Chronic hepatitis B infection—an unmet medical need in New Zealand 35 years after universal neonatal vaccination

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Chronic hepatitis B virus (HBV) infection is a recognised global health priority and in 2016 the World Health Organisation (WHO) adopted the first-ever global hepatitis strategy to eliminate viral hepatitis as a public health threat by 2030.[1] New Zealand is one of the 196 Member States to adopt the WHO strategy and a draft National Hepatitis B Plan has been developed by The Hepatitis Foundation of New Zealand (HFNZ) to support a national strategic approach. HFNZ is a Ministry of Health-funded non-governmental organisation (NGO) that provides a freely accessible, community-based surveillance programme, ensuring timely linkage to appropriate primary and secondary care without stigmatisation.

An estimated 240 million people worldwide have chronic HBV infection, with high endemicity in the Asia-Pacific and sub-Saharan regions.[2] Up to 40% of those with chronic HBV infection will develop inflammation and fibrosis in the liver, which without lifelong antiviral therapy, will progress to cirrhosis and the subsequent complications of, liver failure and hepatocellular carcinoma (HCC). Chronic HBV infection accounts for more than 80% of cases of HCC and more than 50% of liver transplant in the Asia-Pacific region.[3]

Chronic HBV infection is defined as serum HBsAg persistence for more than six months. The natural history of chronic HBV infection can be divided into four distinct phases of infection based on hepatitis B e-antigen (HBeAg) status, HBV DNA level, alanine aminotransferase (ALT) level and the presence or absence of liver inflammation.[4]

Recruitment into long-term monitoring improves survival for individuals with chronic HBV infection through early detection and management of complications such as chronic hepatitis B (CHB) and HCC.[5] All patients should have regular monitoring of serum ALT and HBV DNA level for CHB, at which point therapy to suppress HBV replication with nucleos(t)ide analogues may be commenced in order to prevent disease progression and reduce the risk of HCC.[4,5] HCC surveillance is recommended to identify HCC at an earlier stage when curative options are still available. Six-monthly measurement of serum alpha-fetoprotein (AFP) and ultrasound (USS) is recommended in patients with chronic HBV infection at higher risk for HCC.[4,6]

A New Zealand study demonstrated that patients who present late with advanced HBV-related HCC are more likely to have undiagnosed chronic HBV infection, or have known HBV but not receiving/or receiving suboptimal HCC surveillance. Those who receive optimal HCC surveillance survive longer and are more likely to be treated with transarterial chemoembolisation (TACE).[7,8] The burden of disease for chronic HBV infection is unevenly distributed in New Zealand, accounting for over 50% of liver disease mortality in Māori, Pacific and Asian people, compared to only 10% in Europeans.[9]

The New Zealand Hepatitis B Screening Programme was conducted between 1999 and 2002, performing community-based screening for HBsAg and anti-HBs, targeting at-risk populations (Māori, Pacific and Asian). Screening was limited to individuals over the age of 15 (born prior to universal neonatal vaccination) living in the North Island. The Northern Region Hepatitis Consortium was responsible for screening and follow up of people in the Auckland and Northland regions, with the Hepatitis Foundation conducting screening and follow up for all other regions of the North Island. Approximately one-third of the target population was screened, of which 87% were Māori, Pacific or Asian. Among the target groups, coverage for Māori, Pacific and Asian were 28%, 35% and 20%, respectively. HBsAg prevalence results by ethnicity were Māori (5.6%), Pacific (7.3%) and Asian (6.2%) with prevalence varying within ethnic groups according to region and country of origin. For Asian ethnicity, HBsAg prevalence varied significantly between Chinese, South East Asian and Indian with 8.9%, 8.1% and 0.6%, respectively. Although New Zealand Europeans were not specifically targeted, they have an estimated prevalence rate of 1% (higher than in Australia, Europe and North America).[10] This study provides the largest and most comprehensive prevalence data for New Zealand's at-risk chronic HBV infected population to date.

Social determinants of health play an important role in the health outcomes of individuals and groups, including different ethnic groups. Indexes of deprivation have been used to demonstrate the relationship between health outcomes and socioeconomic deprivation; higher levels of deprivation are associated with increased rates of many diseases and higher mortality rates.[11] Māori and Pacific people are more likely to live in deprived areas; they have higher all-cause mortality rates across all age-groups associated with disparities in socioeconomic position compared with European/Other ethnic groups in New Zealand. Reducing social inequalities in the health of New Zealanders remains an important ongoing challenge.[12]

The aims of this study are to:

- Estimate the number of HBV-infected individuals living in New Zealand
- Describe the recruited HFNZ surveillance population by demographics, including socioeconomic deprivation and regional distribution, virologic and clinical characteristics

Methods

The chronic HBV prevalence for each ethnic group was derived directly from the results of the New Zealand Hepatitis B Screening Programme. These were Māori (5.6%), Pacific Island (7.3%), Asian (8.9%) and Other (2.8%), with Asian comprising only Chinese and South East Asian. A lower prevalence for European (0.5%) was used as HBsAg prevalence varies by region within ethnic groups, and the South Island has a large proportion of New Zealand Europeans, in order to minimise over-estimation of the South Island chronic HBV infected population.[10] The unvaccinated population was estimated from population data, stratified by the 20 DHBs, sourced directly from the publicly available 2018 New Zealand Census. The estimated unvaccinated population for the Māori and European ethnic groups was defined as those aged 30 years and older, as universal infant HBV vaccination was introduced in New Zealand in 1988.[10] A wider age distribution of those aged 20 years and older was used to define the unvaccinated population in the Pacific Islander, Asian and Other ethnic groups. This was due to assumptions made with expert guidance and review of the literature, which confirmed universal infant vaccination was variably introduced later in the Asia-Pacific region.[13,14] The overall HBV-infected population of New Zealand was estimated by applying the prevalence of chronic HBV to the estimated unvaccinated population for each ethnic group. HBV prevalence according to DHB was estimated by dividing the estimated total number of chronic HBV cases by the 2018 total resident population (sourced from 2018 New Zealand Census).

A retrospective review of the HFNZ electronic surveillance database was performed to characterise the known chronic HBV infected population under active follow up as at October 2019. Data was collected by reviewing medical records on the HFNZ database, including gender, age, ethnicity, district health board (DHB) and nucleos(t)ide medication use. The most recent results

were collected for HBeAg status, ALT, and if available HBV DNA viral load, liver stiffness measurements (by either FibroScan or Shear Wave), body mass index (BMI) and diagnosis of diabetes. When results for ALT, HBV DNA level and HBeAg status were all collected for a patient, they were grouped into one of the four EASL-defined phases of chronic HBV infection.[4] An elevated ALT was defined ≥45 U/L, according to local laboratory cut-off values.

Phase 1: HBeAg positive chronic infection, defined as HBeAg detectable, HBV DNA >2,000IU/ml, ALT normal.

Phase 2: HBeAg positive chronic hepatitis, defined as HBeAg detectable, HBV DNA >2,000IU/ml, ALT elevated.

Phase 3: HBeAg negative chronic infection, defined as HBeAg not detectable, HBV DNA <2,000IU/ml, ALT normal or elevated.

Phase 4: HBeAg negative chronic hepatitis, defined as HBeAg not detectable, HBV DNA >2,000IU/ml, ALT elevated.

The New Zealand Deprivation 2018 (NZDep2018) index of socioeconomic deprivation was applied to patient's current address to estimate the relative socioeconomic deprivation of the small area each patient resides in. NZDep2018 incorporates nine 2018 census variables that represent eight deprivation dimensions, providing a deprivation score for each mesh block in New Zealand. A mesh block is the smallest geographical area for which statistical data is collected by Statistics New Zealand. NZDep2018 categorises deprivation scores into deciles represented by ordinal scale 1 to 10. Decile 10 indicates that the mesh block is in the most deprived 10 percent of areas while decile 1 represents a mesh block in the least deprived 10 percent areas of New Zealand.[11]

Results

In 2018, an estimated 93,600 New Zealanders were living with chronic HBV infection, representing approximately 2% of the total population. Table 1 shows the estimated unvaccinated population, prevalence used and number with chronic HBV infection according to ethnic group. The distribution of patients estimated to be living with chronic HBV infection varied considerably across DHBs and regions (Figure 1a), highest in Counties Manukau (19.6%) and lowest in West Coast (0.3%). More than half (51%) reside in the Auckland region compared with the entire South Island accounting for just over 15%. The estimated HBV prevalence according to DHB showed a similar trend with Counties Manukau highest (3.4%) compared with less than 1% in both South Canterbury and West Coast (Figure 1b). Asian (49%), Māori (20%) and Pacific Island (17%) ethnicity groups account for the majority of chronic HBV in New Zealand (Figure 2).

In November 2019, a total of 17,784 New Zealanders with chronic HBV have been recruited into the national surveillance programme, representing just 19% of the estimated total HBV population of New Zealand. Fifty-four percent of individuals recruited into the surveillance programme live in Auckland, while less than 3% live in the South Island. CMDHB holds 20% of the total HBV population and accounts

Table 1: Estimated unvaccinated and chronic HBV infected population by ethnicity in 2018.

Ethnicity (Estimated unvaccinated age group)	Estimated number unvaccinated	Chronic HBV infection prevalence (%)	Estimated number with chronic HBV infection
Māori (≥30 years)	333,906	5.6	18,699
Pacific Islander (≥20 years)	215,238	7.3	15,712
Asian (≥20 years)	519,930	8.9	46,274
European (≥ 30 years)	2,069,856	0.5	10,349
Other (≥20 years)	91,956	2.8	2,575
New Zealand total	3,230,886		93,609

Figure 1a: Estimated total New Zealand HBV population versus recruited HFNZ HBV population by district health board.

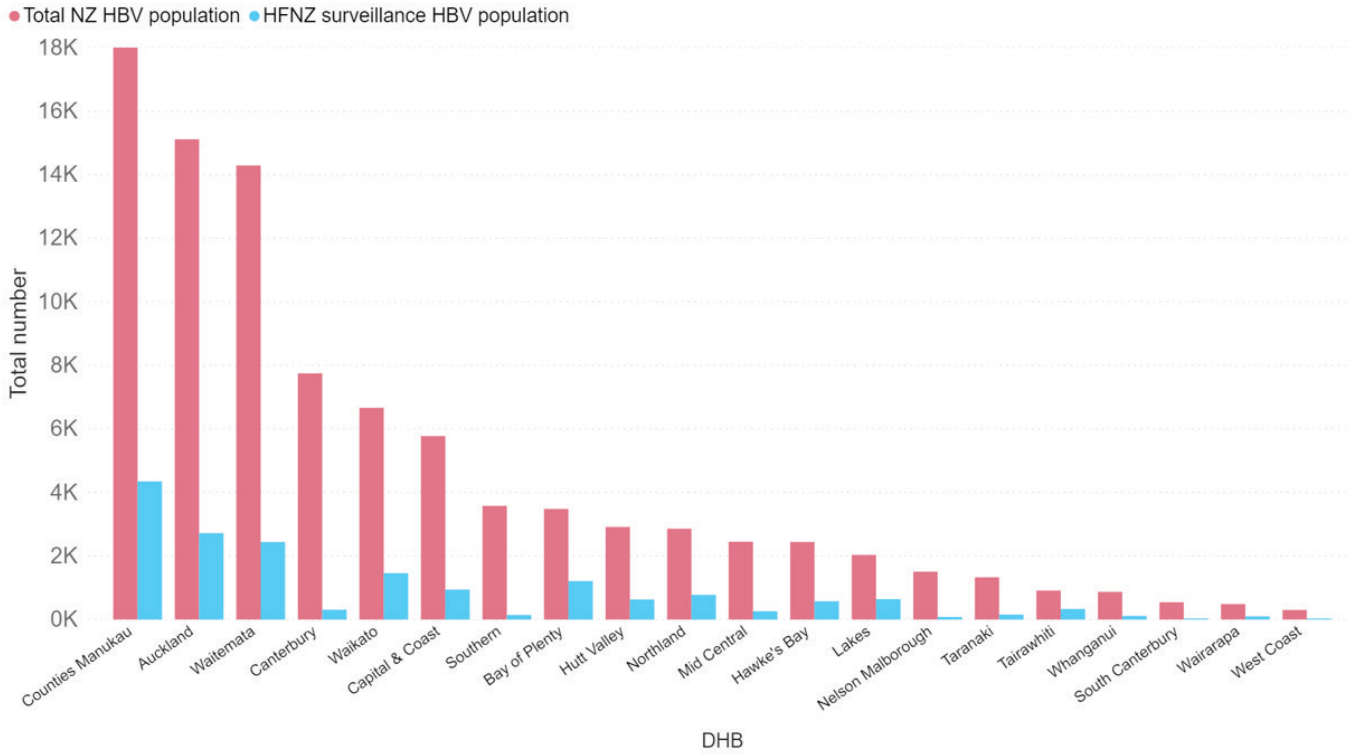


Figure 1b: Estimated HBV prevalence according to district health board.

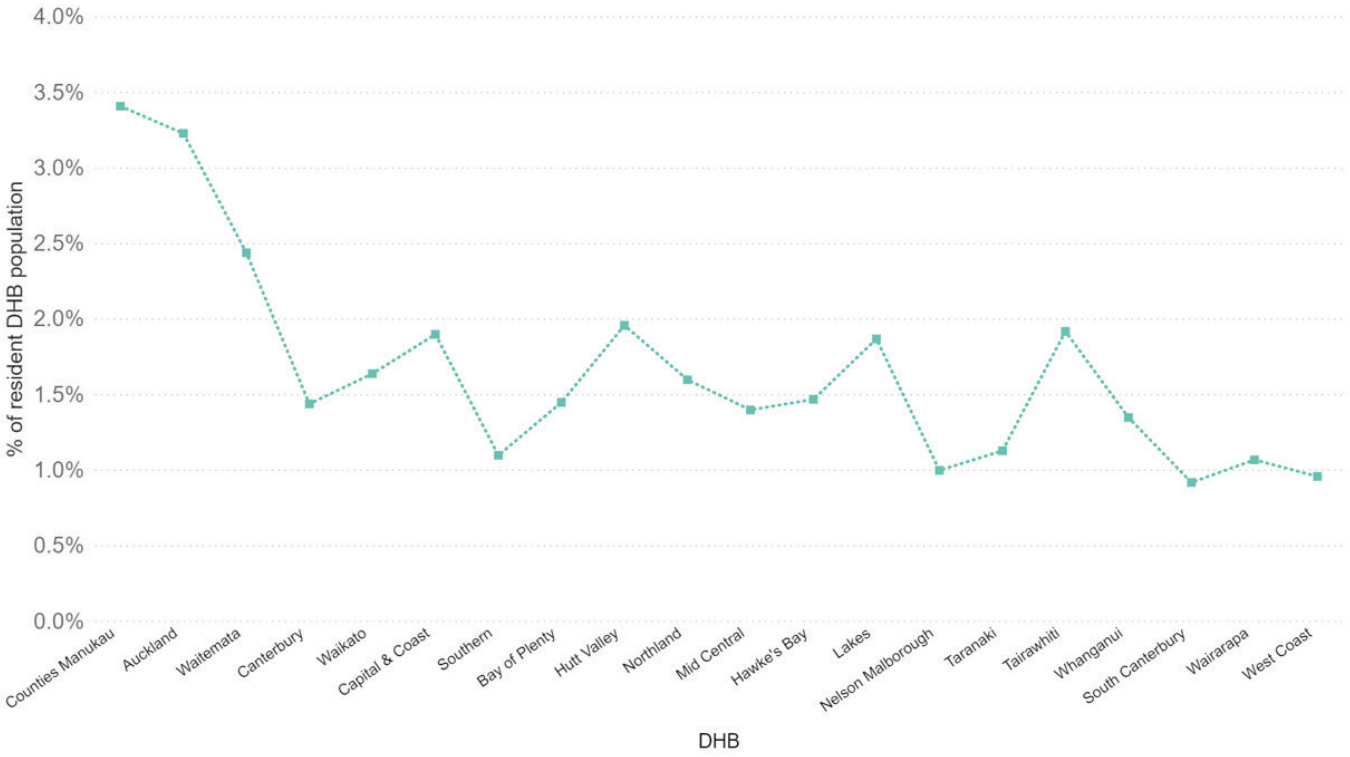


Figure 2: Estimated total New Zealand HBV population versus recruited HFNZ HBV population by ethnicity.

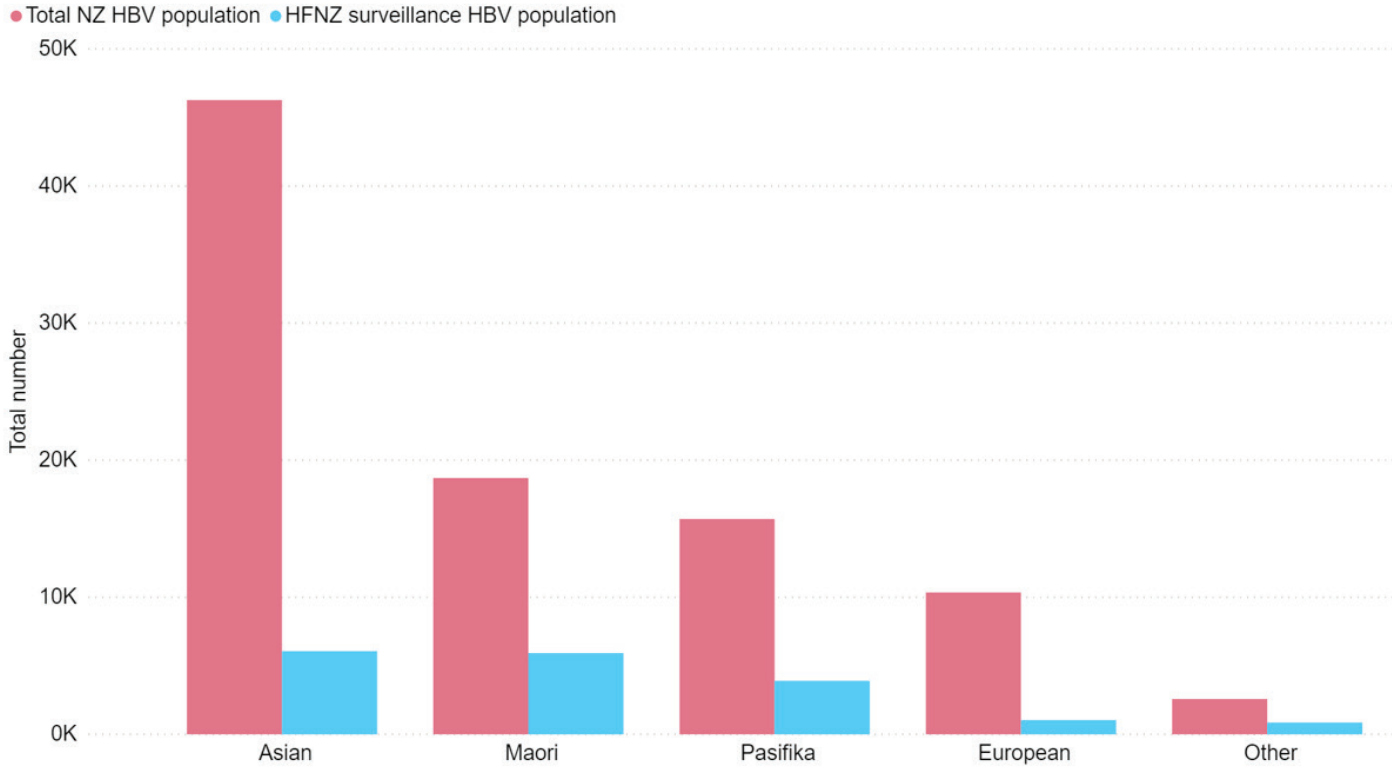


Figure 3: HFNZ population HBeAg status by age.

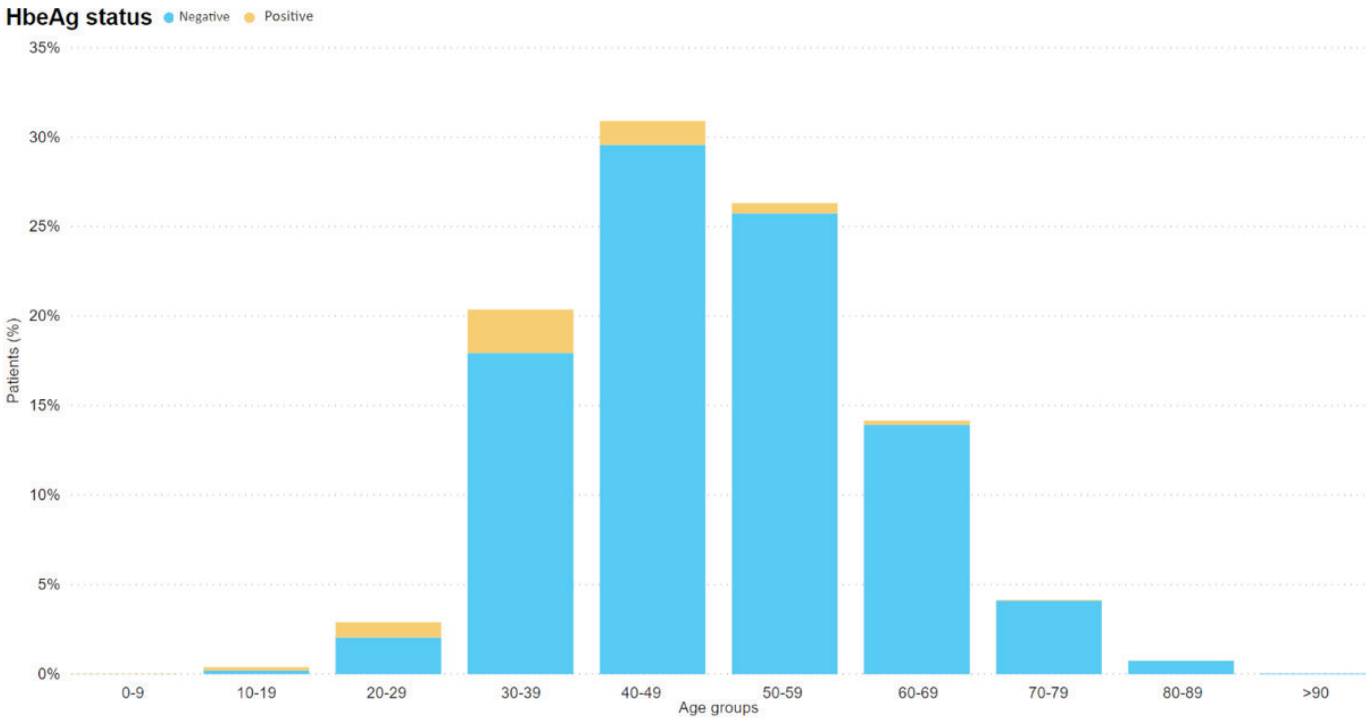


Figure 4: Distribution of HFNZ population by EASL HBV phases of infection.

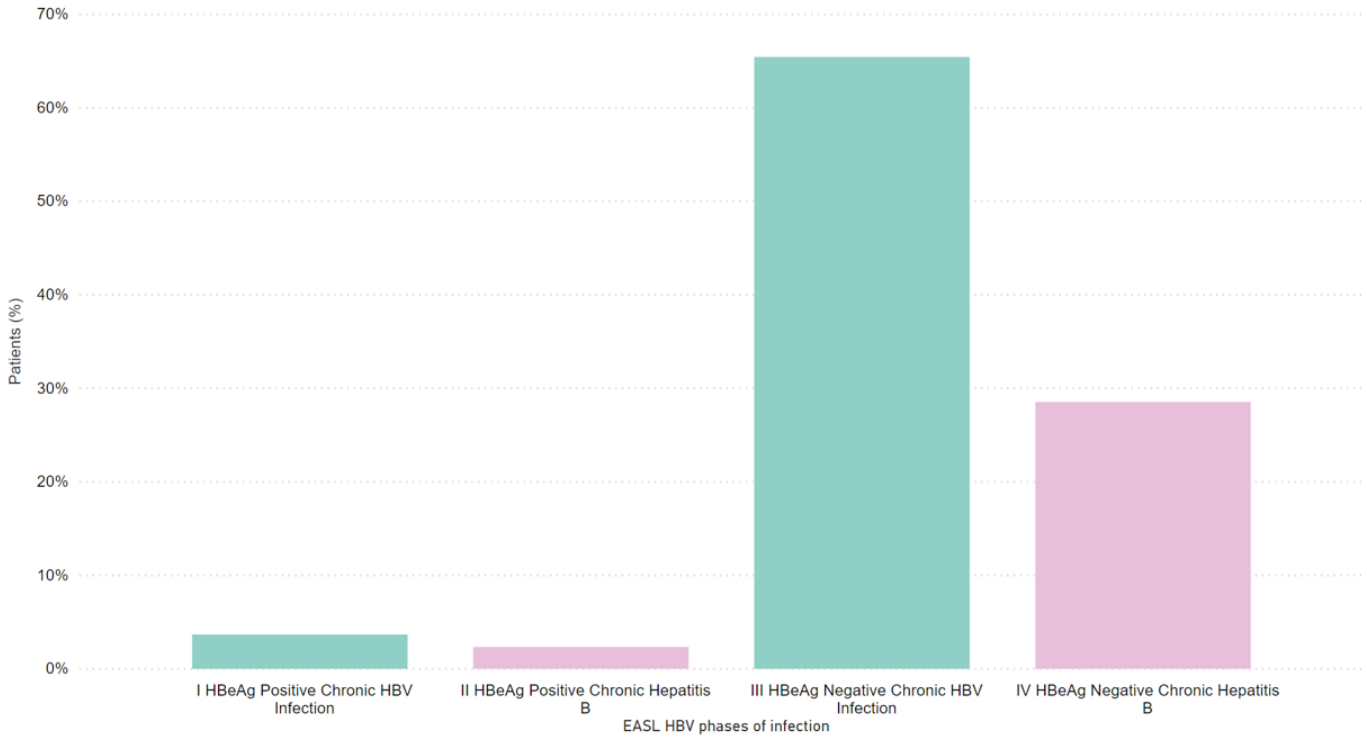


Figure 5: Distribution of HFNZ population by relative socioeconomic deprivation.

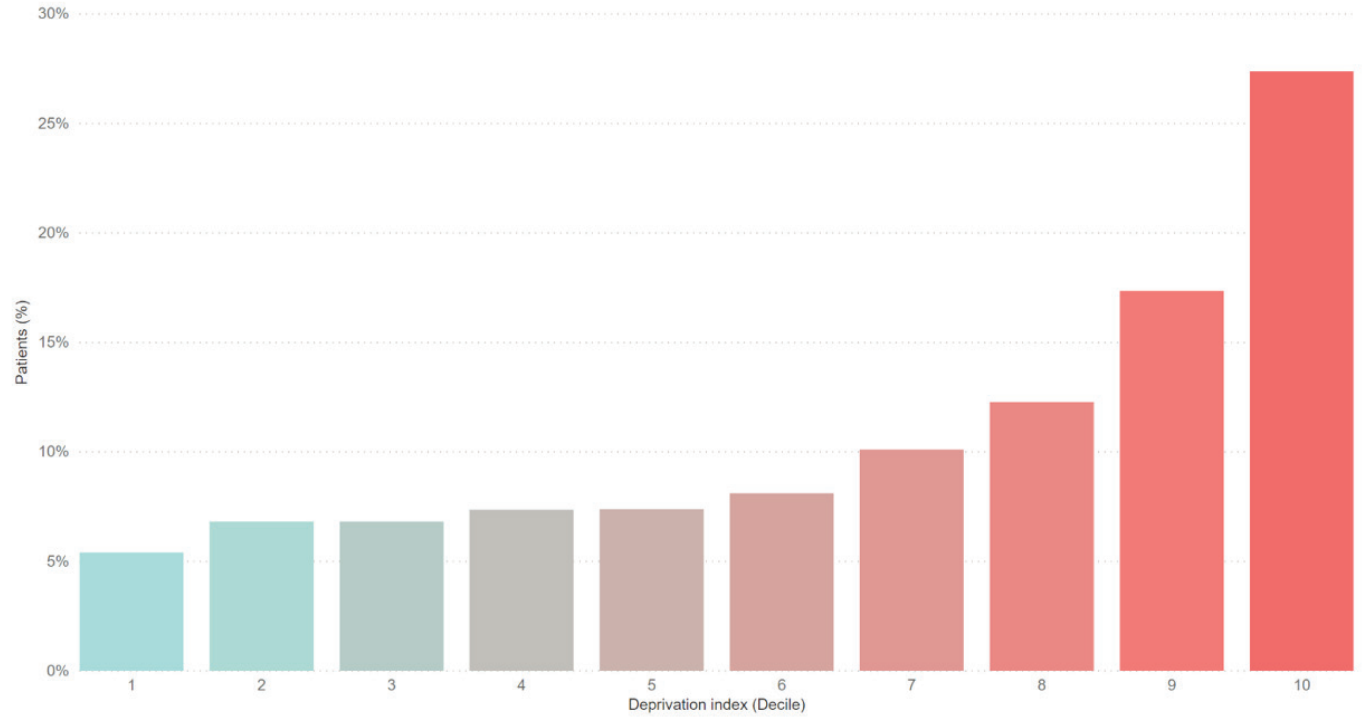
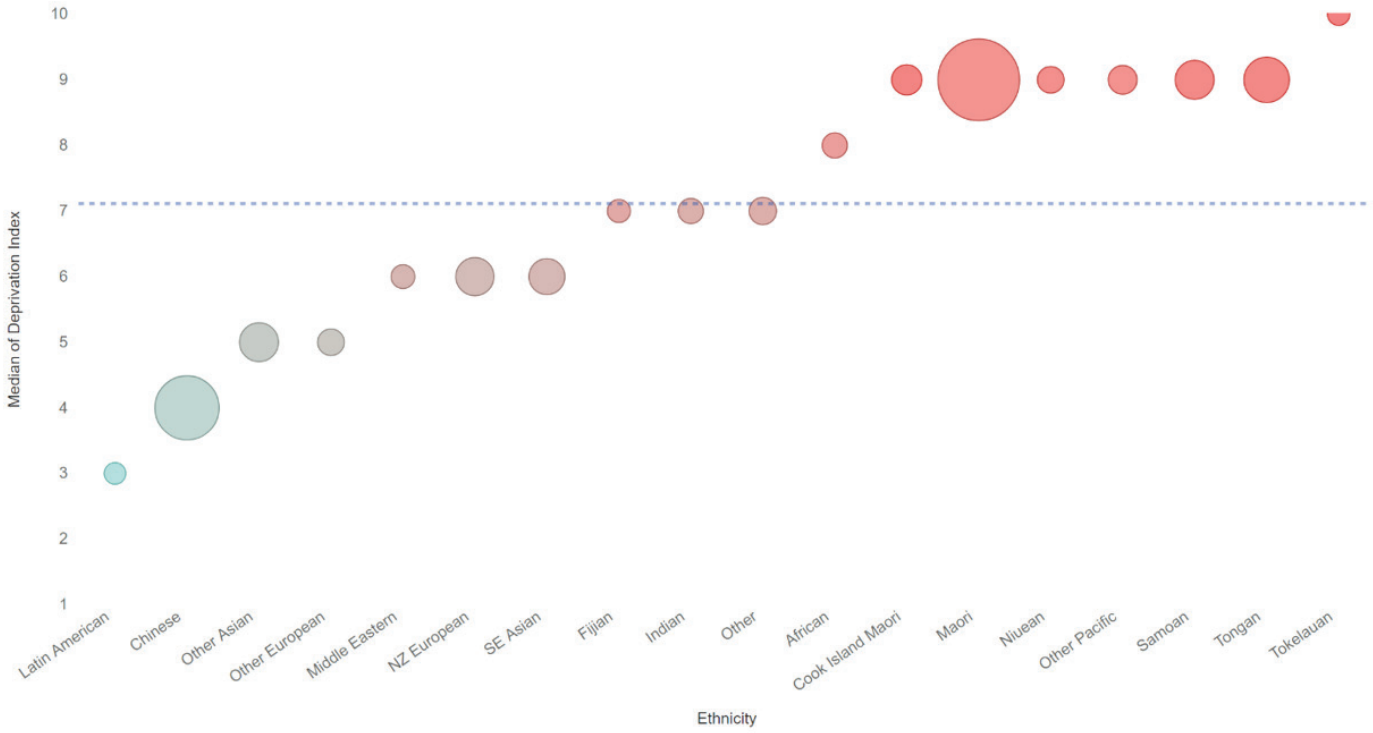


Figure 6: Socioeconomic deprivation of HFNZ population by ethnicity.



for 25% of those on the HFNZ surveillance programme. In comparison the combined four South Island DHBs holds 15% of the total HBV population, but accounts for only 3% of those on the HFNZ surveillance programme (Figure 1a).

Analysing HFNZ's surveillance database, 15,290 individuals are primarily followed up by HFNZ and 2,492 under the care of specialists. The largest source of patient recruitment onto the surveillance database is from general practitioner referrals (38%), while 30% were originally recruited from the New Zealand Hepatitis B Screening Programme. The median age of patients was 49 years with a slight male predominance (53%). The recruited population showed a similar distribution to the overall infected population of New Zealand with 55% living in the Auckland region. Minority ethnic groups account for majority (89%) of patients recruited to HFNZ; Asian 34%, Māori 33%, Pacific 22%. Chinese make up 63% of Asians and Tongan make up 43% of the Pacific Islanders.

All patients had HBeAg status results available; Figure 3 demonstrates the relationship between age and HBeAg status. Forty percent (n=7,352) of patients on the database had had an HBV DNA level performed in the past, majority (71%) of patients were classified into phase III, HBeAg negative chronic HBV infection (Figure 4). Of the 2,458 patients who had liver stiffness measurement results available, the vast majority (75%) had minimal fibrosis, 9% had moderate fibrosis and 10% severe fibrosis based on the measured kPa. Only 25% of patients had a BMI documented, however the average of BMI did increase with a higher kPa. Documentation of diabetes in these patients was incomplete and unable to be analysed.

16,677 patients had a current address available to calculate socioeconomic deprivation. More than one quarter (27%) of patients live in the most deprived areas (decile 10) of New Zealand (Figure 5); when stratified by ethnicity the median deprivation was highest in Pacific and Māori (decile 9) and lowest in Asian (decile 5) (Figure 6).

Discussion

This study suggests a high prevalence of chronic HBV infection within at-risk ethnic groups within New Zealand, which previous literature has shown is associated with high rates of hepatocellular carcinoma, liver transplantation and liver-related death. The morbidity and mortality associated with HBV-related complications can be reduced by earlier detection through regular surveillance. Unfortunately, less than 20% of New Zealanders living with chronic HBV infection have been recruited into the state-funded community-based national surveillance programme, reflecting low awareness and under diagnosis.[7,8]

The prevalence of chronic HBV infection varies across New Zealand reflecting differences in ethnic diversity (Figure 1b). Over half of all New Zealanders estimated to have HBV are living in just three of the 20 DHBs (Auckland, Waitemata and Counties Manukau), while only 15% live in the South Island. This geographic and ethnicity data can be used to target these areas of high burden with the potential to maximise the impact of screening and improvements in diagnosis.

Only one-fifth of the HBV population is under the care of the national surveillance programme. Although this study is unable to determine how many patients are diagnosed and under surveillance by their general practitioner (GP) or local specialist, New Zealand data has shown that in patients who presented with advanced HBV-related HCC, almost 40% were not aware of their HBV status at the time,[7] suggesting that there is almost certainly a significant proportion of patients who are living with undiagnosed HBV in New Zealand. Combining the prevalence analysis with the recruited population data will identify those regions with higher prevalence and low recruitment uptake, including Counties Manukau, Auckland, Waitemata and Canterbury. Prioritising delivery of healthcare resources to these regions would maximise the benefit of educational and targeted screening campaigns.

The lowest proportion of the infected population that were recruited to the national surveillance programme were in the South Island (3%). In comparison, the Auckland region accounted for 54% of HFNZ's recruited population. This reflects the impact of recruitment from the New Zealand Hepatitis B Screening Programme, higher prevalence of disease and current location of the HFNZ headquarters, although suggests geographic variation in access to hepatitis B surveillance.

The large proportion of Asian (34%), Māori (33%) and Pacific (22%) people recruited to HFNZ and undergoing active surveillance, aligns with WHO recommendations on delivering for equity by targeting populations that are vulnerable, at risk and affected. In New Zealand, HBV-related HCC disproportionately affects minority ethnic groups with the incidence of HBV-related HCC highest in Māori, Pacific and Asian men,[7] with chronic HBV infection accounting for more than 50% of liver disease mortality in Māori and Pacific people.[9]

The high level of deprivation in the recruited HBV population, with Māori and Pacific people disproportionately affected, highlights the importance of HFNZ's role in the community. Those living in areas more socioeconomically deprived experience worse overall health outcomes than people living in areas that are the least deprived.[15] Although area-based deprivation should not be applied to individuals, the use of mesh blocks diminishes the extent of measurement error, strengthening the observed associations between socioeconomic position and health outcomes.[11] Improved access to primary healthcare services and providing care in the community is part of the New Zealand Health Strategy's goal to reduce health inequities to improve health outcomes in New Zealanders.[15]

The age distribution of the recruited population showed just a small proportion (3%) of patients under the age of 30, demonstrating the success of the infant immunisation programme implemented in 1988.[16] The older median age is most likely the result of a cohort effect rather than reflecting new infections later in life. Immunisation remains the most cost-effective intervention for the prevention of HBV globally.[1]

The older age associated with HBeAg loss is consistent with previous data showing HBeAg seroconversion occurring at an earlier age in a similar cohort of patients. Māori have predominantly HBV genotype D

which is associated with earlier HBeAg seroconversion than other genotypes.[17] A low proportion (40%) of patients had HBV DNA level results, with majority (71%) classified into HBeAg negative chronic HBV infection. There were low numbers for documented BMI and liver stiffness measurement; however, it was noted that increased BMI was associated with increased kPa, aligning with the known interpretation limitations of liver stiffness measurements in obese individuals. These findings have identified areas for improvement in data collection for the surveillance database, with suggestions to ensure HBV DNA levels are performed in all patients and encourage more thorough data collection including comorbidities such as diabetes and BMI due to the important association with poor liver disease outcomes.[4,6]

Weaknesses for this study include that it is a descriptive analysis dependent on the collection of data from a database where information has been manually entered, subject to inaccuracies and inconsistencies.

The calculation of national, regional and ethnicity unvaccinated population size and HBV prevalence are based on assumptions made from the 2018 New Zealand Census, access to HBV vaccination across the Asia-Pacific region and the New Zealand Hepatitis B Screening Programme. These factors may over or underestimate the true prevalence of disease in New Zealand.

Strengths of this study are that it provides necessary data on chronic HBV burden in New Zealand, required to leverage much-needed political commitment, create awareness and advocate for action and resources. It identifies target regions and ethnic groups for future screening programmes, or for opportunistic screening by general practitioners, to achieve the greatest impact, and improve outcomes.

A partnership approach will be central to the success of making any progress towards elimination of hepatitis B in New Zealand. This includes a broad range of partners from government, primary, secondary, and tertiary care and NGO. Strategies should include government endorsement of the HBV surveillance programme and support for increased opportunistic HBV screening of all Māori, Asian and Pacific Islanders over the age of 35 years. Educational campaigns could be facilitated by HFNZ for primary care providers, as well as by community groups such as The Asian Network Incorporated (TANI), Pasifika and Māori Health Outreach Services who engage directly with at risk populations in order to reduce language and cultural barriers to care. Relaunching a National Hepatitis B Screening Programme for all Māori, Asian and Pacific adults could be considered given that the target population today would be much smaller than in the 2000 Programme, given that almost 200,000 Māori, Asian and Pacific adults were tested and in 2020, the threshold for inclusion has increased from 15 years to 35 years of age thanks to the success of universal neonatal vaccination. However, this would still be a significant investment.

Conclusion

Although New Zealand is a high-income country with first-world healthcare, it has a rising morbidity, mortality and cost burden from endemic chronic HBV infection. Almost half of all New Zealanders living with chronic HBV infection remain undiagnosed. As a direct result, almost half of all HBV-related HCC are diagnosed late when curative intervention is no longer possible and outcome poor. This highlights the need for improved rates of HBV diagnosis, better follow-up of those infected, and the importance of optimal HCC surveillance.

Because HBV-related HCC disproportionately affects New Zealand Māori, Pacific and Asians, including many culturally and linguistically diverse communities, a National HBV Action Plan would reduce health inequalities and improve outcomes for all New Zealanders living with chronic hepatitis B.

Competing interests:
Ed Gane: Ministry of Health Advisor for HBV and HCV. Ahmad Anwar, Susan Hay, Alex Lampen-Smith and Chris Moyes: Employees of The Hepatitis Foundation of NZ.

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