Abstract

Vertical transmission from mother-to-child is an important mode of hepatitis B virus (HBV) infection, accounting for up to half of all incident cases globally. We evaluated the uptake of HBV neonatal vaccination and immunoglobulin delivery in Queensland, Australia, between 2001 and 2013. We identified HBV-positive mothers using linked notifiable conditions, hospitalisation, and perinatal administrative data. Perinatal receipt of monovalent HBV vaccine and hepatitis B immunoglobulin were examined. Of 710,859 live births, with 5,753 infants (0.81%) born to identified HBV-positive mothers; 91.7% received HBV neonatal vaccine. Immunoglobulin uptake was 20.0% in 2012 and 36.6% in 2013. Uptake was higher when the mother's HBV-positive status was recorded in perinatal records (69.6% if maternal HBV status recorded on perinatal data collection vs 9.5% otherwise). Delivery of neonatal HBV vaccination in Queensland was high. Improved identification and documentation of HBV-positive mothers' status during the antenatal period was associated with increased immunoglobulin administration.

Keywords: Hepatitis B; Immunoprophylaxis; Perinatal; Vaccine; Maternal health

Introduction

Chronic infection with hepatitis B virus (HBV) carries a significant global burden of disease, accounting for over 30% of all viral hepatitis-related mortality worldwide [1]. In Australia, HBV notification rates remained relatively high in 2017, at 45/100,000 person years in the 25–29 age group and 53/100,000py for adults aged 30–39 years [2]. In 2015, the estimated number of people living with chronic HBV infection in Australia was approximately 250,000 [2, 3]. Vertical transmission of HBV from mother to child is an important mode of infection, accounting for up to half of all incident cases globally [4]. Without intervention, 70–90% of all infants born to seropositive mothers become chronically infected over their life span [5, 6]. Children who acquire HBV early in life and develop chronic HBV infection are particularly susceptible to serious long-term sequelae, including acute liver failure, cirrhosis, and hepatocellular carcinoma [7].

Perinatal immunoprophylaxis for infants born to HBV-positive mothers can prevent transmission: consisting of hepatitis B immunoglobulin (HBIG) and a monovalent HBV vaccine at birth. It is followed by receipt of the recommended childhood vaccination schedule in Australia (three-dose primary course at 2, 4, and 6 months of age) [8]. The completion of perinatal immunoprophylaxis reduces the risk of vertical transmission by 85–95% [9]. In Australia, targeted vaccination of infants born to HBV-positive mothers was introduced from 1986 [10]. A nationally funded universal program for a birth-dose of monovalent vaccine in all infants was introduced in May 2000, in response to suboptimal coverage rates with the targeted program (Supplementary Material 1) [10].

With this study we sought to assess the completion rate of perinatal HBV vaccination and immunoglobulin administration in infants born to HBV-positive mothers in Queensland, Australia, using a state-wide data linkage of all births from 2001 to 2013.

Material and Methods

We conducted a data linkage study to identify infants born to mothers identified with chronic HBV infection in Queensland, Australia between 01 January 2001 and 30 June 2013 (births in 2001: 47,678; births in 2013: 63,354). We examined HBV vaccination and HBIG receipt at birth. No changes in Queensland policy or program (other than vaccine brand used for the program) occurred over the time period of this study. All linkages were achieved through deterministic and probabilistic matching using personal details from routinely collected data. Linkage was conducted independently of the study investigators by the Statistical and Analysis Linkage Team, Health Statistics Unit, Queensland Health. The study was approved by the Queensland Children's Health Services Human Research Ethics Committee.

Identification of HBV-positive mothers

Data from the Queensland Government administered Perinatal Data Collection (PDC), Notifiable Conditions System (NOCS), Queensland Hospital Admitted Patient Data Collection (QHAPDC) databases, and the Vaccine Information and Vaccine Administration System (VIVAS) were linked to identify HBV-positive mothers, and their infants' perinatal HBV vaccine and HBIG receipt. At the time of the study, VIVAS provided information on the provision of childhood vaccinations directly into the Australian-wide Australian Childhood Immunisation Registry (ACIR). Data from the births registry were used to provide a link between PDC and other datasets.

In Queensland, HBV infection is a mandatory notifiable condition upon laboratory diagnosis under the *Public Health Act 2005* and its subordinate regulation (Supplementary Material 1), with cases recorded in NOCS. The PDC is a record of the pregnancy and birthing experience and contains details of all mothers who give birth in Queensland. It is completed prior to discharge by healthcare professionals using data from the mother's clinical case notes. QHAPDC is a database of all hospital admissions in Queensland. Data on individuals admitted with an ICD-code indication of chronic HBV infection were included in our study. A woman was categorised as HBV-positive if chronic HBV was identified on NOCS prior to delivery, a hospitalisation event with chronic HBV coding was recorded on QHAPDC

prior to delivery, or if chronic HBV infection was recorded as a current medical condition within the PDC. From 2001 to June 2012, chronic HBV infection was recorded on the PDC using a free-text field. From July 2012 onwards, it was recorded via a specific tick-box labelled "Hepatitis B Carrier". Chronic HBV infection was identified from recorded ICD-9/10 codes within the PDC and QHAPDC (Supplementary Material 2). Women with a recorded ICD code of acute HBV infection without evidence of chronic HBV were not included in this study because of the potential resolution prior to their child's birth.

Infant vaccination

Vaccination at birth prior to hospital discharge was recorded in the PDC throughout the study period, while administration of HBIG was recorded in the PDC only from July 2012 onwards. Birth vaccination and HBIG administration data were also captured on VIVAS and were used to supplement PDC data. Following Australian recommendations, vaccine receipt was considered administered if documented as being given within 7 days of birth, and HBIG receipt was considered if administered within 2 days of birth [8].

Data and statistical analysis

Maternal characteristics extracted from the databases included age and year of birth, socio-economic status, location of residence, country of birth, and whether the mother identified as an Aboriginal or Torres Strait Island person (hereafter respectfully referred to as Indigenous). Socio-economic status was categorised into thirds according to postcode of residence using the Australian Bureau of Statistics Socio-Economic Index for Areas (SEIFA), a measure of relative disadvantage [11]. Location of residence was categorised as major city or regional/remote according to the Australian Standard Geographical Classification Remoteness Structure [12]. Mothers were categorised as being Australian Indigenous, non-Indigenous Australian-born, or overseas-born. Indigenous status is routinely collected in a standardised manner in the databases used in this study. Those without a recorded Indigenous status were classified as non-Indigenous in this study.

All births during the study period were analysed. Administration of birth-dose HBV vaccine and/or HBIG in infants was determined and a percentage of total live births to HBV-positive mothers was calculated for each year. Statistical significance of categorical variables was calculated using chi-squared analysis. The association between demographic and social characteristics of the mother and both maternal HBV-positive status and the child's birth vaccination status were investigated using logistic regression. All maternal characteristics were included in the models. Both univariable and multivariable models were constructed. Multivariable models included all reported characteristics as covariables, as well as year of birth of infant. All analysis was conducted in Stata statistical software v15 (StataCorp, College Station, TX, USA).

Results

From January 2001 to June 2013, 710,859 births were recorded on the PDC, with 5,753 infants (0.81%) born to 2,589 identified HBV-positive mothers (Figure 1). Of these births, 1,217 were identified from the PDC. Of the 4,536 remaining births, 3,341 were identified from NOCS only, and 257 from QHAPDC only. Maternal factors associated with greater prevalence of births to HBV-positive mothers are seen in Supplementary Material 3. Notably, the prevalence of births to overseas-born mothers on the PDC increased over time (from 0.28% to 0.46% of all births), reflected in an increase of overall prevalence of HBV-positive mothers (0.80% to 1.75%).

Birth-dose HBV vaccine was administered to 5,271 (91.6%) infants born to HBV-positive mothers (Figure 2). Following an initial rise in vaccine uptake following introduction of the nationally funded universal birth-dose program, annual birth vaccination percentages for these infants ranged from 92.1–95.7% between 2001 and 2013. In comparison, overall birth vaccination was 87.7% from 2001–2013 in infants born to mothers not identified as HBV-positive ($p<0.001$). When investigated by source of HBV identification, 1,160 (95.3%) infants identified on the PDC received birth vaccination, compared to 4,110 (90.6%) infants not identified via the PDC. Of these, 227 (5%) were identified only via QHAPDC.

Documentation of HBIG administration was consistently below 5% from 2001 to 2011 and increased to 20.0% from July–December 2012 and to 36.6% from January–June 2013, the first two six-month periods after HBIG recording began in the PDC. When investigated by source of HBV-positive mother identification, 270 (69.6%) infants of PDC-identified mothers and 63 (9.5%) infants of NOCS and QHAPDC identified mothers received HBIG ($p<0.001$). For 705,106 infants born to mothers not identified as HBV-positive, 41 (0.006%) were recorded as being administered HBIG. All infants who received HBIG also received birth vaccination.

When the association of maternal characteristics in HBV-positive mothers and HBV birth vaccine was examined, infants of Australian-born non-Indigenous mothers were significantly less likely to be

vaccinated at birth after adjusting for potentially confounding variables (Supplementary Material 4). Infants born in a major city were more likely to be vaccinated.

Discussion

In our study of linked datasets in Queensland, we found high HBV vaccination coverage at birth in infants born to HBV-positive mothers. These numbers were similar to studies from other Australian states and national immunisation statistics [13-15], and further, were comparable to data from the United States, Canada, and the UK [16-18]. Vaccination coverage was also significantly higher among infants born to HBV-positive mothers than those born to non-HBV-positive mothers. Birth HBV vaccination coverage differed by population group in HBV-positive mothers, with infants born to Australian Indigenous and overseas-born mothers having the highest reported coverage. This coverage difference highlights a potential healthcare worker and/or maternal bias in risk perception and the need for attention to HBV infection prevention in all children.

Sub-optimal HBIG administration, or possibly sub-optimal documentation, was noted. HBIG administration was significantly higher when the mother's chronic HBV-positive status was identified via the PDC and rose sharply in the twelve months after routine recording on the PDC was introduced. There are several possible reasons for this rise. Previous poor data capture may have led to under-reporting of the actual number of infants administered HBIG, or poor collection of HBV status on the PDC prior to routine recording may have decreased compliance with recommendations. A similar trend was noted in a UK study, which was attributed to "historic data recording issues" [17]. Further, a recent study from New South Wales found similar poor collection of HBV status on the PDC, with only a 65% capture sensitivity [19]. Overall, it seems that poor capture of HBV status is not an isolated phenomenon and may relate to why we found sub-optimal HBIG administration.

Further, we found overall births to HBV-positive mothers increased between 2001–2013, possibly due to the increased number of births in overseas-born mothers. This is consistent with the increasing rate of migration into Australia, primarily from countries where HBV prevalence is high [20]. Notably, there was little change in the proportion of all births to HBV-positive non-Indigenous Australian-born mothers. Identified characteristics of HBV-positive mothers were consistent with recent Australian findings [16, 17].

Somewhat surprisingly, we found a proportion (5%) of HBV-positive mothers who were only identified through linkage with QHAPDC and not identified on the PDC or NOCS. Recent studies from other Australian jurisdictions, the Northern Territory [13] and New South Wales [14], exploring issues around perinatal HBV transmission did not include linkage to previous hospital admissions with HBV-specific coding in the mother. As a consequence, these and similar studies may underestimate the number of HBV-positive women giving birth, which may reflect women less likely to access hospital services or be screened for HBV infection. Alternatively, this may reflect those with previously diagnosed chronic infection, who may only have HBV viral load or e antigen testing; a positive result for either of these is not a specific trigger for notification in Australia.

Reassuringly, in Queensland, the overall prevalence of HBV-positive mothers was 1.75%, in line with World Health Organization (WHO) targets of reducing HBV prevalence to <2% by 2012 and projected to meet target of <0.1% by 2030 [21, 22].

Lastly, children born to mothers not identified on the PDC were observed to receive HBIG less frequently (69.6% vs 9.5% in 2012–2013 for children born to PDC and NOCS/QHAPDC identified mothers, respectively). Recent studies demonstrated that administration of HBV vaccine at birth without HBIG was responsible for over 90% of the combined intervention's protective effectiveness, implying that vaccine alone may be enough in preventing a substantial proportion of vertical HBV transmission [23]. Previous findings have shown HBIG to be a cost-effective strategy which does provide an improvement in preventing HBV transmission when combined with the HBV vaccine [24]. The inclusion and continual improvement of HBIG uptake will further assist in the elimination of HBV and is in line with WHO recommendations [23].

The main strength of our study is the comprehensive identification of HBV-positive mothers via data linkage. Identification using ICD-codes from Queensland-based routinely collected data from hospital and notifiable conditions databases led to the identification of approximately four times more HBV-positive women than would have been attained through the PDC alone. When evaluating program success, our findings highlight the importance of using all available datasets to identify HBV-positive mothers. A limitation of this method of identification is that a proportion of mothers identified on

NOCS/QHAPDC who were subsequently not identified as HBV-positive during antenatal screening may represent those with spontaneous resolution and conversion to being HBsAg negative. Previous studies suggest spontaneous resolution of chronic HBV infection occurs in only 1–3% of infected adults annually [25, 26].

Conclusion

This study assessed uptake of the perinatal preventive program for infants born to HBV-positive mothers using a comprehensive linked dataset. Birth vaccination rates were consistently high, especially when the mother was recorded as HBV-positive in the perinatal data collection record. However, a large proportion of mothers were recorded elsewhere in QHAPDC or NOCs where vaccination rates were lower. HBIG coverage is improving but remains suboptimal. We noted a cohort of infants born to previously identified HBV-positive mothers who were not identified on the PDC and who did not receive HBIG at birth. This highlights the need for improved HBV identification in routine antenatal care. These findings suggest that, similar to US recommendations from the CDC [27-28], Australia may benefit from a programmatic approach to further enhance implementation of the current perinatal HBV prevention recommendations. A more centralised and co-ordinated approach to identifying and treating the infants of HBV-positive mothers may be required to further minimise the risk of perinatal acquisition and subsequent associated risks of chronic HBV infection.

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Figure Legend

Figure 1. Hepatitis B virus carrier women giving birth in Queensland, Australia, January 2001-July 2013.

Figure 2. All births that occurred with a HBV-positive mother, and percentage of births with a HBV-positive mother where birth dose HBV vaccine and HBIG were administered.

Perinatal immunoprophylaxis in babies born to hepatitis B carrier mothers: A data linkage study in Queensland, Australia

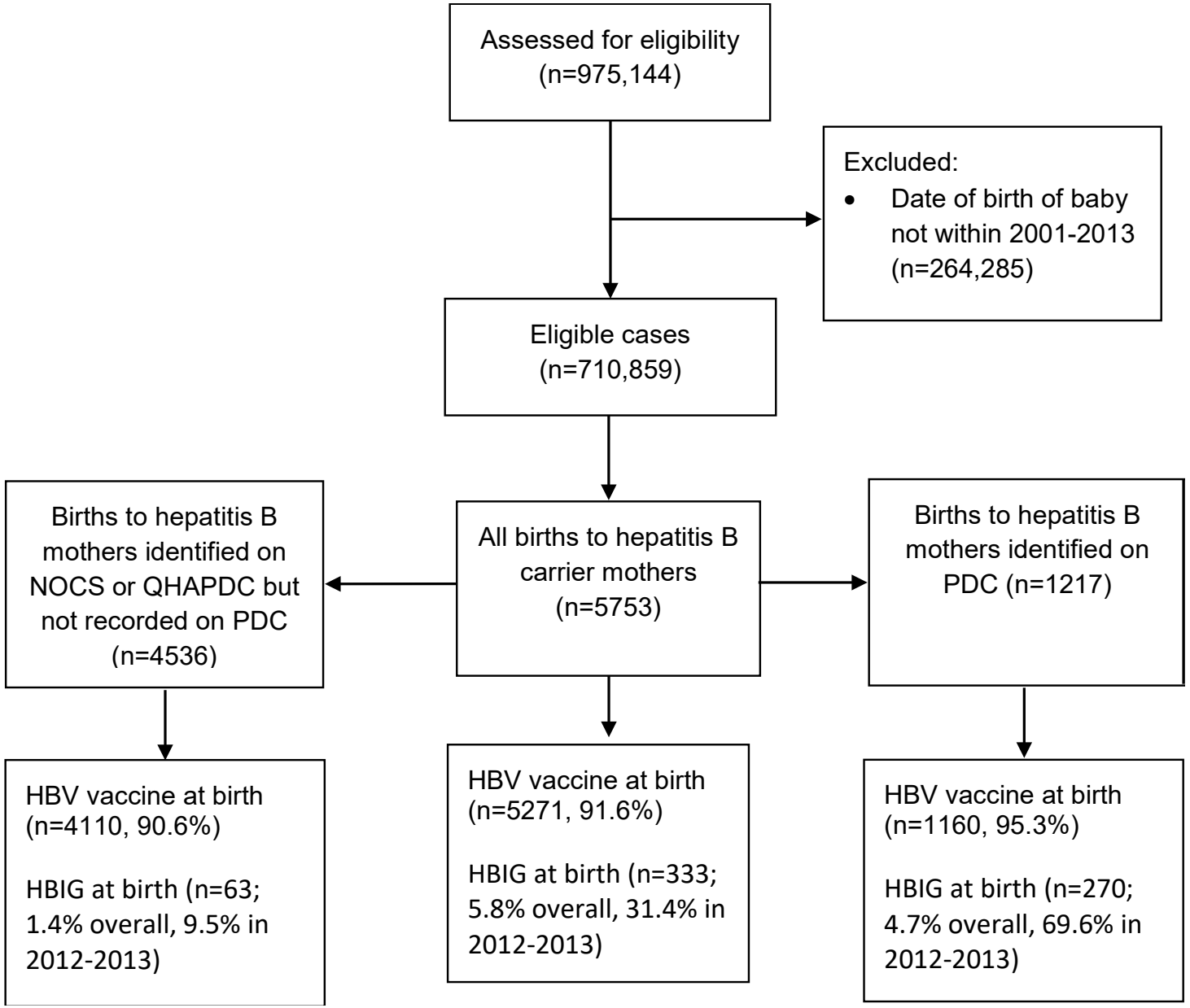

Figure 1. Hepatitis B virus carrier women giving birth in Queensland, Australia, January 2001-July 2013

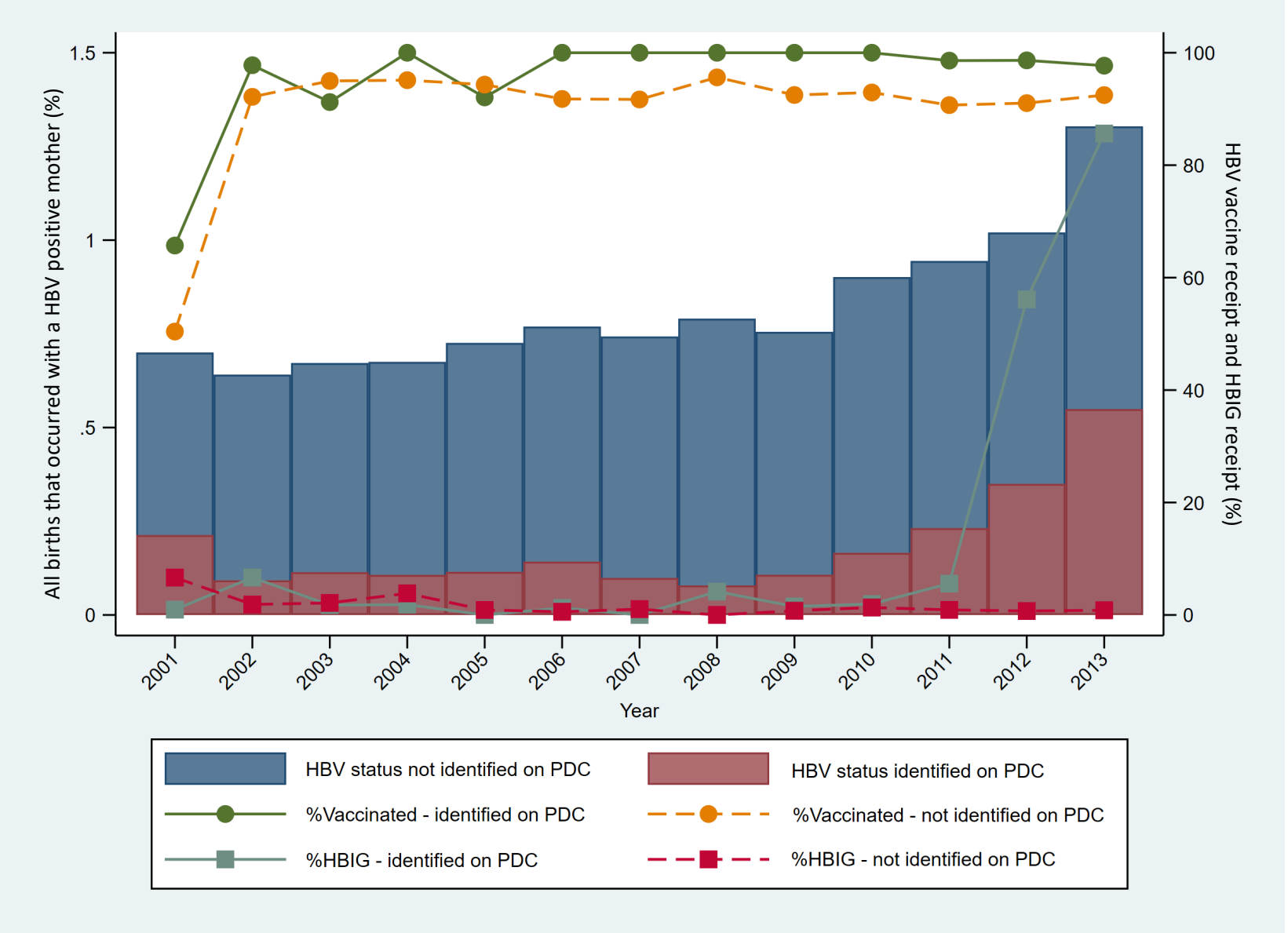

Figure 2. All births that occurred with a HBV positive mother, and percentage of births with a HBV positive mother where birth dose HBV vaccine and HBIG were administered.

Perinatal immunoprophylaxis in babies born to hepatitis B virus-positive mothers: A data linkage study in Queensland, Australia

Supplementary Material

Supplementary Material 1. Summary of relevant hepatitis B vaccination history in Queensland.

1973	Hepatitis B immunoglobulin manufacturing began in Australia
1986	Vaccination recommended for babies born to HBsAg positive mothers (3 doses: birth, 1 month, 6 month) Vaccination recommended for all Aboriginal and Torres Strait Islander children, and children of immigrants and refugees
1996	Hepatitis B vaccination recommended and funded for all adolescents 11–12 years old
2000	Funded vaccination of all infants with a birth dose of monovalent vaccine followed by 3 doses of combination vaccine
2007	Queensland commenced state-wide adolescent vaccination program with school-based delivery (2 doses of adult formulation)
2012	Routine recording of hepatitis B immunoglobulin administration begins on the Perinatal Data Collection

Dates sourced from http://www.ncirs.org.au/sites/default/files/2018-12/Hepatitis-B-history-Dec-2018.pdf and https://www.health.qld.gov.au/__data/assets/pdf_file/0014/161303/pdc_instruction_manual_2012.pdf [accessed 15 April 2019].

Supplementary Material 2. Relevant medical indications of chronic hepatitis B and corresponding ICD-9/10 codes.

ICD-9/10 code	Code description
7052	Hepatitis delta without mention of active hepatitis B
B170	Acute delta infection of hepatitis B carrier
B180	Chronic viral hepatitis B with delta agent
B181	Chronic viral hepatitis B without delta agent

Supplementary Material 3. Association between mother's demographic and social characteristics and HBV carrier status.

	Number of births		Univariable analysis	Multivariable analysis
	N	HBV+ n (%)	Odds ratio (95% CI)	Odds ratio (95% CI)
Maternal age (years)				
<20	39,300	278 (0.7)	1.00 (ref.)	1.00 (ref.)
20−24	121,503	970 (0.8)	1.14 (1.01, 1.29)	1.26 (1.11, 1.43)
25−29	199,928	1,680 (0.8)	1.16 (1.04, 1.30)	1.34 (1.16, 1.53)
30−34	209,940	1,724 (0.8)	1.11 (0.99, 1.24)	1.32 (1.12, 1.56)
35+	128,453	1,101 (0.9)	1.17 (1.04, 1.32)	1.42 (1.16, 1.74)
Maternal year of birth				
<1973	169,537	1,241 (0.7)	1.00 (ref.)	1.00 (ref.)
1973−1977	183,801	1,498 (0.8)	1.11 (1.03, 1.19)	1.12 (1.02, 1.23)
1978−1982	177,830	1,699 (1.0)	1.30 (1.21, 1.39)	1.28 (1.13. 1.45)
1983−1999	167,956	1,315 (0.8)	1.12 (1.04, 1.20)	1.05 (0.88, 1.25)
Place of birth				
Australian non-Indigenous	523,989	2,168 (0.4)	1.00 (ref.)	1.00 (ref.)
Australian Indigenous	39,337	935 (2.4)	5.16 (4.81, 5.54)	4.86 (4.51, 5.24)
Overseas	135,799	2,649 (2.0)	3.97 (3.77, 4.18)	3.96 (3.75, 4.18)
Location of residence				
Regional/remote	368,082	2,790 (0.8)	1.00 (ref.)	1.00 (ref.)
Major city	331,043	2,963 (0.9)	1.17 (1.12, 1.23)	1.18 (1.12, 1.24)
Socio-economic status				
Low	116,724	1,461 (1.3)	1.00 (ref.)	1.00 (ref.)
Medium	255,841	1,994 (0.8)	0.66 (0.62, 0.71)	0.74 (0.69, 0.79)
High	319,674	2,298 (0.7)	0.59 (0.55, 0.63)	0.58 (0.55, 0.62)

Characteristics included in multivariable logistic regression model were maternal age and year of birth, place of birth, location, and socio-economic status

Supplementary Material 4. Association between mother's demographic and social characteristics and the child's HBV vaccine birth-dose status in children born to HBV-positive mothers.

	N	Vaccinated n (%)	Odds ratio (95% CI)	Adjusted Odds ratio (95% CI)
Maternal age (years)				
<20	278	261 (93.9)	1.27 (0.74, 2.17)	1.37 (0.58, 3.27)
20−24	970	896 (92.4)	1.00 (0.72, 1.38)	0.96 (0.50, 1.83)
25−29	1,680	1,526 (90.8)	0.81 (0.62, 1.08)	0.67 (0.42, 1.08)
30−34	1,724	1,557 (90.3)	0.77 (0.59, 1.01)	0.71 (0.52, 0.98)
35+	1,101	1,017 (92.4)	1.00 (ref.)	1.00 (ref.)
Maternal year of birth				
<1973	1,241	1,070 (86.2)	1.00 (ref.)	1.00 (ref.)
1973−1977	1,498	1,362 (90.9)	1.60 (1.26, 2.03)	1.37 (0.97, 1.94)
1978−1982	1,699	1,586 (93.4)	2.24 (1.75, 2.88)	1.53 (0.92. 2.52)
1983−1999	1,315	1,239 (94.2)	2.61 (1.96, 3.46)	1.18 (0.58, 2.39)
Place of birth				
Australian non-Indigenous	2,169	1,889 (87.1)	1.00 (ref.)	1.00 (ref.)
Australian Indigenous	935	873 (93.4)	2.09 (1.57, 2.78)	2.10 (1.54, 2.90)
Overseas	2,649	2,495 (94.2)	2.40 (1.96, 2.95)	2.25 (1.81, 2.78)
Location of residence				
Regional/remote	2,806	2,545 (90.7)	1.00 (ref.)	1.00 (ref.)
Major city	2,947	2,712 (92.0)	1.18 (0.98, 1.42)	1.26 (1.02, 1.55)
Socio-economic status				
Low	1,405	1,295 (92.2)	1.00 (ref.)	1.00 (ref)
Medium	1,994	1,846 (92.6)	1.06 (0.82, 1.37)	1.21 (0.92, 1.59)
High	2,354	2,116 (89.9)	0.76 (0.60, 0.96)	0.79 (0.61, 1.02)

Characteristics included in multivariable logistic regression model were maternal age and year of birth, place of birth, location, and socio-economic status

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Submission Declaration

The submitted work has not been published previously in any form, it is not under consideration for publication elsewhere, its publication has been approved by all authors, and, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Authorship

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the submitted version.

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