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Title:

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Date:

2021-06-01

Citation:

Qama, A., Allard, N., Cowie, B., Davis, J. S. & Davies, J. (2021). Hepatitis B in the Northern Territory: insights into the changing epidemiology of an ancient condition. Internal Medicine Journal, 51 (6), pp.910-922. <https://doi.org/10.1111/imj.15069>.

Persistent Link:

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ORIGINAL ARTICLE

Hepatitis B in the Northern Territory: insights into the changing epidemiology of an ancient condition

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Key words

hepatitis B virus, chronic hepatitis B, Aboriginal and Torres Strait islander peoples, vaccine efficacy, infant vaccination.

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Received 14 June 2020; accepted
10 September 2020.

Abstract

Background: Aboriginal and Torres Strait Islander people are disproportionately affected by hepatitis B virus (HBV) infection. A proposed mismatch between standard vaccines and the HBV/C4 sub-genotype prevalent in Aboriginal people in the Northern Territory (NT) may reduce vaccine effectiveness.

Aims: To determine HBV prevalence in the NT by Indigenous status and to explore patterns of immunity following implementation of universal vaccination, using a large longitudinal diagnostic dataset.

Methods: A retrospective analysis of all available HBV serology results in the NT from 1991 to 2011 was conducted, with HBV prevalence and vaccination status analysed according to indigenous status, age and sex using individuals' patterns of HBsAg, anti-HBs and anti-HBc serology over repeated tests.

Results: 100 790 individuals were tested (33.4% Indigenous) between 1991 and 2011 (26.1% of the 2011 NT population), with a total of 211 802 tests performed. In 2011, the proportion of HBV positive individuals in the NT was 3.17% (5.22% in Indigenous populations) compared to previous 2011 estimates of 1.70% (3.70% in Indigenous populations). The vaccine failure rate was lower than expected with only one presumed vaccinated person subsequently developing HBsAg positivity (0.02%). Evidence of sub-optimal vaccine efficacy by breakthrough anti-HBc positivity in vaccinated individuals was demonstrated in 3.1% of the vaccinated cohort, of which 86.4% identified as Indigenous (HR 1.17). No difference in HBeAg positivity or seroconversion was observed between Indigenous and non-Indigenous individuals living with CHB.

Conclusions: The burden of CHB in Indigenous people in the NT has previously been underestimated. A higher HBV prevalence in the NT than described in previous cross-

Abbreviations: anti-HBc, antibody to hepatitis B core antigen; anti-HBe, antibody to hepatitis B e antigen; anti-HBs, antibody to hepatitis B surface antigen; CHB, chronic hepatitis B; CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBV/C4, hepatitis B virus, sub-genotype C4; HCC, hepatocellular carcinoma; HR, hazard ratio; Indigenous, Australian Aboriginal and/or Torres Strait Islander person; IQR, interquartile range; NT, Northern Territory; OR, odds ratio

Throughout this journal article, 'Indigenous' refers to Australian Aboriginal and Torres Strait Islander peoples. It is understood that there is no single Australian Aboriginal or Torres Strait Islander culture or group. Aboriginal and Torres Strait peoples are the first peoples of Australia and have a strong and resilient history.

Funding: None.

Conflict of interest: None.

Disclosure: The authors declare no conflicts of interest in the data collection, analysis and manuscript preparation. J. S. Davis and J. Davies received an unrestricted educational grant from Gilead for a separate hepatitis B-related project. J. S. Davis and J. Davies received salary support from the Australian National Health and Medical Research Council (NHMRC). J. Davies is a NHMRC Early Career Fellow, and J. S. Davis is a NHMRC Career Development Fellow. The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript. There was no other specific funding for this project.

sectional studies was found, including a higher prevalence in Indigenous people. Evidence of suboptimal vaccine efficacy was demonstrated predominantly in Indigenous individuals.

Introduction

An estimated 250 million people live with chronic hepatitis B virus (HBV) infection worldwide,¹ and of these, over 880 000 people die every year due to the consequences of HBV infection,² primarily hepatocellular carcinoma (HCC) and cirrhosis.³ Chronic hepatitis B (CHB) is estimated to affect 0.95% of Australians, with an estimated population prevalence of 1.90% in the Northern Territory (NT) – the highest CHB prevalence in Australia.⁴ Indigenous Australian¹ communities experience higher CHB prevalence than the non-Indigenous population, with estimates ranging from 2.50% to 3.50%.^{4,5} CHB prevalence has been reported to be even higher in Indigenous communities living in the NT, with a prevalence of 6.08% and a fourfold higher risk of HBsAg positivity.⁶ Further, Indigenous individuals experience significantly higher rates of long-term CHB complications compared to non-Indigenous Australians.⁷

In 2011, the CHB prevalence for Indigenous individuals living in the NT was estimated to be 3.70%.⁸ The vast majority of HBV prevalence studies for Indigenous peoples have utilised cross-sectional serosurveys, primarily in pregnant women.^{5,9,10} These studies may not accurately reflect secular trends in the NT population, population-level changes in vaccination status over time, prevalence in Indigenous men and the dynamic flux in stages of CHB infection. Given Indigenous Australians comprise 30.3% of the NT population,¹¹ identifying trends in HBV infection and vaccination within the NT may help address the health disparities between Indigenous and non-Indigenous Australians living with CHB.

Infant HBV vaccination was introduced in the NT for Indigenous children in 1988 and for all infants in 1990, with a school catch-up programme for students aged between 6 and 16 years conducted in 1998.⁶ Potential issues with the early implementation of these programmes have been identified, including the use of plasma-derived vaccines until 1991, which may have a decreased immunogenic response in infants,¹² and breaches of the cold chain, including freezing of vaccines during transport,^{13,14} making it possible that fully vaccinated infants in the NT have decreased HBV immunity. Indeed, a handful of studies have suggested decreased HBV vaccine efficacy in fully vaccinated Indigenous children in the NT.^{15–17}

An additional challenge to HBV vaccination in the NT is the role of serotype mismatch and suboptimal vaccine efficacy. A unique HBV sub-genotype, HBV/C4, has been identified exclusively in northern Aboriginal communities.^{18,19} The current vaccine is based upon sub-genotype A2, serotype *adw2*,²⁰ whilst HBV/C4 is serotype *ayw3*.^{18,19} A study of Aboriginal individuals vaccinated at birth in the NT found a 67.0% vaccine efficacy against any HBV infection, with breakthrough anti-HBc positivity.¹⁶ Similar results have been noted in fully vaccinated individuals where a genotype and serotype mismatch exists.^{21–27}

The present study aimed to use existing HBV serology test data to assess the prevalence of HBV in the NT and compare these to existing estimates, to compare the CHB trajectory and testing patterns between Indigenous and non-Indigenous individuals and to assess HBV vaccine efficacy in a region of known serotype mismatch.

Methods

This study was a retrospective longitudinal analysis of all available HBV laboratory test data carried out for any reason in the NT between January 1991 and December 2011, including HBsAg, anti-HBs, anti-HBc, HBeAg, anti-HBe and viral load. Data were sourced from three pathology providers, which are responsible for 97.9% of all HBV notifications, and linked as previously described.⁶

Ethical approval for this study was obtained from the Menzies School of Health Research (HREC-12-1745) and the Central Australian Human Research Ethics Committee (HREC-14-244). The decision to use existing diagnostic test data was made at the specific request of Aboriginal communities in the NT to elucidate as much information as possible with currently available data before requesting any new blood samples.

HBV status coding

Participants were classified by their HBV status per testing episode in this dataset to allow changes in disease progression and vaccination status to be captured. For each individual, their HBV status was assumed to remain

Table 1 Hepatitis B virus (HBV) status classification based on serology results for individual testing episodes

Phase	HBsAg	HBsAb	HBcAb	HBeAg	HBeAb
No markers present	Negative	Negative	Negative	Negative	Negative
Vaccinated	Negative	Positive	Negative	Not tested	Not tested
Immune by past exposure	Negative	Positive	Positive	Negative	Negative
Unspecified immunity	Negative	Positive	Not tested	Negative	Negative
Isolated core positive	Negative	Negative	Positive	Negative	Negative
HBV positive	Positive	Negative	Negative	Negative	Negative
eAg positive	Positive	Negative	Positive	Positive	Positive
eAg negative	Positive	Negative	Positive	Negative	Positive
Unknown	Not tested	Negative	Not tested	Negative	Negative
		Positive		Positive	Positive
		Not tested		Not tested	Not tested

eAg, e antigen; HBcAb, hepatitis B core antibody; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen.

consistent until a subsequent test proved otherwise. For each testing episode, participants were classified as: no markers present (susceptible); vaccinated; immune through past exposure; immune with unspecified mechanism; HBV positive, isolated anti-HBc positive; or unknown (Table 1). HBV positive individuals (HBsAg positive) were further stratified into: HBeAg positive, HBeAg negative, or unspecified.

Serological markers were not provided in quantitative format, and anti-HBs titres were not available for analysis. Each serological marker was reported as either: detected; not detected; or not tested. Individual anti-HBc IgM and anti-HBc IgG results were not provided, thus all anti-HBc test results were assumed to be total anti-HBc. Vaccination records were not available so simultaneously positive anti-HBs and negative anti-HBc was assumed to represent vaccine-induced immunity.

Only 25% of individual testing episodes in this dataset included reporting of all three of HBsAg, anti-HBs and anti-HBc, resulting in a large number of episodes where no clear HBV status could be allocated. For participants with an underdetermined status who underwent multiple testing episodes, previous and subsequent test data were used to establish HBV status at these unknown points. Participants that had HBV positive serology were subsequently classified as remaining HBV positive unless later testing demonstrated evidence of HBsAg clearance. Individuals with vaccination serology continued to be classified as vaccinated on later testing episodes, even if

they subsequently returned an undetectable anti-HBs, so long as they had one initial test demonstrating anti-HBs positivity and remained anti-HBc negative, given immunity to HBV persists even as anti-HBs titres wane over time.^{28–30} This longitudinal approach to serology allowed 10 392 unclear test results to be reclassified more accurately, resulting in the clarification of HBV status for 4647 participants.

Yearly HBV prevalence

Prevalence in the cohort was calculated annually based on each individual's HBV status on December 31 of each year. Participants were included in prevalence calculations from the date of their first test and censored at their last recorded interaction with a NT government health service during the study period. HBV prevalence was calculated as the number of people who tested HBsAg positive, with the denominator as the total number of individuals with testing data available for that year, including those with an unknown HBV status. For prevalence calculations where participants were stratified by vaccine eligibility, years 1991 to 1997 were excluded as an insufficient number of tests was conducted.

Vaccination eligibility

Eligibility for standardised vaccination programmes was determined by participants' year of birth. Individuals

born from 1982 to 1992 were classified as eligible for school-based vaccination.³¹ Indigenous individuals born from 1988 and non-Indigenous individuals born from 1990 were classified as eligible for infant vaccination.

Data analysis

Data were analysed in Stata 15.1 (StataCorp, College Station, TX, USA). For descriptive analysis of non-normally distributed data, median and interquartile range (IQR) were used. Differences between groups were assessed using Chi-squared tests for categorical variables and Mann–Whitney *U*-tests for continuous variables, with two-way tests of proportions used for differences within and across groups. Logistic regression was used for multivariable analysis of HBV positivity and

demographic variables, including Indigenous status, sex and age. Survival analysis using Cox proportional hazard models was performed to analyse time-to-event data for HBeAg loss in HBeAg positive individuals, anti-HBc acquisition in vaccinated individuals and anti-HBs loss in vaccinated individuals.

Results

Demographics

There were 100 970 individuals tested for HBV between January 1991 and December 2011, with a total of 211 802 unique testing episodes (Supporting Information Fig. S1). 33.4% of individuals identified as Indigenous, and 58% of individuals were female (Table 2). The

Table 2 Demographic data of people in the Northern Territory who were tested for HBV once or more between January 1991 and December 2011

	Indigenous†	Non-Indigenous	P-value
Number of people tested, <i>n</i> (%)‡	33 658 (33.4)	64 835 (64.3)	<0.0005
Females	18 562 (55.1)	38 575 (59.5)	<0.0005
Males	15 032 (44.7)	26 183 (40.4)	<0.0005
Age at time of first test (years)§	30.2 (23, 40.2)		
Median (IQR)	26.9 (19.2, 39.4)	31.2 (25, 40.6)	0.0001
Age at time of most recent test (years)§	33.2 (25.9, 43.2)		
Median (IQR)	33.2 (24, 44.4)	33.3 (26.6, 42.8)	0.0001
ASGC Remoteness Area, <i>n</i> (%)			<0.0005
Outer regional	3387 (10.1)	33 543 (51.7)	<0.0005
Remote or very remote	21 326 (63.4)	17 040 (26.3)	<0.0005
Not recorded	8945 (26.6)	14 252 (22.0)	<0.0005
People eligible for vaccination programs, <i>n</i> (%)§	10 565 (31.4)	11 047 (17.0)	<0.0005
School catch-up vaccination	8847 (83.7)	10 174 (92.1)	<0.0005
Universal birth vaccination¶	5295 (50.1)	2090 (18.9)	<0.0005
Total number of tests for these individuals, <i>n</i> (%)	99 512 (47.0)	108 822 (51.4)	
Median per person (IQR)	2 (1, 4)	1 (1, 2)	0.0001
Time between subsequent tests (days)	545 (202, 1121)		
Median (IQR)	518 (188, 1088)	582 (231, 1179)	0.0001
Total follow-up time (years)	7.94 (3.97, 12.5)		
Median (IQR)	9.10 (5.15, 13.3)	7.36 (3.54, 12.0)	0.0001
HBV status able to be determined on first test, <i>n</i> (%)‡	14 628 (43.5)	15 032 (23.2)	<0.0005
Females	12 910 (22.1)		<0.0005
Males	17 210 (40.8)		
HBV status on first test, <i>n</i> (%)			<0.0005
No markers	3391 (10.1)	7336 (11.3)	<0.0005
Vaccinated	2014 (5.98)	4191 (6.51)	<0.0005
Immunity by past exposure	5690 (16.9)	2024 (3.12)	<0.0005
Unspecified immunity	1364 (4.05)	6102 (9.41)	<0.0005
HBV positive	2054 (6.10)	861 (1.33)	<0.0005
Isolated anti-HBc	1479 (4.39)	620 (0.96)	<0.0005
Unknown	17 666 (52.5)	43 701 (67.4)	<0.0005

ASGC, Australian Standard Geographical Classification; HBc, hepatitis B core antigen; HBV, hepatitis B virus; IQR, interquartile range.

†2297 people did not have their Indigenous status recorded in the dataset.

‡156 people (64 Indigenous, 77 non-Indigenous, 15 unknown) did not have their sex recorded in the dataset.

§388 people (165 Indigenous, 116 non-Indigenous, 107 unknown) did not have their age recorded in the dataset.

¶4818 people (3577 Indigenous, 1217 non-Indigenous, 24 unknown) were eligible for both vaccination programmes based on their year of birth.

median age at first test was 30.2 years (IQR 23.0–40.2), with 21.9% eligible for standardised vaccination programmes and a median follow-up time of 7.94 years (IQR 3.97–12.5). 51.7% of non-Indigenous individuals had a residential address in an outer regional area (Darwin and suburbs), while the majority (63.4%) of Indigenous individuals were recorded as living in a remote or very remote area (the remainder of the NT).

Most participants (53.8%) were only tested once in this study, although Indigenous people had a median of two tests per person (IQR 1–4, $P < 0.0005$). For individuals who were tested multiple times, the median time between tests was 545 days (IQR 202–1121), with a median of 518 days (IQR 188–1088) for Indigenous individuals ($P < 0.0005$). The majority of participants (62.3%) did not have enough serological markers tested to identify their HBV status on their first testing episode. A significantly higher proportion of Indigenous individuals were able to be classified compared to non-Indigenous people (43.5% and 23.2% respectively, $P < 0.0005$), and a higher proportion of males were able to be classified than females (40.8% vs 22.1%, $P < 0.0005$). A higher proportion of Indigenous people had serology indicating immunity through past exposure (16.9%, $P < 0.0005$) or HBV infection (6.10%, $P < 0.0005$) compared to non-Indigenous participants (3.12% and 1.33% respectively). 55 252 individuals had valid serology results in 2011, representing 26.1% of the total NT population in 2011.³²

HBV prevalence

HBV prevalence was highest in the first year of test results (4.04%), and subsequently fluctuated between 3.03% and 4.04% before reaching its lowest point of 2.81% in 2010 (Fig. 1A). HBV prevalence in Indigenous people peaked in 1999 (8.12%) and continued to decline each year, reaching its lowest point in 2011 (5.22%). For non-Indigenous Australians, HBV prevalence remained between 1.31% and 1.79% for the entirety of the study period. Odds ratios for HBV positivity were 4.59 (4.35–4.84 95% CI, $P < 0.0005$) for Indigenous individuals compared to non-Indigenous Australians, 0.57 (0.55–0.6 95% CI, $P < 0.0005$) for females compared to males and 0.98 (0.97–0.99 95% CI, $P < 0.0005$) for people living in an outer regional area compared to a remote or very remote area.

For people who were eligible for the school catch-up vaccination programme, HBV prevalence steadily decreased over each year of testing, from 5.61% in 1998 to 2.02% in 2010 and 2011 (Fig. 1B). HBV prevalence remained higher in Indigenous Australians compared to

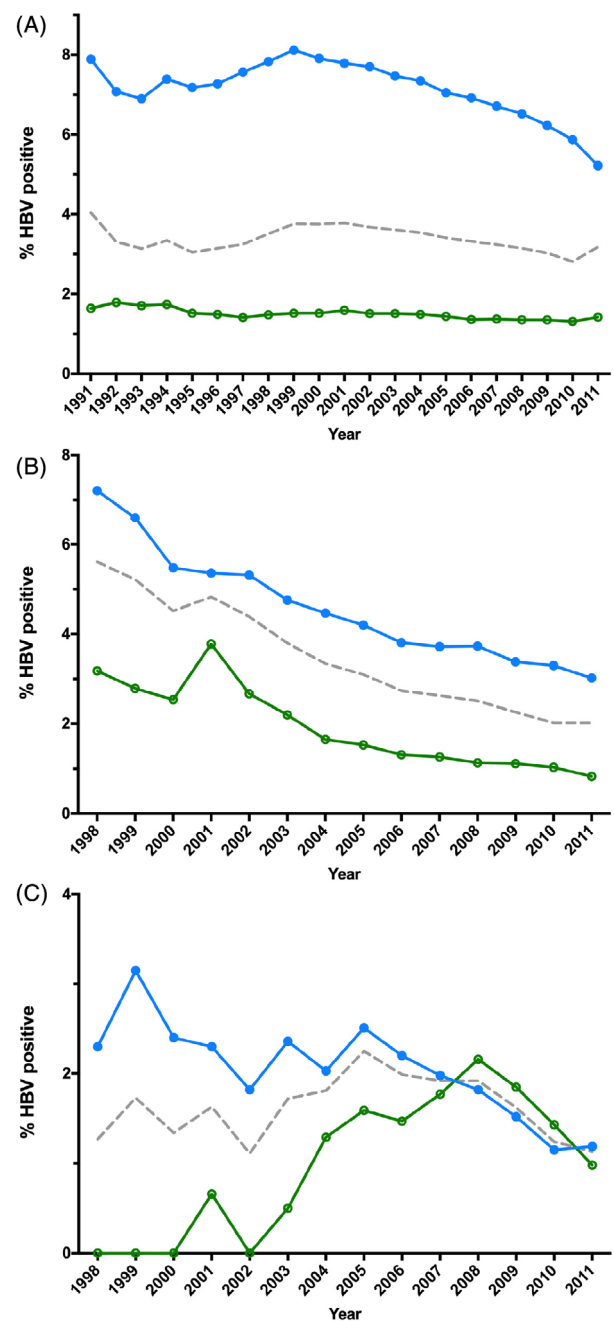


Figure 1 Yearly HBV prevalence in people tested for HBV for any reason in the NT between January 1991 and December 2011, stratified by Indigenous status. (A) Prevalence for all people tested. (B) Prevalence within people eligible for school-based vaccination in 1998. (C) Prevalence within people eligible for universal infant vaccination. (—●—), Indigenous; (—○—), non-Indigenous; (----), total.

non-Indigenous Australians, with an odds ratio of 2.81 (2.42–3.27 95% CI, $P < 0.0005$) for Indigenous people.

For individuals who were eligible to be vaccinated at birth, HBV prevalence fluctuated between 1.11% and

1.81% until reaching its highest in 2005 (2.25%), and subsequently declined each year to 1.13% in 2011 (Fig. 1C). HBV prevalence remained higher in Indigenous individuals until 2007, at which point HBV prevalence became higher in non-Indigenous Australians, although this was not statistically significant, with an overall odds ratio of 1.23 (0.88–1.72 95% CI, $P = 0.228$) for Indigenous people.

HBV diagnoses

A total of 3202 people tested HBsAg positive, with 71.1% of these individuals identifying as Indigenous ($P < 0.0005$) (Table S1). The majority of people (57.8%) who tested HBV positive were male, with a median age of 34.7 years (IQR 24.6–46.9) at the time of their first HBsAg positive test in the study timeframe. A higher proportion of Indigenous Australians who tested HBsAg positive lived in a remote or rural area (68.3%) compared to non-Indigenous Australians (26.9%, $P < 0.0005$). 15.4% of people with HBV were eligible for standardised vaccination programmes, with a greater number of Indigenous people eligible for school-based vaccination ($P = 0.02$). Indigenous people underwent repeat testing slightly more than non-Indigenous individuals, with a median of three tests per person (IQR 2–6, $P < 0.0005$). Indigenous Australians were also tested or engaged in care with a NT government health service for longer periods of time than non-Indigenous Australians, with a median of 10.6 years (IQR 6.67–14.3) compared to 8.82 years (IQR 4.35–13.1, $P < 0.0005$).

The majority of people (61.5%) with an HBV positive test were HBeAg negative on their first HBV positive test, with no difference in HBeAg status on the first HBV positive test between Indigenous and non-Indigenous individuals, regardless of age (Fig. 2A, Table S2). There was no overall difference in the rate of HBeAg seroconversion between Indigenous and non-Indigenous people, even when stratified by age group (Fig. 2B).

Test results of people eligible for standardised vaccination

A total of 22 040 individuals (21.4%) was eligible to be included in vaccination programmes based on their date of birth, with 47.9% of these individuals identifying as Indigenous (Table S2). Of these, only 9384 people (42.6%) had enough serological markers in one testing episode tested during the study period to determine their HBV status without further information or access to clinical records (Table S2). As a result, individuals who were

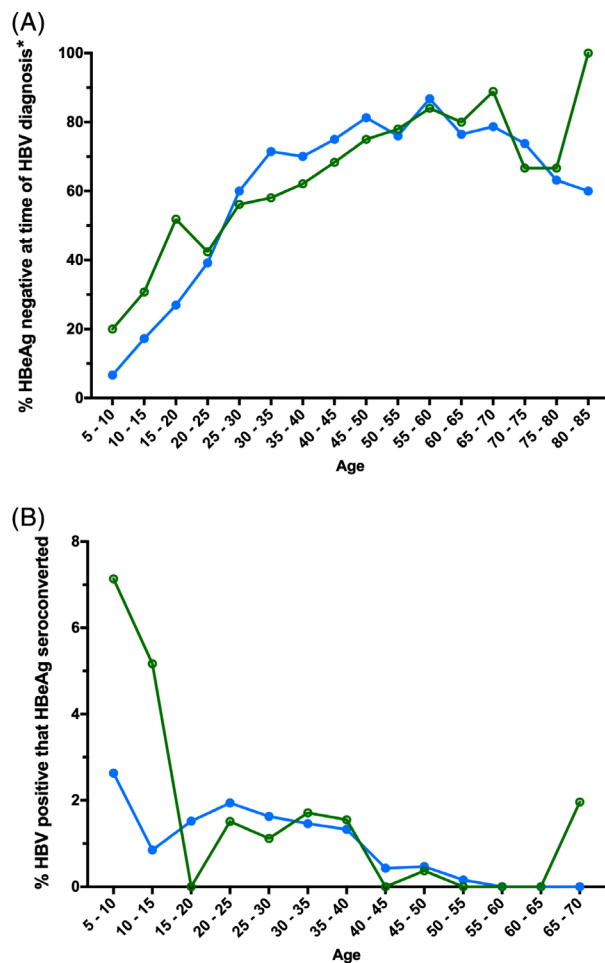


Figure 2 HBeAg serology stratified by Indigenous status and age group at the time of testing. (A) Percentage of individuals who tested HBeAg negative on their first HBV positive test during the study period, by age at the time of their first HBV positive test and by Indigenous status. *'HBV diagnosis' refers to an individual's first positive HBV test in our dataset, although they may have been diagnosed before 1991. (B) Percentage of individuals that HBeAg seroconverted (on their first HBV positive test also tested HBeAg positive, then subsequently tested HBeAg negative), by age at the time of confirmed HBeAg loss and Indigenous status. (—●—), Indigenous; (—○—), non-Indigenous. HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

categorised as immune with an unspecified mechanism or as unknown were excluded from further analysis.

Within the cohort of all individuals eligible for any vaccination programme (infant or school-based) with a known immunity status ($n = 9264$), Indigenous people had a higher proportion of HBsAg positivity on their most recent test (5.39% vs 3.34%, $P < 0.0005$), as well as a lower proportion of vaccination-derived immunity (32.2% compared to 41.5%, $P < 0.0005$), a higher proportion of immunity through past exposure (29.7% vs 7.57%, $P < 0.0005$) and a higher proportion of isolated

anti-HBc positivity than non-Indigenous people (4.22% and 2.44% respectively, $P < 0.0005$) (Fig. 3A).

The pattern of serology results for people eligible for vaccination at school ($n = 8057$) was similar to the overall cohort of all eligible for standardised vaccination programmes. A larger proportion of Indigenous individuals were HBsAg positive on their most recent test (5.81% vs 3.25%, $P < 0.0005$), fewer with markers of vaccination-derived immunity (31.8% vs 43.0%, $P < 0.0005$), a greater proportion with immunity through past exposure (32.8% compared to 7.38%, $P < 0.0005$) and a higher number of isolated anti-HBc positivity than non-Indigenous people (4.48% and 2.38% respectively, $P < 0.0005$) (Fig. 3B).

For individuals eligible for infant vaccination ($n = 3386$), a higher proportion of Indigenous people had vaccine-derived immunity than non-Indigenous people (36.6% vs 32.3%, $P < 0.0005$), and a greater proportion of people with immunity through past infection (15.1% compared to 8.76%, $P < 0.0005$) (Fig. 3C). A statistically significant difference was not seen between Indigenous and non-Indigenous individuals in HBsAg positivity or isolated anti-HBc.

Vaccination efficacy

Changes in immunity status were evaluated over time in the cohort of people who had serology indicative of vaccination on their first HBV test ($n = 6473$) (Table 3). 31.1% of these individuals identified as Indigenous, and 51.1% were female. Individuals in this subgroup had a median age of 29.5 years (IQR 22.9–40.2) on their first HBV testing episode, and a median follow-up time of 4.57 years (IQR 1.95–8.65).

Of these individuals, one Indigenous person subsequently became HBsAg positive (0.02%). A further 198 people subsequently tested anti-HBc positive (3.06%), of which 86.4% were Indigenous (HR 1.29, 1.16–1.43 95% CI, $P < 0.0005$). 42.9% of these people were female (HR 0.55, 0.42–0.73 95% CI, $P < 0.0005$), and 13.1% were eligible for standardised vaccination (HR 0.57, 0.35–0.93 95% CI, $P < 0.0005$). This group that became anti-HBc positive had a median age of 38.4 years old at the time of anti-HBc appearance (IQR 30.4–48.2), and a median follow-up time of 11.9 years (IQR 8.37–15.4), with no significant differences observed between Indigenous and non-Indigenous Australians.

Of the presumed vaccinated cohort, 290 individuals (4.48%) subsequently returned a not detected anti-HBs titre result indicating a waning anti-HBs titre but did not develop HBsAg positivity. 52.1% of these individuals identified as Indigenous (HR 1.06, 0.96–1.14 95% CI, $P = 0.32$), 48.3% of these people were female (HR 0.87,

0.69–1.09 95% CI, $P = 0.21$), and 24.8% were eligible for standardised vaccination (HR 0.57, 0.44–0.74 95% CI, $P < 0.0005$). Indigenous individuals demonstrated an undetectable anti-HBs at a younger median age than non-Indigenous people ($P = 0.002$), and the median follow-up time was 5.70 years (IQR 2.91–8.97), with no difference seen between Indigenous and non-Indigenous individuals.

Discussion

HBV prevalence in the NT

This large longitudinal study has demonstrated a higher proportion of HBV positivity in 2011 across the general NT population (3.17%) and in Indigenous populations (5.22%) compared to previous 2011 estimates of 1.70% (3.70% in Indigenous populations).⁸ HBV prevalence estimates for the NT and for Indigenous peoples have previously been calculated almost exclusively using cross-sectional serosurveys, national notifications data and diagnostic testing results.^{4–6,10} By calculating prevalence through multiple test results over time, this study decreased the proportion of individuals with an unclear HBV status by 12.7%. This approach has allowed for the determination of HBV status for individuals where clinicians have only ordered serological markers informed by their patients' past medical history, and enabled changes in HBV status over time to be tracked. While the prevalence of CHB in those referred for HBV testing is likely to be higher than prevalence in the general population (due to referral bias), testing for Indigenous peoples in the NT is often performed for screening rather than for clinical suspicion as part of an Indigenous adult health check and thus we believe these results are likely to be more accurate than previous estimates, many of which have been based on antenatal screening tests,⁶ and may underestimate the prevalence of HBV in men. Due to the nature of antenatal screening whereby pregnant women in the NT were only routinely tested for HBsAg positivity until 2015,³³ a higher proportion of males were able to have their HBV status determined than females, decreasing the likelihood that we have underestimated the prevalence of HBV in men living in the NT.

HBV prevalence declined from 4.04% to a low of 2.81% over the study period; however, HBV prevalence remained significantly higher in Indigenous Australians than non-Indigenous people (OR 4.59), and significantly lower in women compared to men (OR 0.57). Standardised vaccination programmes resulted in a narrowing of the disparity between Indigenous and non-Indigenous individuals, with an OR of 2.81 for Indigenous people eligible for school-based vaccination, and an

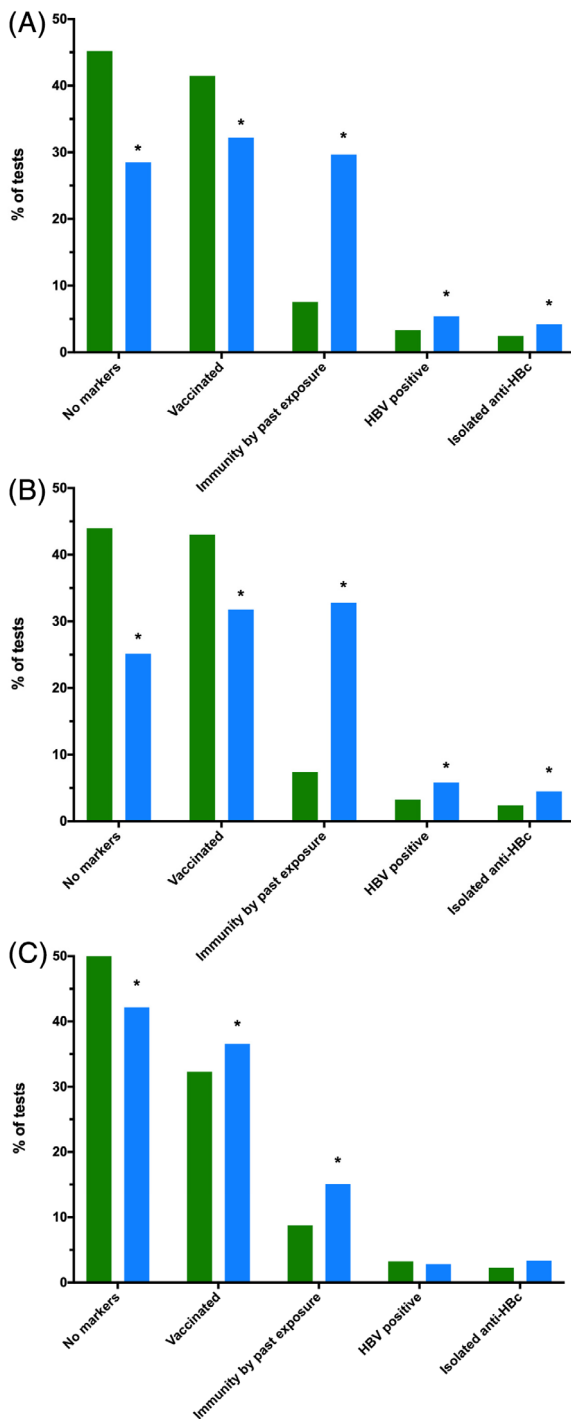


Figure 3 Individuals' most recent hepatitis B virus (HBV) serology results stratified by Indigenous status and eligibility for standardised vaccination, with unknown or inconclusive serology excluded. (A) Individuals eligible for any standardised vaccination programme ($n = 9264$). (B) Individuals eligible for school-based catch-up vaccination ($n = 8057$). (C) Individuals eligible for universal birth vaccination ($n = 3386$). (—○—), Indigenous; (■), non-Indigenous. * $P < 0.0005$. anti-HBc, antibody to hepatitis B core antigen.

OR of 1.23 for Indigenous people eligible for universal infant vaccination. Despite HBV prevalence decreasing prior to standardised vaccination being implemented in the NT,^{6,34} it is clear that vaccination has played a role in reducing the burden of CHB in Indigenous communities. Whilst there are several factors driving this decrease, the increase in the proportion of individuals vaccinated on their most recent test from the general population (23.2%), to those eligible for school-based vaccination (31.5%), to those eligible for universal vaccination (31.8%), and the corresponding decrease in serologic evidence of past exposure (25.6% to 23.0% to 13.5%) suggests that vaccination is playing a role in the prevention of HBV infection. However, the prevalence in those eligible for infant vaccination did not decrease below the national average, which may in part be due to the failure of immunoprophylaxis of children born to HBV positive mothers with high viral loads.³⁵ While these estimates should be interpreted with caution due to the relatively small numbers of people tested who were born after 1982, this shows that vaccination programmes have had an impact in reducing the burden of CHB in younger NT residents.

From 2007, HBV prevalence in non-Indigenous people born since the introduction of universal infant vaccination in the NT eclipsed that of Indigenous individuals. This is likely due to the effects of migration of individuals born in high prevalence areas between 1996 and 2011 to the NT, including from Cambodia, China, and the Philippines.^{6,36} This dataset did not include country of birth information so there is a limited ability to analyse this further.

HBV vaccine efficacy

The present study reports new insights into the role of suboptimal vaccine efficacy in CHB prevention. Of those individuals with serology indicating vaccine-derived immunity on their first test in the dataset, only one (0.02%) person subsequently became HBsAg positive. It is possible that this person's first test returned a falsely negative HBsAg or falsely positive anti-HBs, that this person was incompletely vaccinated, or that this is in fact a true vaccine failure. Regardless, this is substantially lower than expected given the known issues with maintenance of the cold chain and the administration of plasma-derived vaccines in the early years of infant vaccination in the NT.

A small subsection (3.06%) of the presumed vaccinated cohort subsequently developed anti-HBc positivity, of which 86.4% identified as Indigenous (HR 1.17). One potential explanation for this result is that serotype mismatch plays a role in vaccine efficacy. Aboriginal communities in northern Australia have been observed to be

Table 3 Testing patterns of people who had serology indicating vaccination on their first HBV test, and indicators of vaccine efficacy

	Indigenous†(n = 33 658)	Non-Indigenous (n = 64 835)	P value
Demographics			
Number of individuals, n (%)‡	2014 (5.98)	4191 (6.46)	<0.0005
Female	859 (42.8)	2448 (58.5)	<0.0005
Male	1146 (57.2)	1735 (41.5)	<0.0005
Age at time of first HBV test in the study period (years)	29.6 (23.1, 40.2)		
Females	29.6 (23.5, 41.2)		0.008
Males	29.5 (22.4, 39.3)		
Median (IQR)	25.7 (18.8, 40.1)	30.5 (25.1, 40.3)	<0.0005
People eligible for vaccination programmes, n (%)§	897 (44.5)	1119 (26.7)	<0.0005
School catch-up vaccination	690 (76.9)	999 (89.3)	<0.0005
Universal birth vaccination¶	547 (61.0)	235 (21.0)	<0.0005
Time between subsequent tests (days)	400 (157, 943)		
Median (IQR)	386 (166, 879)	413.5 (146, 985)	0.14
Total number of tests for these individuals, n (%)	2 (1, 4)		
Median per person (IQR)	3 (2, 6)	2 (1, 3)	<0.0005
Total follow-up time (years)	4.57 (1.95, 8.65)		
Median (IQR)	5.52 (2.85, 9.65)	4.31 (1.59, 8.07)	<0.0005
Vaccine failure			
Number of people that subsequently became HBsAg positive n (%)	1 (0.05)	0	
Breakthrough HBV infection (anti-HBc appearance)			
Number of people that subsequently became anti-HBc positive, n (%)	171 (8.49)	26 (0.62)	<0.0005
Females	76 (44.4)	9 (34.6)	0.40
Males	95 (55.6)	17 (65.4)	
Age when anti-HBc was detected (years)	38.4 (30.4, 48.2)		
Median (IQR)	38.8 (30.9, 49.5)	34.5 (25.9, 45.7)	0.17
Time to anti-HBc positivity (years)	5.59 (2.51, 9.21)		
Median (IQR)	5.98 (2.57, 9.44)	3.96 (2.29, 7.55)	0.16
Number of tests for these individuals, n (%)	5 (3, 8)		
Median per person (IQR)	5 (4, 9)	4.5 (3, 6)	0.03
People eligible for vaccination programs, n (%)	22 (12.9)	4 (15.4)	0.38
School catch-up vaccination	22 (100)	4 (100)	
Universal birth vaccination	6 (27.3)	0	
Total follow-up time (years)	11.9 (8.37, 15.4)		
Median (IQR)	11.9 (8.45, 15.4)	11.4 (7.04, 14.2)	0.51
Undetectable anti-HBs titre			
Number of people that subsequently had an undetectable anti-HBs titre, n (%)	151 (7.50)	137 (3.27)	<0.0005
Females	54 (35.8)	86 (62.8)	<0.0005
Males	97 (64.2)	51 (37.2)	
Age when anti-HBs was not detected (years)	33.2 (25.4, 43.7)		
Median (IQR)	30.6 (21.4, 42.5)	34.5 (28.2, 45.0)	0.002
Time to undetectable anti-HBs (days)	1142.5 (511, 2360)		
Median (IQR)	1318 (524, 2568)	1087 (501, 2185)	0.27
Number of tests for these individuals, n (%)	4 (3, 5)		
Median per person (IQR)	4 (3, 6)	3 (2, 4)	<0.0005
People eligible for vaccination programmes, n (%)	54 (35.8)	18 (13.1)	<0.0005
School catch-up vaccination	44 (81.5)	18 (100)	0.001
Universal birth vaccination	25 (46.3)	5 (27.8)	0.001
Total follow-up time (years)	5.70 (2.91, 8.97)		
Median (IQR)	6.41 (3.31, 9.96)	5.05 (2.28, 7.81)	0.12

†112 people without their Indigenous status recorded in the dataset demonstrated vaccination serology on their first test.

‡18 people (9 Indigenous, 1 non-Indigenous, 1 unknown) without their sex recorded in the dataset demonstrated vaccination serology on their first test.

§13 people (7 Indigenous, 9 non-Indigenous) did not have their age recorded in the dataset.

¶455 people (340 Indigenous, 115 non-Indigenous) were eligible for both vaccination programmes based on their year of birth. anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IQR, interquartile range.

exclusively infected with HBV/C4, serotype *ayw3*, whilst the current vaccine is genotype A2-based, serotype *adw2*.^{18,19} Several NT-based studies have found high proportions of Aboriginal adolescents who were vaccinated with no detectable immunity,^{15,17} with evidence of acute infection through anti-HBc positivity¹⁶ and with HBsAg positivity.¹⁵ A further study from The Gambia, where a serotype mismatch also exists, reported breakthrough anti-HBc positivity in 27.4% of their fully vaccinated cohort after 20 years.²¹ These studies, in combination with the present data, suggest that the current HBV vaccine is sufficient to protect against chronic infection (and possibly symptomatic acute infection, as demonstrated in a study of Alaska Native people²⁸), but not against acute infection in populations with a serotype mismatch, although a study of vaccinated Indigenous individuals living in Western Australia found a small number of people who developed CHB.³⁷ A recent data linkage study found that 94.1% of people born after 1990 in five NT Indigenous communities received a full vaccination course,³⁸ further suggesting that implementation issues are unlikely to explain the decrease in vaccine efficacy observed.

Anti-HBc breakthrough may have occurred in some participants due to the decreased efficacy of HBV vaccination in adults over the age of 40 years,^{39,40} although the median age of individuals with vaccination serology on their first test was 29.6 years old. It is possible that some of these individuals may have been exposed to HBV before being vaccinated and therefore had a false negative on their first anti-HBc test. However, there is evidence to suggest that acute infection can occur after developing an appropriate response to the vaccine – a previous study found that 58.7% of a fully vaccinated cohort with breakthrough anti-HBc positivity detected at ages 19–21 had been anti-HBs positive and anti-HBc negative at age 10–11, indicating that they had been exposed to HBV well after developing an appropriate anti-HBs response to the vaccine.⁴¹

The presence of anti-HBc in patients who were presumed fully vaccinated presents consequences for individuals who may in the future require immunosuppression. Aboriginal people have higher rates of chronic kidney disease,⁴² liver cancer⁴³ and autoimmune conditions, such as systemic lupus erythematosus⁴⁴ and it is important to screen prior to initiating immunosuppressive therapy.⁴⁵

HBV trajectory and the role of HBV/C4

Genotype C HBV is an independent risk factor for the development of HCC and has been described as an aggressive genotype of HBV,^{46–49} while HBV/C4 has been associated with delayed HBeAg seroconversion, and a more rapid progression to cirrhosis and HCC.⁵⁰ A previous study of Indigenous Australians with HBV/C4

demonstrated a higher than expected proportion of individuals over the age of 40 years that remained HBeAg positive.¹⁸ In the present study, 61.5% of HBV positive individuals tested HBeAg negative on their first test within the dataset, with no difference observed between Indigenous Australians and non-Indigenous Australians. Further, no difference was observed in the rates of HBeAg seroconversion by age between Indigenous and non-Indigenous participants. However, given the increasing numbers of migrants from high prevalence areas to the NT, it is likely that the trajectory of HBV/C4 has been compared to other genotype C variants in this study. Without further clinical or demographic information, this cannot be analysed further.

Limitations

The present study did not include access to detailed demographic data, vaccination history and further clinical information that could stratify individuals living with CHB into the four HBV phases according to disease activity. Without anti-HBs serological titres or vaccination records, it is likely that the number of individuals with vaccination-derived immunity has been underestimated given anti-HBs titres can decrease over time but still offer protection against HBV.^{28,51–53} As clinical guidelines in the NT did not recommend completing a full serological panel when testing for HBV until 2015,³³ a substantial number of individuals did not have enough data available to be serocoded. Country of birth was not available for non-Indigenous people in the infant vaccine eligible cohort and the higher prevalence in later years suggests they may have been born outside the NT.

Conclusion

This analysis has demonstrated a higher HBV prevalence in the NT than described in previous cross-sectional studies, including a higher prevalence in Indigenous people. HBV prevalence and exposure has decreased with the implementation of standardised vaccination programmes, substantially decreasing the disparity in HBV burden that young Indigenous Australians face. Despite known challenges in implementing HBV vaccination in the NT, the failure rate of the vaccine in preventing HBsAg positive infection was low. Evidence of suboptimal vaccine efficacy as determined by breakthrough anti-HBc positivity in vaccinated individuals was demonstrated predominantly in Indigenous individuals, which may be attributable to vaccine serotype mismatch and may have significant clinical implications for Indigenous patients requiring immunosuppressive therapy. No difference in HBeAg positivity or seroconversion

was observed between Indigenous and non-Indigenous individuals living with CHB.

A more complete analysis of HBV status in Indigenous people in the NT is currently underway⁵⁴ which will include clinical data allowing for the exploration of the natural history of CHB in Indigenous people in a way that serological analyses alone cannot. However, this study shows that while the burden of CHB in Indigenous people in the NT is well known, it has previously been underestimated. While ongoing vaccination of infants against HBV is a crucial element of controlling CHB in the NT and Australia, increased efforts to provide care to the substantial number of people living with CHB in the

NT, particularly Indigenous people who represent the majority of those affected by CHB, are of fundamental public health importance.

Acknowledgements

We acknowledge the traditional custodians of the lands where this research was undertaken. We thank the patients whose data contributed to this work. We also thank Dr Margaret Littlejohn and Professor Peter Revill for their insights relating to anti-HBc positivity in vaccinated individuals.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Figure S1 Flow diagram detailing data sources, final dataset creation and total individuals and testing episodes included in this study.

Table S1 Demographic data, testing patterns and first test serology of people who tested positive for HBV during the study period.

Table S2 Demographic data, testing patterns and most recent test serology of people who were eligible for standardised vaccination programs based on their year of birth.