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Long-term impact of childhood hepatitis B vaccination programs on prevalence among Aboriginal and non-Aboriginal women giving birth in Western Australia

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Introduction

Chronic hepatitis B (HBV) infection is a major cause of liver cirrhosis and cancer contributing to a significant burden of disease worldwide[1]. Most cases of chronic infection are acquired early in life, predominantly through maternal transmission[1]. Australia is considered to have low HBV prevalence (<2%), however in Aboriginal and Torres Strait Islander (hereafter referred to as Aboriginal) people[2], some migrant populations[3] and people who inject drugs[4], HBV prevalence is substantially higher.

A vaccine which is 95% effective in preventing HBV has been available since 1982 and since then, various HBV vaccination programs have been implemented across the States and Territories of Australia[5]. Early recommendations were for at-risk adults, and infants and young children from ethnic groups with high HBV carriage rates to be targeted for vaccination[5]. In 1990 a universal neonatal hepatitis B vaccination program, where all babies born were given a 3 dose schedule of HBV vaccine starting from birth, was implemented in the Northern Territory (NT) a region where 28% of the population are Aboriginal (compared with 3% nationally [6]). Subsequently, from May 2000, the HBV vaccine was included in Australia's national infant vaccination schedule, with all babies recommended to receive the first dose at birth. In parallel with the national infant program, schools-based catch-up programs were implemented at various grades and time periods across the Australian States and Territories[5].

Screening pregnant women for HBV, and provision of post-exposure prophylaxis to babies born to HBV-positive mothers remains an important element in prevention of transmission of the virus. Since the late 1990s, screening for HBV with hepatitis B surface antigen (HBsAg) has been recommended and conducted as part of routine care for all pregnant women in Australia[7] with over 90% of pregnant women in WA reported as undergoing HBV screening in 2002[8]. Thus, testing of birthing mothers in Australia provides an opportunity to represent a sentinel population for monitoring chronic HBV prevalence and assessing the impact of HBV prevention programs. Previous analyses using this methodology in two Australian jurisdictions, the NT[2] and New South Wales (NSW)[9], reported decreases in the prevalence of HBV among Aboriginal women giving birth following the introduction of targeted and newborn vaccination programs. However, differences were observed in overall HBV prevalence across the two jurisdictions among both Aboriginal (2.4% in the NT and 0.79% in NSW), and non-Aboriginal women (0.04% in the NT and 0.11% in NSW).

To provide a more complete picture of the ongoing impact of the HBV vaccination programs, and assess the need for additional programs to target high risk populations in Australia, we assessed the impact of HBV vaccination programs in Western Australia (WA) on the

prevalence of HBV infection among mothers giving birth in the State and compared this with the two earlier studies in the NT and NSW[2, 9].

Methods

Data linkage and study population

This study was conducted using population-based record linkage in Western Australia (WA) (population 2.6 million)[10]. The WA Data Linkage Branch has created and maintained probabilistic linkages between core health datasets using personal identifiers such as name, date of birth, address, and sex. Linkage accuracy using this process is high with an error rate estimated at 0.11%[11].

A cohort comprising all women in WA with year of birth between 1974-1995 was determined by selecting any women appearing in either the WA Registry of Births (which contains all birth registrations in WA from 1974 onwards) or the 2014 WA Electoral Commission enrolments database. For women in this cohort, linked data was extracted from two health datasets. The WA Midwives Notification System is a statutory database which receives information from birth attendants about all births attended in the state of WA where the infant has a gestational age of 20 weeks or more, a birthweight of 400g or more, or if gestational age is unknown. Data reported for each birth include maternal year of birth, date of giving birth, maternal postcode of residence, ethnicity and birth details such as parity. The WA Notifiable Infectious Diseases Database contains a record of all notifiable conditions reported to the WA Department of Health under statute including HBV. Both acute and non-acute (unspecified) infections detected by laboratory testing are recorded according to strict case definitions[12] and the date of notification is also recorded.

All women in the cohort resident in WA and who gave birth to their first child (i.e. parity null) between 1st January 2000 and 31st December 2012, as determined from the Midwives Notification System, were included.

Statistical analysis

A woman was defined as having chronic HBV infection at the time of delivery of her first child if she had at least one linked notification of HBV prior to the birthing date. Women whose HBV notification prior to birthing was classified as acute were excluded from the analysis.

The HBV prevalence in birthing women was calculated overall and stratified by Aboriginality as determined from the Indigenous Status Flag created by the WA Data Linkage Branch[13]. HBV prevalence was then examined according to maternal year of birth classified into three

categories based on the likelihood of the mother being included in an HBV vaccination program; (i) pre-HBV vaccine (1974-1981), (ii) HBV vaccine available and recommend for at-risk adults (1982-1987), or (iii) targeted infant and school-based catch-up HBV vaccination programs (1988-1995), (see Appendix for details). No women in our cohort were born during the universal newborn vaccination program which commenced in May 2000. Chi-square tests were used to examine trends in HBV prevalence across maternal birth year categories.

Logistic regression was used to investigate the association between maternal birth year categories and HBV infection adjusted for other characteristics. These included area of residence determined from the mother's residential postcode reported in the Midwives Notification System and classified as metropolitan, regional or remote according to the Australian Standard Geographical Classification[14]; year of giving birth (per 5 year increase from 2000 to 2012), maternal ethnicity for non-Aboriginal women (Caucasian, other). Additional adjustments were made for maternal socioeconomic status based on maternal postcode classified according to the index of relative socioeconomic disadvantage (high, middle, low)[15], and maternal smoking (no, yes).

HBV prevalence in Aboriginal women by maternal year of birth was then compared between the WA cohort, and published data from similar cohorts in the NT and NSW. All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina).

Ethical approval

This study was approved by the Government of WA Department of Health Human Research Ethics Committee (Ref #2012/73) and the WA Aboriginal Health Ethics Committee (Ref 470).

Results

A total of 66,086 women in the study cohort gave birth to their first child between 1st January 2000 and 31st December 2012 in WA. Thirteen women had a notification of acute HBV prior to giving birth and were excluded leaving 66,073 women in the analysis. Of these women 7% (4907) were Aboriginal, with a younger age at the time of giving birth compared to their non-Aboriginal counterparts (mean age 19.1 years compared to 26.5 years, p<.0001) and a higher proportion resident in regional or remote WA (64% vs. 22%, p<.0001).

Among the 66,073 women, 155 linked to a non-acute HBV notification dated prior to giving birth giving an estimated prevalence of chronic HBV of 0.23%, 95%CI 0.20-0.27. Prevalence was substantially higher in Aboriginal women (0.92%, 95%CI 0.65-1.18), than non-Aboriginal

women (0.18%, 95%CI 0.15-0.21). As shown in Figure 1, among Aboriginal women, there was a significant decreasing trend in prevalence of HBV with maternal year of birth (p for trend<.0001). For those born in the pre-HBV vaccine era (year of birth 1974-1981) HBV prevalence was 1.98% (95%CI 0.95-3.01); this fell progressively among those born in the era of vaccination recommended for at-risk adults (1982-1987; 1.22%, 95%CI 0.74-1.69) and in those born in the era that made them eligible for the targeted infant and school based catch-up programs (1988-1995; 0.28%, 95%CI 0.10-0.61). Among non-Aboriginal women, the decline in HBV prevalence across these 3 maternal birth year cohorts was not significant at the 0.05 level (1974-1981: HBV prevalence 0.20% [0.16-0.25]; 1982-1987: 0.17% [0.11-0.23]; 1988-1995: 0.08% [0.03-0.18]; ptrend=0.06).

In logistic regression analyses (Table 1), after adjusting for year of giving birth and region of residence, Aboriginal women born in the two later periods (1982-1987 or 1988-1995) had respectively, a 42% and 89% lower risk of HBV than Aboriginal mothers born between 1974-1981 (adjusted odds ratio [aOR] respectively 0.58 [95%CI 0.30-1.13] and 0.11 [95%CI 0.04-0.33]). Furthermore, Aboriginal women resident in regional and remote WA were three times as likely to have a HBV notification compared to Aboriginal women resident in a major city (aOR 3.06, 95%CI 1.1.36-6.88). These estimates were similar after additional adjustment for maternal smoking and socioeconomic status.

Among non-Aboriginal women, after adjusting for year of giving birth, region of residence and ethnicity, there was no significant difference in HBV prevalence across maternal birth year categories (p=0.20), nor between those living in metropolitan regions and regional/remote areas (p=0.23). However, among non-Aboriginal women, those identifying as non-Caucasian had an estimated HBV prevalence of 1.6% compared to Caucasian women at 0.04%. After adjustments, non-Caucasian women were more than 35 times as likely to have chronic HBV than Caucasian women (aOR 36.08, 95%CI 22.66-57.46).

Comparing the data from WA Aboriginal women to that published from similar cohorts of Aboriginal women giving birth in the NT[2] and NSW[9] we found comparable relative declines in HBV prevalence according to maternal year of birth (Figure 2). However in absolute terms, among women born from 1985 to 1990, HBV prevalence was about one percentage point less among the WA women than in Aboriginal women in the NT, whilst HBV prevalence in WA women was similar to that found in NSW Aboriginal women.

Discussion

This is the first study to report the prevalence of HBV among birthing mothers in WA and examine differences between women born before and after the introduction of targeted HBV vaccination programs. This study estimated the overall HBV prevalence in Aboriginal mothers giving birth for the first time in WA during 2001-2012 to be 0.92%. In Aboriginal women, the risk of HBV infection decreased by 89% in those eligible for at-risk infant and schools-based catch-up vaccination programs compared to women born before the HBV vaccine was available. Among non-Aboriginal women, the HBV prevalence was 0.18%, substantially lower than in their Aboriginal counterparts and with no significant decline in prevalence observed over the study period.

While this was an ecological study design, our results suggest that the targeted at-risk infant and school-based HBV vaccination program has had a significant and long-lasting effect on reducing chronic HBV in the WA Aboriginal population. However, our results also highlight that continued monitoring is needed. Despite the declines in HBV observed in Aboriginal mothers, even in the most recent maternal birth-cohort (1988-1995), the prevalence of HBV remained higher in Aboriginal women compared to their non-Aboriginal counterparts (0.28% versus 0.08%). There were also substantial differences between Aboriginal women living in regional and remote parts of the state with a 3-fold difference compared to Aboriginal women living in cities. Furthermore, in non-Aboriginal women a 35-fold difference was observed between non-Caucasian and Caucasian women.

This study used similar methodology as was used in two previous studies on the prevalence of HBV in birthing mothers in Australia[2, 9]. Consistent across all three studies, was the significant decline (~80%) in HBV prevalence among Aboriginal women associated with the implementation of targeted vaccination programs in each of the jurisdictions (Figure 2). These two earlier studies also noted that despite the large declines, HBV prevalence remained higher in Aboriginal women compared to their non-Aboriginal counterparts of the same birth cohort, and there were marked differences in HBV prevalence between Aboriginal women resident in regional/remote areas compared to cities. While equivalent measures of ethnicity were not available, the WA findings of a significantly higher HBV prevalence among non-Aboriginal women comparing non-Caucasian to Caucasian also broadly mirrors findings in NSW, which showed HBV prevalence of 1.95% among overseas-born women compared to 0.11% in non-Aboriginal Australian-born women.

Despite the similarity in relative decline in HBV prevalence in Aboriginal women between the three Australian jurisdictions that we compared, the absolute HBV prevalence in the NT Aboriginal women was substantially higher than that in WA and NSW for all maternal birth cohorts (Figure 2). According to standard geographic classifications[14], all of the population

in the NT would be classified as regional or remote. Therefore it is interesting that the magnitude of the difference between HBV prevalence among women in similar birth cohorts in WA and NT (eg: for Aboriginal women born around 1990 HBV prevalence in the NT was almost three-times that in WA [0.28 versus 0.80], Figure 2) is about equivalent to that found comparing women living in metropolitan to rural/remote regions of WA (aOR 3.06, Table 1). It suggests geographic factors may underlie the higher prevalence found between jurisdictions such as WA or NSW and the NT.

It is unclear why HBV prevalence in Aboriginal women is much higher among those born in regional/remote areas than in metropolitan areas. Possible reasons include that similar to what has been reported in some African countries,[16, 17] poorer housing and environmental conditions in remote Aboriginal communities, with the associated greater crowding and reduced skin hygiene, leads to higher horizontal transmission in such settings. It has also been suggested that reduced access to health services in more remote populations[9] as well as the potential for differences in circulating HBV genotypes between regions of Australia may be contributing factors[18]. The differences in HBV prevalence in non-Aboriginal non-Caucasian women compared to Caucasian women is almost certainly due to migrant populations from high-HBV prevalence countries[3] however we did not have data on the mothers' country of birth to confirm this hypothesis.

Internationally, other studies assessing the long-term impact of infant and childhood HBV vaccination program impact have reported greater reductions in HBV prevalence associated with universal infant programs than with targeted programs; most assessments of universal programs report reductions in HBV prevalence of 80% or greater [19, 20] whilst targeted (at-risk) programs reported reductions ranging from 25-85%[19, 21]. Our WA findings relate only to women exposed to targeted at-risk and school-based vaccination programs. Therefore, the magnitude of the decline in HBV prevalence is in the upper range of that reported in other studies and comparable to universal programs. While there are no data available on the WA HBV vaccine program coverage during this early period, our results suggest it was very successfully implemented and effective in reducing prevalence.

This study focuses on women giving birth in WA and the results may not be generalisable to men or older women. In Australia[22] and internationally[17] men consistently have higher HBV prevalence reported than women, although assuming that infant and early childhood HBV vaccination programs are equally effective in boys, this difference is unlikely to affect the relative reductions in prevalence estimated here. Also in the WA data, unlike in the earlier NSW studies,[3] we lacked data on country of birth to disaggregate the very high HBV prevalence in the non-Caucasian women according to this variable. Finally, in interpreting our

data the ecological design needs to be considered. We did not have individual data on receipt of HBV vaccine and it is possible that temporal trends other than the introduction of vaccination may have contributed to the decline in HBV prevalence in Aboriginal women. For example, other known risk factors for HBV infection, such as current or previous injecting drug use and overseas travel to high endemicity countries are not routinely collected in the WA Midwives Notification System and thus we were unable to account for these factors.

We demonstrate significant declines in the prevalence of HBV among Aboriginal mothers giving birth for the first time in WA that corresponds with the introduction of targeted vaccination programmes. However, HBV prevalence in Aboriginal mothers remained higher than that of their non-Aboriginal counterparts. Continued screening of pregnant women for HBV and providing babies born to hepatitis B-positive mothers with post-exposure prophylaxis is an important element in prevention of virus transmission. Our cohort consisted of women born between 1974 and 1995 and therefore we were unable to evaluate the impact of the universal newborn vaccination program introduced in May 2000. As these women, born in the universal newborn vaccination era, reach children-bearing age it will be important to continue surveillance to monitor the disparities in HBV prevalence between both Aboriginal and non-Aboriginal women, in Aboriginal women between those resident in regional/remote and cities, and the prevalence of HBV among Australian immigrants. Our findings show that additional efforts are needed to reduce these disparities and these data are vital to inform HBV prevention and treatment programs. Furthermore the methods used here, which are simple and cost effective, could also be used to monitor the impact of vaccination programs in other countries with high HBV prevalence, if antenatal HBV testing is widespread.

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Conflict of Interest

The authors have no conflicts of interest to declare

Highlights

- Infant and childhood hepatitis B vaccination programs have been in place in Australia for many years but less is known about their impact on HBV prevalence.
- A significant decline in HBV prevalence in Aboriginal women was observed following the introduction of HBV vaccination programs in Western Australia.
- Despite this decline, HBV vaccination programs have not eliminated the considerable disparities in HBV prevalence observed in women according to Aboriginality, ethnicity and area of residence.

References

1. World Health Organization, *Hepatitis B, Factsheet No 204.* 2012.
2. Liu B, et al., *The end of the Australia antigen? An ecological study of the impact of universal newborn hepatitis B vaccination two decades on.* Vaccine, 2012. **30**: p. 7309-14.
3. Reekie J, et al., *Country of birth and other factors associated with hepatitis B prevalence in a population with high levels of immigration.* J Gastroenterol Hepatol, 2013. **28**: p. 1539-44.
4. The Kirby Institute, *HIV, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2016.* 2016: The Kirby Institute, UNSW Australia, Sydney NSW 2052.
5. National Centre for Immunistation Research and Surveillance. *Significant events in hepatitis B vaccination practice in Australia*. 2015 November 2015 [cited 2017 14/09/2017]; Available from: http://www.ncirs.edu.au/assets/provider_resources/history/Hepatitis-B-history-November-2015.pdf.
6. Australian Bureau of Statistics, *3238.0.55.001 - Estimates of Aboriginal and Torres Strait Islander Australians, June 2011*. 2013.
7. The royal Australian and New Zealand College of Obstetricians and Gynaecologists, *Management of Hepatitis B in pregnancy*. 2016. p. 1-13.
8. Kwan, K., et al., *Improvement in antenatal testing for sexually transmissible infections and blood-borne viruses in Western Australian hospitals, 2007 to 2010.* Sex Health, 2012. **6**(4): p. 349-54.
9. Deng, L., et al., *Trends in Hepatitis B prevalence among women giving birth in New South Wales Australia* Medical Journal of Australia, 2017.
10. Australian Bureau of Statistics. *http://stat.abs.gov.au/itt/r.jsp?RegionSummary&region=5&dataset=ABS_REGIONAL_ASGS&geoconcept=REGION&datasetASGS=ABS_REGIONAL_ASGS&datasetLGA=ABS_NRP9_LGA&regionLGA=REGION&regionASGS=REGION*. [cited Feb 2018.
11. Holman, C.D., et al., *Population-based linkage of health records in Western Australia: development of a health services research linked database.* Aust N Z J Public Health, 1999. **23**(5): p. 453-9.
12. Australian Government Department of Health. *http://www.health.gov.au/internet/main/publishing.nsf/Content/cdna-casedefinitions.htm#e*.
13. Christensen, D., et al., *Evidence for the use of an algorithm in resolving inconsistent and missing Indigenous status in administrative data collections.* Australian Journal of Social Issues, 2014. **49**(4): p. 423-443.
14. Australian Bureau of Statistics, *Australian Standard Geographic Classification*, ed. A.C.N. 1216.0. 2005, Canberra: Commonwealth of Australia.
15. Australian Bureau of Statistics. *Socio-economic indexes for areas*. [Internet] 2011.
16. Dumpis, U., et al., *Transmission of hepatitis B virus infection in Gambian families revealed by phylogenetic analysis.* J Hepatol, 2001. **35**(1): p. 99-104.
17. Zampino, R., et al., *Hepatitis B virus burden in developing countries.* World J Gastroenterol, 2015. **21**(42): p. 11941-11953.
18. Davies, J., et al., *Molecular epidemiology of hepatitis B in the Indigenous people of northern Australia.* J Gastroenterol Hepatol, 2013. **28**(7): p. 1234-41.
19. Lin, Y., et al., *Serological surveillance and IL-10 genetic variants on anti-HBs titers: Hepatitis B vaccination 20 years after neonatal immunization in Taiwan.* Clinica Chimica Acta, 2011. **412**: p. 766-773.

20. Da Villa, G., et al., *Impact of hepatitis B vaccination in a highly endemic area of south Italy and long-term duration of anti-HBs antibody in two cohorts of vaccinated individuals.* Vaccine, 2007. **25**: p. 3133-6.
21. Lin, C., et al., *Hepatitis B virus infection among pregnant women in Taiwan: comparisons between women born in Taiwan and other southeast countries.* BMC Pub Health, 2008. **8**: p. 49.
22. The Kirby Institute, *Hepatitis B and C in Australia Annual Surveillance Report Supplement 2016*. 2016, The Kirby Institute, UNSW: Sydney Australia.