Gut Online First, published on July 8, 2014 as 10.1136/gutjnl-2013-306247

ORIGINAL ARTICLE

Serological and clinical outcomes of horizontally transmitted chronic hepatitis B infection in New Zealand Māori: results from a 28-year follow-up study

Tien Huey Lim,[1] Edward Gane,[1] Chris Moyes,[2] Barry Borman,[3] Chris Cunningham[4]

ABSTRACT

Background Chronic hepatitis B infection is endemic in New Zealand and has high prevalence in New Zealand Māori. Previous longitudinal studies in populations with predominantly vertically acquired chronic hepatitis B have shown low spontaneous hepatitis B surface-antigen (HBsAg) seroclearance rates: 0.5–1.4% annually (mean age of clearance 48 years). We report the 28-year follow-up data on clinical and serological outcomes in indigenous New Zealand Māori with early horizontally acquired HBV.

Methods In 1984, community seroprevalence study identified 572 HBsAg-positive individuals, followed for 28 years. Liver-related mortality and hepatocellular carcinoma (HCC) incidence were compared between these 572 HBV carriers and 1140 HBsAg-negative matched case-controls. Surviving HBsAg-positive individuals have been followed up in 2012 with clinical assessment, blood tests and liver transient elastography. Rates of hepatitis B e-antigen (HBeAg) and HBsAg seroconversion were determined.

Results After total 13 187.4 person-years follow-up, 15 HBsAg-positive patients have developed HCC compared with none of the HBsAg-negative controls ($p<0.001$). 12 HBsAg-positive patients died from liver-related causes compared with none in the controls ($p<0.001$). Spontaneous HBeAg-seroconversion occurred in 91% of HBeAg-positive patients. Spontaneous HBsAg loss occurred in 33% overall (annual clearance rate 1.34%), with higher rates at older ages (1.05% in patients<20 years at entry vs 4.3% per annum >40 years at entry, $p<0.0001$). Median ages of HBeAg loss and HBsAg loss were 23 years (range 6–66 years) and 40 years (range 4–80 years), respectively.

Conclusions Horizontally transmitted HBV in Maori is similarly associated with increased risk of liver-related mortality and HCC compared with Chinese, although absolute incidence rates are lower. The rates of HBeAg and HBsAg loss are high, and occur at an earlier age than previously reported.

Significance of this study

What is already known on this subject?

- Chronic HBV infection is associated with increased hepatocellular carcinoma (HCC), cirrhosis and liver related mortality.
- Majority of natural history studies are from Asia with vertically transmitted HBV genotypes B and C, few long-term natural history studies of horizontally transmitted HBV exist.
- Spontaneous HBsAg seroconversion in Asian patients is low: annual rate 0.5–1.4%.

What are the new findings?

- Longest duration of follow-up (28 years) in a population infected with HBV through early horizontal rather than vertical transmission, providing new information on natural history of chronic HBV in this population.
- New Zealand Maori with horizontally transmitted HBV have increased risk of HCC and liver related mortality compared with controls, but absolute incidence rates are lower than Asian studies
- HBeAg and HBsAg seroconversion rates are high, and occur at an earlier age than in Asian populations.

How might it impact on clinical practice in the foreseeable future?

- Identify baseline predictors for liver-related complications in patients with early horizontally acquired HBV infection.
- Allow individualised surveillance strategies, stratified according to baseline risk.

OBJECTIVE

An estimated 350 million people worldwide are chronically infected with HBV. Chronic HBV infection is associated with significant health burden, as up to 40% will develop active chronic hepatitis B (CHB), with long-term risks of liver-related complications of cirrhosis, liver failure or hepatocellular carcinoma (HCC). Although the overall rate of chronic HBV infection in New Zealand is low (<2%), it is endemic in certain ethnic groups and areas of North Island.[1] The highest prevalence of CHB is found in the Māori (5.6%), the Pacific Islander Peoples (7.3%) and Asians (6.2%). In contrast, New Zealand European populations generally have rates of CHB of less than 1%.[2 3] There is also a high incidence of HCC in New Zealand, ranging from 6.6/100 000 person-years in the Māori to 20/100 000 person-years in the Chinese.[4] CHB has

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2013-306247).

[1]New Zealand Liver Transplant Unit, Auckland City Hospital, Auckland, New Zealand
[2]The Hepatitis Foundation of New Zealand, Whakatane, New Zealand
[3]Centre for Public Health Research, Massey University, Wellington, New Zealand
[4]Research Centre for Maori Health and Development, Massey University, Wellington, New Zealand

Correspondence to
Dr T H Lim, New Zealand Liver Transplant Unit, Auckland City Hospital, Private Bag 92024, Auckland 1010, New Zealand; tienhuey@gmail.com

Received 10 October 2013
Revised 18 June 2014
Accepted 19 June 2014

To cite: Lim TH, Gane E, Moyes C, *et al*. *Gut* Published Online First: [*please include* Day Month Year] doi:10.1136/gutjnl-2013-306247

been shown to account for over 50% of all chronic liver disease mortality among Māori and Pacific peoples in New Zealand, compared with only 10% among Europeans.[5] In New Zealand, the Government funded a national HBV screening programme in 1999 following wide consultation with international experts. All identified carriers were invited to participate in a long-term follow-up programme, with 6 monthly monitoring for evidence of CHB or HCC. For CHB surveillance, serum alanine aminotransferase (ALT) levels were monitored as these correlate closely with histological activity and rate of progression of fibrosis.[6–8] For HCC surveillance, serum α foetoprotein (AFP) levels were monitored 6 monthly in low-risk patients.[9] In patients considered to be at higher risk for HCC, including those with either significant fibrosis on biopsy or Fibroscan, or a family history of HCC, abdominal ultrasound scans were also performed at 6 monthly intervals.[10]

The most desirable outcome for patients with chronic HBV infection is for HBsAg clearance before development of cirrhosis. However, spontaneous annual HBsAg clearance rates in longitudinal studies in Asians with vertically transmitted HBV have been low, between 0.5% and 1.4%.[11–17] It is important to note that these studies had relatively short duration of follow-up (4–12 years). In these studies, baseline predictors of HBsAg loss include: increasing age, hepatitis B e-antigen (HBeAg) seronegativity, male sex, lower HBV DNA (<5 log copies per mL) and HBV genotype B (compared with genotype C). Recently these baseline predictors have been incorporated into a risk-calculator for HCC in patients with chronic HBV infection[18] to determine HCC risk. Antiviral therapy was also associated with higher rates of HBsAg loss (2.4–5%).[8 19]

The largest longitudinal cohort study of the natural history of CHB infection to date is the Risk Evaluation of Viremia Elevation and Associated Liver Disease (REVEAL) study, conducted in Taiwan in 1991. In this study, 3653 individuals with CHB infection were followed up with abdominal ultrasound and serological tests for a median of 11.4 years. The most important independent predictor for cirrhosis, HCC, overall mortality and liver-related mortality was baseline serum HBV DNA level at study entry.[20–22] This landmark study challenged the current surveillance regimen with ALT and AFP; and raises the question whether monitoring with HBV DNA should be used as it is superior to ALT in determining long-term complications and need for treatment.[23]

However, subsequent papers have questioned whether the findings in the REVEAL study could be generalised to other patient populations. The principal differences between the REVEAL study and this current New Zealand study are patient ethnicity, mode of transmission, age of enrolment and HBV genotype distribution. The REVEAL study population was exclusively Chinese, while the New Zealand study was 79% Polynesian (Māori and Pacific Islander Peoples). A high proportion of transmission in REVEAL was vertical, while in New Zealand it is predominantly early horizontal, with a sharp increase in the prevalence of exposure to hepatitis B markers in early childhood, and very few children infected under the age of 1 year.[24] In Taiwan, the genotype distribution is predominantly B (60%) and C (40%), while New Zealand is predominately C (40%) and D (40%).[25] HBV genotypes have been linked with different risks for progression to cirrhosis, HCC and death.[26–29] Studies in Asia have suggested that HBV genotype B is associated with earlier age of HBeAg seroconversion, less active hepatic necroinflammation, a lower rate of HCC and a slower rate of progression to cirrhosis compared with genotype C. Previous European studies have also reported better outcomes in patients with genotype A compared with those with genotype D.[30] No study to date has compared all major genotypes and conjecture remains as to whether genotypes C and D, which are most predominant in New Zealand, have similar poor outcomes.

The majority of the REVEAL study population was HBeAg-negative (85%) and older (median age at enrolment 45 years). It remains unknown whether similar poor prognosis applies to younger, HBeAg-positive patients.

In summary, the natural history of CHB infection has been reported for older, predominantly e-antigen negative patients, with vertically transmitted HBV genotypes B and C. This case-control cohort study is the first study in young indigenous New Zealand Māori to evaluate the long-term impact of horizontally acquired chronic HBV infection, predominantly genotypes C and D after 28 years of follow-up.

METHODS

The Kawerau township was created in 1953 in the Eastern Bay of Plenty of the North Island of New Zealand to service a newsprint, paper and lumber industry. Nearly all the workforce is employed by the two industrial plants processing timber from the commercial pine forests in the central North Island and Eastern Bay of Plenty. The population of Kawerau at the 1981 census was 8568, comprising 61% European, 35% Māori, and 2% Pacific Islander Peoples. Between February and April 1984, a comprehensive population seroprevalence study was conducted in the Kawerau township whereby all households in the community were tested for current and past hepatitis B infection (HBsAg and antiHBs by reverse passive haemagglutination (RPHA)). Any individual found to be positive for HBsAg was retested 6 months later and if persistently positive was confirmed with chronic HBV infection. Antibodies to hepatitis C virus were not tested. At entry into the Kawerau Study, all participants consented to testing of baseline sera and collection of outcome data. This seroprevalence study was approved by the local ethics committee and funded by the New Zealand Medical Research Council in 1984. The current follow-up study was approved by the Northern Y ethics committee in 2012 and funded by the Health Research Council of New Zealand.

In the original 1984 seroprevalence study, 7901 of 8514 (93%) of the Kawerau population over the age of 6 months were tested, of whom 485 were confirmed as patients with chronic HBV infection (6.1%). An additional 87 individuals, who resided in the Eastern Bay of Plenty but outside Kawerau census boundaries, were also identified with chronic HBV infection through contact tracing and bleeding workers at the local mill.

All HBsAg-positive individuals (n=572) entered into long-term follow-up via the Hepatitis Foundation with 6 monthly blood tests (liver function tests+AFP+hepatitis serology). Ultrasound was only offered to those with the highest risk: patients with cirrhosis or those with a first degree family history of HCC.

For each HBsAg-positive individual from the Kawerau study, we identified two healthy controls from the same cohort case-matched for age, sex and ethnicity (n=1140). Two HBsAg-positive individuals (both Pacific Island women) were unable to be matched as there were no controls of the same age, sex and ethnicity. In New Zealand, all carriers have a National Health Identifier (NHI) number which allows them to be tracked via the Ministry of Health's health and pharmaceutical data set if they have had a health encounter since the NHI system was introduced in the late 1980s. NHI numbers for

HBsAg-negative controls were obtained by inputting demographic information such as name, sex and date of birth into the NHI database. Follow-up of controls was only through the vital status (death/alive) based on death notifications on the NHI system.

The survival status of patients on the NHI database is updated instantly upon receipt of notification of death to the Ministry of Health. 'Cause of death' data on the Ministry of Health Mortality collection is updated to December 2008, after which the cause of death was obtained through direct contact with the patient's General Practitioner, the Coroner's office, or by obtaining death certificates from the Department of Births, Deaths and Marriages. All clinical records of those who presented to hospitals throughout the country were also reviewed to ensure accuracy of the 'cause of death' coded in the Mortality collection. All deaths up to 1 January 2012 were included. The person-years of follow-up for each subject were calculated from the date of enrolment to the date of death, or to 1 January 2012, whichever came first.

In New Zealand, a national hepatoma database has been kept since 1986. All cases and controls were crosschecked with this national hepatoma database to ensure that all HCCs are captured.

HBeAg loss was defined as conversion from HBeAg positivity to HBeAg negativity, which persisted throughout the rest of follow-up. HBsAg loss was defined as two consecutive HBsAg-negative tests.

All patients who were still alive in 2012 were invited to attend local clinics for a clinical interview, physical examination and transient elastography to determine the stage of liver fibrosis after 28 years follow-up. Liver cirrhosis was defined as a liver stiffness measurement (LSM) >11 kPa according to previously published cut-offs for CHB.[31] Only those with >10 valid measurements, IQR/median <30% and success rate >60% were considered reliable measurements.

Statistical analysis

Time-to-events method was used for overall mortality analyses. The cumulative probabilities of survival were analysed by the Kaplan–Meier method and comparison between groups was performed using the log-rank test. Cox proportional hazards models were used to determine independent predictors of outcome. All statistical procedures were performed with SAS V.9.2. p Values less than 0.05 were considered statistically significant.

RESULTS

Of the HBsAg-positive group, 452 (79%) were Polynesian (Māori and Pacific Island peoples), 120 (21%) were Caucasian; 359 (62.8%) were men, 213 (37.2%) were women. The median age at enrolment in 1984 was 17 years (range 1–71 years). At enrolment 41% were HBeAg-positive.

Of 572 HBsAg-positive cases identified in 1984, 565 (98.8%) had follow-up data available in 2012. Total follow-up in the HBsAg-positive group was 13 187.4 person-years, while in the controls the total follow-up was 30 753.5 person-years. The median number of follow-up visits per individual in the HBsAg-positive group over the study period was 15 (range 1–115).

Only 25 of the HBsAg-positive cases (4%) had ever received antiviral therapy; 4 of which received interferon therapy, the rest were treated with nucleoside analogues.

Only one patient was positive for δ co-infection (hepatitis delta virus (HDV)).

Overall mortality

A total of 54 deaths occurred in the HBsAg-positive group by the end of 28 years of follow-up (9.4%), compared with 107 deaths in the HBsAg-negative group (9.4%), (p=0.94). Clinical files were reviewed in 100% of cases and 97 (91%) of controls.

The cumulative probability of survival in the cases was 97.5% and 90.2% at 10 years and 28 years of follow-up, respectively; while in the controls, the cumulative probability of survival was 97.8% and 90.6% at 10 years and 28 years, respectively (figure 1).

Liver-related mortality

Twelve (2%) of HBsAg-positive patients died from a liver-related complication (all due to advanced HCC) compared with none in the HBsAg-negative controls (p<0.0001) (figure 2). No patient died of liver failure or underwent liver transplantation.

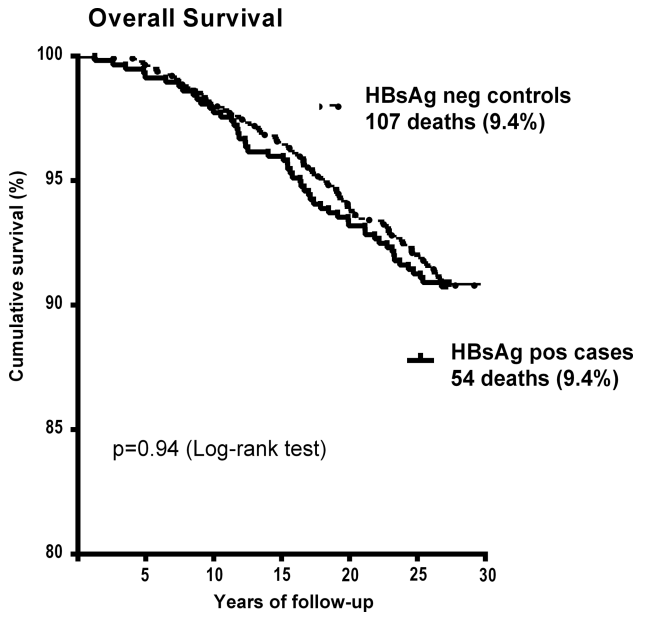

Figure 1 Overall survival in HBsAg-positive cases compared with HBsAg-negative controls. HBsAg, hepatitis B surface-antigen.

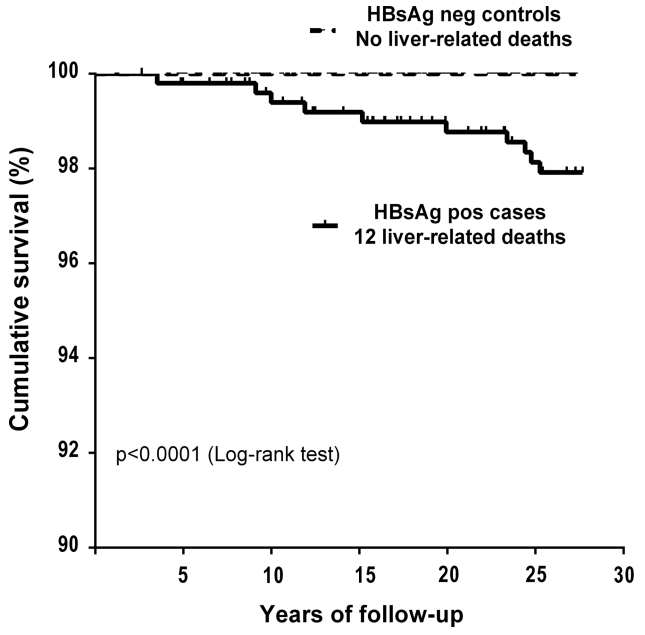

Figure 2 Liver-related mortality.

Table 1 Causes of death

	Carriers (n=572); 13 187.4 person-years	Mortality rate (per 100 000 person-years)	Controls (n=1140); 30 753.5 person-years	Mortality rate (per 100 000 person-year)	Mortality rate ratios (95% CI)	p Value
All cause mortality	54	409	107	348	1.17 (0.85 to 1.63)	NS
Cardiovascular	17	129	28	91	1.45 (0.80 to 2.66)	NS
Injury/poisoning	9	68	24	78	0.86 (0.4 to 1.85)	NS
Sepsis	0	0	6	20	–	NS
HCC	12	91	0*	0	–	<0.0001
Other cancers	10	76	28	91	0.85 (0.41 to 1.74)	NS
Other causes	6	45	21	68	0.68 (0.27 to 1.68)	NS

*Rates of HCC in the New Zealand general population range from 0.3/100 000 in Caucasians to 20/100 000 in Chinese.
HCC, hepatocellular carcinoma.

There was no difference in non-liver related causes of death between the HBsAg-positive patients and HBsAg-negative controls (table 1).

Hepatocellular carcinoma

Fifteen HBsAg-positive individuals developed HCC over 28 years of follow-up (2.6%). No HBsAg-negative controls developed HCC during the study (figure 3). The incidence of HCC was higher in the HBsAg-positive patients compared with HBsAg-negative controls, but there was no difference in the rate of other malignancies.

When the cohort was divided into two groups: <30 years at study entry versus >30 years at study entry, the incidence of HCC was still lower overall than previously reported: 61/100 000 person-years and 327/100 000 person-years, respectively.

The median age at diagnosis of HCC was 52 years (range 28–73 years), 13/15 (87%) were men, 4/15 (27%) had a family history of HCC. Fibrosis stage was available in nine patients, in whom six had cirrhosis and one had advanced fibrosis. To date, 13/15 HCC cases have died, 12 from HCC progression and one from a motor vehicle accident. All had advanced HCC at the time of diagnosis and none were suitable for specific treatment. Two patients are alive at the time of writing—one underwent resection of a single small HCC in 2010 and remains recurrence-free. The other received transarterial embolisation for a large 7 cm HCC in 2010 and now has progressive disease and is receiving palliative care.

Of the 15 patients who developed HCC during the study period, 11 were receiving regular AFP surveillance for this complication, in which 10 were asymptomatic and screen-detected and one was diagnosed as an interval case following the onset of symptoms. All four patients who were not receiving surveillance, presented with symptomatic and advanced HCC.

All patients had elevated serum AFP levels (>10 ng/mL) at diagnosis (median 416, range 40.2–2620 ng/mL), with a trend towards higher levels in the four patients who were not receiving surveillance, (median 163.8 ng/mL vs 517.75 ng/mL), although this did not reach statistical significance (p=0.92).

On multivariate analyses, older age at study entry and Maori ethnicity were significant predictors of HCC and liver-related death. HBeAg positivity was not a predictor of either outcome.

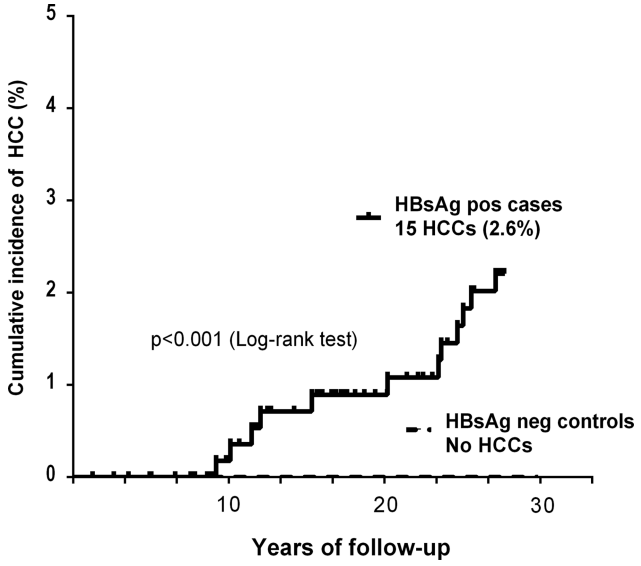

Figure 3 Incidence of hepatocellular carcinoma (HCC). HBsAg, hepatitis B surface-antigen.

Cirrhosis (LSM>11 kPa)

Three hundred and forty-four of the 518 surviving patients underwent transient elastography in 2012 (66%), of which 322 had reliable measurements (94%). There were 33 patients (10%) with cirrhosis after a follow-up of 28 years (9016 patient-years follow-up). The incidence of cirrhosis was 366/100 000 person-years.

On univariate analysis, patients with cirrhosis were more likely to be older: median age 51 years (range 29–73) compared with patients without cirrhosis: 44 years (range 29–85 years). There was no difference in gender, ethnicity, HBeAg status at entry and rate of HBsAg clearance between the two groups. On multivariate analyses, increasing age at baseline was a statistically

Table 2 Baseline characteristics of HBeAg-positive patients compared with HBeAg-negative patients among HBsAg-positive patients (n=572)

Baseline characteristics	HBeAg-positive (n=237)	HBeAg-negative (n=335)	p Value
Age (years) median, range	10.6 (0.5–70.8)	22.5 (0.9–68)	<0.0001
Māori (%)	194 (82%)	250 (75%)	0.0524
Gender (M:F)	1.9:1	1.5:1	0.22

HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface-antigen.

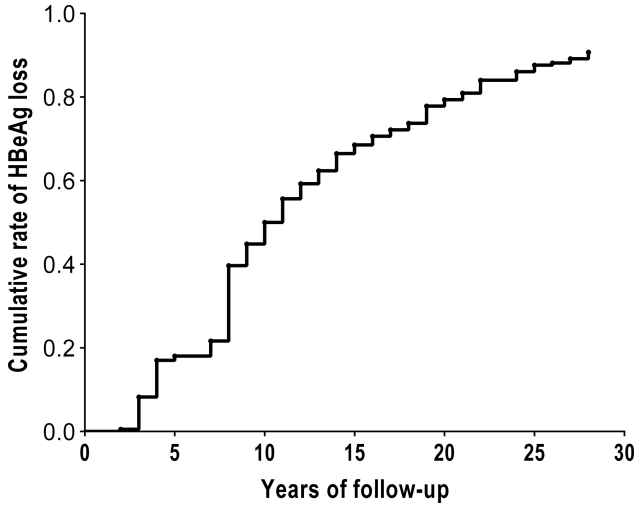

Figure 4 HBeAg loss. HBeAg, hepatitis B e-antigen.

significant predictor for cirrhosis: HR 1.0 (95% CI 1.0 to 1.1), p<0.05.

HBeAg loss

In 1984, 237 patients (41%) were HBeAg-positive. Baseline HBeAg-positive status was associated with younger age and Māori ethnicity (table 2).

In 2012, repeat HBeAg serology was obtained in 201/237 (85%) HBeAg-positive patients. During the 3051 person-years of follow-up, 184 (92%) underwent HBeAg seroconversion, at a median age of 23 years (range 6–66 years) (figure 4). Of those who lost HBeAg 95% developed antibodies to hepatitis B e-antigen (HBeAb). The overall annual rate of HBeAg loss was 6% overall, with a trend to lower HBeAg loss with increasing age at baseline, p=0.98 (table 3).

On univariate analysis, HBeAg loss was associated with younger age and Māori ethnicity. Baseline ALT was not associated with HBeAg loss. On multivariate analysis, Māori ethnicity was the only independent baseline predictor of HBeAg loss (table 4).

Only 6 of the 21 HBeAg-positive patients who received antiviral treatment achieved HBeAg seroconversion (29%).

HBsAg loss

Repeat HBsAg serology was obtained in 438 (77%) patients in 2012. During the 10 849 person-years of follow-up, 145 (33%) became HBsAg-negative, at a median age of 40 years (4–80 years). The overall rate of HBsAg loss was 1.34/100 person-years overall (figure 5), and increased with increasing age at baseline; p<0.0001 (table 5). Of those who lost HBsAg, 95% developed detectable anti-HBs and 78% developed levels >10 IU/L.

On univariate analysis, HBsAg loss was associated with increasing age and HBeAg-negative status at baseline. Baseline ALT level was not associated with HBsAg loss.

On multivariate analysis using Cox proportional hazards models, increasing age at baseline remains a significant baseline predictor of HBsAg loss (table 6)

No patients developed HCC or had a liver-related death after HBsAg clearance.

Table 3 Calculated annual rates of HBeAg loss according to age at study entry

Age at entry (years)	Number of individuals (n)	Māori (%)	Person-years of follow-up	Number with HBeAg loss	Rate of HBeAg loss (per 100 person-years)
<20	193	83	2513	156	6.2
20–39	36	89*	472	26	5.5*
>40	8	25†	76	2	2.6*
Total	237	82	3061	184	6.0

*p=NS for comparisons with <20 years group.
†p<0.0001 for comparisons with <20 years and 20–39 years.
HBeAg, hepatitis B e-antigen.

Table 4 Multivariate analysis of baseline predictors of HBeAg loss (n=237)

Variables	OR (95% CI)
Gender	
Female	1.0 (reference)
Male	1.0 (0.7 to 1.4)
Age at study entry	
1-year increment	1.01 (0.99 to 1.03)
Ethnicity	
Non-Māori	(reference)
Māori	1.7 (1.1 to 2.7)*

*p<0.05; Cox proportional hazards models.
HBeAg, hepatitis B e-antigen.

DISCUSSION

Previous published studies of CHB have been largely cross-sectional studies from specialised hepatology clinics, thereby skewed towards patients with severe liver disease, referred for antiviral therapy. Longitudinal community-based studies are necessary to accurately determine the natural history of untreated CHB. In the recent REVEAL study from Taiwan, population screening identified 3653 HBsAg-positive patients, who were subsequently followed in the community for 11 years.[20–22] All patients were of Chinese ethnicity with predominantly vertically transmitted HBV genotypes B and C. In this

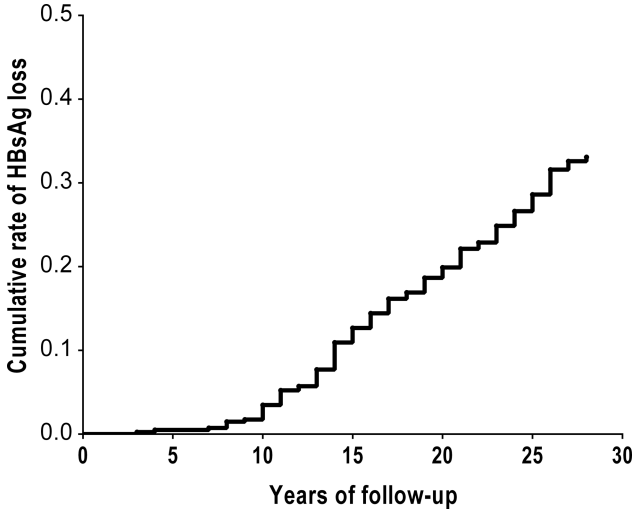

Figure 5 HBsAg loss. HBsAg, hepatitis B surface-antigen.

Table 5 HBsAg loss according to age at study entry

Age at entry (years)	n	Person-years follow-up	No. with HBsAg loss	Rate of HBsAg loss (per 100 person-years)
<20	265	6736	71	1.05
20–39	152	3741	58	1.55*
40 and over	21	372	16	4.3†
Total	438	10 849	145	1.34

*p=0.03 for comparison with <20 years group.
†p<0.0001 for comparison with <20 years group.
HBsAg, hepatitis B surface-antigen.

current New Zealand study, 572 Polynesian patients with presumably horizontally transmitted HBV genotypes C and D, were followed for almost 30 years.

The major strengths of this current study are the longer duration of follow-up and use of transient elastography to stage fibrosis.

The incidence of HCC in this current study is 114/100 000 person-years, which is lower than previous community-based longitudinal studies: 470/100 000 person-years in a study from Toronto, Canada,[32] 822/100 000 person-years in the REVEAL study and 1158/100 000 person-years in the Beasley study from Taiwan.[33] The lower incidence of HCC in this current study may reflect the younger age at study entry (median 17 years in this study compared with 45 years in the REVEAL study). Subgroup analysis for those >30 years of age at study entry revealed an incidence that is still very much lower (327/100 000 person years) than that in the REVEAL study (where all subjects were >30 years old). Difference in ethnicity (Polynesian vs Asian), age of HBV infection (early childhood rather than at birth) and HBV genotype distribution (D vs B/C) may also contribute to the observed differences in HCC incidence in the current and REVEAL studies. All liver-related mortality was due to HCC and not decompensated cirrhosis, again probably due to the young age of the population, with very few patients with cirrhosis.

The incidence of cirrhosis in our cohort is also lower than previously reported: 0.4% overall per annum compared with 0.7–0.9% in other studies. This is despite the use of transient elastography to define cirrhosis, which is expected to be more sensitive at picking up cirrhosis than ultrasound scans used in other studies. This difference seen is again most likely due to the younger age of our population.

Table 6 Multivariate analysis of baseline predictors of HBsAg loss (n=438)

Variables	OR (95% CI)
Gender	
Female	(reference)
Male	1.4 (0.9 to 2.0)
Age at study entry	
1-year increment	1.02 (1.00 to 1.04)†
Ethnicity	
Non-Māori	(reference)
Māori	1.2 (0.7 to 1.8)
HBeAg	
Negative	(reference)
Positive	0.9 (0.4 to 1.8)

†p<0.05, Cox proportional hazards models.
HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface-antigen.

The rate of spontaneous HBeAg loss was higher (6% per annum) and occurred at an earlier age (median 23 years vs 30–39 years) in this current study than in previous Asian studies.[34] The rate of spontaneous HBsAg loss was also higher (1.34% per annum) and occurred earlier (40 years vs 50 years) in this current study. Many different host and viral factors determine spontaneous seroconversion and the differences observed between the current and previous Asian studies may reflect differences in ethnicity, age of HBV infection, median age of the cohort and HBV genotype.[35] In the Alaskan study, where HBV transmission is also through early horizontal infection, the rate of spontaneous loss of HBeAg was higher (7.3% per annum) but rate of HBsAg loss was lower (0.5% per annum) than this current study.[14] The high HBeAg loss in the Alaskan study may reflect the specific HBV genotype (F) found in this population.

The age of HBsAg loss has been shown to be important in determining risk of HCC as many patients who undergo late HBsAg seroconversion will already have advanced fibrosis or cirrhosis. In our cohort, no patients to date have developed HCC after HBsAg loss. Those patients that were found to have severe fibrosis (LSM>8 kPa) or cirrhosis on transient elastography were offered continued lifelong HCC surveillance.[16 36–38]

Limitations of this study include the lack of documentation of other cofactors of liver disease in the original study (alcohol use, aflatoxin or co-infection with hepatitis C/HIV), lack of fibrosis data at baseline and limited availability of ultrasound screening for HCC.

In summary, early horizontally acquired HBV infection in Māori and Pacific Island Peoples is associated with increased liver-related mortality due to an increased rate of HCC compared with non-HBV infected controls. However, the natural history of chronic HBV infection in Māori and Pacific Island Peoples appears to be more benign than that observed in Asian studies, with a lower observed incidence of HCC, liver-related mortality and cirrhosis, and higher rates and earlier age of HBeAg and HBsAg loss. Further studies should investigate which host and viral factors determine this more favourable outcome.

Acknowledgements Helen Purcell and John Hornell at The Hepatitis Foundation of New Zealand. Simon Moyes and Mathu Shanthakumar for their statistical support.

Contributors THL, EG, CM and CC were directly involved in seeing participants and assessing them at each visit. BB was involved right from the conception of the project with planning the study and was responsible for all statistical analyses.

Funding This study is funded by the Health Research Council of New Zealand and the New Zealand Society of Gastroenterology who do not have any role in the study design, collection, analysis or interpretation of data.

Competing interests None.

Ethics approval Northern Y ethics committee.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Robinson T, Bullen C, Humphries W, *et al*. The New Zealand Hepatitis B Screening Programme: screening coverage and prevalence of chronic hepatitis B infection. *N Z Med J* 2005;118:1211.
2 Blakely T, Salmond C, Tobias M. Hepatitis B virus carrier prevalence in New Zealand: population estimates using the 1987 police and customs personnel survey. *N Z Med J* 1998;111:142–4.
3 Tobias MI, Miller JA, Clements CJ, *et al*. Hepatitis B in New Zealand children: the 1985 national immunisation survey. *N Z Med J* 1985;100:203–6.
4 Tukuitonga CF, Solomon N, Stewart A. Incidence of cancer among Pacific Island people in New Zealand. *N Z Med J* 1992;105:463–6.

5 Weir R, Brunton CR, Blakely TA. Chronic liver disease mortality attributable to hepatitis B and C in *New Zealand. J Gastroenterol Hepatol* 2002;17:582–8.
6 Ter Bong F, Ten Kate F, Cuypers H, *et al*. Relation between laboratory test results and histologic hepatitis activity in individuals positive for HBsAg and antibodies to HBeAg. *Lancet* 1998;351:1914–18.
7 Lindh M, Horal P, Dhillon A, *et al*. HBV DNA levels, precore mutations, genotypes and histologic activity in CHB. *J Viral Hepat* 2000;7:258–67.
8 Tai D, Lin S, Chu C, *et al*. Long term outcome of HBeAg negative HBsAg carriers in relation to changes of ALT over time. *Hepatology* 2009;49:1859–67.
9 McMahon BJ, Bulkow L, Harpster A, *et al*. Screening for hepatocellular carcinoma in Alaska natives infected with chronic hepatitis B: a 16-year population-based study. *Hepatology* 2000;32:842–6.
10 Bruix J, Sherman M. Management of Hepatocellular carcinoma—an update. *Hepatology* 2011;53:1020–2.
11 Yuen MF, Hui CK, Cheng CC, *et al*. Long term follow up of interferon alfa treatment in Chinese patients with chronic hepatitis B infection: the effect of hepatitis B e-antigen seroconversion and the development of cirrhosis-related complications. *Hepatology* 2001;34:139–45.
12 Chu Cm, Liaw YF. HBsAg seroclearance in asymptomatic carriers of high endemic areas: appreciably high rates during a long term follow up. *Hepatology* 2007;45:1187–92.
13 Liaw YF, Sheen IS, Chen TJ, *et al*. Incidence, determinants and significance of delayed clearance of serum HBsAg in chronic hepatitis B virus infection: a prospective study. *Hepatology* 1991;13:627–31.
14 McMahon BJ, Holck P, Bulkow L, *et al*. Serologic and clinical outcomes of 1536 Alaska Natives chronically infected with hepatitis B virus. *Ann Intern Med* 2001;135:759–68.
15 Kim JH, Lee JH, Park SJ, *et al*. Factors associated with natural seroclearance of hepatitis B surface antigen and prognosis after seroclearance: a prospective follow-up study. *Hepatogastroenterology* 2008;55:576–81.
16 Simonetti J, Bulkow L, McMahon BJ, *et al*. Clearance of hepatitis B surface antigen and risk of hepatocellular carcinoma in a cohort chronically infected with hepatitis B virus. *Hepatology* 2010;51:1531–7.
17 De Franchis R, Meucci G, Vecchi M, *et al*. The natural history of asymptomatic hepatitis B surface antigen carriers. *Ann Intern Med* 1993;118:191–4.
18 Yang H-I, Yuen M-F, Chan H-L, *et al*. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol* 2011;12:568–74.
19 Flink HJ, van Zonneveld M, Hansen BE, *et al*. Treatment with peg-interferon alpha-2b for HbeAg positive chronic hepatitis B: HBsAg loss is associated with HBV genotype. *Am J Gastroenterol* 2006;101:297–303.
20 Chen CJ, Yang HI, Su J, *et al*. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006;295:65–73.
21 Iloeje UH, Yang HI, Su J, *et al*. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology* 2006;130:678–86.
22 Iloeje UH, Yang HI, Jen CL, *et al*. Risk and predictors of mortality associated with chronic hepatitis B infection. *Clin Gastroenterol Hepatol* 2007;5:921–31.
23 Liaw YF, Leung N, Kao JH, *et al*. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. *Hepatol Int* 2008;2:263–83.
24 Milne A, Allwood GK, Moyes CD, *et al*. A seroepidemiological study of the prevalence of hepatitis B infections in a hyperendemic New Zealand Community. *Int J Epidemiol* 1987;16:84–90.
25 Jazayeri MS, Basuni AA, Cooksley G, *et al*. Hepatitis B virus genotypes, core gene variability and ethnicity in the Pacific region. *J Hepatol* 2004;41:139–46.
26 Fung SK, Lok AS. Hepatitis B virus genotypes: do they play a role in the outcome of HBV infection? *Hepatology* 2004;40:790–2.
27 Chu CM, Liaw YF. Genotype C hepatitis B virus infection is associated with a higher risk of reactivation of hepatitis B and progression to cirrhosis than genotype B: a longitudinal study of hepatitis B e antigen-positive patients with normal aminotransferase levels at baseline. *J Hepatol* 2005;43:411–17.
28 Kao JH, Chen PJ, Lai MY, *et al*. Hepatitis B genotypes correlate with clinical outcomes in patients with chronic hepatitis B. *Gastroenterology* 2000;118:554–9.
29 Sumi H, Yokosuka O, Seki N, *et al*. Influence of hepatitis B virus genotypes on the progression of chronic type B liver disease. *Hepatology* 2003;37:19–26.
30 Sanchez-Tapias JM, Costa J, Mas A, *et al*. Influence of hepatitis B virus genotype on the long term outcome of chronic hepatitis B in western patients. *Gastroenterology* 2002;123:1848–56.
31 Marcellin P, Ziol M, Bedossa P, *et al*. Non-invasive assessment of liver fibrosis by stiffness measurement in patients with chronic hepatitis B. *Liver Int* 2009;29:242–7.
32 Sherman M, Peltekian KM, Lee C. Screening for hepatocellular carcinoma in chronic carriers of hepatitis B virus: incidence and prevalence of hepatocellular carcinoma in a North American urban population. *Hepatology* 1995;22:432–8.
33 Beasley RP, Hwang LY, Lin CC, *et al*. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22,707 men in Taiwan. *Lancet* 1981;2:1129–33.
34 Chu CM, Sheen IS, Lin SM, *et al*. Sex differences in chronic hepatitis B virus infection: studies of serum HBeAg and alanine aminotransferase levels in 10,431 asymptomatic Chinese HBsAg carriers. *Clin Infect Dis* 1993;16:709–13.
35 Ooi E-K, Schroeder B, Gane E, *et al*. High prevalence of precore mutant infection in New Zealand Maori and Pacific Islanders. *Hepatology* 1998;28:214A.
36 Ahn SH, Park YN, Park JY, *et al*. Long term clinical and histological outcomes in patients with spontaneous hepatitis B surface antigen seroclearance. *J Hepatol* 2005;42:188–94.
37 Dragosics B, Ferenci P, Hitchman E, *et al*. Long term follow up study of asymptomatic HBsAg-positive voluntary blood donors in Austria: a clinical and histologic evaluation of 242 cases. *Hepatology* 1987;7:302–6.
38 Arase Y, Ikeda K, Suzuki F, *et al*. Long-term outcome after hepatitis B surface antigen seroclearance in patients with chronic hepatitis B. *Am J Med* 2006;119:e9–15.

GUT

Serological and clinical outcomes of horizontally transmitted chronic hepatitis B infection in New Zealand Maori: results from a 28-year follow-up study

Tien Huey Lim, Edward Gane, Chris Moyes, Barry Borman and Chris Cunningham

Gut published online July 8, 2014