by the NIP. Pregnant women who were tested positive for HBsAg during antenatal screening are informed about the PHBPP and given a booklet of service coupons (Fig. 1). These coupons serve as proof of PHBPP eligibility and are submitted to local PHCs by health service providers whenever an infant receives a service. HBV-infected mothers submit their HBsAg test results to the delivery facility with a coupon, and their infants are given HepB-BD and HBIg. The coupons and case information are submitted to the local PHC. Similarly, each time an infant receives a HepB vaccine or a PVST, a health facility submits its test result or vaccination record and a coupon to the PHC. The PHC then registers the infant and mother and records details including name, national personal identification number, and other case information in the PHBPP Information System (PHBPP-IS), which is managed by the KCDC. Subsequently, the PHC verifies the records and reimburses the fee to the health facilities based on the coupons submitted.

We conducted a retrospective cohort study using registry data of infants born to HBV-infected mothers in the ROK between July 2002 and 2013. Our aim was to evaluate the performance and outcomes associated with the PHBPP and to investigate the impact of the current PEI protocol. Furthermore, we wanted to identify gaps to be filled to accelerate the elimination hepatitis B in the ROK.

2. Materials and methods

2.1. Data sources

The KCDC receives the PHBPP data electronically from every PHC across the country, which enters information into the PHBPP-IS through a secure, controlled-access Internet connection. Data cleaning is done annually at the national level. Vaccination records of infants who have received HepB vaccination through NIP are registered in the Integrated Health Information System (IHIS). The PHBPP data include maternal and infant HepB-related information, as well as the services provided. Individuals are recorded in both registries using their names and national personal identification numbers.

This study used administrative, de-identified data for programme impact assessment and quality assurance purposes; thus, according to the Korean legislation and rules, it did not require ethical review and approval.

2.2. Inclusion criteria and definitions

This study used data of infants registered in the PHBPP-IS between July 2002 and 2013 (Table 1). Their vaccination records were extracted from both PHBPP-IS and IHIS on 14 October 2015. The variables of interest included maternal and infant characteristics, compliance with the PEI protocol, and serologic outcomes. Analysis of factors associated with PEI failure was restricted to data on infants who had been born during 2005–2013 (as data gathered at the beginning of the programme were incomplete), and included information about their mothers’ age, nationality, and HBsAg status, as well as infant’s sex, gestational length, birthweight, delivery type, timing of HepB vaccine and HBIg administration, and who were serologically tested after 4 weeks of age. The eligibility criteria for each data subset are summarised in Table 1.

Maternal age at the time of registration was stratified into: <25 years, 25–29 years, 30–34 years, and ≥35 years. The duration of pregnancy was dichotomised as premature at <37 weeks and ≥37 weeks. Infants born at <24 weeks or >42 weeks of gestation were excluded. Birthweight was categorised into 500–2000 g and 2000–4500 g, and cases outside of these ranges were excluded from the analyses. The delivery type was collected as vaginal delivery or as a Caesarean section. Timing of HepB-BD was categorised as administered on Day 0, Day 1, or on/after Day 2, and timing of
HBIg was categorised as administered on Day 0, Day 1, on/after Day 2, or not administered.

In this study, timely PEI with HBIg or a HepB-BD was defined as administration on the day of birth, as the time data are recorded in days rather than hours in the information system. A threshold concentration of 10 mIU/mL or greater of anti-HBs was assumed to provide seroprotection against HBV, and was defined as a positive anti-HBs test result. PVST intervals and outcomes were analysed with the test results of infants who had received a 3-dose HepB vaccination, who were negative for HBsAg, and whose birthweight was ≥2000 g. PEI failure was defined as an infant who had received PEI but tested positive for HBsAg after four weeks of age.

2.3. Analysis

The programme coverage was calculated by dividing the number of newly registered Korean infants by the estimated number of Korean infants born to HBV-infected mothers in the ROK each year. The annual number of births and the seroprevalence data were extracted from the Statistics Korea (http://kosis.kr/index/index.do) and the Korea National Health and Nutrition Examination Survey (KNHANES) (https://knhanes.cdc.go.kr/knhanes/main.do), respectively [16].

To estimate the number of infants infected with HBV due to perinatal transmission with each intervention, the transmission risk associated with HBeAg-positive and HBeAg-negative mothers without prophylaxis was estimated at 0.85 and 0.31, respectively [13]; following HepB vaccination, the risk was estimated to be reduced to 0.25 and 0.01, respectively [6,17]; with administration of both HepB-BD and HBlg, the risk was further estimated to be reduced to 0.06 and 0.01, respectively [6,17]. The proportion of infants born to HBeAg-positive mothers was calculated from the

Table 1 Datasets used in the analyses.

<table>
<thead>
<tr>
<th>Analytical purpose</th>
<th>Study period</th>
<th>Population dataset</th>
<th>Cases included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>July 2002–2013</td>
<td>Estimated number of infants born to mothers infected with HBV</td>
<td>172,468</td>
</tr>
<tr>
<td>Crude programme coverage</td>
<td></td>
<td>All Korean infants registered for PHBPP</td>
<td>159,983</td>
</tr>
<tr>
<td>PEI failure rate by maternal HBeAg positivity</td>
<td></td>
<td>Excluded: infants of mothers with missing age or HBeAg status</td>
<td>108,877</td>
</tr>
<tr>
<td>Seroconversion rate and kinetics</td>
<td></td>
<td>Excluded: infants (1) with a birthweight &lt;2000 g, (2) without an anti-HBs titre after the third dose of HepB vaccine, or (3) tested positive for HBsAg</td>
<td>103,573</td>
</tr>
<tr>
<td>Overall PEI failure rate</td>
<td></td>
<td>Excluded: infants without PVST (both HBsAg and anti-HBs) result after four weeks of age</td>
<td>100,374</td>
</tr>
<tr>
<td>Factors affecting PEI failure</td>
<td>2005–2013</td>
<td>Infants who received at least one PVST (both HBsAg and anti-HBs) after four weeks of age</td>
<td>43,964</td>
</tr>
<tr>
<td>Factors affecting PEI failure among infants who received appropriate PEI</td>
<td></td>
<td>Excluded: Infants who did not receive appropriate PEI</td>
<td>42,892</td>
</tr>
</tbody>
</table>

Infants with data for all variables needed for sub-analyses (i.e. maternal age, maternal nationality, maternal HBeAg status, infant sex, gestational length, birthweight, delivery type, and timing of administration of HepB-BD and HBlg)

Statistical analyses were conducted using R software version 3.5.1 (R Project for Statistical Computing, Vienna, Austria). Risk factors for PEI failure were evaluated in univariate and multivariate analyses. The PEI failure risk by each factor and proportions of anti-HBs-positive infants by test interval were compared using $\chi^2$-tests. Poisson incidence rate ratio (IRR) was calculated and the Cochrane-Armitage test was applied to test the trend of the HBsAg-positivity over time.

3. Results

3.1. Registration and management rates

From July 2002 through 2013, 159,983 Korean infants were registered with the PHBPP, with an average of 14,050 infants registered annually, except for 2002, when only 5429 infants were registered as the programme was launched in July (Fig. 2 and Table S1). Registered infants were estimated to constitute 3.0–3.4% of the birth cohort for each year in the study period.

The estimated overall programme coverage was 92.8% (annual range: 68.3–99.1%) between July 2002 and 2013 (Fig. 2 and Table S1). Most registered infants (93.9–98.1%) received timely HepB-BD from the beginning of the programme. In contrast, <15% of the registered infants received timely HBIG over the first 2 years of the programme, but this increased to >90% from 2004. Most infants (86.2%) completed a 3-dose HepB vaccination series by 6 months of age. The proportion of PVST recipients stalled at around 55% until 2011, but has since improved and reached 77.9% in 2013. About half of the registered infants (44.0%) received their first PVST at 9–15 months of age.

3.2. Participating health facilities

At the start of the programme, 1203 health facilities participated, comprising 952 private and 251 public facilities. By 2013, the number of participating health facilities had increased to 3300 nationwide, comprising 2949 private hospitals and clinics, and 351 PHC’s and their branch offices, and included facilities located in geographically hard-to-reach areas.

3.3. Acquisition of seroprotection against HBV through PHBPP

Out of the 100,374 infants registered in the programme during the study period who had received at least one PVST after 4 weeks of age (Fig. 2 and Table S1), 80.7% acquired seroprotection against HBV following a primary HepB vaccination series. Additional secondary and, as necessary, tertiary vaccination series were given to non-responders according to a separate protocol, followed by repeated testing for anti-HBs. Of the primary and secondary non-responder infants who had received the second (41.9%) and third PVST (51.6%), 79.9% and 85.7% acquired seroprotection, respectively.

During the study period, 103,573 PHBPP-registered infants with a birthweight of ≥2000 g received a series of HepB vaccinations and had HBsAg-negative PVST results (Table 1). Two-thirds of these infants (64.1%) had PVST performed at between 3 and 8 months after the third dose of HepB vaccine, while 3.5% of these infants had PVST performed sooner than 3 months after the third dose of HepB vaccine (Fig. 3). Anti-HBs positivity was highest (89.1%) among infants who were tested 3–4 months after the third dose of HepB vaccine. The proportion of seroconverted infants was lower among those tested earlier or later in relation to the most recent (last) dose of vaccine received ($p < 0.001$, Cochran-Armitage test for trend).

3.4. Post-exposure immunoprophylaxis failure

3.4.1. Factors affecting PEI failure

Between the programme launch in July 2002 and 2013, the average HBsAg-positivity rate among the 100,374 registered infants who had received PVST at least 4 weeks after birth (Table 1) was 2.8%. This rate decreased over time from 4.2% in 2002 to 1.5% in 2013 (unadjusted Poisson IRR per year = 0.03, 95% confidence interval [CI]: 0.02–0.03). Testing of children for HBsAg was independent of the maternal e-antigen status ($p = 0.18$, Mantel-Haenszel chi-square).
Of the 43,964 infants eligible for inclusion in the analysis (registered between 2005 and 2013) (Table 1), 2.6% of the infants were tested positive for HBsAg (Table S2). Infants born to younger mothers showed a higher HBsAg-positivity rate, specifically, 5.1% among infants with mothers <25 years old were HBsAg-positive, compared to 2.1% among infants with mothers aged 30 years or older \((p < 0.001)\). Infants born to non-Korean mothers had a higher infection rate than infants born to Korean mothers (5.0% vs. 2.4%, \(p < 0.001\)). Of the infants of HBeAg-positive mothers, 5.7% tested positive for HBsAg, compared to 0.8% of infants with HBeAg-negative mothers \((p < 0.001)\). Infants born by vaginal delivery showed a higher prevalence of HBsAg-positivity than infants born by a Caesarean section (2.7% vs. 2.3%, \(p = 0.008\)). In the bivariate analysis, HBsAg-positivity was independent of infant sex, gestational length, birthweight, and timing of HepB-BD or HBIg administration. Among the infants registered between 2005 and 2013, the proportion of HBsAg-positive infants remained similar even with different timing of HepB-BD and HBIg administration.

In univariate analysis, infants with mothers who were younger, non-Korean, HBeAg-positive, or who were born by vaginal delivery had a greater risk of perinatal HBV infection (Table 2). In multivariate analysis, which included the factors associated with a higher risk of transmission (as indicated by a \(p\)-value < 0.05 in univariate analyses), maternal HBeAg-positive status was a strong risk factor for transmission (adjusted odds ratio \([OR]\): 7.55, 95% CI: 6.50–8.78, and \(p < 0.001\)); infants born to mothers <25 years old had 1.45 times higher odds of infection compared to infants born to mothers aged \(\geq 35\) years (95% CI: 1.11–1.91, \(p = 0.007\)); and infants born to non-Korean mothers had 1.46 times higher odds of infection than infants born to Korean mothers (95% CI: 1.14–1.87, \(p = 0.003\)). None of the other factors had strong evidence for an association with perinatal transmission after adjustment.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
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<tr>
<td></td>
<td>Crude OR</td>
<td>95% CI</td>
<td>(p)-value</td>
<td>Adjusted OR</td>
<td>95% CI</td>
<td>(p)-value</td>
<td></td>
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<tr>
<td>Maternal age (vs. ≥35 years)</td>
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<tr>
<td>&lt;25 years</td>
<td>2.49</td>
<td>1.94–2.30</td>
<td>&lt;0.001</td>
<td>1.45</td>
<td>1.11–1.91</td>
<td>0.007</td>
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<tr>
<td>25–29 years</td>
<td>1.34</td>
<td>1.09–1.64</td>
<td>0.005</td>
<td>1.08</td>
<td>0.88–1.33</td>
<td>0.460</td>
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<tr>
<td>30–34 years</td>
<td>0.99</td>
<td>0.81–1.22</td>
<td>0.949</td>
<td>0.90</td>
<td>0.73–1.11</td>
<td>0.325</td>
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<tr>
<td>Non-Korean mother (vs. Korean mother)</td>
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<tr>
<td>Maternal HBeAg-positive (vs. maternal HBeAg-negative)</td>
<td>7.83</td>
<td>6.74–9.10</td>
<td>&lt;0.001</td>
<td>7.55</td>
<td>6.50–8.78</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Male infant (vs. female infant)</td>
<td>1.06</td>
<td>0.94–1.19</td>
<td>0.374</td>
<td>0.96</td>
<td>0.81–1.16</td>
<td>0.937</td>
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<tr>
<td>Short gestational length (24–36 weeks) (vs. 37–42 weeks)</td>
<td>0.80</td>
<td>0.60–1.07</td>
<td>0.128</td>
<td>0.79</td>
<td>0.57–1.09</td>
<td>0.201</td>
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<tr>
<td>Low birthweight (500–2000 g) (vs. 2000–4500 g)</td>
<td>1.09</td>
<td>0.61–1.94</td>
<td>0.771</td>
<td>0.97</td>
<td>0.58–1.61</td>
<td>0.858</td>
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<tr>
<td>Vaginal delivery (vs. Caesarean section)</td>
<td>1.18</td>
<td>1.04–1.34</td>
<td>0.009</td>
<td>1.10</td>
<td>0.97–1.25</td>
<td>0.149</td>
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<tr>
<td>Timing of HepB-BD (vs. Day 0)</td>
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<tr>
<td>Day 1</td>
<td>1.10</td>
<td>0.54–1.65</td>
<td>0.706</td>
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<td></td>
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<tr>
<td>Day 2 or over</td>
<td>0.99</td>
<td>0.62–1.43</td>
<td>0.972</td>
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<td></td>
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<tr>
<td>Timing of HBIg (vs. Day 0)</td>
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<tr>
<td>Day 1</td>
<td>1.02</td>
<td>0.59–1.77</td>
<td>0.940</td>
<td></td>
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<tr>
<td>Day 2 or over</td>
<td>1.03</td>
<td>0.65–1.78</td>
<td>0.913</td>
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<td></td>
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<tr>
<td>Never</td>
<td>1.40</td>
<td>0.76–1.86</td>
<td>0.118</td>
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</tbody>
</table>

*Note.* The analytic dataset contained data on infants who had data for all variables (i.e. maternal age, maternal nationality, maternal HBeAg status, infant sex, gestational length, birthweight, delivery type, timing of administration of HepB-BD and HBIg). This table only includes infants who received a post-vaccination serologic test after 4 weeks of age.
Finally, a total of 108,877 infants registered during the study period had mothers who had been tested for HBeAg (Table 1). One-third of the mothers tested (36.2%) were HBeAg-positive. About half of the mothers aged <25 years (46.1%) were HBeAg-positive, but this proportion decreased as maternal age increased, with rates of 38.1%, 34.1%, and 29.9% in mothers aged 25–29, 30–34, and ≥35 years, respectively (p < 0.001).

3.4.2. HBV infection among infants who had received appropriate PEI

Analysis limited to infants who had received timely HepB-BD and HBIG, and completed a primary HepB vaccination series (Table 1) revealed that the risk of perinatal HBV infection was 5.7% and 0.8% among infants born to HBeAg-positive and HBeAg-negative mothers, respectively. The HBeAg-positive mothers showed a higher risk of perinatal HBV infection regardless of delivery type, maternal age and gestational length (Table 3). In other words, even if they had received appropriate PEI, approximately 9 out of 100 infants were infected if born to mothers who were younger than 25 years and HBeAg-positive, whereas about 1 in 100 infants was infected if born to a mother who was aged ≤25 years and HBeAg-negative. Stratified by the HBeAg status, delivery type did not affect the infection rate among the infants who received appropriate PEI.

3.5. Evolution of HepB prevalence in the ROK

Nationwide coverage surveys in the ROK have shown that childhood 3-dose HepB vaccination coverage has increased from 78.0% in 1989 to 99.4% in 2013 (Fig. 4A). In 2013, the PHBPP-registered infants were more likely to have HepB-BD on the day of birth (98.1%) compared to non-registered infants (86.7%). Concurrently, the HBsAg-positivity rate among teenagers has decreased from 7.0% in the 1980s to 0.3% in 2016, while the prevalence of hepatic carcinoma among children aged <10 years has declined from two cases per million in 2000 to 0 in 2016 (Fig. 4B).

3.6. Overall impact of the PHBPP

Since the PHBPP implementation, the MTCT rate has decreased from 3.7% in 2004 to 1.5% in 2013, and it has remained below 2% since 2012 (Fig. 5). Concurrently, the prevalence of HepB among infants has also decreased, from 0.13% in 2014 to 0.04%, reaching below 0.1% in 2006 and 0.04% in 2013. Without any PEI, 87,272 infants were estimated to be infected through perinatal transmission between July 2002 and 2013. With the annual HepB vaccination coverages, 20,108 infants might have been newly infected in the absence of the PHBPP. Considering the annual PVST rates (Table S1), the estimated number of unregistered infants each year, and annual national vaccination coverage from WUNEIC, a total of 5985 infants were estimated to be newly infected through perinatal transmission in July 2002–2013. The total cost of running the programme during this period was US dollars 16,340,056 (one US dollar equals 1150 Korean won). As such, over the past 11.5 years of the PHBPP, an estimated 14,123 infants were likely directly prevented from perinatal HBV transmission, at a cost of 1157 US dollars per case averted.

4. Discussion

A substantial number of infants have been protected from HBV since the PHBPP was launched in the ROK, where perinatal transmission has been the main transmission route. The programme coverage currently exceeds 90% and an estimated 14,000 infants have been directly protected from perinatal HBV infection between July 2002 and 2013. Considering the intervention is preventing life-long conditions associated with a substantial disease burden, the PHBPP is very cost-effective, which was achieved by mobilising pre-existing health infrastructure, removing financial barriers to access, and promoting the intervention among pregnant women and service providers.

In this study, we examined maternal and infant factors associated with PEI failure. After adjustment, maternal HBeAg was strongly associated with the risk of PEI failure, which was consistent with previous findings [10,13]. Oral antiviral therapy as an additional intervention for mothers at high-risk of PEI failure, who are either HBeAg-positive or highly viraemic in their late pregnancy, has shown high efficacy at preventing transmission to newborns in clinical trials and in clinical settings [18,19]. A cost-effectiveness study in the ROK has suggested that including HBV-DNA testing for HBsAg-positive mothers and maternal antiviral prophylaxis for mothers with a high viral load as part of the PHBPP would not exceed the willingness-to-pay threshold of the gross domestic product per capita in 2014 [20].

In the multiple logistic regression analysis, infants born to younger (<25 years) and non-Korean mothers showed an increased risk of perinatal HBV infection after adjustment for other factors, including maternal HBeAg status. To our knowledge, maternal age has not been previously reported as an independent risk factor for transmission. However, a higher viral load among younger mothers might potentially explain this finding. Younger age of non-Korean compared to Korean mothers could also explain the differences in risk. Further epidemiological studies that take

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Immunoprophylaxis failure rates among infants who had received appropriate post-exposure immunoprophylaxis according to delivery type, maternal age, gestational length and maternal HBeAg status (n = 42,892).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery type</td>
<td>HBeAg-positive mothers</td>
</tr>
<tr>
<td>n/N</td>
<td>%</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>599/10,034</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>287/5,401</td>
</tr>
<tr>
<td>Maternal age</td>
<td></td>
</tr>
<tr>
<td>&lt;25 years</td>
<td>115/1335</td>
</tr>
<tr>
<td>25–29 years</td>
<td>360/6,291</td>
</tr>
<tr>
<td>30–34 years</td>
<td>322/6,293</td>
</tr>
<tr>
<td>≥35 years</td>
<td>89/1606</td>
</tr>
<tr>
<td>Gestational length</td>
<td></td>
</tr>
<tr>
<td>24–36 weeks</td>
<td>38/941</td>
</tr>
<tr>
<td>37–42 weeks</td>
<td>848/14,584</td>
</tr>
</tbody>
</table>

Note. Appropriate post-exposure immunoprophylaxis was defined as receipt of hepatitis B immune globulin and hepatitis B vaccine birth dose in the age of birth (Day 0), and completion of a hepatitis B vaccination series (≥3 doses for infants with a birthweight ≥2000 g; ≥4 doses for infants with a birthweight <2000 g). Infants without information regarding maternal HBeAg status or infant HBsAg status were excluded in this analysis. This table only includes infants who received a post-vaccination serologic test after the age of 4 weeks and registered in the perinatal hepatitis B prevention programme in 2005–2013.
terial viral load, ethnicity and place of birth into account would provide further insight into the role of these factors. Some previous studies have suggested that the rate of HBV MTCT increases during an emergency Caesarean section or a vaginal delivery compared to an elective Caesarean section [10,21]. This association could not be examined in this study, as Caesarean section type data were not available in the PHBPP-IS.

Previous studies have shown that immunocompetent responders at 1–2 months after completion of HepB vaccine series remain protected against acute and chronic hepatitis, even if anti-HBs levels decrease to below 10 mIU/mL over time [22]. In this study, the post-vaccination seroprotection rate peaked at 3–4 months after vaccination (usually at 9–10 months of age) and declined afterwards (Fig. 3). One-quarter of the infants who had ever received PVST underwent a test at age <9 or >15 months. These findings suggest that narrowing the recommended period for PVST and intensifying the follow-up might reduce unnecessary revaccination and additional testing, as demonstrated in a previous study in the United States [23].

The achievements of PHBPP are promising; however, some gaps and uncertainties remain. It is likely that some HBsAg-positive mothers have not been tested during their pregnancy. However, the antenatal care coverage in the ROK is very high and, with the help of the NHI, over 99% of mothers have been delivering babies at health facilities, mostly obstetric clinics, for more than two decades (data from nationwide surveys [24,25]). Moreover, a 2006 survey involving one-third of the country’s obstetricians reported that nearly all respondents (99.5%) provided HepB screening to pregnant women in their care [26]. This implies that linking the NHI and the PHBPP systems could further improve the programme coverage.

The low PVST rate is concerning, as it leaves the HepB vaccination non-responders at risk of acquiring HBV from household contacts in early childhood. Since 2015, the PHC staff have been
encouraged to use post or phone to remind the mothers of infants registered in their catchment area about the test. Adding a verification step in the second well-child visit checklist at 9–12 months of age for all infants could help identify infants who have missed vaccination. Finally, as of 2019, mothers and children with chronic HepB are not provided long-term follow-up care after the PHBPP. A national chronic HepB registry linked to the PHBPP could maximise the coverage of the long-term follow-up and increase the likelihood of timely interventions in this patient group.

To our knowledge, this study is the first comprehensive performance review and impact assessment of the PHBPP in the ROK. The data were extracted from the electronic information systems, using the national personal identification numbers, which link with data on reimbursement of each service, ensuring reliability and completeness of the data. In addition, this operational research examined whether a country has reached the global and regional targets of HepB elimination.

This study has some limitations. First, we were not able to account for factors not captured in the information systems, such as whether the mother was receiving antiviral therapy or not. Second, in our evaluation of the programme impact, we were not able to control for other risk-reducing interventions. For example, the use of single-use dispensable needles was recommended in 1981, and legally enforced in 1985. In the early 1980s, mass vaccination began targeting students and employees, while the universal childhood HepB vaccination started in 1987, and the HepB vaccination was introduced into the NIP in 1995 [27]. Third, there was some uncertainty associated with the programme coverage as the denominators were roughly estimated based on the annual natal-ity and seroprevalence estimates. Individual-level data on HBsAg screening test results were not available for the women giving birth in the ROK.

Improvements have been introduced into the Korean PHBPP over time. In January 2014, an electronic registration process replaced coupons to address issues such as loss of coupons, and to alleviate the administrative workload. The electronic information system also has allowed the PHC staff to track patients who did not complete PEI or PVST and, since 2015, to send periodic reminders every June and October to parents or caregivers of such infants. Since 2016, health professionals can take an online training about the PHBPP before participating in the programme; they also submit an annual self-assessment regarding vaccine management.

Fig. 5. Korean infants with perinatally acquired hepatitis B infection and mother-to-child transmission rate, July 2002–2013. (A) Annual births, and estimated numbers of HBsAg-positive mothers and newborns. Note. The Korean Perinatal Hepatitis B Prevention Programme was launched in July 2002. (B) Estimated percentage of Korean infants with perinatally acquired hepatitis B infection and mother-to-child transmission rate.
The global and regional HepB elimination target is <0.1% sero-prevalence among 5-year-old children by 2030 [28]. The 2006 nationwide serosurvey reported the HBsAg prevalence of 0.2% (95% CI: 0.0–0.4) among the 2920 Korean children aged 4–6 years [29]. Nevertheless, documenting successful elimination of HepB requires a large sample size, which is a significant challenge. In response, the World Health Organization Western Pacific Regional Office Hepatitis B Immunisation Expert Resource Panel suggested a HepB MTCT rate <2% as an alternative target [30]. The present study findings suggest that the ROK has achieved an MTCT HepB rate <2% since 2012, with an estimated HBsAg prevalence among infants <0.1% since 2006. Moreover, our results suggest that the Korean PHBPP is supporting the move towards HepB elimination by improving the implementation of PEI against perinatal HBV transmission.

To consolidate these achievements, efforts should continue to promote the programme among health professionals and the public to identify all eligible infants. Furthermore, an integrated approach to maximise the programme coverage of HBV-infected mothers and further reduce perinatal transmission could be considered; this may include linking different systems, a risk-stratified strategy, and innovations in logistics. Finally, the success of the Korean PHBPP may encourage other comparable countries to implement similar programmes.

Credit authorship contribution statement

Tae Un Yang: Conceptualization, Methodology, Formal analysis, Writing - original draft, Visualization, Writing - review & editing. Chae Won Jung: Methodology, Formal analysis, Writing - review & editing. Dongwook Kim: Data curation, Formal analysis, Writing - review & editing. Hang A Park: Formal analysis, Writing - review & editing. Youngmee Jee: Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributors

TUY conceived the study; DK, CWJ and TUY collected and assembled the data; DK, HAP and TUY did the data analysis; TUY, DK and CWJ contributed to the interpretation of the data; TUY wrote the manuscript, which was critically reviewed and revised by DK, CWJ and YJ. All authors were involved in the approval of the final content before submission.

Appendix A. Supplementary material

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References